Associations between *ADIPOQ* polymorphisms and coronary artery disease: a meta-analysis

Xia Zhang¹, Yan Jun Cao¹, Hong Yu Zhang¹, Hongliang Cong²* and Jian Zhang³*

Abstract

**Background:** Whether adiponectin (*ADIPOQ*) polymorphisms are associated with coronary artery disease (CAD) remain controversial. Therefore, we performed this meta-analysis to better explore potential roles of *ADIPOQ* polymorphisms in CAD.

**Methods:** PubMed, Web of Science, Embase and CNKI were searched for eligible studies. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

**Results:** Totally 45 studies were included for pooled analyses. A significant association with the susceptibility to CAD was detected for rs2241766 (dominant model: \( p = 0.0009, \) OR = 0.82, 95%CI 0.73–0.92; recessive model: \( p = 0.04, \) OR = 1.29, 95%CI 1.02–1.64; allele model: \( p < 0.0001, \) OR = 0.80, 95%CI 0.73–0.88) polymorphism in overall population. Further subgroup analyses by ethnicity showed that rs1501299 polymorphism was significantly associated with the susceptibility to CAD in East Asians, whereas rs2241766 polymorphism was significantly associated with the susceptibility to CAD in Caucasians, East Asians and South Asians.

**Conclusions:** Our findings indicated that rs1501299 and rs2241766 polymorphisms both affect the susceptibility to CAD in certain populations.

**Keywords:** Adiponectin (*ADIPOQ*), Genetic polymorphisms, Coronary artery disease (CAD), Meta-analysis

Background

Coronary artery disease (CAD) is the leading cause of death and disability worldwide [1, 2]. To date, the exact pathogenesis of CAD remains largely unknown. Nevertheless, plenty of evidences demonstrated that genetic factors are crucial for the development of CAD. First, family clustering of CAD was observed extensively, and past twin studies showed that the heredity grade of CAD was over 50% [3, 4]. Second, numerous genetic variants were found to be associated with an increased susceptibility to CAD by previous genetic association studies, and screening of common causal variants was also proved to be an efficient way to predict the individual risk of developing CAD [5, 6]. Overall, these findings jointly indicated that genetic predisposition to CAD is important for its occurrence and development.

Adiponectin (*ADIPOQ*), an adipocytokine that regulates energy and material metabolism, is implicated in the development of multiple metabolic disorders including obesity and type II diabetes. And it was evident that these two common metabolic disorders were associated with an increased risk of CAD [7]. Furthermore, previous studies demonstrated that adiponectin have both anti-atherogenic and anti-inflammatory property [8, 9]. Moreover, the expression level of adiponectin was also significantly decreased in CAD patients [10, 11]. Overall, these evidences jointly suggested that adiponectin might exert favorable protection effects against CAD. Therefore, functional *ADIPOQ* genetic polymorphisms, which may alter the expression level of adiponectin, may also affect individual susceptibility to CAD. Recently, some pilot studies already investigated associations of two common functional *ADIPOQ* polymorphisms, rs1501299...
and rs2241766, with the susceptibility to CAD. However, the results of these studies were not consistent, especially when they were conducted in different populations [12–19]. Previous studies failed to reach a consensus regarding associations between ADIPOQ polymorphisms and CAD partially because of their relatively small sample sizes. Thus, we performed the present meta-analysis to explore the relationship between ADIPOQ polymorphisms and CAD in a larger pooled sample size. Additionally, we also aimed to elucidate the potential effects of ethnic background on associations between ADIPOQ polymorphisms and CAD.

Methods
The current meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist [20–22].

Literature search and inclusion criteria
The combination of following terms: (adiponectin OR ADIPOQ) AND (polymorphism OR variant OR mutation OR genotype OR allele) AND (coronary heart disease OR coronary artery disease OR angina pectoris OR acute coronary syndrome OR myocardial infarction) was used to search for potentially eligible articles that were published prior to December 1, 2018 in PubMed, Web of Science, Embase and China National Knowledge Infrastructure (CNKI). We also reviewed the reference lists of all retrieved articles for other potentially eligible studies.

To test the research hypothesis of this meta-analysis, included studies must meet all the following criteria: (1) case-control study on associations between ADIPOQ polymorphisms (rs1501299 and rs2241766) and CAD; (2) provide genotypic and/or allelic frequency of investigated polymorphisms; (3) full text in English or Chinese available. Studies were excluded if one of the following criteria was fulfilled: (1) not relevant to ADIPOQ polymorphisms and CAD; (2) case reports or case series; (3) abstracts, reviews, comments, letters and conference presentations. In the case of duplicate reports by the same authors, we only included the most recent study.

Data extraction and quality assessment
We extracted the following information from eligible studies: 1. name of the first author; 2. year of publication; 3. country and ethnicity of participants; 4. sample size; and 5. genotypic distributions of ADIPOQ polymorphisms in cases and controls. The probability value (p value) of Hardy-Weinberg equilibrium (HWE) was also calculated.

We used the Newcastle-Ottawa scale (NOS) to evaluate the quality of eligible studies [23]. The NOS has a score range of zero to nine, and studies with a score of more than seven were thought to be of high quality.

Two reviewers conducted data extraction and quality assessment independently (Xia Zhang and YanJun Cao). When necessary, we wrote to the corresponding authors for extra information. Any disagreement between two reviewers was solved by discussion until a consensus was reached.

Statistical analyses
In the current study, Review Manager Version 5.3.3 was used to perform statistical analyses. We calculated ORs and 95% CIs to estimate potential associations between ADIPOQ polymorphisms and CAD in all possible genetic models, and a p value of 0.05 or less was defined as statistically significant. Between-study heterogeneities were evaluated by I² statistic. Random-effect models (REMs) would be used for analyses if I² was greater than 50%. Otherwise, analyses would be performed with fixed-effect models (FEMs). Subgroup analyses by ethnicity and type of disease were subsequently carried out. Stabilities of synthetic results were tested in sensitivity analyses. Publication biases were assessed by funnel plots.

Results
Characteristics of included studies
We found 442 potential relevant articles. Among these articles, totally 45 eligible studies were finally included for pooled analyses (see Fig. 1). Baseline characteristics of included studies were shown in Table 1.

Overall and subgroup analyses
Results of overall and subgroup analyses were summarized in Table 2. To be brief, a significant association with the susceptibility to CAD was detected for rs2241766 (dominant model: $p = 0.0009$, OR = 0.82, 95%CI 0.73–0.92; recessive model: $p = 0.04$, OR = 1.29, 95%CI 1.02–1.64; allele model: $p < 0.0001$, OR = 0.80, 95%CI 0.73–0.88) polymorphism in overall analyses. Further subgroup analyses by ethnicity revealed that rs1501299 polymorphism was significantly associated with the susceptibility to CAD in East Asians, whereas rs2241766 polymorphism was significantly associated with the susceptibility to CAD in Caucasians, East Asians and South Asians. No any other positive results were observed in overall and subgroup analyses (see Table 2 and Fig. 2).

Sensitivity analyses
We performed sensitivity analyses by excluding studies that deviated from HWE. No alterations of results were detected in sensitivity analyses, which suggested that our findings were statistically reliable.
**Publication biases**

Publication biases were evaluated with funnel plots. We did not find obvious asymmetry of funnel plots in any comparisons, which indicated that our findings were unlikely to be impacted by severe publication biases.

**Discussion**

Based on combined analyses of 45 eligible studies, our study showed that rs1501299 and rs2241766 polymorphisms were both significantly associated with the susceptibility to CAD in certain populations, which suggested that these two polymorphisms may be used to identify individuals with higher susceptibility to CAD. There are two possible explanations for our positive findings. First, genetic variations of the *ADIPOQ* gene may lead to alternations in gene expression or changes in *ADIPOQ* protein structure, which may subsequently affect biological functions of *ADIPOQ* and ultimately impact individual susceptibility to CAD. Second, it is also possible that *ADIPOQ* polymorphisms may be linked to each other or even linked to other unidentified genes, which could also impact individual susceptibility to CAD.

There are several points that should be noted about this meta-analysis. Firstly, previous experimental studies demonstrated that mutant alleles of investigated polymorphisms could lead to decreased adiponectin generation, which may partially explain our positive findings [12–19].
| First author, year | Country          | Ethnicity         | Type of disease | Sample size | Genotype distribution | P-value for HWE | NOS score |
|-------------------|------------------|-------------------|-----------------|-------------|-----------------------|-----------------|-----------|
| Al-Daghri 2011    | Saudi Arabia     | South Asian       | CAD             | 123/297     | GG/GT/TT              | 0.897           | 7         |
| Ambrozlak 2018    | Poland           | Caucasian         | MI              | 188/153     | 88/72/28              | 0.933           | 7         |
| Antonopoulos 2013 | Greece           | Caucasian         | CAD             | 462/132     | 220/212/30           | 0.184           | 8         |
| Bacci 2004        | Italy            | Caucasian         | CAD             | 142/234     | 70/65/7              | 0.073           | 7         |
| Boumaiza 2011     | Tunisia          | Caucasian         | CAD             | 213/108     | 105/84/23            | 0.115           | 8         |
| Chen 2011         | China            | East Asian        | CAD             | 93/102      | 54/33/6              | 0.307           | 7         |
| Cheung 2014       | Hong Kong        | East Asian        | CAD             | 182/2010    | 88/75/19             | 0.270           | 7         |
| Chiodini 2010     | Italy            | Caucasian         | MI              | 1002/503    | 530/392/80           | 0.016           | 7         |
| De Caterina 2011  | Italy            | Caucasian         | CAD             | 1833/1821   | 926/746/161         | 0.419           | 7         |
| Esteghamati 2012  | Iran             | South Asian       | CAD             | 114/127     | 76/30/6              | 0.095           | 7         |
| Filippi 2005      | Italy            | Caucasian         | CAD             | 580/466     | 287/241/52           | 0.338           | 8         |
| Gable 2007        | UK               | Caucasian         | CAD             | 504/557     | 266/216/22           | 0.931           | 8         |
| Ghaouari 2018     | Tunisia          | Caucasian         | CAD             | 277/269     | 143/93/41           | <0.001          | 8         |
| Gui 2012          | China            | East Asian        | CAD             | 410/431     | 172/185/53          | 0.072           | 8         |
| Hegener 2006      | USA              | Mixed             | MI              | 341/341     | 183/134/24          | 0.093           | 8         |
| Jung 2006         | Korea            | East Asian        | CAD             | 88/68       | 38/43/7              | 0.399           | 7         |
| Katakami 2012     | Japan            | East Asian        | MI              | 213/2424    | 129/71/13           | 0.209           | 7         |
| Lacquemant 2004   | UK               | Caucasian         | CAD             | 161/309     | 82/66/13            | 0.387           | 7         |
| Li 2018           | China            | East Asian        | CAD             | 201/141     | 67/107/27           | 0.030           | 8         |
| Liang 2011        | China            | East Asian        | CAD             | 78/84       | 30/43/5             | 0.663           | 7         |
| Liang 2017        | China            | East Asian        | CAD             | 960/962     | 490/388/82          | 0.275           | 8         |
| Mohammadzadeh 2016 | Iran             | South Asian       | CAD             | 100/100     | 38/55/7             | 0.063           | 7         |
| Ohashi 2004       | Japan            | East Asian        | CAD             | 383/368     | 185/164/34          | 0.977           | 8         |
| Oliveira 2012     | Brazil           | Mixed             | MI              | 450/153     | 209/197/44          | 0.542           | 7         |
| Piscon 2007       | USA              | Mixed             | MI              | 491/988     | 266/182/43          | 0.869           | 7         |
| Qi 2005           | USA              | Mixed             | MI              | 228/594     | 105/111/12          | 0.930           | 7         |
| Rizk 2012         | Qatar            | South Asian       | ACS             | 142/121     | 58/64/20            | 0.667           | 7         |
| Rodríguez-Rodríguez 2011 | Spain    | Caucasian         | CAD             | 119/555     | 69/44/6             | 0.975           | 7         |
| Wu 2013           | China            | East Asian        | CAD             | 188/200     | 67/108/13           | 0.545           | 7         |
| Zhang 2015        | China            | East Asian        | CAD             | 561/412     | 309/209/43          | 0.459           | 8         |
| Zhang 2018        | China            | East Asian        | CAD             | 717/612     | 583/126/8           | 0.798           | 8         |
| rs2241766 T/G     |                  |                   |                 |             |                      |                 |           |
| Al-Daghri 2011    | Saudi Arabia     | South Asian       | CAD             | 122/298     | 77/35/10            | 0.969           | 7         |
| Antonopoulos 2013 | Greece           | Caucasian         | CAD             | 462/132     | 359/97/6            | 0.309           | 8         |
| Bacci 2004        | Italy            | Caucasian         | CAD             | 130/220     | 90/35/5             | 0.135           | 7         |
| Boumaiza 2011     | Tunisia          | Caucasian         | CAD             | 212/104     | 145/57/10           | 0.111           | 8         |
| Chang 2009        | Taiwan           | East Asian        | CAD             | 600/687     | 316/238/46         | 0.606           | 7         |
| Chen 2011         | China            | East Asian        | CAD             | 93/102      | 68/19/6             | 0.391           | 7         |
| Cheung 2014       | Hong Kong        | East Asian        | CAD             | 184/2012    | 89/83/12            | 0.413           | 7         |
| Chiodini 2010     | Italy            | Caucasian         | MI              | 1002/503    | 679/304/19          | 0.102           | 7         |
| DI 2011           | China            | East Asian        | CAD             | 196/124     | 91/85/20            | 0.884           | 7         |
| Du 2016           | China            | East Asian        | CAD             | 493/304     | 253/190/50         | 0.069           | 8         |
| Esteghamati 2012  | Iran             | South Asian       | CAD             | 114/127     | 48/41/25           | 0.222           | 7         |
| Foucan 2010       | French West Indies | African          | CAD             | 57/159      | NA                  | NA              | 7         |
| Gable 2007        | UK               | Caucasian         | MI              | 526/563     | 360/154/12         | 0.280           | 8         |
### Table 1 The characteristics of included studies (Continued)

| First author, year | Country   | Ethnicity | Type of disease | Sample size | Genotype distribution | P-value for HWE | NOS score |
|--------------------|-----------|-----------|-----------------|-------------|-----------------------|-----------------|-----------|
| Ghazouani 2018     | Tunisia   | Caucasian | CAD             | 277/269     | 181/74/22             | 0.007           | 8         |
| Hegener 2006       | USA       | Mixed     | MI              | 341/341     | 241/95/5              | 0.389           | 8         |
| Jin 2009           | China     | East Asian| CAD             | 110/73      | 53/48/9               | 0.584           | 8         |
| Jung 2006          | Korea     | East Asian| CAD             | 88/68       | 41/40/7               | 0.431           | 7         |
| Lacquemant 2004    | UK        | Caucasian | CAD             | 162/315     | 109/48/5              | 0.015           | 7         |
| Li 2011            | China     | East Asian| CAD             | 118/97      | 51/46/21              | 0.036           | 8         |
| Liang 2017         | China     | East Asian| CAD             | 960/982     | 471/382/107           | 0.387           | 8         |
| Luo 2010           | China     | East Asian| CAD             | 221/100     | 100/99/22             | 0.866           | 7         |
| Mofarrah 2016      | Iran      | South Asian| CAD          | 152/72      | 82/35/35              | 0.072           | 8         |
| Mohammadzadeh 2016 | Iran      | South Asian| CAD           | 100/100     | 75/24/1               | 0.900           | 7         |
| Nan 2012           | China     | East Asian| CAD             | 213/467     | 115/84/14             | 0.953           | 8         |
| Oliveira 2012      | Brazil    | Mixed     | CAD             | 450/153     | 323/114/13            | 0.708           | 7         |
| Oliveira 2012      | Brazil    | Mixed     | CAD             | 482/979     | 374/102/6             | 0.290           | 7         |
| Qi 2005            | USA       | Mixed     | CAD             | 219/599     | NA                    | NA              | 7         |
| Rizk 2012          | Qatar     | South Asian| ACS            | 142/122     | 62/42/38              | 0.245           | 7         |
| Sabouri 2011       | Iran      | South Asian| CAD           | 329/241     | 253/74/2              | 0.703           | 7         |
| Xu 2010            | China     | East Asian| CAD             | 153/73      | 78/65/10              | 0.584           | 8         |
| Zhang 2011         | China     | East Asian| CAD             | 149/167     | 63/60/26              | 0.002           | 7         |
| Zhang 2015         | China     | East Asian| CAD             | 561/412     | 276/235/50            | 0.399           | 8         |
| Zhang 2018         | China     | East Asian| CAD             | 717/612     | 500/184/33            | 0.177           | 8         |

**Abbreviations:** CAD Coronary artery disease, MI Myocardial infarction, ACS Acute coronary syndrome, HWE Hardy-Weinberg equilibrium, NOS Newcastle-Ottawa scale, NA Not available.

### Table 2 Results of overall and subgroup analyses for ADIPOQ polymorphisms and CAD

| Population | Sample size | Dominant comparison | Recessive comparison | Overdominant comparison | Allele comparison |
|------------|-------------|---------------------|----------------------|-------------------------|------------------|
| rs1501299 G/T |            | P value OR (95%CI) | P value OR (95%CI) | P value OR (95%CI) | P value OR (95%CI) |
| Overall    | 11,544/15642 | 0.30 0.94 (0.84–1.05) 73% | 0.42 0.94 (0.80–1.10) 57% | 0.08 0.99 (0.99–1.19) 60% | 0.71 0.98 (0.90–1.08) 76% |
| Caucasian  | 5481/5107   | 0.82 1.01 (0.93–1.09) 39% | 0.12 0.80 (0.61–1.06) 67% | 0.29 1.04 (0.96–1.13) 2%  | 0.47 1.04 (0.93–1.17) 64% |
| East Asian | 4074/7814   | 0.08 0.82 (0.66–1.03) 82% | 0.12 1.20 (1.02–1.42) 40% | 0.10 1.18 (0.97–1.43) 76% | 0.14 0.88 (0.74–1.04) 80% |
| South Asian| 479/645     | 0.88 1.04 (0.61–1.77) 78% | 0.97 0.99 (0.68–1.45) 42% | 0.79 0.95 (0.65–1.38) 55% | 0.90 1.03 (0.68–1.56) 80% |
| MI         | 4159/5883   | 0.67 1.04 (0.87–1.23) 65% | 0.63 0.91 (0.63–1.32) 74% | 0.42 0.96 (0.88–1.05) 47% | 0.71 1.03 (0.88–1.21) 75% |
| rs2241766 T/G |          |                    |                      |                         |                  |
| Overall    | 10,135/11577 | <0.0001 0.82 (0.73–0.92) | <0.0001 1.29 (1.02–1.64) 63% | 0.08 1.12 (0.99–1.27) 71% | <0.0001 0.80 (0.73–0.88) 67% |
| Caucasian  | 2771/2106   | 0.09 0.89 (0.79–1.02) 27% | 0.39 0.87 (0.62–1.20) 0%  | 0.04 1.15 (1.01–1.32) 33% | 0.24 0.93 (0.84–1.05) 20% |
| East Asian | 4856/6280   | 0.02 0.80 (0.66–0.96) 77% | 0.06 1.35 (0.99–1.84) 68% | 0.30 1.12 (0.90–1.40) 83% | 0.0006 0.80 (0.71–0.91) 66% |
| South Asian| 959/960     | 0.04 0.69 (0.48–0.99) 66% | 0.04 0.69 (0.48–0.99) 30% | 0.76 1.05 (0.76–1.46) 56% | 0.01 0.64 (0.45–0.91) 76% |
| MI         | 1869/1407   | 0.19 0.90 (0.77–1.05) 0%  | 0.11 0.68 (0.43–1.09) 18% | 0.06 1.16 (0.99–1.36) 30% | 0.48 0.95 (0.83–1.09) 0%   |

**Abbreviations:** OR Odds ratio, CI Confidence interval, NA Not available, CAD Coronary artery disease, MI Myocardial infarction

The values in bold represent there is statistically significant differences between cases and controls.
Fig. 2 (See legend on next page.)
Secondly, it is also worth noting that for rs1501299 polymorphism, the trends of associations in different ethnicities were not always consistent, and this may be attributed to ethnic differences in genotypic distributions of investigated polymorphisms. However, it is also that these inconsistent findings may be resulted from a complex interaction of both genetic and environmental factors. Thirdly, it should be noted that significant between-study heterogeneities were observed in all genetics comparisons of overall analyses, which may partially attributed to ethnic and racial differences of eligible studies. To overcome between-study heterogeneities, REMs were used for pooled analyses, and in further subgroup analyses, we noticed that between-study heterogeneities among studies that were conducted in Caucasians were relatively small, which also supported that ethnic background could impact individual susceptibility to CAD. Fourthly, a recent meta-analyses conducted by Hou et al. [24] also tried to explore potential associations between ADIPOQ polymorphisms and CAD. However, our findings should be considered as more conclusive compared to that of previous meta-analysis since many related studies were published in the last three years, which warranted an update meta-analysis. Totally 10 more eligible studies were enrolled in our pooled analyses, and the sample sizes of our analyses were also significantly larger than that of previous meta-analyses, which could significantly reduce the risk of obtaining false positive or false negative results. Compared with the previous meta-analysis, similar positive results were detected for rs2241766 polymorphism in overall and subgroup analyses. However, positive results in Caucasians for rs1501299 polymorphism were no longer observed in our meta-analysis. Instead, we found that rs1501299 polymorphism could impact individual susceptibility to CAD in East Asians under recessive genetic model. Therefore, future studies with larger sample sizes are still needed to test the potential associations between ADIPOQ polymorphisms and CAD, especially for rs1501299 polymorphism. Fifthly, our study only focused on two mostly investigated ADIPOQ polymorphisms, and future meta-analyses should try to investigate the associations between CAD and other common ADIPOQ polymorphisms such as rs266729, rs822395 and rs17300539. These polymorphisms were not analyzed by us because we failed to find any additional eligible studies compared to the previous meta-analysis conducted by Hou et al. [24].

Some limitations of this meta-analysis should also be acknowledged when interpreting our findings. First, our pooled analyses were based on unadjusted estimations due to lack of raw data, and failure to perform further adjusted analyses may impact the reliability of our findings [25, 26]. Second, since our pooled analyses were based on retrospective case-control studies, despite our positive findings, future perspective studies are still needed to examine whether there is direct causal relationship between ADIPOQ polymorphisms and CAD [27, 28]. Third, associations between ADIPOQ polymorphisms and CAD may also be modified by gene-gene and gene-environmental interactions. However, due to lack of raw data, we could not conduct relevant analyses [29, 30]. Fourth, our analyses were based on retrospective case-control studies. Thus, despite the relatively high NOS score, it was still possible that our findings might be impacted by potential selection, measurement and confounding biases. Taking the above mentioned limitations into consideration, our findings should be interpreted with caution.

Conclusions
In conclusion, our meta-analysis suggested that rs1501299 and rs2241766 polymorphisms were both significantly associated with the susceptibility to CAD in certain populations. However, further well-designed studies are still warranted to confirm our findings.

Abbreviations
ADIPOQ: Adiponectin; CAD: Coronary artery disease; HWE: Hardy-Weinberg equilibrium; NOS: Newcastle-Ottawa scale

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Availability of data and materials
The current study was based on results of relevant published studies.

Authors’ contributions
XZ, HC and JZ conceived of the study, participated in its design. XZ and YC conducted the systematic literature review. HZ performed data analyses. XZ, HC and JZ drafted the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Ethics approval and consent to participate
Not applicable.
Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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