Genetic variations associated with coronary artery disease and myocardial infarction in the Arab world: a systematic review and meta-analysis

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Abstract

Coronary artery disease (CAD) and myocardial infarction (MI) have reached epidemic levels in the Arab world. The well-recognized familial clustering of CAD implies that genetics plays a key role in its development. Several CAD/MI genetic association studies have been conducted, but the outcomes have been inconsistent. In this study, we aimed to systematically review and quantitatively summarize the current evidence on genetic polymorphisms associated with CAD/MI risk in the Arab world. We systematically searched five literature databases (Science Direct, PubMed, Scopus, EMBASE, and Web of Science). We included all genetic polymorphisms with odds ratio (OR) > 1 that were significantly associated with CAD/MI risk among Arabs. Review Manager software v5.02 was used to conduct the meta-analysis. Publication bias was measured using Begg’s funnel plot and Egger’s test based on STATA software v15.1. The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were computed to estimate the association. I²-statistic was used to assess heterogeneity. In total, 75 studies comprising 36,125 cases and 31,730 controls were included, and 62 studies were eligible for meta-analysis. A total of 80 captured variants within or near 59 genes were found to be associated with an increased CAD/MI susceptibility. We performed 46 individual meta-analyses tests for 46 variants. The pooled OR of association with CAD/MI ranged from 1.14 to 7.57, with a median (interquartile range) of 1.83 (1.64 – 2.57). With the few studies published so far, there appears to be a unique genetic and clinical susceptibility profile for Arab patients with CAD/MI. The findings of this study will pave the way to perform future genetic association studies that will help identify potential therapeutic targets against CAD/MI.

Keywords: Coronary artery disease, Myocardial infarction, Genetic variations, Genotype-phenotype correlations, Arab countries.

Introduction

Coronary artery disease (CAD), also referred to as ischemic heart disease (IHD), is a complex multifactorial disorder characterized by insufficient oxygen supply to the cardiac muscles due to narrowing of the coronary artery by fatty plaques. CAD encompasses a spectrum of clinical events, including asymptomatic subclinical atherosclerosis, angina pectoris, myocardial infarction (MI) and sudden cardiac death [1]. Over the past ten years, large-scale genome-wide association studies (GWAS) and similar research have identified a large number of genetic polymorphisms associated with CAD and/or MI [2-13].
However, to date, the identified loci altogether explain a small fraction of CAD and/or MI risk [10]. Furthermore, these studies have been conducted almost exclusively in populations of Eastern Asian or European descent [7, 8, 14-19], and because of the well-evidenced genetic differences among different ethnic groups, the identified loci might not explain CAD susceptibility in other populations. Environmental factors, such as diet, hypertension, dyslipidemia, diabetes, physical activity, and smoking are known to alter a person's risk of developing CAD. Nevertheless, it has been estimated that approximately 40–50% of subjects with CAD do not have any conventional risk factors [20, 21], suggesting that genetics play a crucial role in the predisposition to CAD. Family and twin studies provide convincing evidence that CAD clusters in families [22, 23]; it is now universally accepted that CAD has a significant hereditary component accounting for approximately 50% to 60% of susceptibility to the disease [20, 22, 24-27].

CAD is recognized as a major global health problem with significant mortality and morbidity worldwide [28]. It is estimated that by 2020, CAD will be responsible for a total of 11.1 million deaths globally, and it is predicted to reach 23.4 million in 2030 [29]. In developing countries, CAD is considered the leading cause of death [30]. Arab countries bear a heavy burden from CAD and its subsequent complications. Arab patients present with MI at a younger age compared to patients of Western European descent [31]. The projected future burden of CAD-related mortality in Arab countries is set to exceed that seen in other geographic areas [32]. Age-standardized mortality rates collected by the World Health Organization (WHO) have shown higher rates of cardiovascular death in seven Arab countries (United Arab Emirates, Kuwait, Jordan, Tunisia, Lebanon, Saudi Arabia and Egypt) compared to the United Kingdom, Germany and the United States, with ischemic heart disease being the leading cause of death [33].

Arabs are a major panethnic group, and their union, the Arab League, comprises 22 countries [34]. The Arab world has historically been a crossroads for different cultures that has significantly altered its ethnic composition, yielding a high degree of genetic heterogeneity [35]. Given that certain ethnic groups and specific populations living in particular geographical areas in the Arab world are more prone to CAD/MI than others [31, 32, 36-42], this suggests that genetic factors may predispose Arabs to CAD and/or MI in a unique way that is different from other ethnic groups.

During the last decade, extensive research on different genetic polymorphisms associated with CAD and/or MI have yielded inconclusive results [43-48]. This is mainly because of two critical issues: 1) the multifactorial nature of CAD, involving different pathways and intermediate phenotypes with different genes involved; and 2) the wide heterogeneity of investigations related to study design, sample size, clinical endpoints, typology of included patients, and diversities in multiple ethnic cohorts [47]. In addition, there has been relatively little attention devoted to comprehensively assess the effect of CAD/MI-associated genetic polymorphisms among Arabs. A meta-analysis, which combines CAD/MI genetic association studies in the Arab world, could be helpful to explain the association of genetic polymorphisms with high CAD and/or MI susceptibility. Therefore, in this study, we aimed to systematically review and quantitatively summarize current evidence on genetic polymorphisms associated with CAD/MI risk in the Arab world.

Methods

To ensure the rigor of the current systematic review, it was designed and implemented based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [49]. The described search method and selection strategy was used to identify studies investigating the effect of CAD/MI genetic polymorphisms, including single nucleotide polymorphisms (SNPs), variable number tandem repeats (VNTRs), deletions, insertions, and copy-number variants on CAD and/or MI risk as primary outcomes among Arab patients residing in any of the 22 Arab countries.

Search strategy

Five literature databases (Science Direct, PubMed, Scopus, EMBASE, and Web of Science) were searched from inception until May 2019 for relevant studies. Literature searches were performed using a combination of text words and MeSH terms, such as: (“coronary artery disease” OR “ischemic heart disease” OR “coronary heart disease” OR “myocardial infarction” OR “cardiovascular disease”) AND (“polymorphism” OR “genetic” OR “SNPs” OR “mutation” OR “variant”) AND (“Arab” OR “Bahrain” OR “Algeria” OR “Comoros” OR “Egypt” OR “Egypt” OR “Emirates/UAE” OR “Djibouti” OR “Iraq” OR “Kuwait” OR “Lebanon” OR “Jordan” OR “Libya” OR “Morocco” OR “Oman” OR “Mauritania” OR “Palestine” OR “Qatar” OR “Saudi” OR “Somali” OR “Sudan” OR “Syria” OR “Tunisia” OR “Yemen”).

Study selection

The selection criteria for the articles were as follows: (1) studies reporting genetic polymorphisms associated with CAD and/or MI susceptibility; (2) patients clinically diagnosed with CAD or who have experienced MI; (3) studies conducted on human subjects only; (4) Arab subjects residing in Arab countries; (5) studies that reported odd ratios (OR) and 95% confidence intervals (CI); and (6)
variants with significant genetic association ($P < 0.05$) data and $OR > 1$. The exclusion criteria were as follows: (1) CAD and/or MI not the primary outcomes; (2) studies performed exclusively in patients with familial hypercholesterolemia, diabetes mellitus, or hypertension; and (3) reviews articles, comments or animal studies. Studies resulting from the search strategy were all exported to Endnote X9, and duplicates were removed. Articles that remained after duplicate removal have been screened in two stages (Figure 1).

![PRISMA flow diagram of the included studies](image)

Figure 1. PRISMA flow diagram of the included studies. Our search strategy resulted in 5,608 studies. A total of 75 studies were eligible for inclusion in the systematic review, and 62 were included in the meta-analysis.

The first stage involved performing the initial screening of the title, abstract and keywords of studies and assessing relevance for the scope of the systematic review according to the selection criteria. The second stage involved retrieval of the full text of each potentially relevant study and screening for content to decide on its inclusion. For conference abstracts and articles for which full-text articles could not be retrieved, the abstracts were reviewed thoroughly for content and were considered as eligible if they met the selection criteria and required data were available in the abstract. Study authors were contacted to obtain the required data if not included in the abstract. Any disagreement about inclusion was referred to a second reviewer (HZ) and were resolved through discussion.

**Data collection**

The collected information were reviewed independently by two scientists (SY and HZ), and relevant data were extracted. A consensus through discussion was reached to collect all the information related to the genetic polymorphisms that were significantly associated with CAD and/or MI with an OR > 1 among Arab patients. The following data were extracted from each eligible study: author(s), year, study design, country of origin, phenotype, number of cases, number of controls, genotyping method, gene, nucleotide change, protein change, dbSNP ID, associated allele/genotype, crude [OR, 95% CI, P-value], adjusted [OR, CI 95% CI, P-value] (Figure 1. Table 1, Supplementary Table S1).

All genetic polymorphisms collected from the 75 included studies were reviewed to obtain relevant information on the pathogenicity and ethnic distribution to determine whether they were distinctive to Arab populations. For that purpose, the following databases were used: ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/index.php), and Leiden Open Variation Database http://databases.lovd.nl/whole_genome/genes.

**Statistical analysis**

Review Manager software v5.02 (The Cochrane Collaboration, 2009) was used to conduct the meta-analysis. Publication bias was measured using Begg’s funnel plot and Egger’s test based on STATA software v15.1 (StataCorp, College Station, TX, USA). We used a random or fixed effect model to summarize study estimates (ORs and 95% CI) if there were two or more observations for an individual variant. For assessment of heterogeneity, we used the I² statistics. When $I^2 < 50\%$, a fixed-effect model was used; otherwise, a random-effect model was used.

**Results**

**Search findings**

The initial search yielded 5,608 potentially relevant articles, and after duplicate removal, 4,954 articles remained, of which 4,493 irrelevant articles were excluded by screening the abstracts and titles and 461 potentially eligible articles remained; of these, 75 studies conducted in eight countries between 2006 and 2019 met the inclusion criteria and were eligible for the systematic review, of which 62 studies were eligible for meta-analysis (Figure 1, Table 1, Supplementary Table S1). The 75 studies included in this systematic review were conducted in eight Arab countries: Algeria (n = 1) [50], Egypt (n = 18) [51-68], Iraq (n = 1) [69], Lebanon (n = 1) [70], Morocco (n = 3) [71-73], Qatar (n = 1) [74], Saudi Arabia (n = 18) [75-92], and Tunisia (n = 32) [93-124]. The total number of cases was 36,125 and the number of controls was 31,730 (Supplementary Table S1)
| Reference | Gene  | Variant | SNP ID     | Country     | Phenotype | Cases (\#) | Controls (\#) | Allele/Genotype | OR    | 95% CI    | P value | Clinical Significance |
|-----------|-------|---------|------------|-------------|-----------|-------------|---------------|-----------------|-------|-----------|---------|----------------------|
| [59]      | ABCA1 | G>A     | rs2230806  | Egypt       | PCAD      | 116         | 119           | R               | 1.43  | 0.99–2.07 | 0.03    | B                    |
| [79]      | ABCA1 | G>A     | rs2230806  | Saudi Arabia| CAD       | 990         | 618           | KK              | 1.42  | 1.06–1.91 | 0.017   | B                    |
| [53]      | ACE   | I/D     | rs4646994  | Egypt       | CAD       | 60          | 50            | D               | 2.538 | 1.468–4.388 | <0.0001 | NA                   |
| [66]      | ACE   | I/D     | rs4646994  | Egypt       | MI        | 79          | 238           | ID              | 1.81  | 1.07–3.04 | 0.027   | NA                   |
| [83]      | ACE   | I/D     | rs4646994  | Saudi Arabia| CAD       | 225         | 110           | DD vs II        | 2.45  | 1.26–4.78 | 0.008   | NA                   |
| [105]     | ACE   | I/D     | rs4646994  | Tunisia     | CAD       | 341         | 316           | Ins/ins         | 1.9   | 1.07–3.49 | 0.02    | NA                   |
| [121]     | ACE   | I/D     | rs4646994  | Tunisia     | MI        | 119         | 238           | del/del         | 4.27  | 2.65–6.86 | <0.0001 | NA                   |
| [64]      | ADIPOQ| T>G     | rs2241766  | Egypt       | MI        | 60          | 60            | G               | 5.8   | 1.92–17.54 | 0.001   | NR                   |
| [69]      | ADIPOQ| T>G     | rs2241766  | Iraqi       | CAD       | 150         | 150           | GG              | 5.04  | 1.04–24.40 | 0.044   | NR                   |
| [88]      | ADIPOQ| T>G     | rs2241766  | Saudi Arabia| CAD       | 123         | 295           | GG              | 4.7   | 1.6–13.5  | 0.003   | NR                   |
| [81]      | ADRB2 | C>G     | rs1042714  | Saudi Arabia| CAD       | 773         | 528           | C/G             | 2.53  | 1.97–3.24 | <0.001  | B                    |
| [105]     | AGT   | C>T     | rs4762     | Tunisia     | CAD       | 341         | 316           | MM              | 1.8   | 1.12–2.94 | 0.001   | LB                   |
| [82]      | AGT   | A>G     | rs5051     | Saudi Arabia| CAD       | 3246        | 1001          | –               | 1.17  | 1.05–1.29 | 0.004   | B                    |
| [53]      | AGT   | T>C     | rs699      | Egypt       | CAD       | 60          | 50            | T               | 2.915 | 1.666–5.097 | <0.0001 | B                    |
| [105]     | AGT   | T>C     | rs699      | Tunisia     | CAD       | 341         | 316           | MT              | 1.79  | 1.11–2.86 | 0.02    | B                    |
| [120]     | AGT   | T>C     | rs699      | Tunisia     | AMI       | 123         | 144           | TT              | 1.9   | 1.09–3.29 | 0.022   | B                    |
| [83]      | AGTR2 | A>C     | rs11091046 | Saudi Arabia| CAD       | 225         | 110           | CC and AA vs CA | 7.21  | 4.31–12.04 | <0.0001 | NR                   |
| [67]      | AGXT2 | C>A     | rs16899974 | Egypt       | CAD       | 100         | 50            | CA + AA         | 2.1   | –         | 0.0192  | NR                   |
| [67]      | AGXT2 | C>T     | rs37369    | Egypt       | CAD       | 100         | 50            | CT + TT         | 2.4   | –         | 0.005   | Affects              |
| [72]      | APOA5 | T>C     | rs662799   | Morocco     | MI        | 118         | 184           | CC              | 2.6   | 1.18–5.66 | 0.03    | –                    |
| [110]     | APOB  | I/D     | rs17240441 | Tunisia     | MI        | 318         | 368           | D/D             | 2.95  | 1.40–6.22 | 0.004   | B/LB                 |
| [114]     | ApoC3 | C>G     | rs5128     | Tunisia     | MI        | 326         | 361           | S2S2            | 8.28  | 1.01–67.80 | 0.049   | NR                   |
| [111]     | ARG1  | G>T     | rs2781666  | Tunisia     | MI        | 318         | 282           | TT              | 2.2   | 1.20–4.04 | 0.01    | NR                   |
| [112]     | ARG1  | G>T     | rs2781666  | Tunisia     | MI        | 321         | 436           | TT              | 2.05  | 1.19–3.52 | 0.009   | NR                   |
| [94]      | ATR1  | A>C     | rs5186     | Tunisia     | AMI       | 118         | 150           | CC              | 2.06  | 1.02–4.18 | 0.045   | B                    |
| [97]      | C3    | C>G     | rs2230199  | Tunisia     | MI        | 170         | 95            | allele frequency | 2.616 | 1.738–3.938 | 2.742E-06 | B                    |
| [75]      | C9orf84| G>A     | rs10981012 | Saudi Arabia| CAD       | 2668        | 3000          | A               | 1.34  | 1.17–1.52 | 0.000   | NR                   |
| [119]     | CCL2  | A>G     | rs1024611  | Tunisia     | MI        | 319         | 467           | AG+GG           | 1.34  | 1.00–1.79 | 0.04    | P, RF                |
| [58]      | CCL5  | G>A     | rs2107538  | Egypt       | AMI       | 100         | 100           | GG vs AG/AA     | 2.1   | 1.2–3.8  | 0.0185  | NR                   |
| [123]     | CD40  | C>T     | rs1883832  | Tunisia     | MI        | 273         | 219           | T               | 1.45  | 1.09–1.94 | 0.008   | B                    |
| Reference | Gene     | Variant | SNP ID    | Country     | Phenotype | Cases (n) | Controls (n) | Allele/Genotype | OR   | 95% CI     | P value   | Clinical Significance |
|-----------|----------|---------|-----------|-------------|-----------|-----------|--------------|-----------------|------|------------|-----------|-----------------------|
| [74]      | CDKN2B-AS1| A>G     | rs10757274| Qatar       | CAD       | 236       | 152         | G               | *   | *          | NR        |                       |
| [68]      | CDKN2B-AS1| A>G     | rs10757278| Egypt       | CAD       | 100       | 50          | AG              | 3.92 | 1.86–8.27  | 0.002     | NR                    |
| [74]      | CDKN2B-AS1| A>G     | rs10757278| Qatar       | CAD       | 236       | 152         | G               | *   | *          | NR        |                       |
| [84]      | CDKN2B-AS1| A>G     | rs1333042  | Saudi Arabia| CAD      | 250       | 252         | A               | 2.2012 | 1.69–2.86  | 5.14E-09  | NR                    |
| [74]      | CDKN2B-AS1| A>G     | rs2383207  | Qatar       | CAD       | 236       | 152         | GG/AA+AG        | 1.8  | 1.04–3.12  | 0.03      | NR                    |
| [84]      | CDKN2B-AS1| A>G     | rs2891168  | Saudi Arabia| CAD      | 250       | 252         | G               | 2.1908 | 1.6920–2.8368 | 1.85E-10 | NA                    |
| [146]     | CDKN2B-AS1| A>G     | rs4977574  | Lebanon     | MI        | 222       | 1,727       | GG              | 1.86 | 1.17–3.07  | 0.012     | NR                    |
| [84]      | CDKN2B-AS1| A>G     | rs4977574  | Saudi Arabia| CAD      | 250       | 252         | C               | 1.4917 | 1.0345–2.1511 | 0.0315   | NR                    |
| [79]      | CETP      | G>A     | rs5882     | Saudi Arabia| CAD      | 990       | 618         | VI              | 1.45 | 1.12–1.88  | 0.005     | B                     |
| [59]      | CETP      | C>T     | rs708272   | Egypt       | PCAD      | 116       | 119         | B1B1<sup>1</sup> | 2.25 | 1.06–4.77  | 0.02      | NR                    |
| [51]      | CPR2      | C>T     | rs1926447  | Egypt       | MI        | 46        | 54          | G              | 3.26 | 1.82–5.83  | 0.001     | NR                    |
| [55]      | CPR2      | C>T     | rs1926447  | Egypt       | MI        | 46        | 54          | CT/TT           | 4.95 | 1.80–13.63 | 0.0001    | NR                    |
| [60]      | CYP2R1    | G>A     | rs10766197 | Egypt       | MI        | 185       | 138         | AA              | 2    | 1.1–3.8    | 0.04      | NR                    |
| [60]      | CYP2R1    | C>A     | rs1993116  | Egypt       | MI        | 185       | 138         | GG              | 8.5  | 3.7–19.9   | <0.0001   | NR                    |
| [60]      | CYP2R1    | G>A     | rs2060793  | Egypt       | MI        | 185       | 138         | AA              | 2.3  | 1.2–4.5    | 0.02      | NR                    |
| [75]      | DCLK2     | A>G     | rs9985766  | Saudi Arabia| CAD      | 2668      | 3000        | G              | 1.35 | 1.2–1.52   | 0.000 NR  |                       |
| [67]      | DDAH1     | T>C     | rs997251   | Egypt       | CAD      | 100       | 50          | CT+CC           | 2.3  | –          | 0.0063    | NR                    |
| [64]      | ENPP1     | C>A     | rs1044498  | Egypt       | MI        | 60        | 60          | K              | 3    | 1.45–6.20  | 0.004     | B                     |
| [71]      | F2        | G>A     | rs1799963  | Morocco     | MI        | 100       | 182         | A              | 238.83 | 4.48–12581.7 | <0.001 P |                       |
| [109]     | F2        | G>A     | rs1799963  | Tunisia     | MI        | 399       | 608         | A              | 3.6  | 1.29–10.53 | 0.005     | P                     |
| [117]     | F2        | G>A     | rs1799963  | Tunisia     | MI        | 88        | 195         | A              | 4.68 | 1.6–14.26  | 0.001     | P                     |
| [73]      | F5        | C>T     | rs118203908| Morocco     | MI        | 100       | 211         | TT              | 3.16 | 1.29–7.71  | 0.03      | P                     |
| [61]      | F5        | G>A     | rs6025     | Morocco     | MI        | 44        | 211         | AA              | 8.2  | 1.91–35.21 | 0.0094    | CIP, RF                |
| [113]     | F5        | G>A     | rs6025     | Tunisia     | CAD      | 200       | 300         | GA              | 4.03 | 2.1–7.6    | <0.001    | CIP, RF                |
| [90]      | GATA4     | C>T     | rs1062219  | Saudi Arabia| CAD      | 857       | 3,421       | CT+TT           | 1.15 | 1.01–1.31  | 0.034     | US                    |
| [90]      | GATA4     | A>G     | rs3729856  | Saudi Arabia| MI        | 2890      | 1388        | G              | 1.34 | 1.04–1.72  | 0.024     | B                     |
| [91]      | GATA4     | A>G     | rs3729856  | Saudi Arabia| CHD      | –         | –           | G              | 1.48 | 1.06–2.08  | 0.023     | B                     |
| [90]      | GATA4     | A>C     | rs804280   | Saudi Arabia| MI        | 2890      | 1388        | AC+CC           | 1.17 | 1.07–1.29  | 0.02      | P                     |
| Reference | Gene | Variant | SNP ID   | Country         | Phenotype | Cases (n) | Controls (n) | Allele/Genotype | OR    | 95% CI       | P value | Clinical Significance |
|-----------|------|---------|----------|-----------------|-----------|-----------|--------------|----------------|-------|--------------|---------|-----------------------|
| [101]     | Hsp70-2 | G>A    | rs1061581 | Tunisia         | CAD       | 252       | 151          | P2/P2            | 2.498 | 1.284–4.859 | 0.006   | NR                    |
| [57]      | ICAM1  | A>G    | rs5498   | Egypt           | CHD       | 100       | 50           | KK               | 8.6   | 1.8–57.2    | 0.003   | NR                    |
| [62]      | IL-10  | A>G    | rs1800896 | Egypt           | CAD       | 108       | 143          | GG               | 8.02  | 2.87–22.46  | <0.0001 | NR                    |
| [62]      | IL-6   | C>G    | rs1800795 | Egypt           | CAD       | 108       | 143          | GC               | 3.95  | 2.16–7.22   | <0.0001 | NR                    |
| [104]     | IL10   | A>C    | rs1800872 | Tunisia         | CAD       | 291       | 291          | A/A              | 3.33  | 1.27–9.09   | 0.015   | Pr, RF                 |
| [87]      | JCAD   | A>G    | rs2487928 | Saudi Arabia    | CAD       | 500       | 504          | G                | 1.4161| 1.0930–1.8348| 0.0084  | NR                    |
| [75]      | KCNA1  | C>T    | rs13082914| Saudi Arabia    | CAD       | 2668      | 3000         | T                | 1.21  | 1.09–1.34   | 0.000   | NR                    |
| [59]      | LCAT   | C>T    | rs5923   | Egypt           | PCAD      | 116       | 119          | TT               | 4.27  | 1.97–9.24   | 0       | LB                    |
| [75]      | LOC10192892 | C>T | rs17775862 | Saudi Arabia | CAD | 2668 | 3000 | T | 1.55 | 1.3–1.85 | 0.000 | NR |
| [75]      | LOC392232 | C>T | rs12541758 | Saudi Arabia | CAD | 2668 | 3000 | T | 1.25 | 1.15–1.36 | 0.000 | NR |
| [89]      | MEF2A  | G>C    | rs1059759 | Saudi Arabia    | CAD       | 1156      | 859          | G>C              | 1.21  | 1.02–1.43   | 0.029   | NR                    |
| [77]      | MEF2A  | G>T    | rs325400 | Saudi Arabia    | CAD       | 120       | 100          | GT               | 2.0102| 1.3405–3.0146| 0.00048| NR |
| [65]      | MMP3   | 5A/6A  | rs3025058 | Egypt           | AMI       | 40        | 40           | 5A5A             | 13    | 1.576–107.233| 0.009  | NA                    |
| [56]      | MMP9   | C>T    | rs3918242 | Egypt           | AMI       | 184       | 180          | CT+TT            | 3.21  | 1.28–8.02   | 0.012   | NR                    |
| [58]      | MTHFR  | C>T    | rs1801133 | Egypt           | AMI       | 100       | 100          | TT vs CC/CT      | 6.1   | 1.3–28.0    | 0.0184  | Drug response         |
| [102]     | MTHFR  | C>T    | rs1801133 | Tunisia         | CAD       | 352       | 390          | TT               | 2.78  | 1.61–4.80   | <0.001  | Drug response         |
| [106]     | MTHFR  | C>T    | rs1801133 | Tunisia         | CAD       | 173       | 78           | TT               | 1.85  | 0.99–3.4    | 0.033   | Drug response         |
| [106]     | MTR    | A>G    | rs1805087 | Tunisia         | CAD       | 173       | 78           | GG               | 2.94  | 0.98–8.8    | 0.032   | B                     |
| [118]     | MTR    | A>G    | rs1805087 | Tunisia         | MI        | 321       | 343          | AG+GG            | 1.6   | 1.11–2.30   | 0.01    | B                     |
| [50]      | NOS3   | G>T    | rs1799983 | Algeria         | MI        | 68        | 115          | GT & TT          | 1.2   | 1.03–1.32   | 0.025   | B                     |
| [72]      | NOS3   | G>T    | rs1799983 | Morocco         | MI        | 118       | 184          | TT               | 2.57  | 0.87–7.52   | 0.01    | B                     |
| [72]      | NOS3   | G>T    | rs1799983 | Morocco         | MI        | 118       | 184          | Reccessive model | 2.15  | 0.74–6.16   | 0.03    | B                     |
| Reference | Gene     | Variant | SNP ID   | Country  | Phenotype | Cases (n) | Controls (n) | Allele/Genotype | OR          | 95% CI    | P value | Clinical Significance |
|-----------|----------|---------|----------|----------|-----------|-----------|--------------|----------------|-------------|-----------|---------|-----------------------|
| [86]      | NOS3     | G>T     | rs1799983| Saudi Arabia | CAD | 142 | 145 | – | 4.39 | 1.69–11.42 | <0.0001 | B |
| [196]     | NOS3     | G>T     | rs1799983| Tunisia | CAD | 332 | 368 | Dominant model | 2.84 | 2.09–3.86 | <0.001 | B |
| [86]      | NOS3     | T>C     | rs2070744| Saudi Arabia | CAD | 142 | 145 | CC + TC | 3.41 | 1.98 – 5.87 | <0.001 | Pr, RF |
| [96]      | NOS3     | T>C     | rs2070744| Tunisia | MI | 303 | 225 | Codominant CC | 1.15 | 0.66–2.02 | 0.612 | Pr, RF |
| [96]      | NOS3     | 4a/4b   | rs61722009| Tunisia | MI | 303 | 225 | Codominant model 4a4a | 4.38 | 1.24–15.41 | 0.021 | NR |
| [100]     | NOS3     | 4a/4b   | rs61722009| Tunisia | MI | 303 | 225 | 4a | 1.76 | 1.25–2.49 | 0.0007 | NR |
| [115]     | NOS3     | 4a/4b   | rs61722009| Tunisia | MI | 310 | 250 | 4a4a | 3.61 | 1.18–11.09 | 0.03 | NR |
| [107]     | PCSK9    | A>G     | rs505151 | Tunisia | CAD | 192 | 66 | G | 3.39 | 1.55–7.37 | 0.001 | B/LB |
| [75]      | PDZD2    | A>G     | rs32793  | Saudi Arabia | MI | 2668 | 3000 | G | 1.25 | 1.14–1.37 | 0.000 | NR |
| [54]      | PLAT     | I/D     | rs4646972| Egypt | AMI | 184 | 184 | II | 3.2 | 1.48–7.3 | 0.002 | NA |
| [78]      | PON1     | A>G     | rs662    | Saudi Arabia | CAD | 121 | 108 | GG | 3.2 | 1.4–7.4 | <0.01 | A, RF |
| [93]      | PON1     | A>G     | rs662    | Tunisia | MI | 310 | 375 | RR | 1.93 | 1.24–3.02 | 0.004 | A, RF |
| [95]      | PON1     | A>G     | rs662    | Tunisia | MI | 303 | 408 | RR | 1.93 | 1.24–3.02 | – | A, RF |
| [103]     | PON1     | A>G     | rs662    | Tunisia | MI | 382 | 380 | RR | 1.89 | 1.21–2.94 | – | A, RF |
| [103]     | PON1     | C>T     | rs705381 | Tunisia | MI | 382 | 380 | T | 1.29 | 1.05–1.58 | 0.011 | NR |
| [124]     | PPARD    | T>C     | rs2016520| Tunisia | CAD | 112 | 113 | TC/CC | 2.77 | 1.24–6.19 | 0.001 | NR |
| [122]     | PPARG    | C>G     | rs1801282| Tunisia | CAD | 239 | 244 | Pro | 1.694 | 1.190–2.413 | 0.003 | LB |
| [85]      | PSMA6    | A>G     | rs4981283| Saudi Arabia | MI | 1135 | 866 | – | 1.16 | 1.01–1.33 | 0.035 | NR |
| [75]      | RNF13    | G>A     | rs41141047| Saudi Arabia | MI | 2668 | 3000 | A | 1.51 | 1.3–1.76 | 0.000 | NR |
| [76]      | SELE     | A>C     | rs5361   | Saudi Arabia | CAD | 556 | 237 | R | 1.76 | 1.14–2.72 | 0.007 | NR |
| [54]      | SERPINE1 | A>G     | rs1799889| Egypt | AMI | 184 | 184 | 4G/4G | 3.33 | 1.5–7.5 | 0.003 | NR |
| [72]      | SERPINE1 | A>G     | rs1799889| Morocco | MI | 118 | 184 | 4G/5G | 11.2 | 8.3–15.08 | <0.001 | NR |
| [75]      | SLC5A3/MRPS 6/KCNE2 | C>T | rs9982601| Saudi Arabia | MI | 2668 | 3000 | T | 1.38 | 1.23–1.55 | 0.000 | NR |
| [63]      | SOD2     | T>C     | rs4880   | Egypt | AMI | 100 | 100 | VV | 3.614 | 1.943 – 6.725 | <0.0001 | Drug response |
| [99]      | SOD2     | T>C     | rs4880   | Tunisia | CAD | 164 | 203 | Val/Val | 2.19 | 1.21–3.97 | 0.009 | Drug response |
| [52]      | THBD     | C>T     | rs1042579| Egypt | AMI | 102 | 110 | TT | 8.03 | 0.97–66.47 | 0.026 | B |
| [116]     | TP53     | A>G     | rs1625895| Tunisia | MI | 246 | 230 | M2 | 1.43 | 1.05–1.95 | 0.017 | B |

Clinical significance was measured using the ClinVar databases. A = association; B = benign, LB = likely benign; P = pathogenic; LP = likely pathogenic; RF = risk factor, Pr = protective, CIP = conflicting interpretations of pathogenicity, NA = not available (for novel variants), NR = not reported in ClinVar. * reported significant adjusted ORs. Variants unique to Arabs are in bold characters.
No significant genetic association data were captured from 14 of the 22 Arab countries (Bahrain, Comoros, Djibouti, Jordan, Kuwait, Libya, Mauritania, Oman, Palestine, Somalia, Sudan, Syria, United Arab Emirates, and Yemen). We captured 80 variants reported to have significant associations with CAD or MI risk in eight Arab countries (Figure 2. Supplementary Table S1). The NOS3 gene was the most frequently reported gene among Arab patients with CAD and/or MI (n=7), it was reported in four Arab countries: Saudi Arabia, Tunisia, Algeria and Morocco, with three different genetic variants identified (Supplementary Table S1). Of the three variants identified in NOS3, two variants were SNPs (c.894G>T; rs1799983 and c.-786T>C; rs2070744) and one variant was a 27-base pair VNTR in intron-4 (4b/a 27bp VNTR; rs61722009). The most frequent variant detected among Arab patients was NOS3: c.894G>T (rs1799983), which was reported with significant positive CAD/MI associations in four different Arab countries, followed by the variants ADIPOQ: c.45T>G (rs2241766) and ACE: insertion/deletion (I/D) (rs4646994), which were reported with significant positive CAD/MI associations in three different Arab countries (Figure 2, Table 1).

Quantitative synthesis, sensitivity analysis, and publication bias
46 variants captured from 62 studies were individually meta-analyzed (Supplementary Figures S1-S46). A summary of all the individual meta analyses is shown in Figure 3, the pooled ORs of association of the 46 variants with CAD/MI ranging from 1.14 to 7.57, with a median (interquartile range) of 1.83 (1.64 – 2.57).

Since publication bias could affect the meta-analysis, we assessed for publication bias in one eligible variant (rs1799983), which was reported with 11 observations in four studies (Figure 4). Both the funnel plot and Egger’s test suggested a publication bias. Significant heterogeneity was found in five meta-analyses. Figure (5) shows the 29 variants that reported ORs > 1 but were ineligible for inclusion in the meta-analysis, the ORs for CAD and/or MI among these studies ranged from 1.13 to 3.39, with a median of 1.49 (interquartile range 1.25-2.19).
Table 1. Summary of the 46 individual meta-analyses. 46 variants captured from 62 studies were individually meta-analyzed. The pooled OR of association with CAD/MI of all captured variants ranged from 1.14 to 7.57, with a median (interquartile range) of 1.83 (1.64–2.57). SNP: single nucleotide polymorphism; CI: confidence interval; OR: odds ratio.

| Gene      | SNP      | Variant | Number of studies | OR (95% CI) |
|-----------|----------|---------|-------------------|-------------|
| HNF1A     | rs2383207| C>T     | 3                 | 1.14 (1.06, 1.23) |
| HNF1A     | rs2259820| C>T     | 2                 | 1.14 (1.06, 1.23) |
| GATA4     | rs804280 | A>C     | 3                 | 1.15 (1.09, 1.22) |
| GATA4     | rs3726856| A>G     | 3                 | 1.23 (1.10, 1.38) |
| ABCA1     | rs2230806| G>A     | 3                 | 1.24 (1.09, 1.40) |
| CCL2      | rs1024611| A>G     | 2                 | 1.32 (1.09, 1.60) |
| CETP      | rs5882   | G>A     | 3                 | 1.42 (1.22, 1.65) |
| CDKN2B-AS1| rs4977574| A>G     | 3                 | 1.43 (1.19, 1.71) |
| CD40      | rs1883832| C>T     | 2                 | 1.44 (1.18, 1.76) |
| MTR       | rs1800587| A>G     | 5                 | 1.61 (1.33, 1.96) |
| IL10      | rs1800872| A>C     | 4                 | 1.62 (1.31, 1.97) |
| PON1      | rs662    | C>T     | 8                 | 1.64 (1.45, 1.87) |
| ApoC3     | rs5128   | C>G     | 3                 | 1.64 (1.23, 2.19) |
| CETP      | rs708227  | C>T    | 3                  | 1.64 (1.22, 2.21) |
| PPP4R2    | rs1801282| C>G     | 2                 | 1.67 (1.26, 2.17) |
| APOB      | rs1724041| Ins>Del | 2                 | 1.68 (1.25, 2.25) |
| NOS3      | rs61722099| 27-bp VNTR| 7               | 1.74 (1.46, 2.08) |
| Hsp70-2   | rs1065181| G>A     | 2                 | 1.75 (1.23, 2.49) |
| ATR1      | rs5186   | A>C     | 2                 | 1.75 (1.27, 2.42) |
| ARG1      | rs2781666| G>T     | 5                 | 1.80 (1.56, 2.09) |
| SELE      | rs5361   | A>C     | 2                 | 1.82 (1.19, 2.80) |
| MMP9      | rs3918242| C>T     | 4                 | 1.83 (1.42, 2.36) |
| APOA5     | rs662799 | T>C     | 3                 | 1.83 (1.37, 2.45) |
| AGT       | rs699    | T>C     | 6                 | 1.84 (1.50, 2.25) |
| MTHFR     | rs180133 | C>T     | 8                 | 1.94 (1.67, 2.24) |
| NOS3      | rs2070744| T>C     | 5                 | 2.00 (1.16, 3.46) |
| F5        | rs11820908| C>T   | 4                  | 2.04 (1.55, 2.70) |
| NOS3      | rs1799863| G>T     | 11                | 2.08 (1.56, 2.79) |
| ADIPOQ    | rs2241766| T>G     | 7                 | 2.12 (1.68, 2.67) |
| PLAT      | rs4646972| Ins>Del | 3                 | 2.21 (1.50, 3.24) |
| ADRB2     | rs1042714| C>G     | 3                 | 2.25 (1.93, 2.62) |
| LCAT      | rs5923   | C>T     | 3                 | 2.25 (1.68, 3.02) |
| IL-10     | rs1800896| A>G     | 2                 | 2.34 (1.56, 3.51) |
| ACE       | rs4646994| Gln/Del | 9                 | 2.44 (2.06, 2.89) |
| TM4D      | rs1042579| C>T     | 4                 | 2.57 (1.86, 3.54) |
| SOD2      | rs4880   | T>C     | 4                 | 2.58 (1.98, 3.37) |
| CDKN2B    | rs10757278| A>G   | 3                  | 2.70 (1.83, 3.99) |
| MNP3      | rs3025058| Ins>Dal | 2                 | 2.80 (1.41, 5.56) |
| CPB2      | rs1926447| C>T     | 3                 | 3.46 (2.36, 5.06) |
| IL-6      | rs1800795| C>G     | 2                 | 3.60 (2.55, 5.08) |
| TCAM1     | rs5498   | A>G     | 3                 | 3.76 (2.11, 6.68) |
| F5        | rs6025   | G>A     | 6                 | 3.93 (2.99, 5.16) |
| SERPINE1  | rs1799889| A>G     | 6                 | 4.36 (2.82, 6.42) |
| AGTR2     | rs11091046| A>C   | 2               | 5.06 (3.50, 7.33) |
| CYP2R1    | rs1993116| A>G     | 3                 | 6.34 (3.90, 10.31) |
| F2        | rs1799963| G>A     | 8                 | 7.57 (3.22, 17.77) |

Figure 4. Funnel plot for the rs1799983. Egger’s test, p=0.043. Begg’s test, p=0.586. Based on Egger’s test, there was a publication bias.
Figure 5. Summary of the OR (95% CI) for the 29 variants ineligible for inclusion in the meta-analysis. Single observations which were not meta-analyzed are presented in the Figure. The ORs ranged from 1.13 to 3.39, with a median of 1.49 (interquartile range 1.25-2.19).

Discussion

This is the first systematic study designed to comprehensively assess all genetic variations that are significantly associated with a high risk of CAD and/or MI in Arab countries. In this systematic review, we evaluated the association between 80 genetic variants and CAD/MI captured from 75 eligible studies, comprising 36,125 cases and 31,730 controls (Supplementary Table S1). The NOS3 gene was the most affected gene among Arab patients with CAD/MI-associated variants reported in Saudi Arabia, Tunisia, Algeria, and Morocco. The NOS3: c.894G>T (rs1799983) was the most commonly studied variant, demonstrating a two-fold increased risk for CAD/MI among Arab patients (Table 1, Figure 2).

In this study, gene variants were found to increase the risk of CAD and/or MI by 206% based on the median of the OR comparing individuals with and without CAD and/or MI. We conducted 46 meta-analyses for 46 variants in 39 genes (Figure 3, Supplementary Figures S1-S46) which demonstrated a potential risk of developing CAD and/or MI. The NOS3: c.894G>T (rs1799983) has previously been shown to be associated with ischemic heart disease [125, 126], coronary artery spasm [127], ischemic stroke [128], hypertension [129, 130], metabolic syndrome [131], and Alzheimer’s disease [132-134]. However, the evidence for an association of this SNP with CAD or MI risk remain conflicting and inconclusive, with several studies reporting a lack of association with the disease [135-140]. The pooled meta-analysis for the individual 46 meta-analyses (Figure 3) showed that there was no heterogeneity in most of the captured studies, and the pooled effect of the variants was potentially conferring a significant risk of developing CAD and/or MI among Arabs. The median (interquartile range) of
the pooled OR was 1.83 (1.64-2.57). 7 of the 80 variants captured in this systematic review were located in the \textit{CDKN2B-AS1}, also referred to as \textit{ANRIL}. This gene is located within the p15/CDKN2B-p16/CDKN2A-p14/ARF cluster at the 9p21 locus. The 9p21 locus was reported to be associated with both CAD and/or MI risk in Arabs and revealed significant associations with CAD in subjects from Qatar [74], Saudi Arabia [84], and Egypt [68], and with MI in Lebanon [70]. 4 of the 7 variants captured in \textit{CDKN2B-AS1} (rs564398, rs4977574, rs2891168, and rs1333042) have been previously validated to confer CAD risk in other ethnic groups, including Hispanic, Chinese, European, white American, and Turkish populations [5, 12, 141-157]. Moreover, \textit{CDKN2B-AS1} rs10757278 variant which was reported in Qatar and Egypt was previously reported to carry the highest CAD risk among Europeans, Africans, East Asians, South Asians, and Koreans [158]. Given that the risk of CAD and MI may vary among different ethnic groups, it is crucial to examine SNP associations in different ethnic groups to help resolve which SNP is most likely to be causative.

Genotype-phenotype correlation in Arab patients with CAD/MI

We captured 80 CAD/MI-associated variants in 36,125 Arab patients diagnosed with moderate to severe CAD, which included patients who had undergone coronary revascularization (coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI)). The included studies comprised patients who presented with conventional CAD risk factors, including family history, diabetes, smoking, alcohol, hypertension, dyslipidemia, along with high levels of fasting glucose, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) compared to controls (Supplementary Table S1).

The genotype–phenotype correlation for Arab patients harboring most of the CAD/MI-associated variants is still difficult to interpret, and a meaningful correlation remains questionable. This is in part due to the heterogeneity and multifactorial nature of the disease, as well as the substantial differences in the mutational spectra among the various racial groups. In addition, there is a limited number of CAD/MI genetic association studies conducted in the Arab world, and the phenotypes studied varied greatly between studies for a certain polymorphism. Therefore, many of the associations found for the studied CAD/MI-associated variants need to be confirmed in future studies before firm conclusions about genotype-phenotype correlation can be drawn. Nevertheless, some variants are believed to be causative for the disease and were more frequently reported with high CAD/MI susceptibility in certain racial groups compared to others.

Among the six Gulf Cooperation Council (GCC) countries (Kuwait, Bahrain, Qatar, Saudi Arabia, Oman, and United Arab Emirates), 36 variants with significant positive associations to CAD/MI phenotypes were reported in Saudi Arabia and Qatar (Table 1, Supplementary Table S1). The variant \textit{ADRB2}: c.79C>G (rs1042714) was reported to be an independent predictor of severe CAD in a study that comprised 773 Saudi patients who presented with “severe” phenotypes of early onset CAD with angiographically determined narrowing of the coronary vessels \(\geq 70\%\); the results suggested a strong association of \textit{ADRB2}: c.79C>G with CAD/MI manifestations. Similarly, a meta-analysis performed by Wang et al. [159], suggested that the \textit{ADRB2}: c.79C>G variant is associated with an increased risk of both CAD and MI in Asians and Caucasians. A recent meta-analysis, however, revealed that \textit{ADRB2} c.79C>G is positively associated with cardiovascular events but not with all-cause mortality in CAD patients [160], implying that the it might be associated with the presence but not severity of the disease.

Another variant reported with significant positive association in the GCC region was \textit{GATA4} c.997+56A>C (rs804280). This variant was reported to be an independent risk factor for CAD in a study that comprised 2,274 Saudi patients with angiographically determined narrowing of the coronary vessels \(\geq 50\%\), of whom 971 presented with more than two diseased vessels [90]. In addition, this variant was reported to be associated with hypercholesterolemia and elevated LDL-C, which are well-established risk factors for atherosclerosis [90]. Moreover, this variant has been previously associated with cardiac malformations in different populations [161-165], and was previously reported as “pathogenic” for congenital heart disease in the ClinVar database.

The variant, described as \textit{AGTR2}: c.3123A>C (rs11091046), was found to confer the highest risk in the GCC region, reported with a 7.21-fold increased risk of CAD in a study that comprised 225 Saudi patients who presented with traditional CAD risk factors, such as diabetes (64.4%), dyslipidemia (57.8%), hypertension (73.3%), and smoking (39.6%) [83]. A Japanese study has previously reported a positive association of \textit{AGTR2}: c.3123A>C (rs11091046) with MI [166]. Conversely, two other studies have previously demonstrated lack of an association in Iranian subjects [167, 168]. The variant, described as \textit{CDKN2B-AS1} rs2383207, located in the 9p21 locus, was reported in Qatar and Saudi Arabia with significant positive associations to CAD in patients who presented with > 50% luminal stenosis in at least one vessel [74, 84]. Among Arab patients residing in Qatar, the \textit{CDKN2B-AS1}: rs2383207 G allele conferred a 15.26-fold increased risk of CAD. This variant was previously shown to be associated with other CAD-related phenotypes in other ethnic groups, including stroke [169-171] and sudden cardiac death [172, 173].
Another variant, described as TRPA1: rs12541758, was found to be unique to Saudis (Table 1, Supplementary Table 1). This variant was reported for the first time to be significantly associated with CAD and MI in a GWAS by Wakil et al. [75] conducted among Saudi patients; the variant displayed a suggestive GWAS association (P<1x10^-5), and was found to exhibit the most conspicuous association with CAD among the other variants identified in the study. More importantly, according to medical literature, HGMD, dbSNP, EVS, and LOVD databases, this variant has not been previously reported in other ethnic groups, suggesting that it is unique to the Saudi population. This variant is located near the TRPA1 gene, which acts as an excitatory ion channel and is known to play a role in diverse pathophysiological processes, including inflammation, pain, tissue injury and tissue repair. However, further investigation is needed to be able to establish a clear genotype-phenotype correlation for this variant in association to CAD and MI. Other two variants that were identified as unique were KCNAB1 rs13082914, as well as the intergenic variant rs17775862 located in chromosome 6 (Table 1, Supplementary Table 1). These variants were identified in the same GWAS conducted by Wakil et al. [75], however they displayed slightly weaker association with the disease compared to the other variants identified in the study.

In the Levant countries (Egypt, Iraq, Jordan, Lebanon, Palestine and Syria), positive associations between genetic polymorphisms and CAD/MI were reported in Egypt, Lebanon and Iraq, with a total of 28 variants captured (Supplementary Table S1). Most of the captured variants in the Levant region were located in the CYP2R1 gene. Interestingly, Sedky et al. [60] demonstrated a link between CYP2R1 variants and MI risk in 185 Egyptian patients, of whom 72% suffered ST elevated myocardial infarction (STEMI). Three CYP2R1 variants (rs1993116, rs2060793, rs10766197) were reported with significant associations to MI among the Egyptian patients, with rs1993116 conferring the strongest association among all three CYP2R1 variants, with an 8.5-fold increased risk of MI [60]. CYP2R1 variants have been previously linked to vitamin D among European [174, 175], Chinese [176] and few Arab populations [177]. However, there is a lack of evidence of the association of CYP2R1 variants with CAD/MI in other ethnic groups.

In the Maghreb countries (Algeria, Tunisia, Morocco and Libya), significant positive associations were reported in Algeria, Tunisia, and Morocco, with a total of 30 variants captured (Supplementary Table S1). The variant NOS3: c.894G>T (rs1799983) was the most frequently reported, with significant CAD/MI associations among Tunisians [108], Moroccans [72], Algerians [50], and Saudis [86]. In these studies, all patients presented with traditional CAD risk factors such as dyslipidemia, hypertension, diabetes, and smoking. Our meta-analysis demonstrated an aggregated OR of 2.08 (95% CI 1.56 – 2.79) for this variant (Figure 3). This is consistent with a meta-analysis conducted by Rai et al. [178], which comprised subjects from European, African, Asian, and Asian-Indian ancestries, and revealed a significant association between NOS3: c.894G>T (rs1799983) and CAD, with the highest degree of association observed among Middle Easterners, and thus a strong genotype-phenotype correlation is believed to exist for this variant. Interestingly, despite the crucial role of NOS3 in nitric oxide (NO) production and the function of NO in the regulation of blood pressure, NOS3: c.894G>T (rs1799983) was not associated with blood pressure variations among Algerians [50] or Moroccans [72]. Conversely, a study by Shahid et al. [179], which comprised Pakistani subjects with typical biochemical and clinical profiles of CAD, revealed that NOS3: c.894G>T (rs1799983) is significantly associated with blood pressure variations but not with CAD. The phenotypic variations and divergence of results among the different studied groups can be explained by differences in sample size, allele frequency, culture, and lifestyle.

Other variants that were reported with significant CAD/MI associations in the Maghreb region, include CCL2: -2518A>G (rs1024611), F5: c.2491C>T (rs118203908), and F2: c.20210G>A (rs1799963), which were previously reported as “pathogenic” for CAD/MI or CAD-related events in the ClinVar database. The variant CCL2: -2518A>G (rs1024611), which was reported with significant association to MI in Tunisians [119]; was previously reported in the ClinVar database as a “risk factor” of CAD [180] and as “pathogenic” for CAD development in HIV-infected individuals [181], a meaningful genotype-phenotype relationship is believed to exist for this variant. Several studies have demonstrated the association between CCL2: -2518A>G (rs1024611) and increased risk of CAD [180]; however, the results were conflicting among different ethnicities, showing positive associations among Taiwanese and Indians [182, 183] but negative associations in the Chinese population [184]. In the Arab world, the association between CCL2: -2518A>G (rs1024611) and CAD/MI has been investigated in Egypt [58] and Tunisia [84] and was reported to be significantly associated with MI in Tunisians but not Egyptians [84]. Thus, more studies are needed to be able to understand the genotype-phenotype correlations for this variant among Arabs.

The variant F5: c.2491C>T (rs118203908), also described in literature as C2491T, was reported with significant association to MI phenotype for the first time in a study conducted by hmimech et al. [73], which comprised 100 Moroccan patients, including subjects of both genders who presented with stenosis (66%), valvulopathy (28%), severely abnormal LVEF (15%), moderately abnormal LVEF (41%), diabetes (39%), dyslipidemia (27%),...
hypertension (44%), family history of MI (3%), obesity (22%), and smoking history (45%) [73]. Interestingly, C2491T was first discovered in a patient of Moroccan origin by van Wijk et al. [185], and was found to be associated with type I factor V deficiency. Hamzi et al. [186] assessed its frequency in the general Moroccan population, and it has been shown to be associated with ischaemic stroke among Moroccans [187]. C2491T has not been described in the medical literature, HGMD, dbSNP, EVS, or LOVD databases in any other ethnic groups, suggesting that it might be unique to Moroccans, however, further investigation is needed. Furthermore, the association of C2491T with CAD/MI is not yet well-established, thus further studies are needed to establish a rigid genotype-phenotype correlation.

The variant, F2: c.20210G>A (rs1799963), which was reported with positive CAD/MI associations in MI patients from Morocco [71] and Tunisia [109, 117], was previously reported in the ClinVar database as “pathogenic” for venous thrombosis and as a “risk factor” for ischemic stroke. Nevertheless, the detrimental role of c.20210G>A in increasing the risk of MI remains controversial [188]. A meta-analysis investigating the association between F2: c.20210G>A (rs1799963) and CAD showed significant associations in individuals of European descent but not in Americans or Asians [190], suggesting a potential role of ethnic differences in genetic backgrounds and the environment in which they lived. More studies are needed in the Arab region to correctly characterize the genotype-phenotype relationship of c.20210G>A with CAD/MI.

Although there is an overlap between the genetic profile of Arabs and patients from other ethnic groups, Arabs appear to have distinctive disease susceptibility genotypes that are responsible for their CAD/MI phenotypes. This could be explained by the significant history of admixing that has significantly altered their ethnic composition. This ethnic variability can be attributed to gene-gene and gene-environment interactions. Despite the fact that CAD/MI rates in Arabs are among the highest in the world, with CAD ranked among the top ten leading causes of deaths in Egypt, Morocco, Iraq, Yemen, Algeria, Syria, and Tunisia [191, 192], there are few CAD/MI studies. We believe that current efforts to unravel the Arab genome [193, 194] will help to characterize Arabs with CAD/MI, which will potentially personalize treatments for Arab patients with CAD/MI [195]. Moreover, subsequent analyses will help identify Arab-specific variants, which may help in understanding the molecular pathology of CAD and thus in identifying meaningful genotype-phenotype correlations among Arabs.

Limitations

We encountered some limitations in our study. First, the included studies varied in the degree they controlled for potential confounders, such as age, gender, smoking, family history, diabetes, hypertension and dyslipidemia. Thus, we were not able to include them into the pooled analysis. Second, because of insufficient data, our meta-analysis was conducted using crude estimates, and a more precise analysis stratified by clinical manifestation and environmental factors was not performed. Third, there is a limited number of genetic association studies on CAD/MI risk in the Arab world. Thus, we were not able to perform a sensitivity analysis to confirm the stability and reliability of our meta-analysis. Fourth, meta-analysis was not carried out for 34 variants because of lack of studies. Finally, there was an indication of publication bias, which necessitates well-controlled studies. Despite these limitations, we believe that this study will be of value in informing future genetic association studies.

Conclusion

This is the first systematic review and meta-analysis designed to comprehensively assess all genetic variations significantly associated with CAD/MI risk in Arab countries. Overall, we found that Arabs have a distinct disease susceptibility genotypes that are responsible for CAD and/or MI phenotypes, which makes them different from other ethnic groups, potentially explaining the regional variation in disease prevalence. Although some of the CAD/MI-associated variants mentioned in this study were reported in other ethnic groups, the combination with the unique interaction of the environment, diet, marriage traditions, might allow for the enrichment of these genotypes, and thus predisposing the individuals of these ethnic groups to CAD/MI. Our study creates a paradigm for future well-controlled epidemiological studies which will allow the dissection the genetic architecture that that renders Arabs susceptible to CAD/MI, and thus may serve as a platform to design a gene panel for early, accurate, and pre-symptomatic diagnosis of CAD and MI. Despite our comprehensive search strategy, the dearth of genetic association studies related to CAD and MI in the Arab world, suggests a need for more and well-designed genetic-association studies that serve as a basis for understanding the genetic architecture that renders Arabs susceptible to CAD.

Supplementary Files

The Supplementary Material for this article can be found online at: https://doi.org/10.36462/H.BioSci.20213

Supplementary Table S1:
Clinical and genetic characterization of Arab patients with CAD/MI.

Supplementary Figures S1-S46: Individual meta-analyses for 46 different variants that were significantly associated (OR>1) with Arab patients with CAD/MI.
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