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*Meta-Analysis*

# miR-146a rs2910164 polymorphism might be associated with coronary artery disease risk in Asians

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**Abstract:** Recently, several studies reported the association between miR-146a rs2910164 polymorphism and coronary artery disease (CAD) risk. However, the results were inconclusive. We therefore did a meta-analysis to investigate this association. Electronic databases, including PubMed, EMBASE, and China National Knowledge Infrastructure (CNKI) databases, were searched. The strength of association was assessed by calculating odds ratios (OR) and 95% confidence interval (CI). Five eligible studies included in this meta-analysis. The total sample size of this meta-analysis was 1565 cases and 1541 controls. We found that miR-146a rs2910164 polymorphism was significantly associated with an increased CAD risk (OR = 1.19; 95% CI 1.07 – 1.32; *P* = 0.002). In the subgroup analysis by race, miR-146a rs2910164 polymorphism was significantly associated with an increased CAD risk in Asians (OR = 1.18; 95% CI 1.04 – 1.33; *P* = 0.008). However, we did not find significant result in Caucasians (OR = 1.22; 95% CI 0.86 – 1.74; *P* = 0.25). In the subgroup analysis by age, we found that miR-146a rs2910164 polymorphism increased CAD risk in old population (OR = 1.22; 95% CI 1.09 – 1.38; *P* = 0.0008). In conclusion, this meta-analysis found that miR-146a rs2910164 polymorphism was significantly associated with CAD risk.

***Key words:*** Coronary artery disease; MicroRNA; Polymorphism.

## Introduction

Coronary artery disease (CAD) is one of the most common causes of death in the developed world (1). Risk factors for atherosclerotic disease include chronic inflammation, immunology, and genetic and environmental factors, all of which interact with each other to promote the formation of atherosclerosis and atherosclerotic cardiovascular diseases (2). Finding genetic risk factors of CAD is very important of understanding the pathogenesis of CAD.

MicroRNA (miRs) are a class of noncoding RNA with the length of 18–25 nucleotides. MiR-146a was studied well in many diseases. For example, He et al. indicated the protective roles of miR-146a/b in hepatic schistosomiasis through regulating the differentiation of macrophages into M2 cells (3). Czajka et al. found that miR-146 family directly regulate the retinoic acid receptor beta in papillary thyroid carcinoma (4). Shi et al. indicated a crucial role of miR-146a in the development of acquired drug resistance to cisplatin in non-small cell lung cancer cells (5).

Recently, several studies reported the association between miR-146a rs2910164 polymorphism and CAD risk. However, the results were inconclusive (6-10). We therefore did a meta-analysis to investigate this association.

## Materials and Methods

### Publications Search

Electronic databases, including PubMed, EMBASE, and China National Knowledge Infrastructure (CNKI) databases, were searched up to Feb 10, 2017. Search terms included “coronary artery disease” and “miR-146a”. There was no language restriction.

### Inclusion and exclusion criteria

The following criteria were used to select the eligible studies: (a) case-control study evaluating of the association between miR-146a rs2910164 polymorphism and CAD risk; (b) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI). When reports used the same patient population, only the largest one was included.

### Data extraction

Two investigators extracted the data from included studies independently. The following data were collected from each study: the first author, year, race, age, gender, and sample size.

### Statistical analysis

A statistical test for heterogeneity was performed based on the Q statistic. The P > 0.10 of the Q-test indicated a lack of heterogeneity among studies. The summary OR estimate of each study was calculated by the random-effects model (the DerSimonian and Laird method). Stratified analysis was performed by race and

**Table 1.** Characteristics of the studies included in this meta-analysis.

| Study | Year | Ethnicity | Age (years) | Gender | N°. of case | N°. of control | HWE |
|---|---|---|---|---|---|---|---|
| Chen | 2013 | Asian | 64 | Mixed | 658 | 658 | Yes |
| Hamann | 2014 | Caucasian | NA | Mixed | 206 | 200 | Yes |
| Ramkaran | 2014 | Asian | 37 | Male | 106 | 100 | Yes |
| Xiong | 2014 | Asian | 65 | Mixed | 295 | 283 | Yes |
| Bastami | 2016 | Caucasian | 61 | Mixed | 300 | 300 | Yes |

NA, not available; HWE, Hardy–Weinberg equilibrium.

age. Cumulative meta-analysis and sensitivity analysis were conducted. Potential publication bias was examined by Egger's test. All statistical tests were performed with the software STATA version 11.0 (Stata Corporation, College station, TX, USA). A P value < 0.05 was considered statistically significant.

## Results

### Characteristics of the included studies

After including these studies, we selected five eligible studies for this meta-analysis. Two studies used Caucasians and three studies used Asians. The total sample size of this meta-analysis was 1565 cases and 1541 controls. Characteristics the included studies are summarized in Table 1.

### Meta-analysis results

As shown in Figure 1, we found that miR-146a rs2910164 polymorphism was significantly associated with an increased CAD risk (OR = 1.19; 95% CI 1.07 – 1.32; $P$ = 0.002). In the subgroup analysis by race, miR-146a rs2910164 polymorphism was significantly associated with an increased CAD risk in Asians (OR = 1.18; 95% CI 1.04 – 1.33; $P$ = 0.008). However, we did not find significant result in Caucasians (OR = 1.22; 95% CI 0.86 – 1.74; $P$ = 0.25). In the subgroup analysis by age, we found that miR-146a rs2910164 polymorphism increased CAD risk in old population (OR = 1.22; 95% CI 1.09 – 1.38; $P$ = 0.0008). All these results are listed in Table 2.

Result from the cumulative meta-analysis suggested that the evidence was consistent over time (Figure 2). In the sensitivity analysis, the result was not changed (Figure 3). Furthermore, no significant publication bias was found by funnel plot (Figure 4) and Egger's test ($P$ = 0.9).

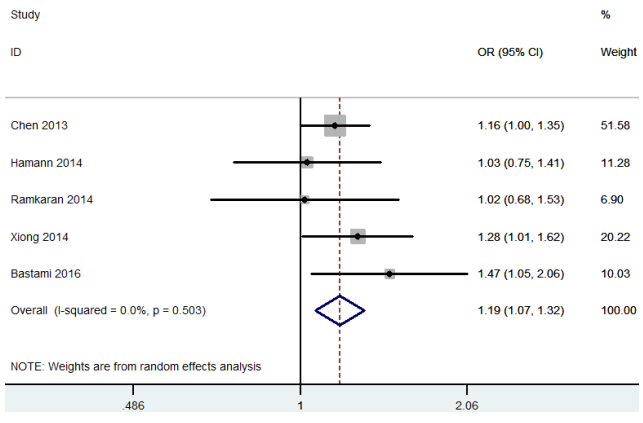


**Figure 1.** The association between miR-146a rs2910164 polymorphism and CAD risk.

## Discussion

This meta-analysis assessed the association between miR-146a rs2910164 polymorphism and CAD risk. We found that miR-146a rs2910164 polymorphism was significantly associated with an increased CAD risk. In the subgroup analysis by race, miR-146a rs2910164 polymorphism was significantly associated with an increased CAD risk in Asians. However, we did not find significant result in Caucasians. It should be highlighted that ethnic differences can occur in genotype frequencies. In the subgroup analysis by age, we found that miR-146a rs2910164 polymorphism increased CAD risk in old population.

Wang et al. showed that the plasma miR-146a level is significantly increased in CAD patients with good coronary collateral circulation and significantly decreased in those with poor coronary collateral circulation (11). Alipoor et al. suggested that miR-146a rs2910164 polymorphism might be associated with type 2 diabetes and its cardiovascular risk factors in an Iranian population (12). Yin et al. suggested that miR-146a rs2910164 polymorphism may influence susceptibility to lung cancer in Chinese nonsmoking females (13). Bogunia-Kubik et al. indicated that miR-146a might be involved in pathogenesis of rheumatoid arthritis and implied that miR-146a-3p polymorphism may be associated with miR-146a-5p levels in serum (14).

Some limitations in this meta-analysis should be ad-

**Table 2.** Results of this meta-analysis.

| | OR (95% CI) | *P* Value | $I^2$ (%) |
|---|---|---|---|
| Overall | 1.19 (1.07-1.32) | 0.002 | 0 |
| Caucasian | 1.22 (0.86-1.74) | 0.25 | 56 |
| Asian | 1.18 (1.04-1.33) | 0.008 | 0 |
| Old | 1.22 (1.09-1.38) | 0.0008 | 0 |

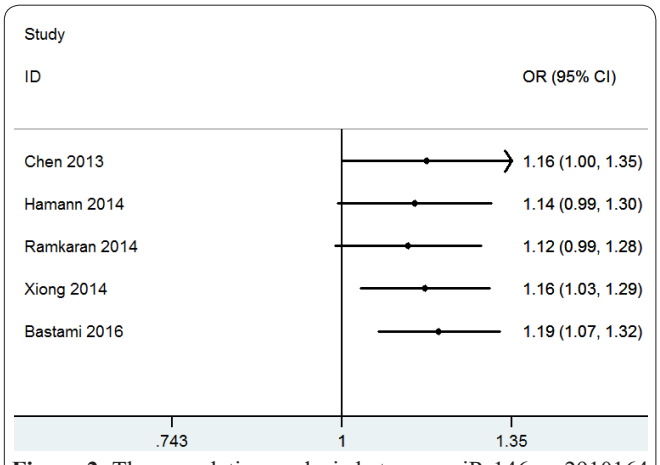


**Figure 2.** The cumulative analysis between miR-146a rs2910164 polymorphism and CAD risk.

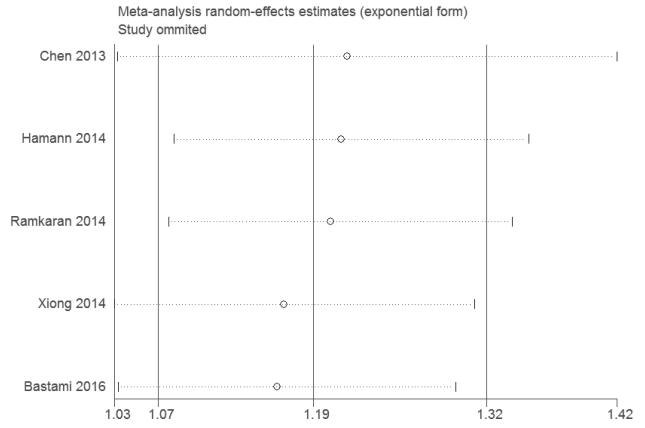


**Figure 3.** Sensitivity analysis of the association between miR-146a rs2910164 polymorphism and CAD risk.

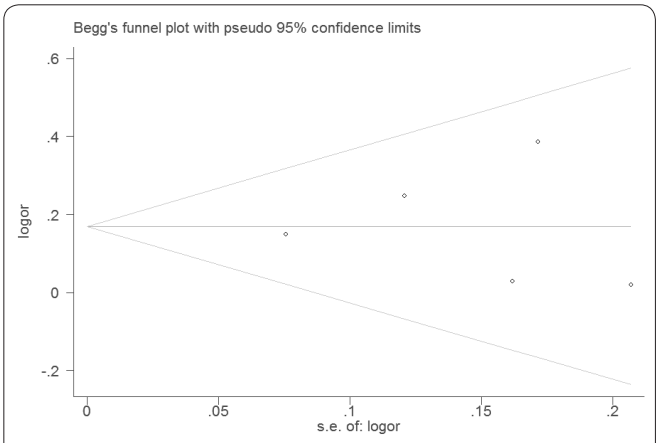


**Figure 4.** Publication bias of the association between miR-146a rs2910164 polymorphism and CAD risk.

dressed. First, only published studies that were included in this meta-analysis. Second, the studies included in our meta-analysis were small. Thus this meta-analysis had little statistical power. Third, we should take into account the general inability of observational studies to prove causation, due to their high potential for bias particularly in the field of nutritional epidemiology. Finally, all of the included studies were retrospective.

In conclusion, this meta-analysis found that miR-146a rs2910164 polymorphism was significantly associated with CAD risk.

## Disclosure of conflict of interest

The authors have declared that no competing interests exist.

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