The Relationship between CYP4A11 and CYP4F2 Gene Polymorphisms and Coronary Heart Disease in Chinese: A Meta-analysis

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Abstract

Aim: To investigate the correlation between CYP4A11 and CYP4F2 polymorphisms and coronary heart disease in Chinese. Methods: The related research data of CYP4A11 and CYP4F2 gene polymorphism and coronary heart disease were searched through the Internet and analyzed by Review Manager 5.3 software. Results: A total of 6 articles were included. Meta-analysis shows that there is heterogeneity between CYP4A11 gene rs3890011 genotype and coronary heart disease risk research. The CC and GG genotypes of CYP4A11 gene rs3890011 had statistical significance with the occurrence of coronary heart disease. The AA and AG genotypes of CYP4A11 gene rs9332978 had statistical significance with the occurrence of coronary heart disease. TT, CT and CC genotypes of CYP4A11 gene rs1126742 had no statistical significance with coronary heart disease. Heterogeneity exists in studies on CC and TT genotypes of CYP4F2 gene rs2108622 and the risk of coronary heart disease. The CC and TT genotypes of CYP4F2 gene rs2108622 had statistical significance with the occurrence of coronary heart disease, while the CC, CT and TT genotypes of CYP4F2 gene rs1558139 had no statistical significance with the occurrence of coronary heart disease. Conclusion: Based on the results of this paper, CYP4A11 and CYP4F2 gene polymorphisms are associated with coronary heart disease in Chinese.

Keywords

CYP4A11; CYP4F2; Gene Polymorphism; Coronary Heart Disease; Meta-analysis.

1. Introduction

Coronary heart disease (CHD) is a heart disease caused by narrowing or obstruction of vascular lumen caused by atherosclerotic lesions in coronary arteries, resulting in myocardial ischemia, hypoxia or necrosis. According to the investigation report of the World Health Organization, coronary heart disease is one of the main causes of human death, and the incidence rate is increasing year by year, and its treatment, especially prevention, is extremely important.

Cytochrome 450 is a heme thioferrin enzyme system that exists widely in organisms, and it plays a very important role in the metabolism of exogenous and endogenous compounds [1]. Studies [2-3] confirmed that CYP catalyzed arachidonic acid (AA) to produce epoxy eicosatrienoic acid (EETs), 20-hydroxy 24 enoic acid (20-HETEs) and prostacyclin. 20-HETEs plays an important role in regulating vascular dynamics by mediating vasoconstriction and vascular remodeling caused by angiotensin II, norepinephrine and Pituitrin. Among them, CYP4A11 and CYP4F2 gene polymorphisms can affect the metabolism of AA to produce 20-HETEs. There are many mutation sites in CYP4A11 and CYP4F2, such as rs9332978, rs3890011, rs1126742, rs2108622, rs1558139 and so on. Studies have found that these loci may be associated with coronary heart disease, but do not come to a consistent conclusion, so it is of important scientific value and extensive social benefits to study the relationship between CYP4A11 and CYP4F2 gene polymorphism and coronary heart disease. However, there are few clinical studies on the relationship between CYP4A11 and CYP4F2 gene polymorphism and coronary heart disease in Chinese population. The purpose of this study is to

enlarge the sample size by summarizing the literature on the relationship between CYP4A11 and CYP4F2 gene polymorphisms and coronary heart disease in Chinese, hoping to find out the relationship between CYP4A11 and CYP4F2 gene polymorphisms and coronary heart disease in Chinese more accurately.

2. Materials and Methods

2.1 Search Strategy

The five researchers conducted a comprehensive search of Chinese (CNKI, VIP, wanfang) and English (PubMed, Web of Science) databases to find relevant Chinese and English research articles published before December 15, 2020 (the date of completion of the search).A literature review was performed using the terms "CYP4A11", "CYP4F2", "Gene polymorphism" AND " coronary heart disease ".

2.2 Study selection

Inclusion criteria: (1) Literature on the relationship between CYP4A11 and CYP4F2 gene polymorphisms and coronary heart disease; (2)Each article reported the distribution of genotype frequency in coronary heart disease group and control group;(3)The genotypic distribution of each was in accordance with the genetic balance of Hardy-Weinberg.

Exclusion criteria: (1) Literature that cannot provide valid data;(2)Literature published with duplicate data; (3) Non-Chinese and English literature.

Completed independently by 5 researchers, they searched the literature by title or key word respectively to obtain the full text. By reading the abstract, the documents that did not meet the standard were excluded, and the full text was read to further exclude the literature that did not meet the standards and the research quality was low.

2.3 Quality assessment

Potential risks of bias were evaluated, using the Cochrane tool developed for this purpose [4]. This tool assesses bias in different domains: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and study staff (performance bias); blinding of outcome assessors (detection bias); incomplete results data (attrition bias); selective reporting of results (reporting bias); and other sources of bias. Each domain was rated as “High”, “Low” or “Unclear” depending on the judgment of each author following the recommendations.[5]

2.4 Literature data analysis

Make Excel table and extract relevant data from the final included literature: author, publication time, nationality, sex, number of genotypes, distribution of genotypes in cases and controls.

Review Manager 5.3 (http://ims.cochrane.org/revman/download) was used for Meta analysis, and the combined effect amount of each genotype combination and 95% confidence interval (95%CI) were calculated. Using I^2 statistics for heterogeneity test, when $I^2 < 50\%$, it is considered that there is no heterogeneity among the studies, and the fixed effect model is used to analyze the literature data; when $I^2 > 50\%$, it is considered that there is heterogeneity. Random effect model is used. $P \leq 0.05$ means that the difference is statistically significant, and forest map is used for statistical description. Publication bias was evaluated by funnel chart.

3. Result

3.1 Literature screening results and quality evaluation results

A total of 70 articles were obtained from each literature database. After reading the full text to exclude the literature that did not meet the requirements, lack of inter-group data and duplicated data, 6 articles and 5535 subjects were obtained. As shown in Figure 1.

The basic characteristics of the literature are included. As shown in Table 1.

Included in the quality evaluation of the literature, see the quality evaluation chart. As shown in Figure 2.

Table 1. Incorporate into the basic characteristics table of literature.

Name	Time	Nation	Sex	Genotype	CAD		Control	
					Events	Total	Events	Total
Zhenyan Fu	2012	Han	Men	rs9332978 A/A	172	276	120	180
				rs9332978 A/G	90	276	54	180
				rs9332978 G/G	14	276	6	180
		Han	Women	rs9332978 A/A	51	85	94	135
				rs9332978 A/G	28	85	38	135
				rs9332978 G/G	6	85	3	135
		Uigur	Men	rs9332978 A/A	210	277	97	132
				rs9332978 A/G	61	277	29	132
				rs9332978 G/G	6	277	6	132
		Uigur	Women	rs9332978 A/A	35	54	36	50
				rs9332978 A/G	18	54	13	50
				rs9332978 G/G	1	54	1	50
		Han	Men	rs3890011 C/C	78	276	46	180
				rs3890011 C/G	121	276	102	180
				rs3890011 G/G	77	276	32	180
		Han	Women	rs3890011 C/C	19	85	42	135
				rs3890011 C/G	45	85	66	135
				rs3890011 G/G	21	85	27	135
		Uigur	Men	rs3890011 C/C	107	277	53	132
				rs3890011 C/G	122	277	60	132
				rs3890011 G/G	48	277	19	132
		Uigur	Women	rs3890011 C/C	17	54	21	50
				rs3890011 C/G	21	54	20	50
				rs3890011 G/G	16	54	9	50
		Han	Men	rs1126742 T/T	186	276	118	180
				rs1126742 T/C	72	276	56	180
				rs1126742 C/C	18	276	6	180
		Han	Women	rs1126742 T/T	59	85	84	135
				rs1126742 T/C	19	85	43	135
				rs1126742 C/C	7	85	8	135
		Uigur	Men	rs1126742 T/T	183	277	93	132
				rs1126742 T/C	85	277	35	132
				rs1126742 C/C	9	277	4	132
		Uigur	Women	rs1126742 T/T	33	54	33	50
				rs1126742 T/C	17	54	14	50
				rs1126742 C/C	4	54	3	50
Svetlana Sirotina	2018	Russia		rs3890011 C/C	338	637	404	686
				rs3890011 C/G	244	637	236	686
				rs3890011 G/G	55	637	46	686
				rs9332978 A/A	477	637	526	686
				rs9332978 A/G	160	637	158	686
				rs9332978 G/G	0	637	0	686
LIU Junhua	2012	Han		rs9332978 A/A	111	168	225	297
				rs9332978 A/G	53	168	68	297
				rs9332978 G/G	4	168	4	297
				rs1126742 T/T	100	168	150	297
				rs1126742 T/C	53	168	123	297
				rs1126742 C/C	15	168	24	297

A. Basic characteristics of CYP4A11 gene polymorphism and coronary heart disease.

Name	Time	Nation	Genotype	CAD		Control	
				Events	Total	Events	Total
DAN San-li	2009	Han	rs2108622 C/C	252	420	193	412
			rs2108622 C/T	152	420	186	412
			rs2108622 T/T	16	420	33	412
LIU Junhua	2012	Han	rs1558139 C/C	58	168	105	297
			rs1558139 C/T	85	168	148	297
			rs1558139 T/T	25	168	44	297
WANG Xiao-huan	2017	Han	rs2108622 C/C	306	514	104	198
			rs2108622 C/T	183	514	78	198
			rs2108622 T/T	25	514	16	198
ZHAO Ping	2016	Han	rs1558139 C/C	81	285	76	264
			rs1558139 C/T	137	285	135	264
			rs1558139 T/T	67	285	53	264
		Mongolian	rs2108622 C/C	173	285	159	264
			rs2108622 C/T	97	285	115	264
			rs2108622 T/T	15	285	10	264

B. Basic characteristics of CYP4F2 gene polymorphism and coronary heart disease.

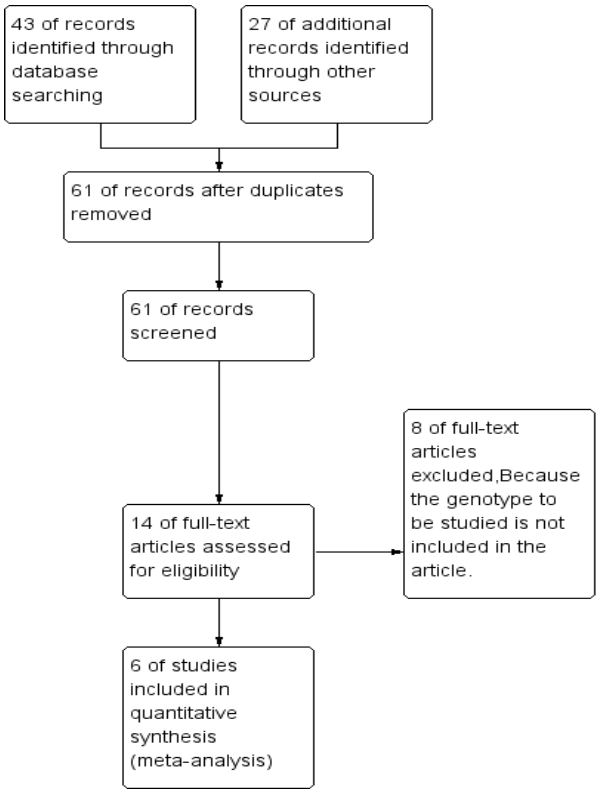
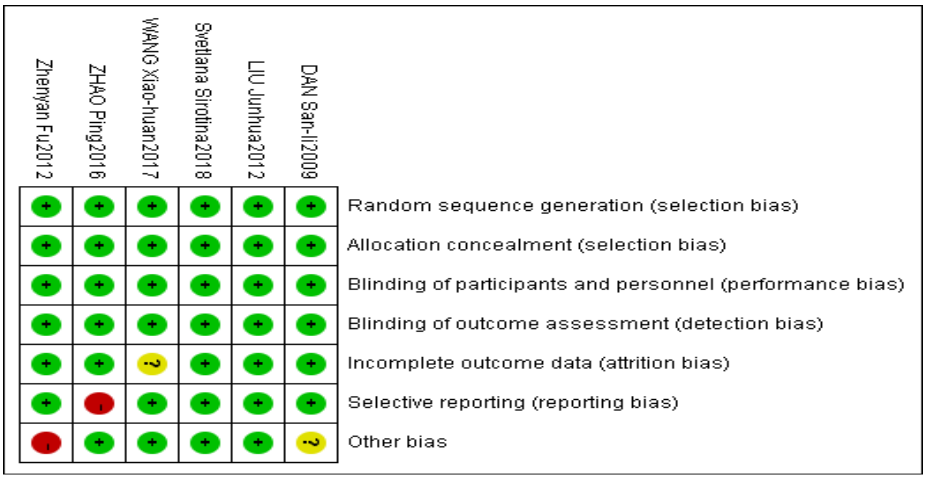
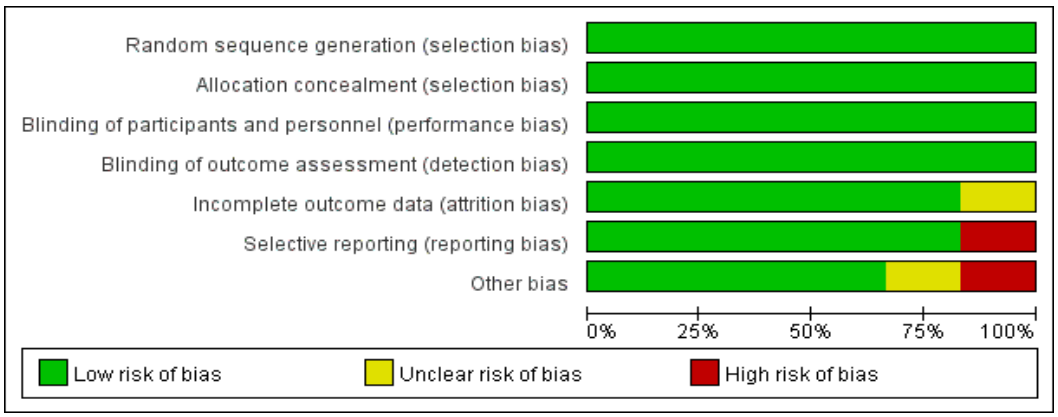


Figure 1. Flow chart of literature screening.



A. Individual bias assessment of included studies.



B. Summary bias assessment of included studies.

Figure 2. Risk of bias summary.

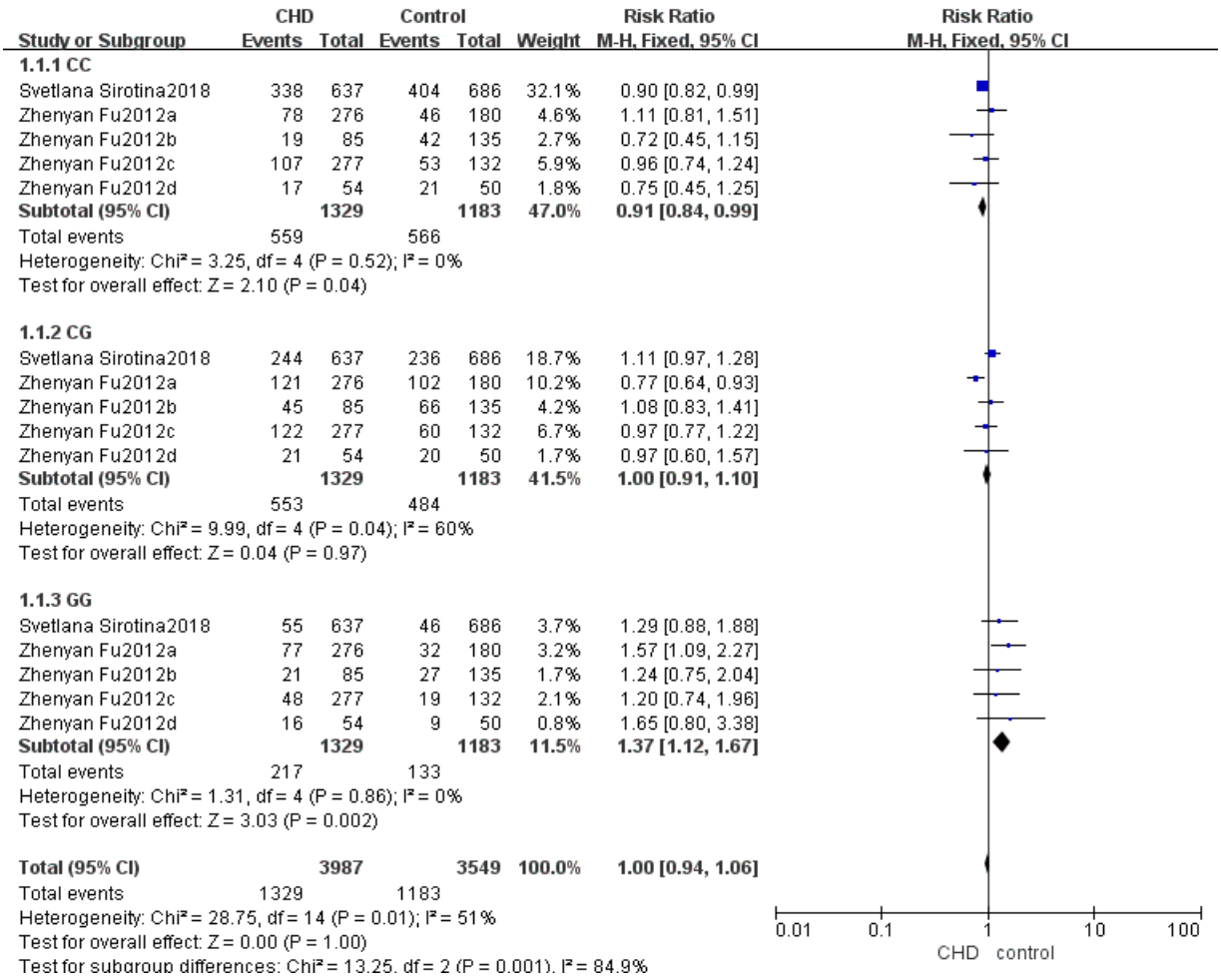


Figure 3. Forest map of the relationship between CC, CG, GG genotypes of CYP4A11 gene rs3890011 and coronary heart disease.

3.2 Gene polymorphism and risk analysis and heterogeneity analysis of coronary heart disease

3.2.1.Genetic polymorphism of CYP4A11 and risk analysis and heterogeneity analysis of coronary heart disease

Comparing the CC, CG and GG genotypes of CYP4A11 gene rs3890011 between the coronary heart disease group and the control group, the results showed that there was heterogeneity between patients with CG genotype and the risk of coronary heart disease (I^2=60%). Patients with CC genotype had a lower risk of coronary heart disease (OR = 0.91,95% CI: 0.84-0.99, P = 0.04), while patients with GG genotype had an increased risk of coronary heart disease (OR = 1.37,95% CI: 1.12-1.67, P = 0.002). As shown in Figure 3.

The TT, CT and CC genotypes of CYP4A11 gene rs1126742 in the coronary heart disease group and the control group were compared. the results showed that there was no correlation between patients with TT, CT and CC genotypes and the risk of coronary heart disease (OR = 1.04,95% CI: 0.97-1.12, P = 0.27; OR = 0.787,95% CI: 0.75-1.01, P = 0.07). OR = 1.31,95% CI: 0.88-1.96, P = 0.19). As shown in Figure 4.

The genotypes of AA, AG and GG of CYP4A11 gene rs9332978 in coronary heart disease group and control group were compared. The results showed that patients with AA genotype had a lower risk of coronary heart disease (OR = 0.95,95% CI: 0.91-1.00, P = 0.03), while patients with AG genotype had an increased risk of coronary heart disease (OR = 1.13,95% CI: 1.00-1.28, P = 0.04). The risk of developing coronary heart disease in patients with GG allele did not exist in correlation (OR = 1.31,95% CI: 0.77-2.24, P = 0.32). As shown in Figure 5.

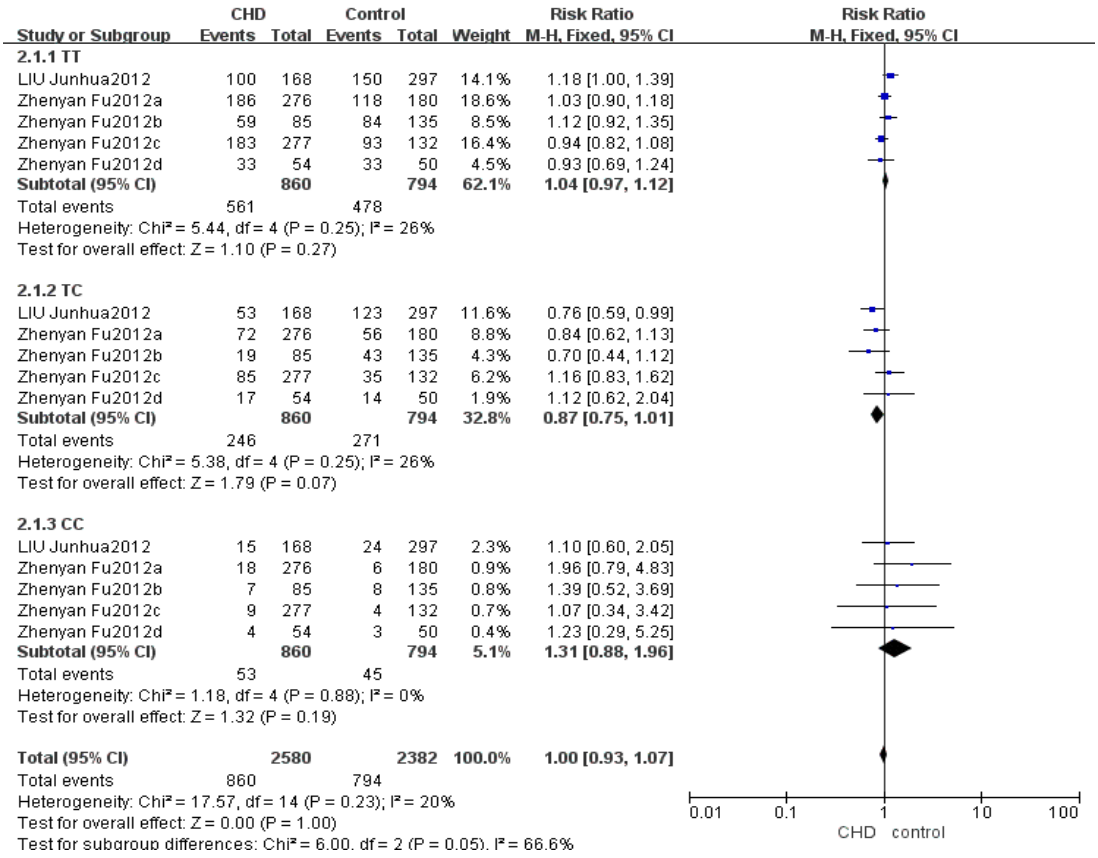


Figure 4. Forest map of the relationship between TT, CT, CC genotypes of CYP4A11 gene rs1126742 and coronary heart disease.

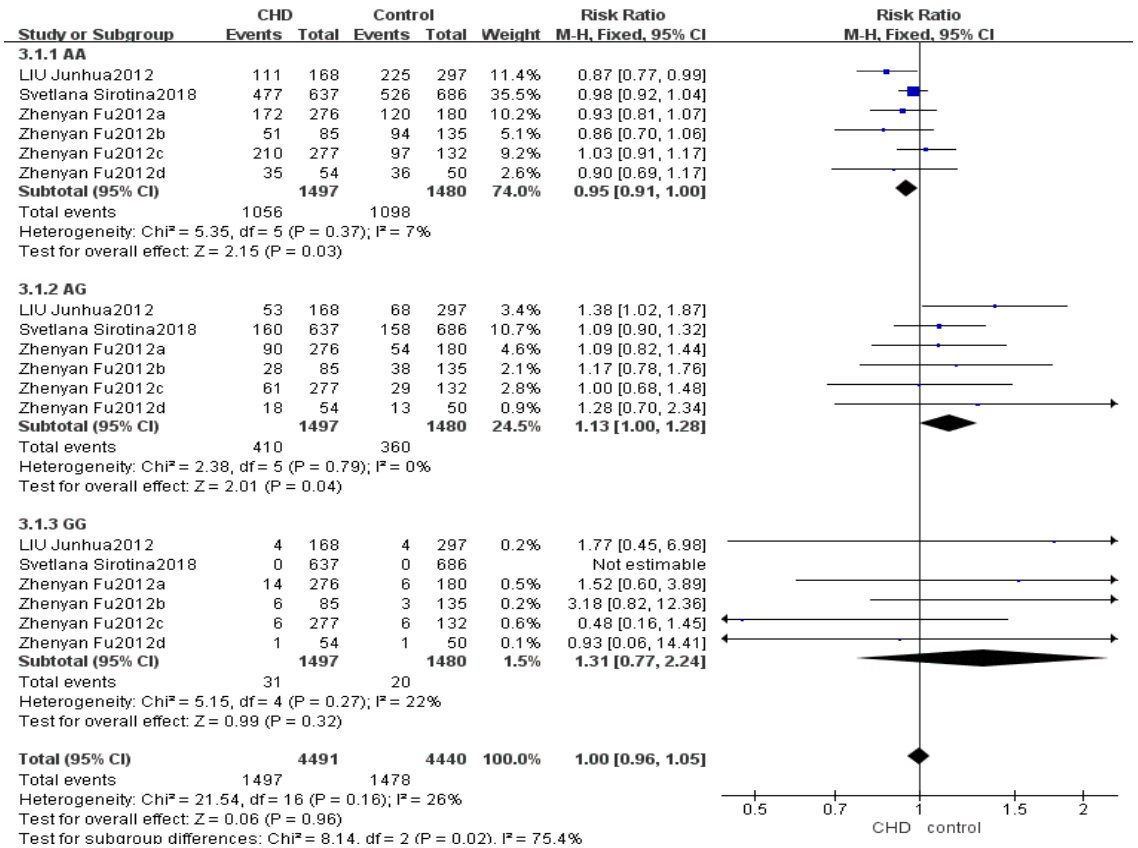


Figure 5. Forest map of the relationship between AA, AG, GG genotypes of CYP4A11 gene rs9332978 and coronary heart disease.

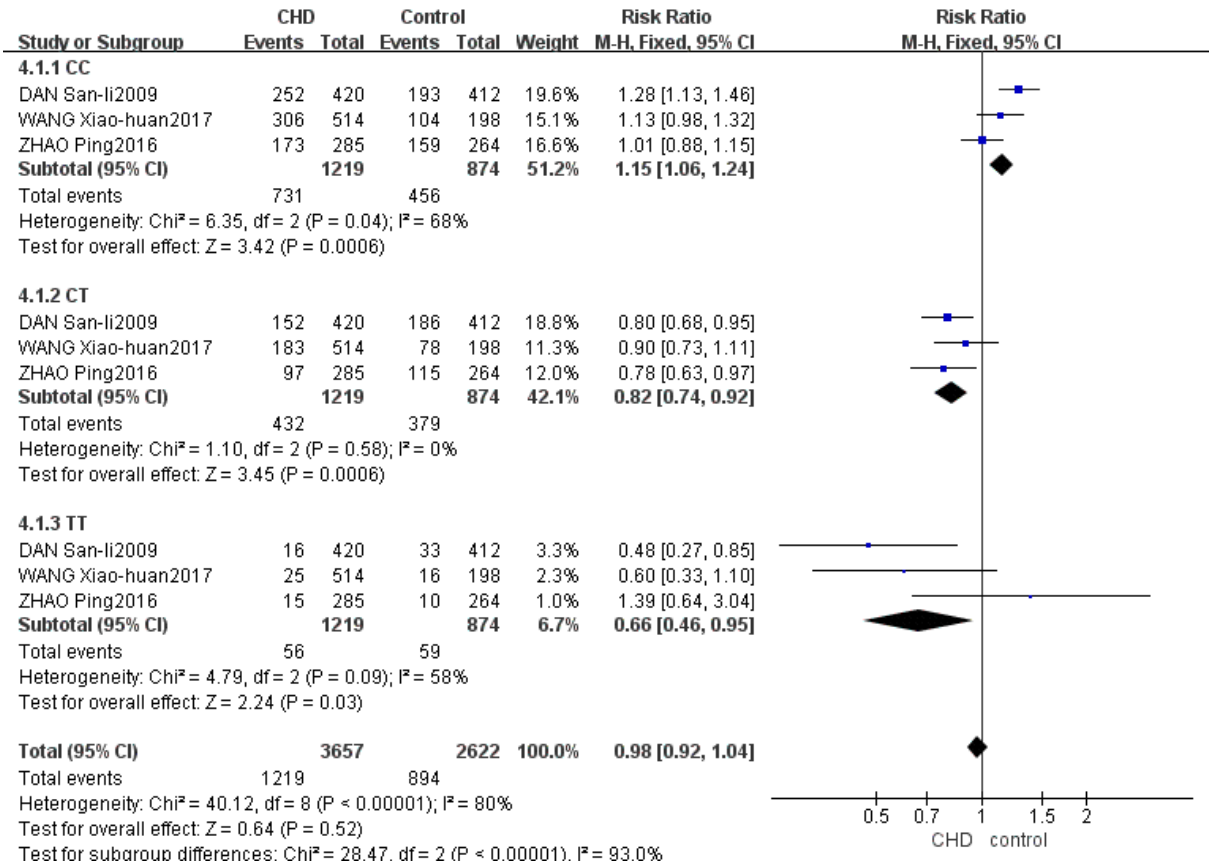


Figure 6. Forest map of the relationship between CC, CT, TT genotypes of CYP4F2 gene rs2108622 and coronary heart disease.

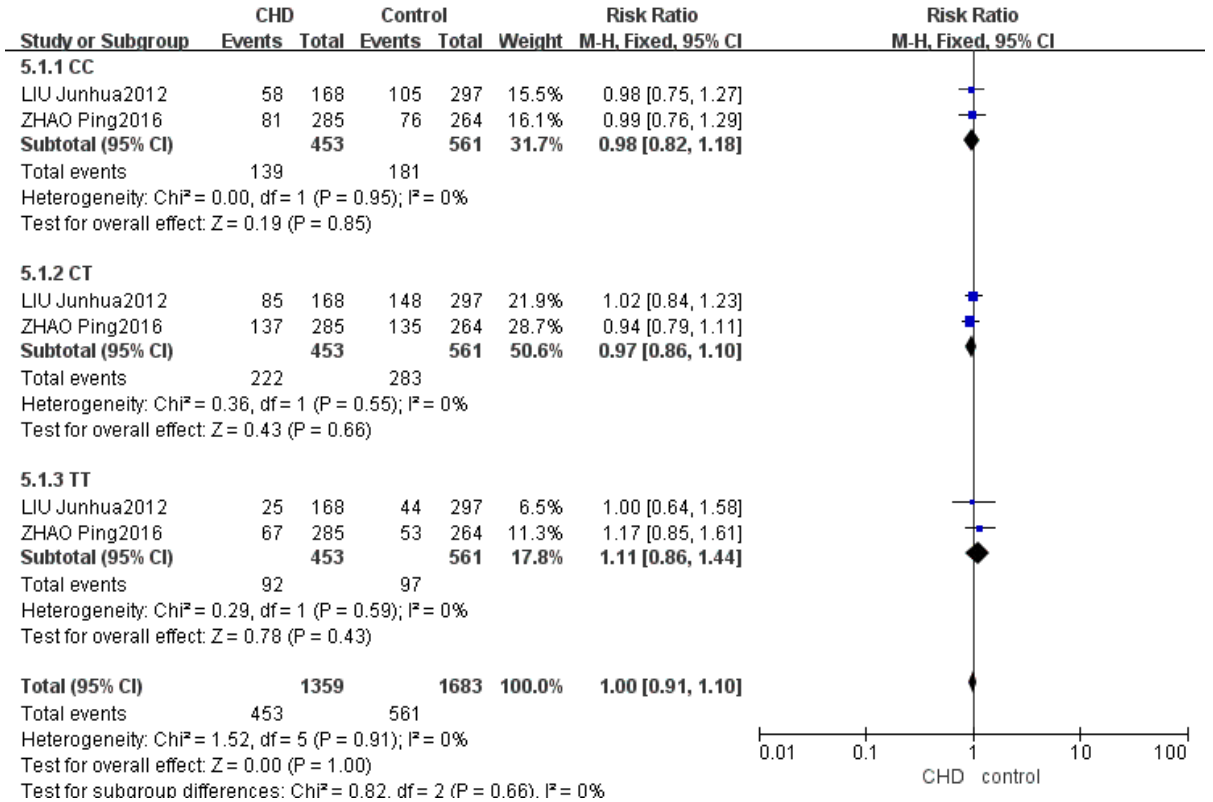


Figure 7. Forest map of the relationship between CC, CT, TT genotypes of CYP4F2 gene rs1558139 and coronary heart disease.

3.2.2.Genetic polymorphism of CYP4F2 and risk analysis and heterogeneity analysis of coronary heart disease

Comparing the CC, CT and TT genotypes of CYP4F2 gene rs2108622 between the coronary heart disease group and the control group, the results showed that the patients with CC and TT genotypes and the wind risk patients with coronary heart disease existed in heterogeneity (I^2=68%). Patients with CT genotype had a reduced risk of coronary heart disease (OR = 0.82, 95% CI: 0.74-0.92, P = 0.0006). As shown in Figure 6.

Comparing the CC, CT and TT genotypes of CYP4F2 gene rs1558139 between the coronary heart disease group and the control group, the results showed that there was no correlation between patients with CC, CT and TT genotypes and the risk of coronary heart disease (OR = 0.998,95% CI: 0.82-1.18, P = 0.85; OR = 0.97,95% CI: 0.86-1.10, P = 0.66). OR = 1.11,95% CI: 0.86-1.44, P = 0.43). As shown in Figure 7.

3.3 Subgroup analysis

The study found that there was heterogeneity between patients with CG genotype of CYP4A11 gene rs3890011 and the risk of coronary heart disease. Subgroup analysis was performed on patients with CG genotypes according to gender factors. The results showed that there was no heterogeneity between women with CG genotype and the risk of coronary heart disease (I^2=0%), as shown in Figure 8. Therefore, gender may be the reason for the heterogeneity between patients with CG genotype and the risk of coronary heart disease.

It was found that there was heterogeneity between patients with CC and TT genotypes of CYP4F2 gene rs2108622 and the risk of coronary heart disease. The patients with CC and TT genotypes from different nationalities were analyzed by subgroup analysis. The results showed that Han patients with CC genotype had an increased risk of coronary heart disease (OR=1.21,95%CI:1.08-1.37), while patients with TT genotype had a lower risk of coronary heart disease (OR=0.53,95%CI:0.35-0.81), as shown in Figure 9. Therefore, ethnic factors are the cause of heterogeneity between patients with CC and TT genotypes and the risk of coronary heart disease.

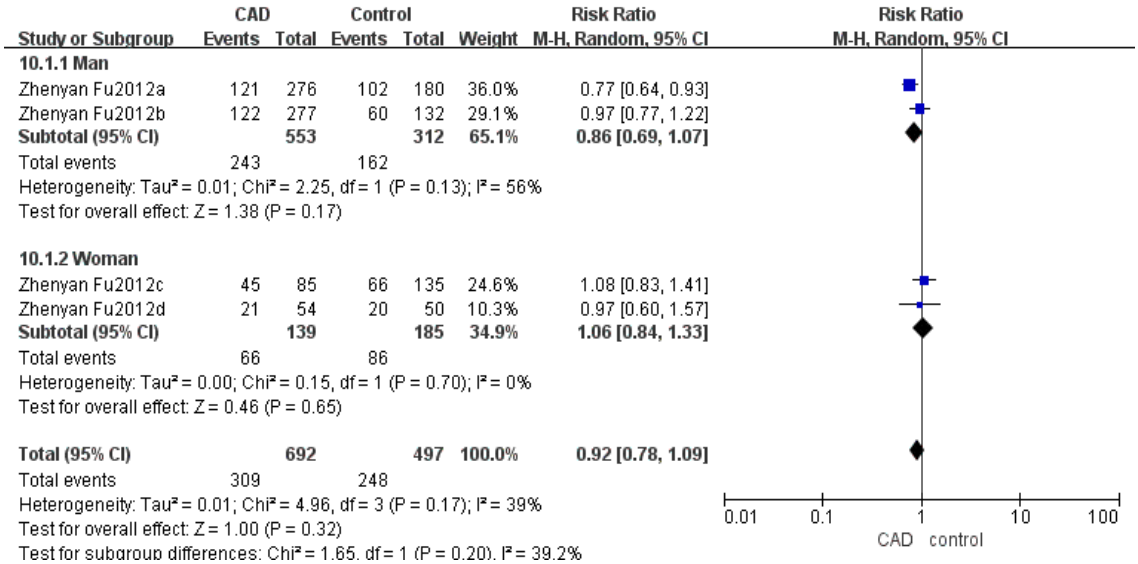
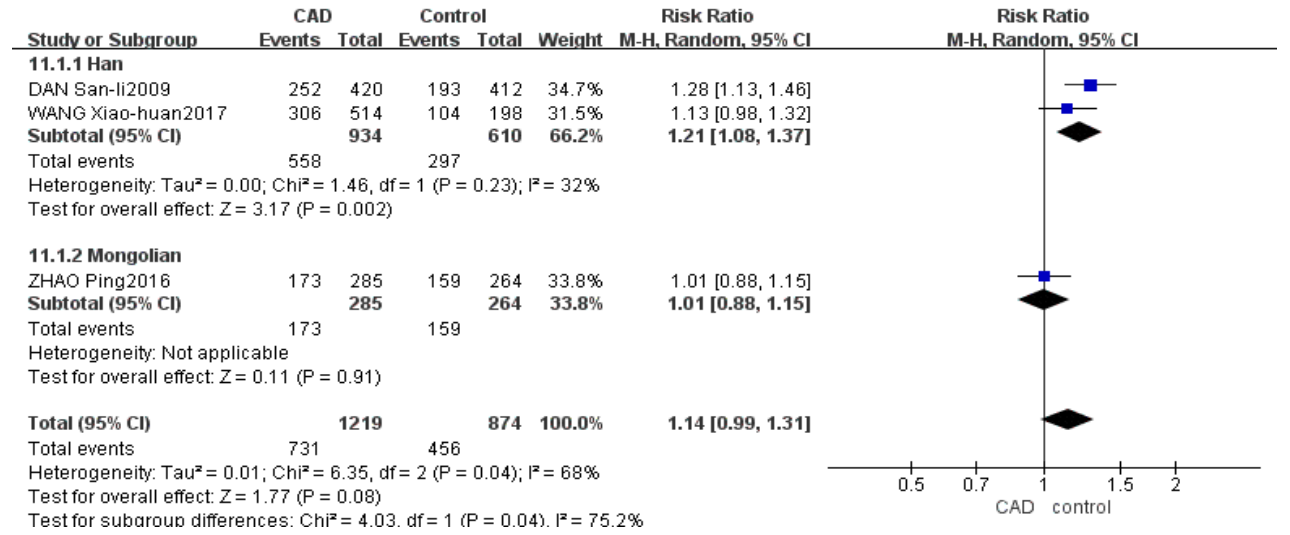


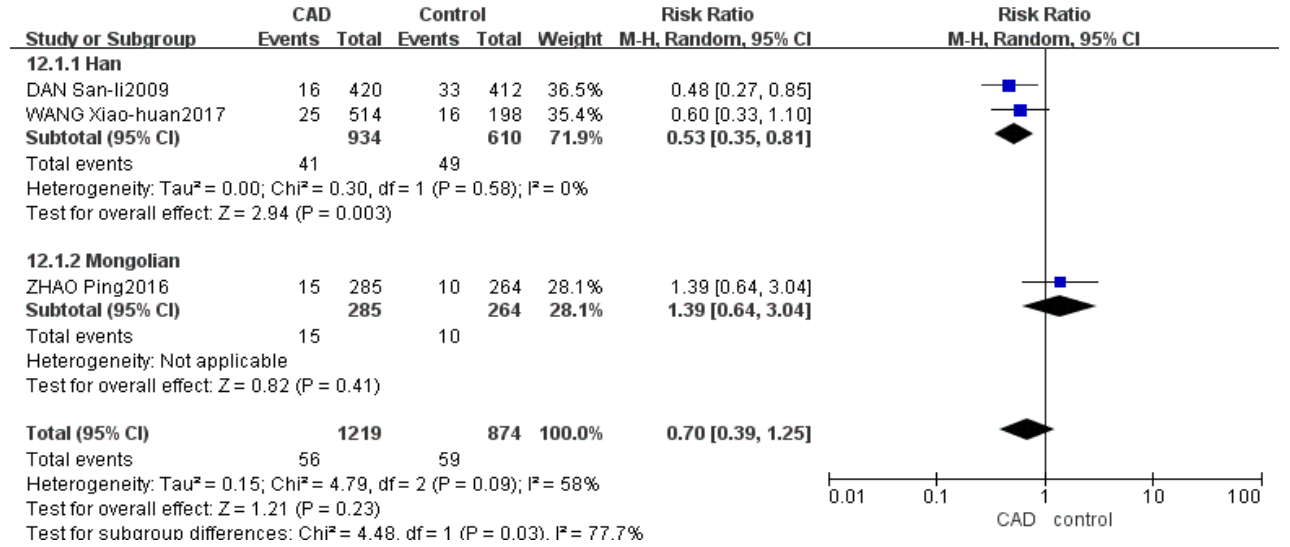
Figure 8. Subgroup analysis of gender factors in patients with CG genotype.

3.4 Sensitivity analysis

In the study of the relationship between the CG genotype of CYP4A11 gene rs3890011 and coronary heart disease, excluding a group of data from Zhengyuan Fu, the heterogeneity of each study changed, and the results were not statistically significant (OR = 1.07,95% CI:0.96-1.19, P = 0.23). As shown in Figure 10.



A. Effect of ethnic factors on CC genotypes.



B. Effect of ethnic factors on TTgenotypes.

Figure 9. Subgroup analysis of CC and TT genotypes in patients with ethnic factors.

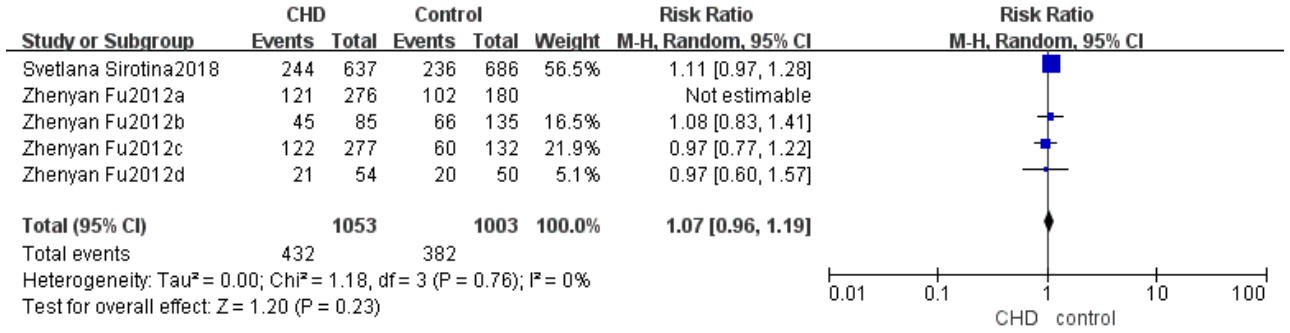


Figure 10. Forest Map of the relationship between CG Genotype of CYP4A11 Genotype rs3890011 and Coronary Heart Disease.

In the study of the relationship between CC and TT genotypes of CYP4F2 gene rs2108622 and coronary heart disease, the heterogeneity of each study changed after the removal of one literature, and the results were statistically significant (OR = 1.22,95% CI: 1.10-1.34, P < 0.0001 / OR = 0.53, 95% CI: 0.35-0.80, P = 0.003). As shown in Figure 11.

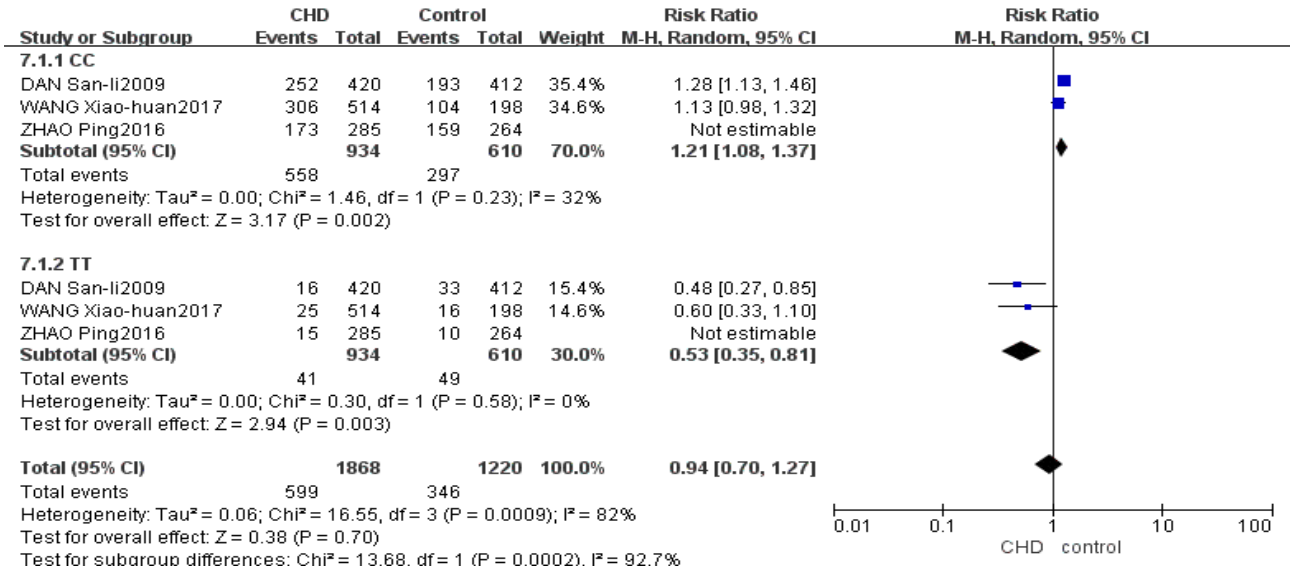
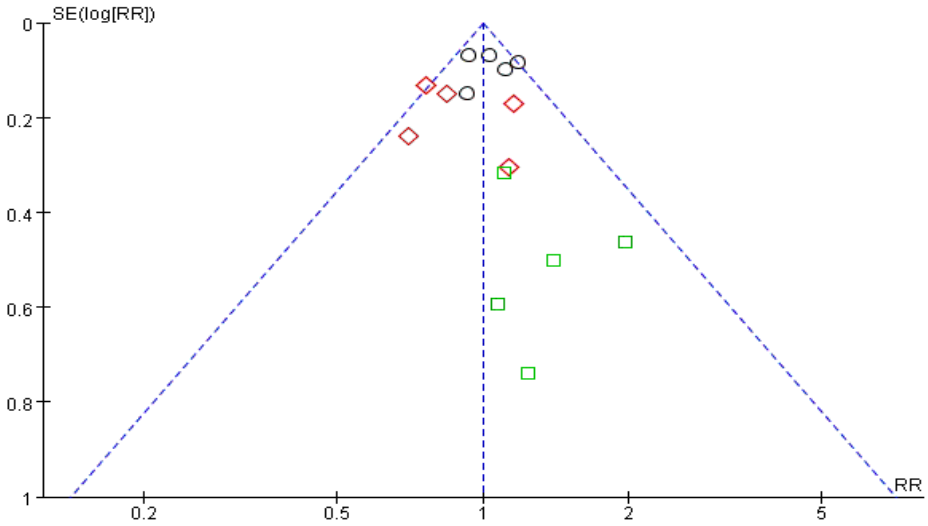
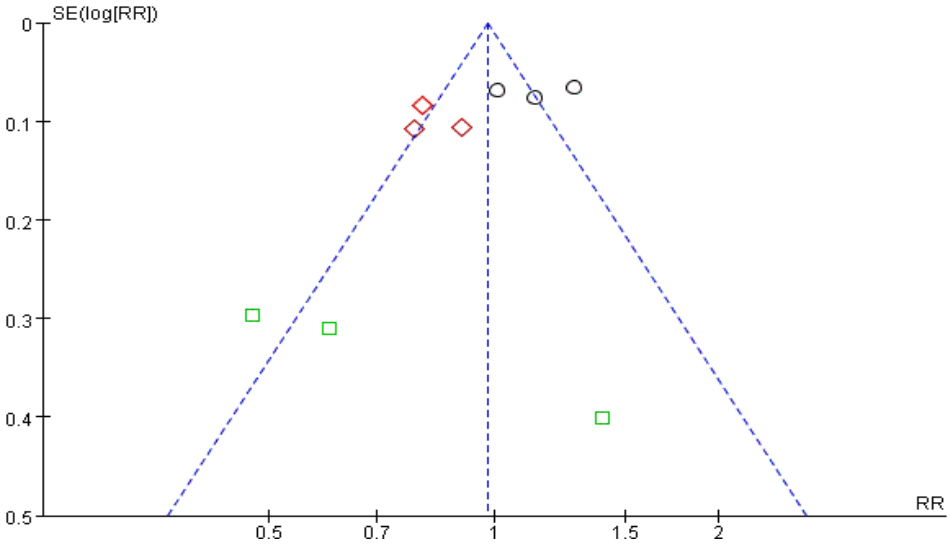


Figure 11. Forest map of the relationship between CC, TT genotypes of CYP4F2 gene rs2108622 and coronary heart disease.



A. CYP4A11 gene and publication bias of coronary heart disease study.



B. CYP4F2 gene and publication bias of coronary heart disease study.

Figure 12. Literature research published biased funnel chart.

For other analysis results, the results of the meta-analysis were replicated excluding in each step one of the studies included in the review. The analysis was considered robust when the results obtained were similar.

3.5 Published bias estimates

Publication bias was evaluated using Cochrane tool developed for this purpose. The funnel chart shows that the distribution of scattered spots on the left and right sides is asymmetrical and there is publication bias. As shown in Figure 12.

4. Discussion

To the best of our knowledge, this is the first meta-analysis to evaluate the association between CYP4A11 and CYP4F2 gene polymorphisms and coronary heart disease. In this study, we collected data from 6 literatures and 5535 subjects. To evaluate the relationship between CYP4A11 and CYP4F2 gene polymorphisms and coronary heart disease. The results showed that patients with CC genotype with CYP4A11 gene rs3890011 had a lower risk of coronary heart disease, while patients with GG genotype had an increased risk of coronary heart disease. Therefore, homozygous genotypes (CC, GG) of CYP4A11 gene rs3890011 were associated with coronary heart disease. The TT, CT and CC genotypes of CYP4A11 gene rs1126742 were not associated with coronary heart disease, the risk of coronary heart disease decreased in patients with AA genotype carrying CYP4A11 gene rs9332978, and increased in patients with AG genotype, and there was no correlation between GG genotype and the risk of coronary heart disease. Therefore, the dominant genes (AA, AG) of CYP4A11 gene rs9332978 are associated with coronary heart disease. Patients with CT genotype carrying CYP4F2 gene rs2108622 had a lower risk of coronary heart disease, while CC, CT and TT genotypes of CYP4F2 gene rs1558139 were not associated with coronary heart disease.

Cardio-cerebrovascular disease is a common disease that seriously threatens the health of human beings, especially the middle-aged and elderly over 50 years old. it has the characteristics of high prevalence rate, high disability rate and high mortality rate. Even with the application of the most advanced and perfect treatment, more than 50% of the survivors of cerebrovascular accidents can not take care of themselves. The number of people who die from cardiovascular and cerebrovascular diseases is as high as 15 million every year, ranking first in all causes of death. Common cardiovascular and cerebrovascular diseases are hypertension, hyperlipidemia, coronary heart disease and so on. Therefore, it is particularly important to prevent the occurrence of cardiovascular and cerebrovascular diseases such as coronary heart disease. At present, many studies have shown that cytochrome P450 (CYP450) gene is associated with the pathogenesis of coronary heart disease [6-10]. Cytochrome P450 mainly includes four families of CYP1-4 and subfamilies A, B, C, D, E and F, which are involved in the biotransformation of a variety of endogenous substrates, exogenous compounds and drugs. Arachidonic acid is one of the most abundant endogenous substances in human body. CYP4A and CYP4F families are the main isoenzymes that catalyze the ω-hydroxylation of arachidonic acid to 20-HETE. [11] exogenous administration of 20-HETE can inhibit coronary vasodilation induced by vascular endothelial hyperpolarizing factor, aggravate the degree of myocardial injury caused by coronary artery ischemia, and then lead to coronary heart disease. [12]

In this paper, through sensitivity analysis, the heterogeneity of each study changed after removing a literature from the study on the relationship between CC and TT genotypes of CYP4F2 gene rs2108622 and coronary heart disease(I^2=32%,I^2=0%). it can be concluded that the homozygous genotypes of CYP4F2 gene rs2108622 (CC, TT) are related to the occurrence of coronary heart disease, the CC genotype is positively correlated with the occurrence of coronary heart disease, and the TT genotype is negatively correlated with the occurrence of coronary heart disease. The main difference between the deleted literature and other literature is that the research object is different. ZHAOPing's article studies the genes of Mongolian population, so we have reason to believe that ethnic factors have a great influence on the relationship between CYP4F2 gene rs2108622 and coronary heart diseas. In the study of the correlation between CG genotype of CYP4A11 gene

rs3890011 and coronary heart disease, the heterogeneity of each study changed after removing a set of data (I^2=0%). The difference between the removed set of data and other data studies lies in the difference of the research objects, and the research object of removing a set of data from ZhengyuanFu is Han male. Therefore, we believe that the relationship between CG genotype of CYP4A11 gene rs3890011 and coronary heart disease is related to gender. Because of the small sample size, it is impossible to determine whether it is related to men or women.

5. Limitations

The calculated results were obtained after excluding the studies with heterogeneity, which would undoubtedly contribute to drawing some scientific conclusions in the present meta-analysis. However, the main limitation of this meta-analysis is that the sample size is small, the conclusion may not be accurate, and the pathogenesis of coronary heart disease is not clear. In the future work, we should further expand the sample size, in order to further clarify the possible pathogenesis of coronary heart disease and find genetic susceptibility genes, and then take effective intervention measures to prevent or delay the occurrence of coronary heart disease.

6. Conclusions

Based on the results of this paper, it can be concluded that the homozygous genotypes of CYP4A11 gene rs3890011 (CC, GG) are related to the occurrence of coronary heart disease in Chinese. The dominant genes of CYP4A11 gene rs9332978 (AA, AG) are related to the occurrence of coronary heart disease in Chinese. There was no correlation between TT, CT, CC genotypes of CYP4A11 gene rs1126742 and coronary heart disease in Chinese. Homozygous genotypes of CYP4F2 gene rs2108622 (CC, TT) are associated with coronary heart disease in Chinese, while CC, CT and TT genotypes of CYP4F2 gene rs1558139 are not associated with coronary heart disease in Chinese. Therefore, CYP4A11 and CYP4F2 gene polymorphisms are associated with coronary heart disease in Chinese.

References

[1] Winkelmann BR,Hager J.Genetic variation in coronaryheart disease and myocardial infarction: methodological overview and clinical evidence [J]. Pharmacogenomics, 2000,1(1):73-9 4.

[2] LIU Lu, CAO Jian.Research progress of epoxy eicosatrienoic acid in the prevention and treatment of cardiovascular diseases[J]. Chin J Geriatr Heart Brain Vessel Dis, 2014,16(12):1329.

[3] Yan Lulu,Zhang Yongzhen. Research advance of the role of cytochrome P450 in heart failure[J]. Chin J Cardiovasc Med, 2015,20(2):151-154.

[4] Bukoh MX, Siah C-JR. A systematic review and meta-analysis on the structured handover interventions in improving patient safety outcomes. J Nurs Manag. 2020;28(3):744–55.

[5] Walter Masson, Martin Lobo, Daniel Siniawski, et al. Role of non-statin lipid-lowering therapy in coronary atherosclerosis regression: a metaanalysis and meta-regression[J]. Lipids in Health and Disease, (2020) 19:111. https://doi.org/10.1186/s12944-020-01297-5

[6] Yu C, Yan Q. Fu C, et al. CYP4F2 genetic polymorphisms are associated with coronary heart disease in a Chinese population [J]. Lipids Health Dis, 2014,13:83.

[7] Deng S, Zhu G, Liu F, et al. CYP4F2 gene V433 M polymor - phism is associated with ischemie stroke in the male Northern Chinese Han population] Prog Neuropsychopharmacol Biol Psychiatry, 2010, 34(4):664-668.

[8] Zordoky BN. EIKadi AO. Effect of cytochrome P450 polymor -phism on arachidonic acid metabolism and their impact on cardiovas - cular diseases] Pharmacol Ther. 2010.25(3):446-463.

[9] Huang D. Fu ZY, Yang YN, et al. Association on the haplo-types of CYP4F2 gene and m yocardial infarction [J]. Zhong - hua Liu Xing Bing Xue Za Zhi .2009.30(7):733-736 .

[10] Fu Z. Nakayama T. Sato N. et al. A haplotype of the CYP 4 F 2 gene associated with myocardial infarction in Japanese men [J]. Mol Genet Metab. 2009,96(3):145-147.

[11] LIU Junhua. Association of CYP4A11 and CYP4F2 polymorphism with Essential hypertension and Coronary heart disease[D]. Guangzhou:Southern Medical University, 2012.

[12] Mayer B, Lieb W, Gotz A, et al. Association of a functional polymorphism in the CYP4A11 gene with systolic blood pressure in survivors of myocardial infarction [J]. JHypertens, 2006;24:1965-1970.