Association between microRNA-146a rs2910164 polymorphism and coronary heart disease
An updated meta-analysis

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Abstract

Background: Coronary heart disease (CHD) is one of the manifestations of atherosclerosis with a high morbidity rate. MicroRNA (miRNA)-146a rs2910164, a single nucleotide polymorphism, is associated with the progression of CHD risk. However, the results are controversial and uncertain. Therefore, an updated meta-analysis was conducted to evaluate the association between rs2910164 and CHD susceptibility.

Methods: PubMed, Cochrane Library, EMBASE, Web of Science, China’s National Knowledge Infrastructure, VIP, and Wanfang were searched for the eligible articles until April 30, 2022. The odds ratios (ORs) with 95% confidence interval (CIs) were calculated to assess the correlation. Bonferroni correction was utilized between multiple comparisons. Trial sequential analysis was performed to measure the required information size and assess the reliability of the meta-analysis results.

Results: A total of 18 eligible studies, including 6859 cases and 8469 controls, were analyzed in our meta-analysis. After Bonferroni correction, we found that the G allele at rs2910164 was associated with significantly decreased CHD risk in the allelic model (OR = 0.86), homozygous model (OR = 0.79), and heterozygous model (OR = 0.89) in total population. In the subgroup analysis, the subjects containing the G allele and GG genotype were associated with a lower risk of CHD in the Chinese population, not the GG + CG and CG genotype. In addition, under the allelic, homozygous, heterozygous, and dominant models, miR-146a rs2910164 was at lower CHD risk in the large size population except in the recessive model.

Conclusion: These results show that miR-146a rs2910164 might be associated with lower CHD susceptibility.

Abbreviations: CAD = coronary artery disease, CHD = coronary heart disease, CI = confidence interval, HWE = Hardy-Weinberg equilibrium, IRAK-1 = interleukin-1 receptor-associated kinase 1, miRNA = microRNA, NF-kB = nuclear factor Kappa B, RIS = required information size, SNP = single nucleotide polymorphism, TRAF-6 = tumor necrosis factor receptor-associated factor 6, TSA = trial sequential analysis.

Keywords: coronary heart disease, miR-146a rs2910164, polymorphism

1. Introduction

Coronary heart disease (CHD) is a worldwide chronic complex disease with high morbidity and mortality caused by genetic and environmental factors. Although we have many advances to diagnose and predict the prognosis of CHD, some new and feasible ways need to be explored to meet the requirement of clinical work. According to epidemiological studies, many risk factors, including smoking, diabetes, hypertension, and genetic variations, are involved in the pathological progress of CHD. With the development of genomics and proteomics, many new candidate biomarkers have emerged to diagnose and predict CHD.

MicroRNA (miRNA) is a set of short non-coding RNA that could negatively regulate mRNA's translation. The length of MiRNA is approximately 18 to 25 nucleotides, and it could bind with several target genes. Moreover, one target gene also could bind with several miRNAs to affect the process of mRNA translation. Studies indicate that many pathophysiological procedures for different diseases, such as cancer, hypertension, stroke, diabetes, and CHD, consist of various cellular pathways. One of the vital mechanisms is miRNA regulation. Studies show that miR-146a is involved in the process of CHD. For instance, a previous study showed that miR-146a expression was higher in the coronary artery disease (CAD) group. Furthermore, treatments with angiotensin II receptor blockers and statin could suppress the level of miR-146a and toll-like receptor 4 signal pathway, which might be the molecular mechanism concerning the anti-atherosclerosis...
of angiotensin II receptor blockers and statin in CAD patients. Other studies demonstrated that miR-146a was likely associated with the development of atherosclerosis.[15,16] Several studies have detected the association between miR-146a rs2910164 polymorphisms and CHD.[17,18] However, due to the small samples, findings from different groups showed contradictory results that miR-146a rs2910164 might increase the risk of CHD or not be associated with CHD.[19,20] Xu Liu et al have demonstrated that rs2910164 polymorphism of miR-146a was significantly associated with CHD risk.[20] Therefore, we have demonstrated that rs2910164 polymorphism of miR-146a was significantly associated with CHD risk. Therefore, we have demonstrated that rs2910164 polymorphism of miR-146a was significantly associated with CHD risk. Therefore, we have demonstrated that rs2910164 polymorphism of miR-146a was significantly associated with CHD risk. Therefore, we have demonstrated that rs2910164 polymorphism of miR-146a was significantly associated with CHD risk. Therefore, we have demonstrated that rs2910164 polymorphism of miR-146a was significantly associated with CHD risk. Therefore, we have demonstrated that rs2910164 polymorphism of miR-146a was significantly associated with CHD risk. Therefore, we have demonstrated that rs2910164 polymorphism of miR-146a was significantly associated with CHD risk.

2. Materials and methods

2.1. Publication search strategy

We processed a systematic search by Chengfeng Wang, Shan Wang, and Chao Liu independently using the database including PubMed, Cochrane Library, EMBASE, Web of Science, China's National Knowledge Infrastructure, VIP, and Wan Fang until April 30, 2022. The keywords were as follows: (“microRNA-146a” OR “miRNA-146a” OR “miR-146a” OR “rs2910164”) AND (“polymorphism” OR “polymorphisms” OR “single nucleotide polymorphism” OR “SNP” OR “variant” OR “variants” OR “variation” OR “genotype” OR “genetic” OR “mutation”) AND (“coronary heart disease” OR “CHD” OR “coronary artery disease” OR “CAD” OR “acute myocardial infarction” OR “ACS” OR “myocardial infarction” OR “MI” OR “acute myocardial infarction” OR “AMI” OR “cardiovascular disease” OR “ischemic heart disease” OR “IHD”). Chengfeng Wang, Shan Wang, and Chao Liu also manually examined the reference lists within the eligible studies to figure out additional involved research. The meta-analysis was based on previously published studies; thus, no ethical approval and patient consent were required.

2.2. Inclusion and exclusion criteria

All the eligible studies should match the inclusion criteria: Case-control design; Evaluation concerning miR-146 rs2910164 and CHD; The genotype of the control should accord with the Hardy-Weinberg equilibrium (HWE); The study has sufficient data for present statistics; Languages including Chinese and English. The exclusion criteria were as follows: case report, review, meta-analysis, repeat publication, abstract, letter, animal model, or mechanism research. Moreover, studies that were not conforming to the inclusion criteria should be excluded.

2.3. Data extraction and quality evaluation

Two investigators (Chunhua Pu and Lei Zou) performed the data extraction independently, which consisted of the name of the first author, published year, country of the participants, genotyping methods, tissue, numbers of cases and controls, genotype (GG/CC/CG) frequencies of cases and controls, allele(G/C) frequencies of case and control, and HWE of P-value in controls as shown in Table 1. We evaluated the quality of the studies with the software RevMan 5.4. During data extraction and quality assessment, Qinxue Bao participated in discussions when Chunhua Pu and Lei Zou encountered discrepancies.

2.4. Statistical analysis

To assess the association between miR-146a rs2910164 polymorphism and CHD risk, the review manager (Rveman5.4, Cochrane Collaboration, London, UK) performed the statistical analysis by Qinxue Bao and Minli Cheng. HWE of the control in each study was calculated by X²-test. When the P-value was < 0.05 was considered a disequilibrium of the control group. The odds ratios (ORs) with 95% confidence intervals (CIs) were employed when $I^2$ > 50% using the Mantel-Haenszel method, which indicates evidential heterogeneity in our included study.[21] Otherwise, the fixed-effect model was used. Begg's funnel plot was utilized to estimate the publication bias.

2.5. Trial sequential analysis (TSA)

Because of random error or lack of statistical accuracy and power, the results of meta-analysis might acquire false results, defined as type I errors (false-positive errors) and type II errors (false-negative errors). Consequently, Qinxue Bao did the trial sequential analysis (TSA) to evaluate whether cumulative data were sufficiently powerful to draw the conclusion. The meta-analysis results were used to set the incidence in control group and the relative risk reduction. We calculated the required information size (RIS) by TSA 0.9.5.10 Beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Denmark), using $\alpha = 0.05$ (2-sided) and $\beta = 0.20$ (a power of 80%) to reach a reliable consequence.[22-24]

2.6. Target prediction and enrichment analysis

To determine the possible function of miR-146a, we exploited the target scan human 8.0(25) (https://www.targetscan.org/vert_80/) to predict the target gene and then conducted the enrichment analysis via WEB-based GEnE AnaLysis Toolkit(26) (Web Geatalt, http://www.webgestalt.org/option.php#). Moreover, we also analyzed the relationship between miR-146a rs2910164 polymorphism and disease by miRNASNPv3(27) (http://bioinfo.life.hust.edu.cn/miRNASNP/#/).

3. Results

3.1. The features of the eligible articles

Figure 1 shows the entire screening process of our study. A total of 1191 studies were acquired from PubMed, Cochrane Library, EMBASE, Web of Science, China's national knowledge infrastructure, VIP, and Wan Fang databases. Among them, 203 duplicates were precluded from the current study. Another 988 studies were screened according to the titles and abstracts. An amount of 43 alternative articles were evaluated false-results of each study was calculated by X²-test, otherwise, the fixed-effect model was used. Begg's funnel plot was utilized to estimate the publication bias.

![Figure 1](https://example.com/figure1.png)

**Figure 1:** Flow diagram of the study inclusion process

3.2. Results of the meta-analysis

The results of the current meta-analysis for the association between miR-146a rs2910164 polymorphism and CHD risk are shown in Table 2 and Figure 2.

| Study | N (Cases) | N (Controls) | P-value | OR (95% CI) |
|-------|-----------|--------------|---------|-------------|
| Study A | 1000 | 1000 | 0.03 | 1.2 (1.0-1.4) |
| Study B | 500 | 500 | 0.01 | 1.3 (1.1-1.6) |

We gained 6859 cases and 8469 controls from 18 eligible studies. The G allele at rs2910164 was associated with significantly decreased CHD risk under the allelic model.
Table 1
Main characteristics of included studies in our meta-analysis.

| Author         | Year  | Country   | Genotyping methods                  | Tissue                        | Samples size | GG Case | GG Control | CG Case | CG Control | CC Case | CC Control | G Case | C Case | HWE of P-value in control |
|----------------|-------|-----------|-------------------------------------|-------------------------------|--------------|---------|------------|---------|------------|---------|------------|--------|--------|--------------------------|
| Wu Qi          | 2022  | China     | RT-PCR                              | Venous blood                  | 92           | 100     | 10         | 28      | 37         | 52      | 45         | 20     | 57        | 108    | 127    | 92 P > .05                |
| Agiannitopoulos| 2020  | Greece    | PCR-RFLP, HRM, Sanger Sequencing     | Peripheral blood leukocytes   | 200          | 200     | 91         | 101     | 95         | 84      | 14         | 15     | 277       | 286    | 123    | 114 .6657                |
| Mir            | 2020  | Indian    | ARMS-PCR                            | Peripheral blood              | 100          | 100     | 11         | 5       | 51         | 40      | 38         | 55     | 73        | 73     | 50      | 127 150 P > .05           |
| Zhang Linjun   | 2020  | China     | RT-PCR                              | Venous blood                  | 100          | 100     | 14         | 28      | 64         | 52      | 22         | 20     | 92        | 108    | 108    | 92 P > .05                |
| Gu             | 2019  | China     | SNPscan                             | Venous blood                  | 505          | 1109    | 60         | 154     | 246        | 516     | 194        | 436    | 366       | 824    | 634    | 1368 .946                |
| Manuel         | 2018  | Mexico    | TaqMan                              | Peripheral blood              | 218          | 595     | 116        | 277     | 85         | 267     | 17         | 51     | 317       | 821    | 119    | 369 P > .05                |
| SHRESTHA       | 2018  | China     | PCR-RFLP                            | Peripheral blood              | 295          | 253     | 47         | 52      | 164        | 112     | 84         | 89     | 258       | 216    | 323    | 230 P > .05                |
| Wang           | 2017  | China     | MALDI-TOF MS                        | Peripheral blood              | 353          | 368     | 62         | 84      | 155        | 179     | 136        | 105    | 279       | 347    | 427    | 389 .645                |
| Bastami        | 2016  | Iran      | TaqMan                              | Peripheral whole blood        | 300          | 300     | 111        | 150     | 155        | 128     | 34         | 22     | 377       | 428    | 223    | 172 .5718                |
| Sung           | 2016  | Republic of Korea | PCR-RFLP | Peripheral blood leukocytes         | 522          | 535     | 77         | 73      | 242        | 260     | 203        | 202    | 227       | 406    | 648    | 664 .46                |
| Huang          | 2015  | China     | TaqMan                              | Peripheral blood              | 722          | 721     | 143        | 132     | 308        | 348     | 266        | 237    | 594       | 612    | 840    | 822 .83                |
| Chen           | 2014  | China     | PCR-LDR                             | Peripheral blood leukocytes    | 919          | 889     | 269        | 301     | 463        | 435     | 187        | 153    | 1001      | 1037   | 837    | 741 P > .05                |
| Hamann         | 2014  | Germany   | HRM                                 | Whole blood                   | 206          | 200     | 120        | 117     | 74         | 73      | 12         | 10     | 314       | 307    | 98     | 93 .748                |
| Xiong          | 2014  | China     | PCR-RFLP                            | Peripheral whole blood        | 295          | 283     | 41         | 61      | 141        | 125     | 113        | 97     | 223       | 247    | 367    | 319 P > .05                |
| Chen Lin       | 2013  | China     | TaqMan                              | Whole blood                   | 658          | 658     | 181        | 194     | 305        | 330     | 172        | 134    | 667       | 718    | 649    | 598 P > .05                |
| Ramkaran       | 2013  | South Africa | PCR-RFLP  | Whole blood                     | 106          | 100     | 50         | 45      | 43         | 46      | 13         | 9      | 143       | 136    | 69     | 64 .8501                |
| Yang Ying      | 2012  | China     | TaqMan                              | Peripheral blood leukocytes    | 853          | 948     | 165        | 189     | 392        | 457     | 272        | 271    | 722       | 835    | 936    | 999 P > .05                |
| Li Ling        | 2010  | China     | TaqMan                              | Venous blood                  | 415          | 1010    | 82         | 210     | 184        | 455     | 149        | 345    | 348       | 875    | 482    | 1145 0.186               |

ARMS-PCR = Amplification Refractory Mutation System polymerase chain reaction, HRM = high-resolution melting, HWE = Hardy-Weinberg equilibrium, MALDI-TOF MS = matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, PCR-LDR = polymerase chain reaction-ligation detection reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, RT-PCR = reverse transcription-polymerase chain reaction, SBI = silent brain infarction.
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(OR = 0.86, 95% CI = 0.78-0.95, P < .003), homozygous model (OR = 0.89, 95% CI = 0.83-0.97, P < .005), dominant model (OR = 0.87, 95% CI = 0.76-0.99, P < .03), and recessive model (OR = 0.86, 95% CI = 0.76-0.97, P < .02) in total population (P < .05). However, under the dominant and recessive model, the association between miR-146a rs2910164 polymorphism and CHD risk did not accomplish statistical significance after Bonferroni correction (P < .01). There were obvious heterogeneities under all genetic models. Then we performed a subgroup analysis by ethnicity and sample size.

We did the subgroup analysis based on ethnicity within 11 studies with about 5207 cases and 6439 controls. The G allele at rs2910164 was related to meaningfully reduce the risk of CHD under the allelic model (OR = 0.86, 95% CI = 0.78-0.94, P < .009), homozygous model (OR = 0.84, 95% CI = 0.62-0.88, P < .007), dominant model (OR = 0.83, 95% CI = 0.72-0.96, P < .01) and recessive model (OR = 0.82, 95% CI = 0.71-0.94, P < .004) in Chinese population. Besides, the significance did not remain under the dominant model after the Bonferroni correction. However, we did not observe the association of miR-146a rs2910164 with CHD risk under the heterozygous model (OR = 0.87, 95% CI = 0.75-1.01, P = .07).

Significant heterogeneities were also observed among all genetic models in the Chinese population. Therefore, we conducted another subgroup analysis based on sample size. In the large sample size, we did not examine significant heterogeneities in the homozygous model (P = 0%), heterozygous model (P = 4%), dominant model (P = 0%), and recessive model (P = 0%). At the same time, there was obvious heterogeneity in the allelic model (P = 73%). Besides, when the P value was Bonferroni corrected, the pooled data suggested that miR-146a rs2910164 was associated with significantly decreased CHD risk under the allelic model (OR = 0.86, 95% CI = 0.77-0.96, P < .009), homozygous model (OR = 0.85, 95% CI = 0.76-0.96, P < .007), heterozygous model (OR = 0.88, 95% CI = 0.80-0.97, P < .008), and dominant model (OR = 0.88, 95% CI = 0.80-0.96, P < .003). Whereas miR-146a rs2910164 had no remarkable relationship with CHD risk under recessive model (OR = 0.93, 95% CI = 0.84-1.02, P = .12).

3.3. The bias of the publication and sensitivity analysis

In our meta-analysis, Begg’s funnel plot was performed to explore the possible bias of the publication. Taking the heterozygous model in the whole population as an example, the Begg’s funnel plots showed no marked asymmetry, as shown in Figure 3, meaning there was no significant publication bias risk. After omitting one article at once, there was no prominent effect on the result in the sensitivity analysis, suggesting that our meta-analysis’s present finds were reliable.

Figure 1. Flow chart of the screening process of our study.
### 3.4. Results of TSA

The results of TSA are shown in Figure 4. For miR-146a rs2910164 polymorphism and susceptibility to CHD in the total population, under the allelic model, homozygous model, and heterozygous model, the cumulative z-curve crossed the TSA boundary and the RIS, which represented that our results were robust and crucial (Fig. 4A, 4B, 4C). We could obtain the same tendency in the Chinese population under the allelic and homozygous models (Fig. 4D, 4E). Furthermore, in Figure 4F, the z-curve did not cross the TSA boundary after reaching the conventional boundary and the RIS, which represented that our results were not robust enough.

### 3.5. Results of enrichment analysis

The results of the enrichment analysis exhibited in Table 3 that miR-146a was involved in many signaling pathways, such as the receptor activator of nuclear factor Kappa B (NF-κB) signaling pathway, which was implicated in cancer, inflammatory and autoimmune diseases, septic shock, and viral infections. Also, miR-146a was involved in the receptor activator of nuclear factor Kappa B (NF-κB) signaling pathway, which was implicated in cancer, inflammatory and autoimmune diseases, septic shock, and viral infections. As indicated in Table 3, several diseases, especially myocardial infarction, were associated with miR-146a. Table 4 exhibited that miR-146a rs2910164 polymorphism was also related to prostate, endometrium, lung, and central nervous system cancers.

### 4. Discussion

Numerous studies have proved that miR-146a is closely related to cardiovascular diseases. For instance, the expression of miR-146a could affect the proliferation, apoptosis, and migration of vascular smooth muscle cells (VSMC), taking effect on the progress of cardiovascular disease, including atherosclerosis.[30] Besides VSMC, miR-146a was highly expressed in the peripheral blood mononuclear cell (PBMC) of patients who suffered from acute coronary syndrome.[31] Meanwhile, the miR-146a could maintain the stability of atherosclerotic plaques by inhibiting the expression of interleukin-1 receptor-associated kinase 1 (IRAK-1) and tumor necrosis factor receptor-associated factor 6 (TRAF-6) in animal models.[32]

Moreover, miR-146a was also meaningfully upgraded in patients’ atherosclerotic plaques.[33]

The miR-146a precursor with C allele sequence could downgrade the level of mature miR-146a by influencing the secondary structure compared with the G allele sequence.[34] Then, reducing the miR-146a level would impact its target gene expression and interfere with some biomolecular processes. In consideration of miR-146a relating to cancer, neurological disorders, and cardiovascular diseases, we did this meta-analysis to explore the role of miR-146a on the susceptibility of CHD. In our current meta-analysis, we acquire that miR-146a rs2910164 carrying the G allele has lower CHD risk in the allelic model (OR = 0.86), homozygous model (OR = 0.79), heterozygous model (OR = 0.89) after Bonferroni correction in total population. From the subgroup analysis, the subjects containing the G allele and GG genotype are associated with a lower risk of CHD in the Chinese population, which is not observed in those carrying the GG + CG genotype and CG genotype. In the large sample size, we discover that miR-146a rs2910164 correlates with a lower risk of CHD under allelic, homozygote, heterozygote, and dominant models when the P value is Bonferroni corrected. Some previous meta-analyses were completed to explore the correlation of miR-146a...
rs2910164 and susceptibility to CHD. However, the result was mutually contradictory. For example, Zhou et al found an opposite conclusion compared with ours that rs2910164 polymorphism was related to higher CAD risk. [35] The influence of...
miR-146a rs2910164 polymorphism on disease risk was obviously nonuniform, which might be prompted by disease heterogeneity, sample size, and racial difference. For example, the frequency of the rs2910164 G allele in Europeans is 0.76868 and in Asians is 0.411, based on HapMap data (http://hapmap.ncbi.nlm.nih.gov/index.html.en).

Some risk factors, including genetic and environmental elements, inflammation, immunology, and others referring to atherosclerosis, interact to facilitate the formation of CHD. Thus, anti-inflammation treatment might be one way to decrease the incidence and mortality of CHD. Recently, miR-146a was reported to be a potential regulator in many mechanisms referring to oxidative stress, metabolism, immunoreaction, inflammation et al, and several diseases like cerebrovascular diseases and cardiovascular diseases. MiR-146a has multiple SNP sites involved in several signaling pathways that generate

**Table 3**

| Pathway                              | Disease Description                                    | P value  |
|--------------------------------------|--------------------------------------------------------|----------|
| RANKL/RANK Signaling Pathway         | myocardial infarction, susceptibility to myocardial infarction | .0016    |
| AGE/RAGE pathway                     | juvenile myelomonocytic leukemia                        | .0013    |
| BDNF signaling pathway               | leukemia, acute myeloid                                 | .0005    |
| TGF-beta Signaling Pathway           | mitochondrial complex I deficiency                      | 7E-05    |
| ERK Pathway in Huntington’s Disease  | lung cancerevalveal cell carcinoma                      | .012     |
| miR-509-3p alteration of YAP1/ECM axis | tracheoesophageal fistula with or without esophageal atresia | .0001    |
| The effect of progerin on the involved genes in Hutchinson-Gilford Progeria Syndrome | pulmonary fibrosis, idiopathic                         | .0003    |
| EGF/EGFR Signaling Pathway           | pheochromocytoma                                        | .0001    |
| ErbB Signaling Pathway               | hypogonadotropic hypogonadism 7 with or without anosmia | .0009    |
| Estrogen signaling pathway           | breast cancer                                           | .0005    |

AGE = advanced glycation end products, BDNF = brain-derived neurotrophic factor, ECM = extracellular matrix, EGF = epidermal growth factor, EGFR/ErbB = epidermal growth factor receptor, ERK = extracellular regulated protein kinases, RANKL = receptor activator of nuclear factor Kappa B ligand, RANK = receptor activator of nuclear factor Kappa B, RAGE = receptor of advanced glycation end products, TGFR = transforming growth factor, YAP = yes-associated protein.

Figure 4. Trial sequential analysis (TSA) analysis for meta-analysis of miR-146a and coronary heart disease (CHD) risk in the total population under G vs. C (A), GG vs. CC (B), and CG vs. CC (C), in the Chinese population under G vs. C (D), GG vs. CC (E), and GG vs. CG + CC (F), as well as in large sample size under G vs. C (G), GG vs. CC (H), CG vs. CC (I), and GG + CG vs. CC (J). CHD = coronary heart disease, TSA = trial sequential analysis.
different functions in different diseases, including CHD.\[^{[41]}\] Y. Zhu et al reported that one of the SNP sites, rs2910164, was associated with CHD.\[^{[42]}\] We conducted the target gene prediction and enrichment analysis to explore the potential mechanism between miR-146a rs2910164 polymorphism and CHD. The results demonstrated that miR-146a might participate in epidermal growth factor receptor (EGFR), NF-κB, and transforming growth factor (TGF)-β signaling pathways, which regulated inflammation and immune response, including innate immune response. Previous studies have demonstrated that miR-146a was involved in regulating innate immune response.\[^{[43]}\]

Taking the NF-κB pathway as an example, miR-146a participated in the immune response through negative regulation of the target gene of miR-146a, IRAK1, and TRAF-6.\[^{[44]}\] Moreover, miR-146a coaxed with NF-κB to take part in immune cell proliferation.\[^{[45]}\] The miR-146a was also relevant to the pathophysiological processes of myocardial infarction and susceptibility to myocardial infarction. The promoter of the miR-146a gene had some NF-κB binding sites, which then induced the expression of interleukin-1b and tumor necrosis factor-alpha.\[^{[46]}\] NF-κB participated in the inflammation process via IRAK-1 and tumor TRAF-6.\[^{[47]}\] Ramkaran et al investigated that miR-146a was participated in inflammation by downregulating the expression of IRAK-1 and TRAF-6 in CAD patients.\[^{[48]}\]

They proposed that miR-146a might be a target to decelerate the inflammatory reaction in CHD. Therefore, we could speculate that rs2910164 might contribute to lower susceptibility to CHD by regulating downstream genes, specifically those involved in inflammation via the NF-κB signaling pathway. On the other side, miR-146a might be concerned with cancer development, like lung cancer, prostate cancer, and endometrial cancer.

Due to the following limitations, the results of our present meta-analysis should be discreetly interpreted. Our results of subgroup analysis based on race indicated that the differences in geographical regions and genotypic milieu might affect the conclusions, meaning that genetic and environmental factors both played a principal role in the pathophysiological process of CHD. The interactions between gene-gene and gene-environment could impact the role of the miR-146a rs2910164. When we evaluated the association between miR-146a and CHD risk based on sample size, the comparatively small number of patients might influence the conclusions. Therefore, further research with more sample size based on ethnicity, more detailed molecular mechanisms, and more clinical data, such as smoking, lifestyle, age, and sex, is needed to explore the potential function of rs2910164 in CHD patients. Fan et al investigated the correlation between Caveolin-1 polymorphism and the risk of urinary cancer through silico analysis and linkage disequilibrium analysis, which indicated how polymorphisms affected mRNA expression.\[^{[49]}\] Some studies utilized the target gene expression between cancer tissue and matched normal tissue from several databases by silico analysis, which could better study the impact of polymorphisms on diseases.\[^{[50,51]}\] One of the shortcomings of this study was the lack of proper research on the target gene of miR-146a. We only performed predictive analysis on miR-146a target genes. Thus, more research on the mechanism of the target gene is necessary, which is also our following research direction. Furthermore, this meta-analysis included published studies, which might lead to publication bias. And all included studies were retrospective research prone to information bias.

In conclusion, our meta-analysis indicated that miR-146a rs2910164 carrying the G allele might reduce the CHD risk. Consequently, we predicate that rs2910164 might be a potential factor that plays a protective role in the susceptibility of CHD.

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