Effects of ADIPOQ polymorphisms on individual susceptibility to coronary artery disease: a meta-analysis

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ABSTRACT

Whether adiponectin (ADIPOQ) polymorphisms affect individual susceptibility to coronary artery disease (CAD) remains controversial. Therefore, we performed this meta-analysis to better analyse associations between ADIPOQ polymorphisms and CAD. PubMed, Web of Science, Embase and CNKI were searched for eligible studies. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Totally, 51 studies were eligible for analyses. In overall analyses, significant associations with the susceptibility to CAD were detected for rs266729 (overdominant model: \( p = 0.03, OR = 1.11, 95\% CI 1.01–1.22 \)), rs822395 (recessive model: \( p = 0.007, OR = 1.21, 95\% CI 1.05–1.40 \)) and 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: \( p < 0.0001, OR = 0.80, 95\% CI 0.73–0.88 \)) polymorphisms. Further subgroup analyses by ethnicity revealed that rs1501299 polymorphism was significantly associated with the susceptibility to CAD in East Asians, while rs2241766 polymorphism was significantly associated with the susceptibility to CAD in Caucasians, East Asians and South Asians. In summary, our findings indicated that rs266729, rs822395, rs1501299 and rs2241766 polymorphisms were all significantly associated with the susceptibility to CAD in certain populations.

Introduction

Coronary artery disease (CAD) is the leading cause of death and disability worldwide [1,2]. So far, the exact aetiology of CAD is still unclear. Nevertheless, plenty of evidence supported that genetic factors may play a crucial part in its development. First, family clustering of CAD was observed extensively, and past twin studies proved 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 supported that genetic predisposition to CAD is important for its occurrence and development.

Adiponectin (ADIPOQ), a multifunctional adipokine that is predominantly secreted by adipocytes, plays a central role in regulating energy and material metabolism [7]. Previous studies showed that adiponectin has both anti-atherogenic and anti-inflammatory properties [8,9]. Furthermore, the expression level of adiponectin was also significantly decreased in patients with CAD [10,11]. In summary, these pieces of evidence jointly suggested that adiponectin might exert favourable protection effects against CAD. Therefore, functional ADIPOQ genetic polymorphisms, which may alter the expression level of adiponectin, may also affect individual susceptibility to CAD. So far, several studies already tried to investigate associations between ADIPOQ polymorphisms and CAD, but the results of these studies were controversial, 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.

Materials and methods

Literature search and inclusion criteria

The current meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [20]. PubMed, Web of...
Science, Embase and China National Knowledge Infrastructure (CNKI) were searched for potentially eligible articles using 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). We also reviewed the reference lists of all retrieved articles to identify other potentially eligible studies. The initial search was conducted in July 2018 and the latest update was performed in December 2018.

To test the research hypothesis of this meta-analysis, included studies must satisfy the following criteria: (1) case–control study on associations between ADIPOQ polymorphisms and CAD; (2) provide genotypic and/or allelic frequency of investigated ADIPOQ polymorphisms; and (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; and (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 for analyses.

**Data extraction and quality assessment**

We extracted the following information from eligible studies: (a) name of the first author; (b) year of publication; (c) country and ethnicity of participants; (d) sample size; and (e) 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 [21]. The NOS has a score range of 0 to 9, and studies with a score of more than 7 were thought to be of high quality.

Two reviewers conducted data extraction and quality assessment independently. 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, we performed statistical analyses by using Review Manager Version 5.3.3. We calculated ORs and 95% CIs to estimate potential associations between ADIPOQ polymorphisms and CAD in dominant, recessive, overdominant and allele models, and statistical significances of pooled analyses were determined by the Z test, with a p value of 0.05 or less was defined as statistically significant. All investigated ADIPOQ polymorphisms contain a major allele (M) and a minor allele (m), and the definitions of all genetic comparisons were as follows: dominant comparison is defined as MM versus Mm + mm, recessive comparison is defined as mm vs. MM +Mm, overdominant comparison is defined as Mm versus MM + mm, and the allele comparison is defined as M versus m. Between-study heterogeneities were evaluated by $I^2$ statistic. Random-effect models would be used for analyses if $I^2$ was greater than 50% (Der Simonian–Laird method). Otherwise, analyses would be conducted with fixed-effect models (Mantel–Haenszel method). Subgroup analyses were subsequently carried out by ethnicity and type of disease. Stabilities of synthetic results were tested in sensitivity analyses. Publication biases were assessed by funnel plots.

**Results**

**Characteristics of included studies**

We found 434 potentially relevant articles. Among these articles, totally 51 eligible studies were finally included for synthetic analyses (see Figure 1). The NOS score of eligible articles ranged from 7 to 8, which indicated that all the included studies were of high quality. Baseline characteristics of the included studies are summarized in Table 1.

**Overall and subgroup analyses**

Results of overall and subgroup analyses are summarized in Table 2. To be brief, significant associations with the susceptibility to CAD were detected for rs266729 (overdominant model: $p = 0.03$, odds ratio [OR] = 1.11, 95% confidence interval [CI] 1.01–1.22), rs822395 (recessive model: $p = 0.007$, OR = 1.21, 95% CI 1.05–1.40) and rs2241766 (dominant model: $p = 0.009$, OR = 1.82, 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) polymorphisms in overall analyses. Further subgroup analyses by ethnicity revealed that rs1501299 polymorphism was significantly associated with the susceptibility to CAD in East Asians, while 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 supplementary Figure 1).

**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 (see supplementary Figure 2).

Discussion

To the best of our knowledge, this is so far the most comprehensive meta-analysis on associations between ADIPOQ polymorphisms and CAD, and our pooled analyses demonstrated that rs266729, rs822395, rs1501299 and rs2241766 polymorphisms were all significantly correlated with the susceptibility to CAD in certain populations.

There are several points that need to be addressed about this meta-analysis. First, previous experimental studies showed that mutant alleles of investigated polymorphisms were correlated with decreased adiponectin generation, which may partially explain our positive findings [12–19]. Second, it is also notable that 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 possible that these inconsistent findings may have resulted from a complex interaction of both genetic and environmental factors. Third, the pathogenic mechanism of CAD is highly complex, and hence, it is unlikely that a single genetic polymorphism could significantly contribute to its development. As a result, to better illustrate potential
Table 1. The characteristics of included studies.

| First author, y | Country | Ethnicity | Type of disease | Sample size | Genotype distribution | p-Value for HWE | NOS score |
|-----------------|---------|-----------|-----------------|-------------|-----------------------|----------------|-----------|
| rs266729 G/C    |         |           |                 |             |                       |                |           |
| Cheung 2014     | Hong Kong | East Asian | CAD             | 184/2007    | CC/CG/GG              | 0.327          | 7         |
| Chiodini 2010   | Italy    | Caucasian | MI              | 1002/503    | 1016/617/108         | 0.717          | 7         |
| De Caterina 2011| Italy    | Caucasian | MI              | 1855/1855   | 1063/684/108         | 0.883          | 7         |
| Du 2016         | China    | East Asian | CAD             | 493/304     | 278/175/40           | 0.069          | 8         |
| Gable 2007      | UK       | Caucasian | MI              | 340/342     | 197/123/20           | 0.548          | 8         |
| Hetgener 2006   | USA      | Mixed     | MI              | 161/313     | 89/65/7              | 0.870          | 7         |
| Lacquemant 2004 | UK       | Caucasian | CAD             | 111/65/8    | 675/379/60           | 0.478          | 7         |
| Oguri 2009      | Japan    | East Asian | MI              | 722/1114    |                       | 0.239          | 8         |
| Persson 2010    | Sweden   | Asian     | MI              | 278/175/40  | 272/172/28           | 0.383          | 8         |
| Prior 2009      | UK       | Caucasian | CAD             | 127/100/17  | 130/101/13           | 0.241          | 8         |
| Prior 2011      | UK       | Caucasian | MI              | 197/123/20  | 158/114/26           | 0.406          | 8         |
| Rodríguez-Rodríguez 2011 | Spain | Caucasian | MI              | 329/197/38  | 327/197/38           | 0.717          | 7         |
| Zhang 2015      | Japan    | East Asian | CAD             | 174/118/21  | 174/118/21           | 0.791          | 8         |
| Zhang 2018      | China    | East Asian | CAD             | 110/72/16   | 146/76/15            | 0.239          | 8         |
| Zhang 2010      | China    | East Asian | CAD             | 198/237     | 198/237/16           | 0.239          | 8         |
| rs822395 A/C    |         |           |                 |             | AA/AC/CC              | 0.371          | 7         |
| Cheung 2014     | Hong Kong | East Asian | CAD             | 184/2009    | 144/527/41           | 0.750          | 7         |
| De Caterina 2011| Italy    | Caucasian | MI              | 1855/1854   | 848/811/196          | 0.750          | 7         |
| Lacquemant 2004 | UK       | Caucasian | MI              | 342/189/20  | 335/242/32           | 0.184          | 8         |
| Pischon 2000    | USA      | Mixed     | MI              | 496/989     | 450/467/72           | 0.001          | 7         |
| Qi 2005         | USA      | Mixed     | MI              | 104/101/29  | 296/280/76           | 0.793          | 8         |
| Zhang 2015      | China    | East Asian | MI              | 274/114/8   | 274/114/8            | 0.328          | 8         |
| Zhang 2018      | China    | East Asian | MI              | 252/281/79  | 252/281/79           | 0.962          | 8         |
| Zhang 2010      | China    | East Asian | MI              | 143/48/7   | 175/59/3             | 0.424          | 8         |
| rs1501299 G/T   |         |           |                 |             | GG/GT/TT              | 0.897          | 7         |
| Al-Dagher 2011  | Saudi Arabia | South Asian | MI              | 123/297     | 111/142/44           | 0.933          | 7         |
| Ambrozlak 2018  | Poland   | Caucasian | MI              | 188/72/28   | 84/59/10             | 0.184          | 8         |
| Antonopoulos 2013| Greece | Caucasian | MI              | 220/212/30  | 66/50/16             | 0.073          | 7         |
| Bacci 2004      | Italy    | Caucasian | MI              | 142/234     | 118/88/28            | 0.115          | 8         |
| Boursina 2011   | Tunisia  | Caucasian | MI              | 213/108     | 45/41/18             | 0.307          | 7         |
| Chen 2011       | China    | East Asian | MI              | 93/102      | 61/38/3              | 0.424          | 8         |
| Cheung 2014     | Hong Kong | East Asian | MI              | 182/2010    | 1103/759/148         | 0.270          | 7         |
| Chiodini 2010   | Italy    | Caucasian | MI              | 1002/503    | 239/198/66           | 0.016          | 7         |
| De Caterina 2011| Italy    | Caucasian | MI              | 1853/1821   | 906/767/148          | 0.419          | 7         |
| Esteghamati 2012| Iran     | South Asian | CAD             | 114/127     | 63/47/17             | 0.095          | 7         |
| Filippi 2005    | Italy    | Caucasian | MI              | 504/557     | 289/225/43           | 0.338          | 8         |
| Gable 2007      | UK       | Caucasian | MI              | 266/166/22  | 266/166/22           | 0.338          | 8         |
| Ghazouani 2018  | Tunisia  | Caucasian | MI              | 143/93/41   | 138/88/43            | 0.001          | 7         |
| Gui 2012        | China    | East Asian | MI              | 341/141     | 181/141/17           | 0.093          | 8         |
| Hegener 2006    | USA      | Mixed     | MI              | 88/47/17    | 31/32/5              | 0.399          | 7         |
| Jung 2006       | Korea    | East Asian | MI              | 213/242     | 129/71/13            | 0.209          | 7         |
| Katakami 2012   | Japan    | East Asian | MI              | 201/141     | 64/53/24             | 0.030          | 8         |
| Lacquemant 2004 | UK       | Caucasian | MI              | 161/309     | 169/115/25           | 0.387          | 7         |
| Li 2018         | China    | East Asian | MI              | 82/66/13    | 64/53/24             | 0.030          | 8         |
| Liang 2011      | China    | East Asian | MI              | 78/84       | 48/30/6              | 0.663          | 7         |
| Liang 2017      | China    | East Asian | MI              | 960/962     | 617/300/45           | 0.275          | 8         |
| Mohammadzadeh 2016 | Iran | East Asian | MI              | 100/100     | 56/42/2              | 0.063          | 7         |
| Ohashi 2004     | Japan    | East Asian | MI              | 383/368     | 190/149/29           | 0.977          | 8         |

(Continued)
| First author, y | Country | Ethnicity | Type of disease | Sample size | Genotype distribution | p-Value for HWE | NOS score |
|-----------------|---------|-----------|-----------------|-------------|----------------------|----------------|-----------|
| Oliveira 2012   | Brazil  | Mixed     | CAD             | 450/153     | 209/197/44          | 0.542          | 7         |
| Pischon 2007    | USA     | Mixed     | CAD             | 491/988     | 266/182/43          | 0.869          | 7         |
| Qi 2005         | USA     | Mixed     | CAD             | 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 | East Asian 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| East Asian CAD  | 561/412     | 309/209/43          | 0.459          | 8         |
| Zhang 2018      | China   | East Asian| East Asian CAD  | 717/612     | 583/126/8           | 0.798          | 8         |
| rs2241766       |         |           |                 |             | TT/TG/GG            |                |           |
| Al-Daghri 2011  | Saudi Arabia | South Asia | CAD | 122/298 | 77/35/10 | 220/72/6 | 0.969 | 7 |
| Antonopoulos 2013 | Greece | Caucasian | CAD | 462/132 | 359/97/6 | 99/29/4 | 0.309 | 8 |
| Bacci 2004      | Italy   | Caucasian | CAD | 130/220 | 90/35/5 | 149/60/11 | 0.135 | 7 |
| Boumaiza 2011   | Tunisia | East Asian| CAD | 212/104 | 145/57/10 | 75/24/5 | 0.111 | 8 |
| Chang 2009      | Taiwan  | East Asian| East CAD | 600/687 | 316/238/46 | 309/399/79 | 0.606 | 7 |
| Chen 2011       | China   | East Asian| East CAD | 93/102 | 68/19/6 | 59/35/8 | 0.391 | 7 |
| Cheung 2014     | Hong Kong | East Asian| East CAD | 184/2012 | 89/83/12 | 1007/822/183 | 0.413 | 7 |
| Chiodini 2010   | Italy   | Caucasian | East MI | 1002/503 | 679/304/19 | 359/126/18 | 0.102 | 7 |
| Di 2011         | China   | East Asian| MI | 196/124 | 91/85/20 | 65/50/9 | 0.884 | 7 |
| Du 2016         | China   | East Asian| East CAD | 493/304 | 253/190/50 | 185/97/22 | 0.069 | 8 |
| Esteghamati 2012 | Iran  | East Asian| East South CAD | 114/127 | 48/41/25 | 68/46/13 | 0.222 | 7 |
| Foucan 2010     | French West Indies | East African| CAD | 57/159 | NA | NA | NA | 7 |
| Gable 2007      | UK      | Caucasian | MI | 526/563 | 360/154/12 | 384/168/11 | 0.280 | 8 |
| Ghazouani 2018  | Tunisia | East Asian| CAD | 277/269 | 181/74/22 | 182/70/17 | 0.007 | 8 |
| Hegener 2006    | USA     | Mixed     | MI | 341/341 | 241/95/5 | 252/80/9 | 0.389 | 8 |
| Jin 2009        | China   | East Asian| East CAD | 110/73 | 53/48/9 | 50/20/3 | 0.584 | 7 |
| Jung 2006       | Korea   | East Asian| East CAD | 88/68 | 41/40/7 | 34/30/4 | 0.431 | 7 |
| Lacquemant 2004 | UK      | Caucasian | East CAD | 162/315 | 109/48/5 | 249/57/9 | 0.015 | 7 |
| Li 2011         | China   | East Asian| CAD | 118/97 | 51/46/21 | 54/31/12 | 0.036 | 8 |
| Liang 2017      | China   | East Asian| East CAD | 960/982 | 471/382/107 | 608/308/46 | 0.387 | 8 |
| Luo 2010        | China   | East Asian| East CAD | 221/100 | 100/99/22 | 50/41/9 | 0.886 | 7 |
| Mofarrah 2016   | Iran    | East Asian| South CAD | 152/72 | 82/35/35 | 56/13/3 | 0.072 | 8 |
| Mohammadzadeh 2016 | Iran  | East Asian| South CAD | 100/100 | 75/24/1 | 65/31/4 | 0.900 | 7 |
| Nan 2012        | China   | East Asian| East CAD | 213/467 | 115/84/14 | 237/191/39 | 0.953 | 8 |
| Oliveira 2012   | Brazil  | Mixed     | CAD             | 450/153     | 323/114/13          | 0.708          | 7         |
| Pischon 2007    | USA     | Mixed     | CAD             | 482/979     | 374/102/6          | 0.290          | 7         |
| Qi 2005         | USA     | Mixed     | CAD             | 219/599     | NA                 | NA            | NA        |
| Rizk 2012       | Qatar   | South Asian| ACS             | 142/122     | 62/42/38           | 0.245          | 7         |
| Sabouri 2011    | Iran    | East 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         |
| rs17300539      |         |           |                 |             | GG/GA/AA           |                |           |
| Ambroziak 2018  | Poland  | Caucasian | MI | 193/153 | 169/23/1 | 130/23/0 | 0.315 | 7 |
| Chiodini 2010   | Italy   | Caucasian | MI | 1002/503 | 827/165/10 | 414/87/2 | 0.252 | 7 |
| Gable 2007      | UK      | Caucasian | MI | 529/568 | 446/78/5 | 458/107/3 | 0.220 | 8 |

(Continued)
associations of certain genetic polymorphisms with CAD, we strongly recommend further studies to perform haplotype analyses and explore potential gene–gene interactions.

Some limitations of this meta-analysis should also be noted when interpreting our findings. First, our pooled analyses were based on unadjusted estimations due to lack of raw data, and we have to admit that failure to perform further adjusted analyses may impede the reliability of our findings [22,23]. Second, since our pooled analyses were based on case–control studies, despite our positive findings, future prospective studies are still needed to examine whether there is a direct causal relationship between ADIPOQ polymorphisms and CAD [24,25]. Third, associations between ADIPOQ polymorphisms and CAD may also be modified by gene–gene and gene–environmental interactions. However, most studies did not consider these potential interactions, which impeded us to conduct relevant analyses [26,27]. Considering the above-mentioned limitations, our findings should be interpreted with caution.

In conclusion, our meta-analysis suggested that rs266729, rs822395, rs1501299 and rs2241766 polymorphisms were all significantly correlated with the susceptibility to CAD in certain populations. However, further well-designed studies are still warranted to confirm our findings.

**Authors’ contributions**

Zhiyuan WANG and Jingquan ZHONG conceived the study and participated in its design. Zhiyuan WANG and Jinglan DIAO conducted the systematic literature review. Xin YUE performed data analyses. Zhiyuan WANG and Jingquan ZHONG drafted the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.
Disclosure statement

No potential conflict of interest was reported by the authors.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this type of study, formal consent is not required.

References

[1] Moran AE, Forouzanfar MH, Roth G, et al. The global burden of ischemic heart disease in 1990 and 2010: the global burden of disease 2010 study. Circulation. 2014;129:1493–1501.

[2] Global burden of disease study 2013 collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the global burden of disease study 2013. Lancet. 2015;386:743–800.

[3] Mayer B, Erdmann J, Schunkert H. Genetics and heritability of coronary artery disease and myocardial infarction. Clin Res Cardiol. 2007;96:1–7.

[4] Evans A, Van Baal GC, McCarron P, et al. The genetics of coronary heart disease: the contribution of twin studies. Twin Res. 2003;6:432–441.

[5] Sayols-Baixeras S, Lluis-Ganella C, Lucas G, et al. Pathogenesis of coronary artery disease: focus on genetic risk factors and identification of genetic variants. Appl Clin Genet. 2014;7:15–32.

[6] Dai X, Wiernek S, Evans JP, et al. Genetics of coronary artery disease and myocardial infarction. World J Cardiol. 2016;8:1–23.

[7] Wang ZV, Scherer PE. Adiponectin, the past two decades. J Mol Cell Biol. 2016;8:93–100.

[8] Katsiki N, Mantzoros C, Mikhailidis DP. Adiponectin, lipids and atherosclerosis. Curr Opin Lipidol. 2017;28:347–354.

[9] Ohashi K, Ouchi N, Matsuzawa Y. Anti-inflammatory and anti-atherogenic properties of adiponectin. Biochimie. 2012;94:2137–2142.

[10] Persson J, Lindberg K, Gustafsson TP, et al. Low plasma adiponectin concentration is associated with myocardial infarction in young individuals. J Intern Med. 2010;268:194–205.

[11] Piestrzieniewicz K, Luczak K, Komorowski J, et al. Obesity and adiponectin in acute myocardial infarction. Cardiol J. 2007;14:29–36.

[12] Zhang Z, Li Y, Yang X, et al. Susceptibility of multiple polymorphisms in ADIPOQ, ADIPOR1 and ADIPOR2 genes to myocardial infarction in Han Chinese. Gene. 2018;658:10–17.

[13] Zhong C, Zhen D, Qi Q, et al. A lack of association between adiponectin polymorphisms and coronary artery disease in a Chinese population. Genet Mol Biol. 2010;33:428–433.

[14] Liang C, Yawei X, Qinwan W, et al. Association of AdipoQ single-nucleotide polymorphisms and smoking interaction with the risk of coronary heart disease in Chinese Han population. Clin Exp Hypertens. 2017;39:748–753.

[15] Mohammadzadeh G, Ghaffari MA, Heibar H, et al. Association of two common single nucleotide polymorphisms (+457T/G and +276G/T) of ADIPOQ gene with coronary artery disease in type 2 diabetic patients. Iran Biomed J. 2016;20:152–160.

[16] Rizk NM, El-Menyar A, Marei I, et al. Association of adiponectin gene polymorphism (+T45G) with acute coronary syndrome and circulating adiponectin levels. Angiology. 2013;64:257–265.

[17] Ambrozjak M, Kolanowska M, Bartoszewicz Z, et al. Adiponectin gene variants and decreased adiponectin plasma levels are associated with the risk of myocardial infarction in young age. Gene. 2018;642:498–504.

[18] Chiiodini BD, Specchia C, Gori F, et al. Adiponectin gene polymorphisms and their effect on the risk of myocardial infarction and type 2 diabetes: an association study in an Italian population. Ther Adv Cardiovasc Dis. 2010;4:223–230.

[19] Hegener HH, Lee IM, Cook NR, et al. Association of adiponectin gene variations with risk of incident myocardial infarction and ischemic stroke: a nested case-control study. Clin Chem. 2006;52:2021–2027.

[20] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264–269.

[21] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603–605.

[22] Xie X, Shi X, Liu M. The roles of TLR gene polymorphisms in atherosclerosis: a systematic review and meta-analysis of 35,317 subjects. Scand J Immunol. 2017;86:50–58.

[23] Sun H, Li Q, Jin Y, et al. Associations of tumor necrosis factor-α polymorphisms with the risk of asthma: a meta-analysis. Exp Mol Pathol. 2018;105:411–416.

[24] Dong J, Ping Y, Wang Y, et al. The roles of endothelial nitric oxide synthase gene polymorphisms in diabetes mellitus and its associated vascular complications: a systematic review and meta-analysis. Endocrine. 2018;62:412–422.

[25] Shi X, Xie X, Jia Y, et al. Associations of insulin receptor and insulin receptor substrates genetic polymorphisms with polycystic ovary syndrome: a systematic review and meta-analysis. J Obstet Gynaecol Res. 2016;42:844–854.

[26] Zhu Y, Zheng G, Hu Z. Association between SERT insertion/deletion polymorphism and the risk of irritable bowel syndrome: a meta-analysis based on 7039 subjects. Gene. 2018;679:133–137.

[27] Xie X, Shi X, Xun X, et al. Endothelial nitric oxide synthase gene single nucleotide polymorphisms and the risk of hypertension: a meta-analysis involving 63,258 subjects. Clin Exp Hypertens. 2017;39:175–182.