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Associations between miR-146a rs2910164 polymorphisms and risk of ischemic cardio-cerebrovascular diseases

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Abstract

Background: Many studies investigated the association between miR-146a rs2910164 polymorphisms and risk of ischemic cardio-cerebrovascular diseases. However, the results were inconsistent.

Methods: We searched the PubMed, EMBASE, Cochrane library, Web of Science, Chinese National Knowledge Infrastructure, VIP, and Wanfang databases for appropriate studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the associations. Heterogeneity, sensitivity, and publication bias were conducted to measure the robustness of our findings.

All analyses were based on previous published studies, thus, no ethical approval and patient consent are required.

Results: We conducted a meta-analysis to evaluate the relationship between miR-146a rs2910164 polymorphisms and risk of ischemic cardio-cerebrovascular diseases. A total of 26 related studies involving 11,602 cases and 14,016 controls were identified and included in our meta-analysis. After considering the heterogeneity of the global analysis, we inferred that rs2910164 polymorphisms were associated with a lower risk of coronary heart disease (CHD) significantly in all genetic models. In addition, it was also found that the miR-146a rs2910164 polymorphisms were associated with the low risk of ischemic cardio-cerebrovascular diseases in large sample size subgroup analysis.

Conclusion: These results indicate that miR-146a rs2910164 polymorphisms were significantly associated with a lower risk of ischemic cardio-cerebrovascular. The miR-146a rs29101164 might be recommended as a predictor for susceptibility of ischemic cardio-cerebrovascular diseases.

Abbreviations: ACS = acute coronary syndrome, CAD = coronary artery disease, CHD = coronary heart disease, CI = confidence interval, HWE = Hardy–Weinberg equilibrium, IS = ischemic stroke, OR = odds ratio, SNP = single-nucleotide polymorphism.

Keywords: ischemic cardio-cerebrovascular diseases, meta-analysis, miR-146a, single nucleotide polymorphism

1. Introduction

Ischemic cardio-cerebrovascular disease is a chronic disease that develops imperceptibly throughout life and usually progressing to an advanced stage when symptoms occur.[1] It is a concept of a series of diseases with the same pathological basis and different clinical manifestations, including coronary heart disease (CHD),

ischemic cerebrovascular disease, and other diseases.[2,3] Although scientific progress has been made in disease prevention, diagnosis, and treatment, ischemic cardiovascular and cerebro-vascular diseases are still the main causes of morbidity and mortality in developed and developing countries.[4–6] It has been estimated that more than 80% of ischemic cardio-cerebrovascular diseases now occur in developing countries.[7] Etiologically, ischemic cardio-cerebrovascular disease was supposed to be a highly complex disease caused by multiple environmental and genetic risk factors.[8] To date, more and more attention has been paid to the study of susceptibility genes, increasing molecular epidemiological studies also have revealed the important role of genetic factors in ischemic cardio-cerebrovascular diseases.

MicroRNAs (miRNAs and miRs) are endogenous, conservative, small (about 22-nucleotide), single-strand, non-coding RNA molecules, attaching to the 3′untranslated region (3′-UTR) of target mRNAs, which regulate gene expressions through translation repression or degradation of target genes.[9] Epidemiological studies demonstrated that miRNA-associated genetic sequence polymorphism played an important role in the development and progression of diseases including neurological disorders, cardiovascular diseases, autoimmune diseases, and cancers.[10] Accumulating evidences have demonstrated that miR-146a participates in inflammatory processes to interfere with the pathology of cardiovascular diseases. In addition, miR-146a also exerts a neuroprotective effect through astrocytes to

downregulated miR-146a in patients with ischemic stroke (IS) in the acute phase.[11,12]

Some studies have examined the associations between miR-146a rs2910164 polymorphisms and ischemic cardio-cerebrovascular diseases. However, the results of these studies were inconsistent due to the limited sample size in a single study. Therefore, we conducted a meta-analysis of all eligible case–control studies to investigate the relationship between single-nucleotide polymorphisms (SNPs) in the miR-146a rs2910164 polymorphisms and ischemic cardio-cerebrovascular diseases.

2. Materials and methods

2.1. Search strategy and eligibility of relevant studies

We conducted a systematic search using the PubMed, EMBASE, Cochrane library, Web of Science, Chinese National Knowledge Infrastructure, VIP, and Wanfang databases. The last search was performed on July 2018, with keywords including ("miR146a" OR "miR-146a" OR "miRNA146a" OR "microRNA146a" OR "rs2910164") AND ("ischemic cardio-cerebrovascular diseases" OR "ischemic heart and cerebrovascular diseases" OR "ischemic stroke" OR "IS" OR "cerebral ischemic stroke" OR "CIS" OR "cerebral infarction" OR "CI" OR "lacunar infarction" OR "LI" OR "coronary heart disease" OR "CHD" OR "ischemic heart disease" OR "IHD" OR "coronary atherosclerotic heart disease" OR "coronary artery disease" OR "CAD" OR "acute coronary syndrome" OR "ACS" OR "acute myocardial infarction" OR "AMI" OR "myocardial infarction" OR "MI") AND ("gene" OR "genetic" OR "single-nucleotide polymorphism" OR "SNP" OR "allele" OR "variation" OR "variant" OR "mutation"). We also manually searched the reference lists of relevant reports to identify additional studies. All identified studies that met the inclusion criteria have been assessed by 2 independent reviewers using standardized forms.

2.2. Inclusion and exclusion criteria

Eligible studies should conform with the following criteria: the design was accordance with case–control study; the exposure was miR-146a rs2910164; the outcome was incident of ischemic cardio-cerebrovascular diseases; and study provided sufficient published data to calculate odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Exclusion criteria were as follows: reviews, case reports, meta-analysis, and animal model research; repeated publications; not relevant to ischemic cardio-cerebrovascular diseases; not a case–control study; and lacking sufficient data for quantitative analyses. Moreover, non-English and non-Chinese articles were also excluded.

2.3. Data extraction and quality assessment

Data were extracted independently by 2 reviewers (Zhao and Li). All discrepancies were resolved by discussion with a 3rd reviewer (Ma). The following information was extracted: first author's name, published year, country of origin and ethnicity of study participants, type of ischemic cardio-cerebrovascular diseases, genotyping methods, number of cases and controls, and genotype frequency of case and control, Hardy–Weinberg equilibrium (HWE) for controls by 2 independent researches (Zhao and Li). Detailed characteristics of included studies were shown in Table 1. We assessed the quality of all included studies according

to the Newcastle–Ottawa quality assessment scale.[13] Quality score ranged from 0 to 9, a final score ≥6 was regarded as high quality.

2.4. Statistical analysis

HWE was assessed via Chi-square test in the control populations of each study, which could be considered disequilibrium when P value is less than .05. Pooled ORs and corresponding 95% CIs were calculated to estimate associations between miR-146a rs2910164 polymorphism and ischemic cardio-cerebrovascular diseases. The strength of the association was determined using the following models: allelic model (G vs C), homozygote model (GG vs CC), heterozygous model (CG vs CC), dominant model (CG + GG vs CC), and recessive model (GG vs CG + CC). Subgroup analyses were conducted by ethnicity (Asian and Caucasian), disease types (IS and CHD subgroups), and sample size (small sample: the total number of controls and cases less than 1000; large sample: the total number of controls and cases not less than 1000). We used the Cochran Q-statistic and the I^2 statistic to evaluate statistical heterogeneity among studies.[13] $P \geq .1$ suggested a lack of heterogeneity among studies. A random-effect model (the DerSimonian and Laird method) was used in the presence of heterogeneity ($P < .1$); otherwise, a fixed-effect model using the Mantel–Haenszel method was utilized. We conducted a sensitivity analysis to assess the stability of the results. Furthermore, Begg funnel plot and Egger test were used to evaluate publication bias among included studies. Z-test was used to assess the overall effect and $P < .05$ was considered statistically significant difference. Analyses were carried out with Review Manager 5.3 and Stata 12.0 software (Stata Corporation, College Station, TX).

3. Results

3.1. Characteristics of included studies

Figure 1 shows our study selection process. In total, 2540 studies were retrieved from the PubMed, EMBASE, Cochrane library, Web of Science, Chinese National Knowledge Infrastructure, VIP, and Wanfang databases. Of these, 405 duplicates were excluded from this study. Another 1932 studies were excluded after reviewing the titles and abstracts. A total of 203 eligible studies were evaluated for full-text review. A total of 179 of them were excluded due to nonreporting of available data, duplicate data, meta-analyses, and case reports. Twenty-four original articles containing 26 studies were retained after reviewing the full text (Table 1).[14–37]

HWE was assessed via Chi-square test in the control subjects of each study. Genotype distributions among controls were consistent with HWE in only 23 studies.[15–30,32–37] These 23 studies investigated 2 diseases (IS and CHD) and were included in the final meta-analysis. However, there were 3 types of CHDs have been hit after literature review as coronary artery disease (CAD), acute coronary syndrome (ACS), and myocardial infarction. There were 3 types of ISs, which were silent brain infarction, lacunar infarction, and atherosclerotic cerebral infarction (ACI). The 23 studies included 9780 cases and 10411 controls, 12 studies focused on IS and 11 focused on CHD. Subgroup analyses were also conducted by ethnicity (Asian and Caucasian) and sample size (the total number of controls and cases less than 1000 was used as small, otherwise as large).
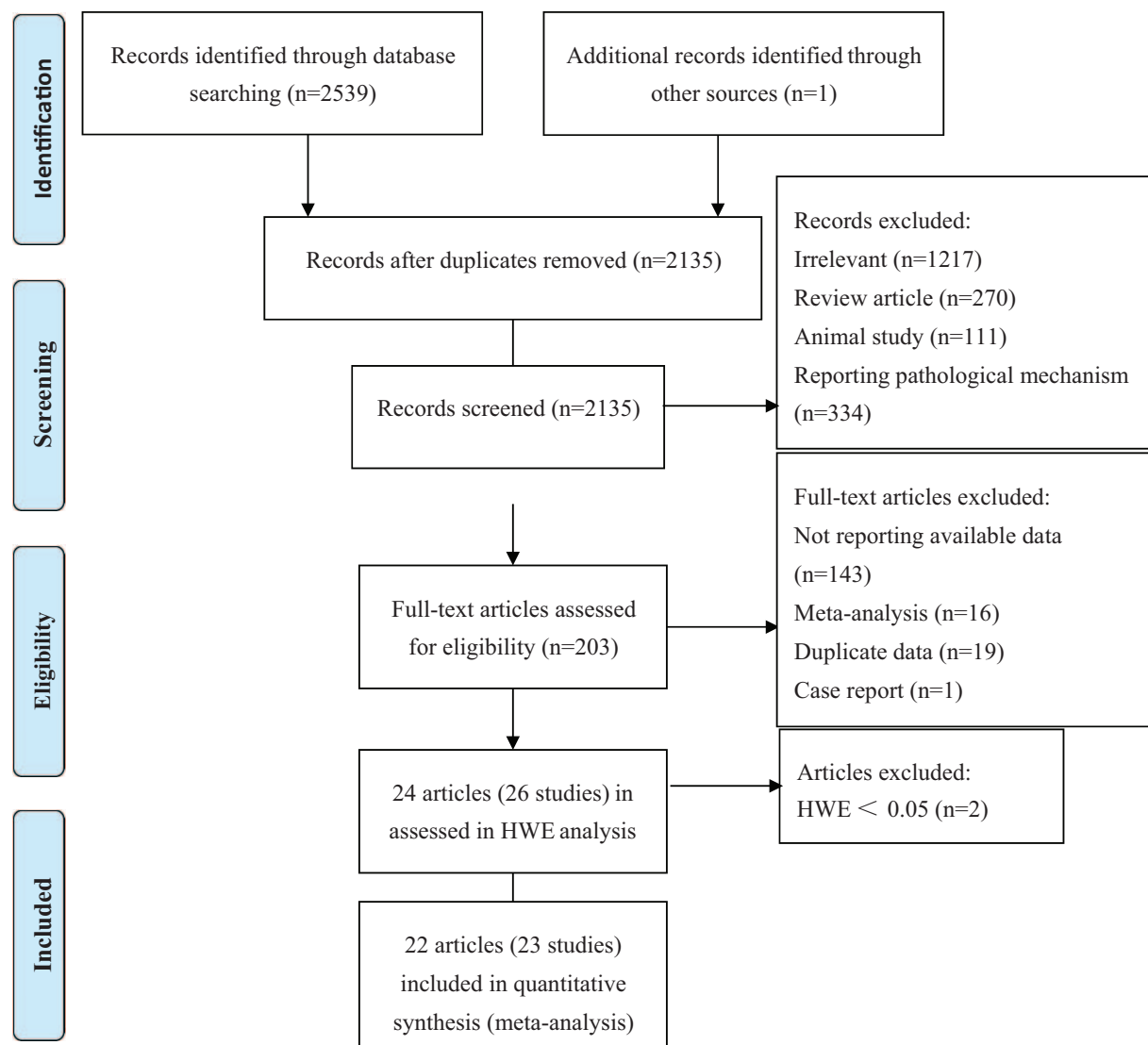
Figure 1. Study selection flow chart.

According to the Newcastle–Ottawa quality assessment scale, the summarized quality scores ranged from 6 to 9, which suggested that the evidence had a good quality.

3.2. Results from meta-analysis

The results of meta-analysis for the association between miR-146a rs2910164 polymorphism and ischemic cardio-cerebrovascular diseases risk are shown in Figures 2 and 3 and Table 2.

Twenty-three eligible studies including 9780 cases and 10411 controls were included in this analysis. Heterogeneities were observed in 5 types of genetic models' analysis. We used the random-effect model to evaluate the association between rs2910164 polymorphisms and the risk of ischemic cardio-cerebrovascular diseases in all genetic models, there was no significant associations based on the global analysis of these studies (allelic model: OR = 0.95, 95%CI = 0.87–1.03, P = .19; homozygote model: OR = 0.90, 95%CI = 0.76–1.07, P = .24; heterozygous model: OR = 0.93, 95%CI = 0.85–1.01, P = .09; dominant model: OR = 0.92, 95%CI = 0.83–1.02, P = .12; and

recessive model: OR = 0.95, 95%CI = 0.84–1.08, P = 0.45) (Fig. 2, Table 2).

However, because of the heterogeneity of the global meta-analysis, we cannot infer that rs2910164 polymorphism was completely unrelated to ischemic cardio-cerebrovascular diseases only from the results of global analysis. Therefore, to reduce the influence of heterogeneity and further clarify the relationship between rs2910164 polymorphisms and the risk of ischemic cardio-cerebrovascular diseases, we performed subgroup analysis based on the type of disease, ethnic origin, and sample size.

For the analysis of IS, heterogeneities were observed in allelic (I^2 = 78%, P < .00001), homozygote (I^2 = 79%, P < .00001), dominant (I^2 = 66%, P = .0007), and recessive (I^2 = 72%, P < .0001) models, while there was no significant heterogeneity in heterozygous (I^2 = 34%, P = .12) model. And there was also no significant association among all kinds of genetic models as allelic, homozygote, heterozygous, dominant, and recessive models (allelic model: OR = 1.04, 95%CI = 0.92–1.18, P = .55; homozygote model: OR = 1.08, 95%CI = 0.82–1.42, P = .59; heterozygous model: OR = 1.04, 95%CI = 0.95–1.14, P = .37;

Table 1

Main characteristic of studies included in the meta-analysis.

Author	Year	Country	Ethnicity	Disease	Genotyping methods	Sample size (case/control)	GG (case/control)	CG (case/control)	CC (case/control)	G (case/control)	C (case/control)	HWE of control	NOS
Li (1)	2010	China	Asian	IS	PCR-RFLP	268/1010	79/210	110/455	79/345	268/875	268/1145	0.009	8
Li (2)	2010	China	Asian	CAD	PCR-RFLP	415/1010	82/210	184/455	149/345	348/875	482/1145	0.009	8
Sun	2011	China	Asian	IS	PCR-RFLP	381/650	65/118	170/304	146/228	300/540	462/760	0.345	6
Yang	2012	China	Asian	CHD	Taqman	829/917	165/189	392/457	272/271	722/835	936/999	0.885	8
Chen	2013	China	Asian	CHD	Taqman	658/658	181/194	305/330	172/134	667/718	649/598	0.769	8
Jeon (1)	2013	Korea	Asian	IS	Taqman	678/553	128/76	327/266	223/211	583/418	773/688	0.589	7
Jeon (2)	2013	Korea	Asian	SBI	Taqman	373/553	57/76	179/266	137/211	293/418	453/688	0.589	7
Chen	2014	China	Asian	MI	PCR-LDR	919/889	269/301	463/435	187/153	1001/1037	837/741	0.846	8
Hamann	2014	German	Caucasian	CAD	HRM	206/200	120/117	74/73	12/10	314/307	98/93	0.748	7
Hu	2014	China	Asian	IS	PCR-RFLP	196/205	34/26	87/82	75/97	155/134	237/276	0.193	6
Li	2014	China	Asian	LI	SNaPshot	173/298	15/51	85/136	73/111	115/238	231/358	0.401	6
Liu	2014	China	Asian	IS	PCR-RFLP	296/391	52/77	159/198	85/116	263/352	329/430	0.650	7
Ramkaran	2014	South Africa	Asian	CAD	PCR-RFLP	106/100	50/45	43/46	13/9	143/136	69/64	0.569	7
Xiong	2014	China	Asian	CAD	PCR-RFLP	295/283	41/61	141/125	113/97	223/247	367/319	0.086	7
Zhu	2014	China	Asian	IS	PCR-LDR	368/381	50/64	173/185	145/132	273/313	463/449	0.952	6
Huang (1)	2015	China	Asian	IS	Taqman	531/531	81/55	261/257	189/219	423/367	639/695	0.106	7
Huang (2)	2015	China	Asian	ACS	Taqman	717/717	143/132	308/348	266/237	594/612	840/822	0.830	9
Bastami	2016	Iran	Caucasia n	CAD	Taqman	300/300	111/150	155/128	34/22	377/428	223/172	0.454	8
Lv	2016	China	Asian	IS	Taqman	378/378	61/38	198/187	119/153	320/263	436/493	0.079	7
Qu	2016	China	Asian	IS	PCR-LDR	1139/1585	166/233	618/869	355/483	950/1335	1328/1835	<0.001	8
Sung	2016	Korea	Asian	CAD	PCR-RFLP	522/535	77/73	242/260	203/202	396/406	648/664	0.460	8
Zhong	2016	China	Asian	ACI	SNaPshot	297/300	28/35	128/152	141/113	184/222	410/378	0.133	7
Zhu	2016	China	Asian	IS	PCR-RFLP	396/378	71/45	194/179	131/154	336/269	456/487	0.521	7
Luo	2017	China	Asian	IS	PCR-LDR	298/303	39/45	130/139	129/119	208/229	388/377	0.672	6
Wang	2017	China	Asian	CAD	PCR-LDR	353/368	62/84	155/179	136/105	279/347	427/389	0.645	7
Zhu	2017	China	Asian	IS	Taqman	510/523	55/86	251/267	204/170	361/439	659/607	0.272	6

ACI = atherosclerotic cerebral infarction, ACS = acute coronary syndrome, CAD = coronary artery disease, CHD = coronary heart disease, HRM = high-resolution melting, HWE = Hardy–Weinberg equilibrium, IS = ischemic stroke, MI = myocardial infarction, PCR-LDR = polymerase chain reaction-ligation detection reaction, LI = lacunar infarction, NOS = Newcastle–Ottawa quality assessment scale, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, SBI = silent brain infarction.

dominant model: OR = 1.05, 95%CI = 0.91–1.22, P = .49; and recessive model: OR = 1.05, 95%CI = 0.85–1.31, P = .64) (Table 2).

For the analysis of CHD, there was no significant heterogeneities among allelic, homozygote, heterozygous, and dominant models, while heterogeneity was observed in recessive (I^2 = 41%, P = .07) model. Significant association was found under all genetic models (allelic model: OR = 0.87, 95%CI = 0.82–0.92, P < .00001; homozygote model: OR = 0.77, 95%CI = 0.69–0.87, P < .0001; heterozygous model: OR = 0.81, 95%CI = 0.74–0.89, P < .00001; dominant model: OR = 0.80, 95%CI = 0.73–0.87,

P < .00001; and recessive model: OR = 0.86, 95%CI = 0.76–0.98, P = .02) (Fig. 3, Table 2).

In Asian populations, no association was observed in any genetic models (allelic model: OR = 0.96, 95%CI = 0.88–1.04, P = .34; homozygote model: OR = 0.93, 95%CI = 0.78–1.10, P = .39; heterozygous model: OR = 0.93, 95%CI = 0.85–1.02, P = .12; dominant model: OR = 0.93, 95%CI = 0.84–1.04, P = .19; and recessive model: OR = 0.97, 95%CI = 0.86–1.11, P = .70) (Table 2).

When the number of total sample size is small, the results of analysis are often inaccurate due to the influence of random

Table 2

Meta-analysis of miR-146a rs2910164 polymorphism with ischemic cardio-cerebrovascular diseases.

		G vs C				GG vs CC				CG vs CC				CG + GG vs CC				GG vs CG + CC		
	N	OR (95%CI)	P_H	I^2	P	OR (95%CI)	P_H	I^2	P	OR (95%CI)	P_H	I^2	P	OR (95%CI)	P_H	I^2	P	OR (95%CI)	P_H	I^2
Overall	26	0.96[0.89,1.03]	<.00001	74%	.29	0.93[0.80,1.08]	<.00001	72%	.35	0.93[0.87,1.01]	.050	34%	.07	0.94[0.85,1.02]	<.0001	61%	.15	0.97[0.87,1.10]	<.00001	67%
HWE																				
YES	23	0.95[0.87,1.03]	<.00001	74%	.19	0.90[0.76,1.07]	<.00001	73%	.24	0.93[0.85,1.01]	.02	41%	.09	0.92[0.83,1.02]	<.0001	63%	.12	0.95[0.84,1.08]	<.00001	66%
Disease																				
IS	12	1.04[0.92,1.18]	<.00001	78%	.55	1.08[0.82,1.42]	<.00001	79%	.59	1.04[0.95,1.14]	.12	34%	.37	1.05[0.91,1.22]	.0007	66%	.49	1.05[0.85,1.31]	<.0001	72%
CHD	11	0.87[0.82,0.92]	.18	27%	<.00001	0.77[0.69,0.87]	.26	19%	<.0001	0.81[0.74,0.89]	.83	0%	<.00001	0.80[0.73,0.87]	.69	0%	<.00001	0.86[0.76,0.98]	.07	41%
Ethnicity																				
Asian	21	0.96[0.88,1.04]	<.00001	74%	.34	0.93[0.78,1.10]	<.00001	74%	.39	0.93[0.85,1.02]	.01	46%	.12	0.93[0.84,1.04]	<.0001	65%	.19	0.97[0.86,1.11]	<.0001	64%
Caucasian	2	0.80[0.56,1.13]	.080	66%	.20	0.57[0.35,0.93]	.28	13%	.03	0.80[0.49,1.31]	.89	0%	.38	0.68[0.43,1.09]	.55	0%	.11	0.75[0.45,1.26]	.05	75%
Sample size																				
≥1000	9	0.96[0.86,1.06]	.0001	74%	.42	0.94[0.75,1.17]	<.0001	76%	.56	0.89[0.82,0.97]	.10	40%	.009	0.91[0.79,1.03]	.004	64%	.14	1.00[0.85,1.18]	.002	67%
<1000	14	0.94[0.82,1.07]	<.00001	76%	.33	0.87[0.67,1.14]	<.0001	73%	.31	0.96[0.84,1.10]	.05	42%	.56	0.93[0.79,1.10]	.0005	64%	.40	0.91[0.75,1.11]	.0002	67%

CHD = coronary heart disease, 95%CI = 95% confidence interval, HWE = Hardy–Weinberg equilibrium, IS = ischemic stroke, N = number of comparisons, OR = odds ratio, P = P-value. P_H: P-value of heterogeneity test random-effects model was used when P value for heterogeneity test $P_H < .1$; otherwise, fixed-effect model was used.
I^2 means quality assurance measure of the degree of difference between multiple research effects.
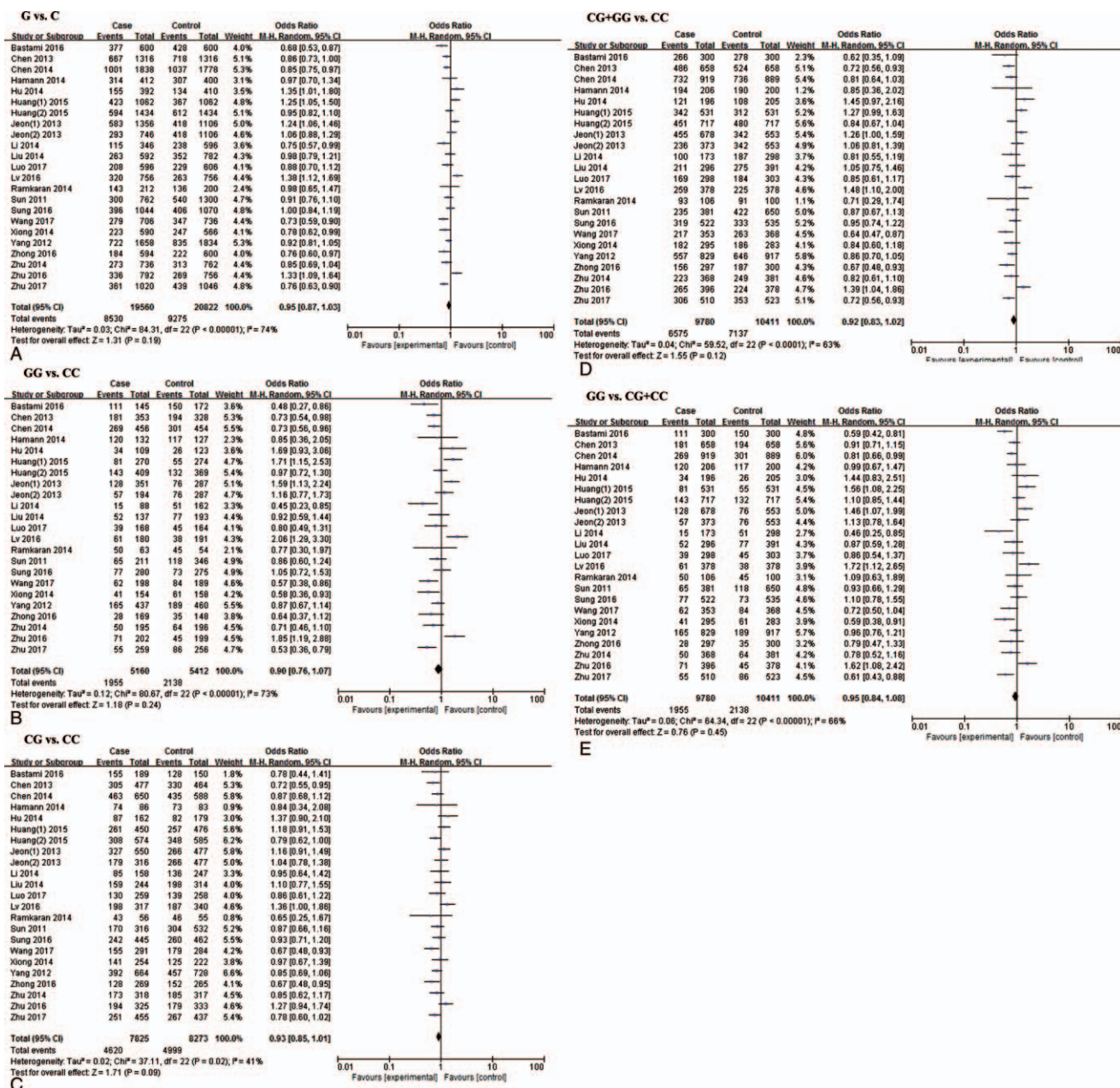
Figure 2. Forest plots of odds ratios for the association between miR-146a rs2910164 and risk of overall ischemic cardio-cerebrovascular diseases. (A) G versus C; (B) GG versus CC; (C) CG versus CC; (D) CG + GG versus CC; and (E) GG versus CG + CC.

errors. Therefore, we conducted stratified subgroup analysis based on sample sizes to further analyze the relationship between miR-146a rs2910164 polymorphisms and ischemic cardio-cerebrovascular diseases, which showed that miR-146a rs2910164 polymorphisms were associated with decreased risk of ischemic cardio-cerebrovascular diseases in a large sample size (N ≥ 1000) under the heterozygous model (OR = 0.89, 95%CI = 0.82–0.97, P = .009). We found there was no association in small sample size (N < 1000) under all genetic models (allelic model: OR = 0.94, 95%CI = 0.82–1.07, P = .33; homozygote model: OR = 0.87, 95%CI = 0.67–1.14, P = .31; heterozygous model: OR = 0.96, 95%CI = 0.84–1.10, P = .56; dominant model: OR = 0.93, 95%CI = 0.79–1.10, P = .40; and recessive model: OR = 0.91, 95%CI = 0.75–1.11, P = .35) (Table 2).

3.3. Sensitivity and publication bias analyses

Sensitivity analysis was performed by omitting each study to examine the impact on the pooled ORs. The corresponding pooled OR was not significantly altered in all genetic models, suggesting that our meta-analysis results were accurate (Fig. 4). Potential publication bias in the current study was evaluated with Begg funnel plot and Egger test. No obvious asymmetry of funnel plots was observed in any comparisons, which indicated that no publication bias was observed in the current meta-analysis (Fig. 5 and Table 3).

4. Discussion

In the present meta-analysis, we found that the miR-146a polymorphisms were not significantly associated with the risk of
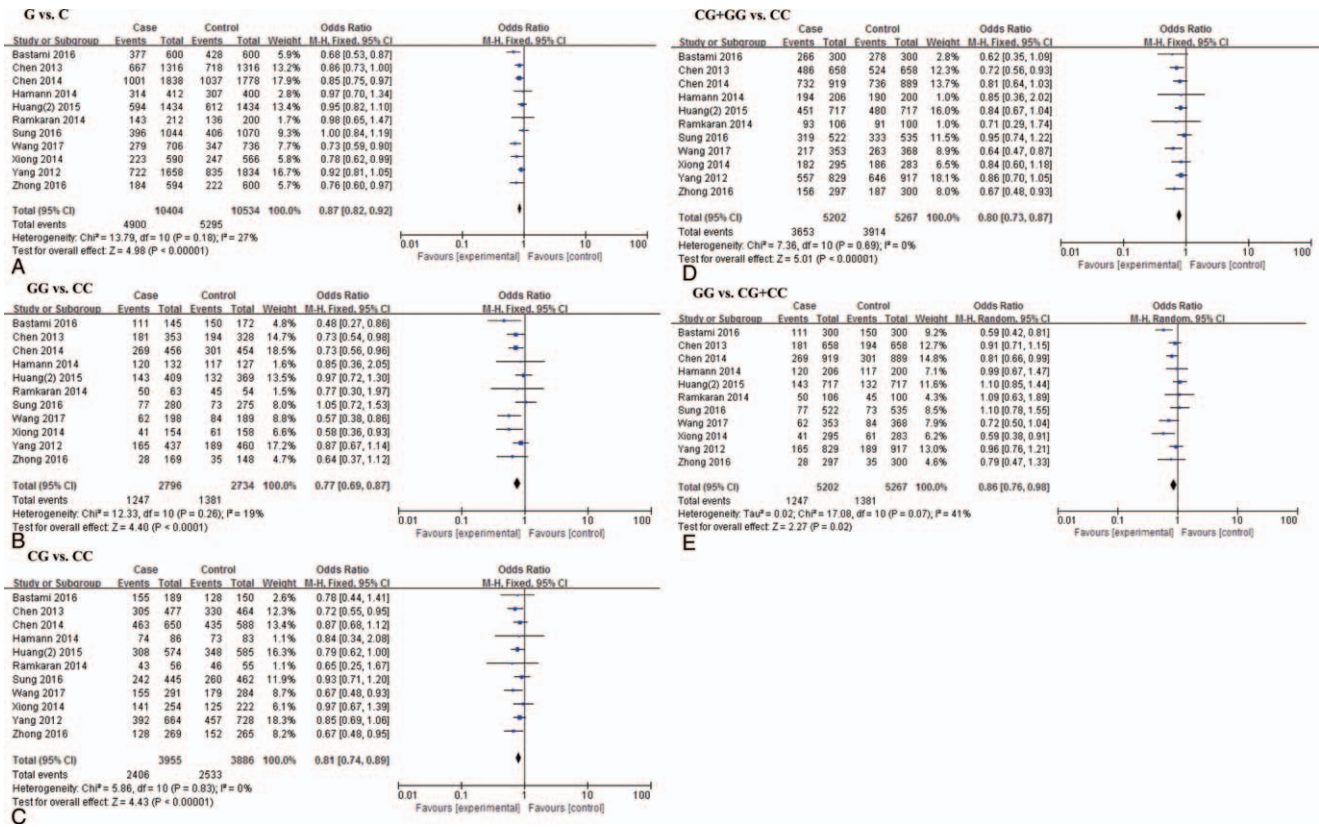
Figure 3. Forest plots of odds ratios for the association between miR-146a rs2910164 and risk of coronary heart disease (CHD). (A) G versus C; (B) GG versus CC; (C) CG versus CC; (D) CG+GG versus CC; and (E) GG versus CG+CC.
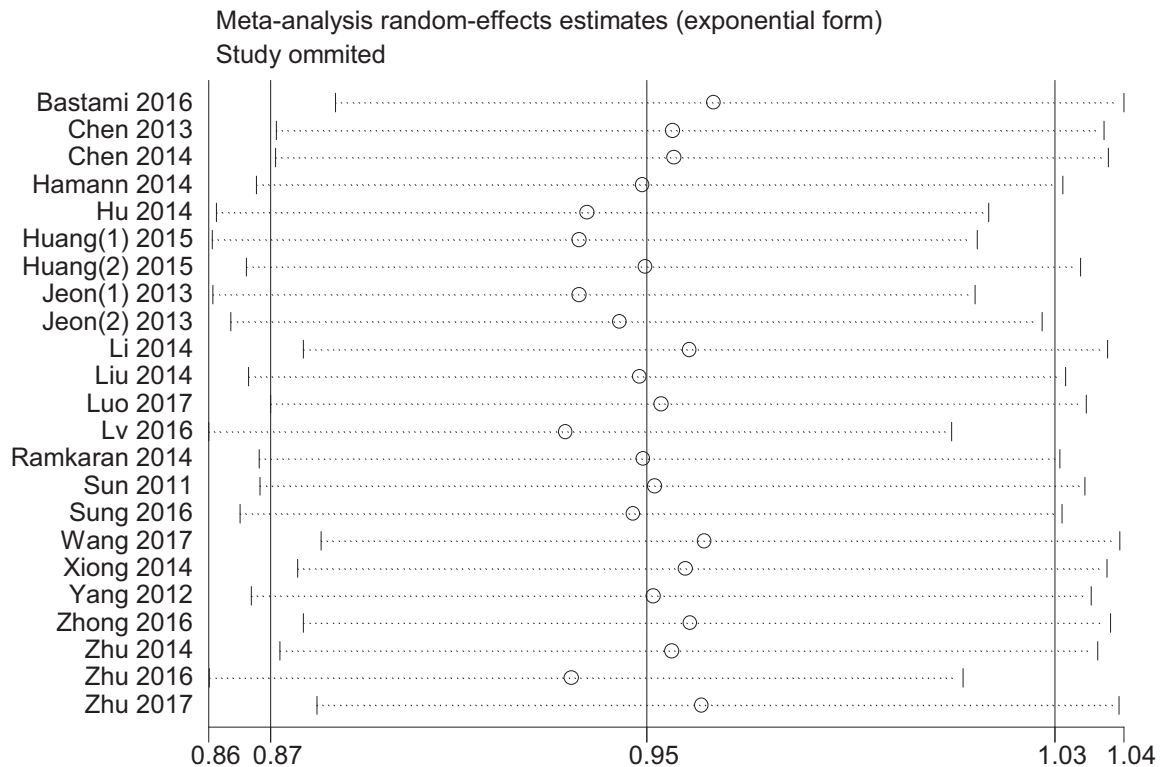

Figure 4. Sensitivity analysis of each study performed by omitting each data from the analysis (G vs C).
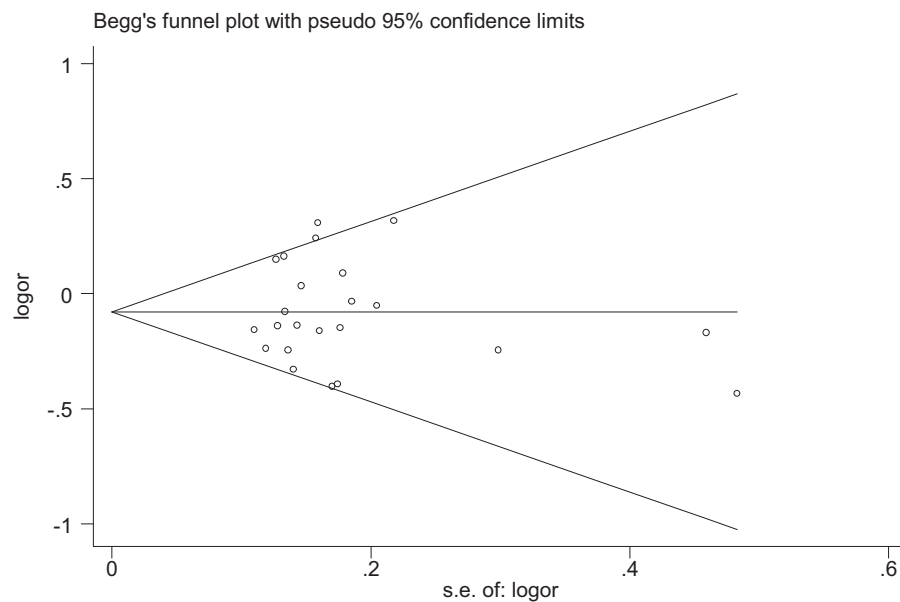
Figure 5. Begg funnel plot of publication bias for heterozygous model of miR-146a rs2910164 polymorphism.

ischemic cardio-cerebrovascular diseases in all genetic models. Our subgroup study stratified by disease type showed that rs2910164 polymorphisms were associated with CHD. We found an association between these polymorphisms and CAD based on 2 studies evaluated CAD in Caucasian populations, demonstrating that lower risks for GG carriers versus CC carriers, while rs2910164 was not associated with ischemic cardio-cerebrovascular diseases in Asian populations. Subgroup analysis based on sample size also revealed that the CG of rs2910164 was associated with the lower risks of ischemic cardio-cerebrovascular diseases in the large sample group.

Several studies have assessed the effects of miR-146a SNPs on ischemic cardio-cerebrovascular diseases, but the results were inconsistent. Although a recent meta-analysis was performed to reveal the relationship of miR-146a polymorphisms and CAD and IS,[11] little study has been included on ischemic cardiovascular and cerebrovascular diseases. To obtain conclusive results on the relationship between miR-146a polymorphisms and ischemic cardio-cerebrovascular diseases, we included 18 more studies with 8464 cases and 10919 controls for ischemic cardio-cerebrovascular diseases analysis. We found a similar lower CHD

risk for the G allele and GG, CG, CG+GG of rs2910164, our meta-analysis also provided further evidence for the lower risk of ischemic cardio-cerebrovascular diseases for CG of rs2910164 in large sample size. In the sensitivity analysis, no significant effects were altered after omitting each study at a time, suggesting that our meta-analysis results were reliable.

Because of the common characteristics diseases such as similar pathophysiology of ischemic events, we combine the cardiovascular and cerebrovascular diseases to analyses and draw corresponding conclusions. Considering that the heterogeneity of the overall meta-analysis, and the risk factors and treatment effects of cardiovascular and cerebrovascular are quite different, we performed subgroup analysis of cardiovascular and cerebrovascular diseases, respectively. We observed that rs2910164 was associated with the risk of ischemic cardio-cerebrovascular diseases analysis in the large sample group, so the rs2910164 was associated with the risk of CHD. In addition, we also found a lower risk of ischemic cardio-cerebrovascular diseases in Caucasian. However, only 2 studies were included in the Caucasian subgroup and 2 studies focused on CAD. Although the subgroup analysis for Caucasian population in this study

Table 3

Egger linear regression test for funnel plot asymmetries.

Group	G vs C P_B	G vs C P_E	GG vs CC P_B	GG vs CC P_E	CG vs CC P_B	CG vs CC P_E	CG+GG vs CC P_B	CG+GG vs CC P_E	GG vs CG+CC P_B	GG vs CG+CC P_E
Overall	.673	.943	.751	.850	.833	.966	.916	.717	.958	.834
Disease										
IS	.732	.704	.945	.593	.631	.735	.837	.963	.732	.474
CHD	.436	.405	.436	.263	.640	.491	.161	.235	.876	.683
Sample size										
≥1000	.602	.459	.602	.436	.754	.992	.466	.954	.466	.322
<1000	.381	.659	.743	.538	.511	.461	.661	.425	.511	.690
Ethnicity										
Asian	.928	.847	.976	.894	.566	.816	.976	.992	.880	.844

P_B = P-value of Begg test, P_E = P-value of Egger test.

found that rs2910164 was associated with the risk of ischemic cardio-cerebrovascular diseases, the conclusions drawn in this subgroup analysis are still not broadly representative, further studies are still needed to confirm the associations.

Ischemic cardio-cerebrovascular diseases are a series of diseases caused by atherosclerosis. Atherosclerosis is a chronic inflammatory disease of the arteries, it is principally a lipid-driven process initiated by the accumulation of lipoprotein particles and an inflammatory process in focal areas of arteries as well.[38] Recently, miR-146a was recognized as a potent regulator in many physiological and pathological processes, including immune function, inflammatory reaction, metabolism, oxidative stress, neurodegenerative, and cardiovascular diseases.[39] Recent studies have shown that miR-146a can regulate the synthetic phenotype and proliferation of vascular smooth muscle cells by targeting Krüppel-like factor 4.[40,41] In addition, Eyileten et al suggested the combination of plasma high-sensitivity C-reactive protein and serum miR-146b gained a better sensitivity/specificity for the prediction of IS.[42] MiR-146a expression has been reported to mediate inflammatory response and promote astrocyte proliferation.[43] In several studies, the expression level of miR-146a in peripheral blood mononuclear cells was significantly increased in patients with CHD.[44] The high level of miR-146a concentration in peripheral blood mononuclear cells may directly affect the differentiation and activities of Th1 cells, which has been implicated in the progression and the onset of the ACS.[28] Pordzik et al demonstrated that hyperglycemia-associated downregulation of miR-146a mediates platelet activation in diabetics, favoring IS.[45] In addition, other studies also revealed that miR-146a could reduce the production of pro-inflammatory cytokines via downregulating inerleukin-1 receptor-associated kinase 1 and tumor necrosis factor (TNF) receptor associated factor 6 in macrophages.[46,47] Therefore, the down-regulation of miR-146a may increase vascular damage response and inflammation-related atherosclerosis by increasing the levels of inerleukin-1 receptor-associated kinase 1, TNF receptor associated factor 6, and TNF-α. SNP rs2910164 involves a C-to-G nucleotide substitution, which can cause a mismatch in the stem structure of the miR-146a precursor, then decrease the expression of miR-146a.

The results of our meta-analysis should be interpreted attentively because of the following limitations. First of all, the relatively small number of patients may affect the outcomes. After a comprehensive literature search, only 26 eligible studies were included. Genotype distributions among controls were consistent with HWE in only 23 studies. Secondly, there was limited information about clinicopathological features or disease sub-types in the original studies, which made it difficult to conduct more subgroup meta-analysis. Thirdly, ischemic cardio-cerebro-vascular diseases were multifactorial disease influenced by both genetic and environmental factors, the gene–gene and gene–environment interactions may significantly affect the function of miR-146a rs2910164 SNP. Fourthly, most of the patients in this study were Asian, which would limit the comprehensiveness and veracity of the results. Finally, an SNP might be in linkage disequilibrium with other genetic variations of susceptibility genes to ischemic cardio-cerebrovascular diseases, which may present stronger effect when considered together with other variations.

In conclusion, our meta-analysis suggests the CG genotype of rs2910164 may be a decreased risk of ischemic cardio-cerebrovascular diseases. Thus, we suggest rs2910164 could be recommended as a protective factor for the susceptibility of ischemic cardio-cerebrovascular diseases.

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