Effects of paraoxonase 1 gene polymorphisms on heart diseases

Systematic review and meta-analysis of 64 case-control studies

Yazmín Hernández-Díaz, MDa,b, Carlos Alfonso Tovilla-Zárate, PhDc, Isela Esther Juárez-Rojop, PhDd, Thelma Beatriz González-Castro, MDa,b, Candelario Rodríguez-Pérez, MDb, María Lilia López-Narváez, MDb, José Manuel Rodríguez-Pérez, PhDd, José Francisco Cámara-Álvarezc

Abstract

Background: Associations between paraoxonase 1 (PON1) gene polymorphisms and heart diseases (HD) risk remain inconsistent. In order to obtain address this issue we performed a meta-analysis to assess the association between the L55M and Q192R polymorphisms of PON1 gene and heart diseases risk.

Methods: Relevant studies were enrolled by searching databases systematically. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to calculate the strength of association. Subgroup analyses were conducted for diagnostic and ethnicity. The heterogeneity among each of the studies was calculated by using Cochran Q test and the inconsistency index (I²), and Begg’s funnel plot and Egger’s tests were performed to evaluate publication bias.

Result: Sixty-four studies involving a total of 19,715 cases and 33,397 controls were included in this meta-analysis. We found that the L55M polymorphism showed a significant association with heart diseases in Europeans (OR 1.44, 95%CI 1.33–1.56) and Asians (OR 1.18, 95%CI 1.03–1.35). This meta-analysis also showed a protective association of Q192R polymorphism with HD in Asian (OR 0.49, 95%CI 0.37–0.66) and African populations (OR 0.67, 95%CI 0.53–0.84). The 192R allele significantly decreased the risk of myocardial infarction (OR 0.75, 95%CI 0.57–0.99) and coronary artery disease (OR 0.91, 95%CI 0.84–0.98); however, individuals with 192O allele had a markedly increased risk of coronary artery disease development (OR 1.38, 95%CI 1.22–1.56).

Conclusion: This study demonstrated that the genetic risk for heart diseases is associated with the PON1 gene polymorphisms. L55M polymorphism is a risk factor and Q192R polymorphism is protective in certain populations. It is worth noting that the 192O allele may be a risk factor to develop coronary artery disease.

Abbreviations: CAD = coronary artery disease, CHD = coronary heart disease, GRADE = grading of recommendations assessment, development and evaluation, HD = heart diseases, HWE = Hardy–Weinberg equilibrium, MI = myocardial infarction, NOS = Newcastle-Ottawa Scale, PON1 = paraoxonase 1.

Keywords: ethnicity, heart disease, paraoxonase 1, polymorphisms, positive association, systematic review

1. Introduction

Obesity, diabetes, hypertension, alcohol, and genetic factors have an effect in the cause of heart diseases. Heart diseases (HD) such as coronary heart disease (CHD), coronary artery disease (CAD), and myocardial infarction (MI) are leading causes of morbidity and mortality globally.[1,2] To date, a low plasma concentration of high density lipoprotein (HDL) is one of the strongest risk factors for heart disease. The antioxidant activity of HDL is largely due to the paraoxonase (PON) which has the ability to metabolize lipid peroxides.[3,4] The PON1 gene in humans is located on the long arm of chromosome 7 between q21.3 and q22.1.[5,6] PON1 is a calcium-dependent antioxidant glycoprotein with a molecular mass of 43kDa and is found in serum as a component of the HDL. PON1 hydrolyzes organophosphate insecticides and is responsible for determining the toxicity of these compounds in mammals.[7,8] PON1 has two polymorphisms in the coding region: L55M (163T>G) that results in a substitution from leucine (L) to methionine (M) at codon 55, and Q192R (575A>G) polymorphism that results in a substitution from glutamine (Q) to arginine (R) at position 192. The –192 position polymorphism is the major determinant of the PON1 activity, however, the –55 position polymorphism also modulates its activity.[4,9] Numerous case-control studies have been
| Allele          | Sample size | Cases/Control | Cases/Control | Gender | Cases/Control | p HWE | Gender | Cases/Control | Gender | Cases/Control | Grade quality | NOS score |
|-----------------|-------------|---------------|---------------|--------|---------------|-------|--------|---------------|--------|---------------|---------------|-----------|
| L55M Polymorphism |             |               |               |        |               |       |        |               |        |               |               |           |
| Zama, T.[9]     | 1997        | Asian CAD     | PCR           | 75/115 | 140/10        | 20/21 | —      | —             | —      |               | 1.00/0.59     | Moderate 8 |
| Hasselwander, O.[12] | 1999      | European CHD  | POR-RFLP      | 103/388 | 133/73        | 50/175 | 70/33  | 20/42/154    | 0.28/0.26 | Moderate 7    |               |           |
| Ayub, A.[13]    | 1999        | European MI   | POR-RFLP      | 50/48  | 71/29         | 60/36  | 38/12  | 37/11        | 0.29/0.36 | Moderate 7    |               |           |
| Heilman, B.[14] | 2000        | European CHD  | POR-RFLP      | 364/250 | 472/256       | 317/183 | 115/249 | 139/111      | 0.20/0.78 | High 7        |               |           |
| Imas, Y.[15]    | 2000        | Asian CAD     | POR-RFLP      | 210/431 | 387/33       | 79/65  | 18/42  | 32/110       | 0.36/0.08 | Moderate 8    |               |           |
| Siv-Banerjee, S.[16] | 2000      | American MI   | POR-RFLP      | 492/518 | 265/29        | 72/764 | 211/241 | 25/264       | 0.55/0.01 | Moderate 6    |               |           |
| Mackness, B.[17] | 2001       | European CHD  | POR-RFLP      | 427/382 | 538/256       | 360/204 | 302/115 | 147/135      | 0.39/0.01 | High 8        |               |           |
| Arcs, M.[17]    | 2002        | European CAD  | PCR           | 585/178 | 736/438       | 233/123 | 413/180 | 84/94        | 0.18/1.00 | Moderate 7    |               |           |
| Fére, N.[18]    | 2002        | European MI   | POR-RFLP      | 215/215 | 263/167       | 263/167 | 215/0  | 215/0        | 0.56/0.11 | Moderate 8    |               |           |
| Yamada, Y.[19]  | 2002        | Asian MI      | PCR           | 445/464 | 837/53        | 36/80  | —      | —             | —      |               | 0.39/0.24     | Moderate 7 |
| Robertson, K.S.[20] | 2003      | European CHD  | PCR-RFLP      | 172/221 | 227/17        | 20/42/40 | 17/20  | 211/0        | 0.30/0.89 | Moderate 7    |               |           |
| Oliveira, S.A.[21] | 2004      | European CAD  | PCR           | 377/379 | 497/257       | 485/273 | 232/119 | 24/132       | 0.00/0.37 | Moderate 7    |               |           |
| Tobin, M.D.[22] | 2004        | European MI   | POR-RFLP      | 547/505 | 682/412       | 643/367 | 372/175 | 31/192       | 0.12/0.32 | Moderate 7    |               |           |
| Martineau, N.[23] | 2005       | European CHD  | PCR           | 642/273 | 705/498       | 328/218 | 520/122 | 187/66       | 0.15/0.70 | Moderate 7    |               |           |
| Kerkeni, M.[24] | 2006        | African CAD   | POR-RFLP      | 100/120 | 151/49        | 18/59  | 74/26  | 87/33        | 1.00/0.04 | Moderate 7    |               |           |
| Blatner, J.[25] | 2006        | American CAD  | PCR-RFLP      | 710/199 | 840/574       | 261/137 | 564/146 | 100/99       | 0.69/0.52 | Moderate 7    |               |           |
| Rios, D.[26]    | 2007        | African CAD   | POR-RFLP      | 148/127 | 196/100       | 16/68  | 99/49  | 56/71        | 0.00/0.03 | Moderate 7    |               |           |
| Saxe, E.[27]    | 2007        | Asian MI      | PCR           | 201/350 | 322/80        | 54/152  | 153/58 | 25/112       | 0.00/0.11 | Moderate 7    |               |           |
| Troughton, J.[28] | 2008       | European CHD  | PCR           | 433/247 | 329/165       | 59/307  | 43/30  | 24/70        | 0.06/0.46 | Moderate 8    |               |           |
| Khatib, H.[29]  | 2008        | Asian CHD     | PCR-RFLP      | 310/129 | 167/111       | 104/33  | 19/100 | 65/76        | 0.00/0.00 | Moderate 7    |               |           |
| Bjornholm, R.S.[30] | 2009       | European CHD  | AS-POR        | 1019/2161 | 1334/766   | 267/1458 | 655/436 | 1270/846    | 9.49/0.59 | Moderate 8    |               |           |
| Agrawal, S.[31] | 2009        | European CHD  | PCR-RFLP      | 279/190 | 412/46        | 262/118 | 244/41 | 163/37       | 0.08/0.23 | Moderate 7    |               |           |
| Kaman, D.[32]   | 2009        | European CHD  | POR-RFLP      | 277/922 | 369/85        | 103/91  | 189/89 | 54/38        | 1.00/0.67 | Moderate 7    |               |           |
| Votava, E.[33]  | 2009        | African CHD   | PCR-RFLP      | 112/918 | 127/55        | 183/33  | 64/27  | 59/59        | 0.45/0.42 | Moderate 7    |               |           |
| Ayub, M.[34]    | 2009        | European MI   | PCR           | 218/131 | 287/55        | 120/43 | 119/22 | 80/32        | 0.76/0.00 | Moderate 7    |               |           |
| Mukamal, K.[35] | 2009        | American MI   | Taqman        | 482/971 | 616/584       | 1251/691 | 263/243 | 528/490      | 0.84/0.40 | Moderate 7    |               |           |
| Lakshmy, R.[36] | 2010        | Asian CAD     | PCR-RFLP      | 124/154 | 201/47        | 239/69  | 108/16 | 199/25       | 0.56/0.03 | Moderate 7    |               |           |
| Gupta, N.[37]   | 2011        | Asian CAD     | POR-RFLP      | 350/300 | 593/107       | 487/113 | 269/64 | 151/149      | 0.09/0.09 | Moderate 7    |               |           |
| Bournafas, A.[38] | 2015       | African ACS   | PCR           | 205/100 | 257/153       | 146/54  | 125/80 | 52/48        | 0.23/0.61 | High 7        |               |           |

(continued)
| Author                  | Year | Ethnicity | Diagnosis | Genotype method | Sample size | Cases/Control | Allele | Gender | p HWE | Grade quality | NOS score |
|------------------------|------|-----------|-----------|-----------------|-------------|---------------|--------|---------|------|---------------|-----------|
| Hasselwander, O. [12]  | 1999 | European  | CAD       | PCR-RFLP        | 103/388     | 144/62        | 534/422| M/F     | 70/3 | 0.00/0.19     | 7         |
| Ayub, A. [13]         | 1999 | European  | MI        | PCR-RFLP        | 210/431     | 228/84        | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Imai, Y. [10]         | 2000 | Asian     | CAD       | PCR-RFLP        | 210/431     | 228/84        | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Aynacioglu, A.S. [47] | 2000 | Asian     | CAD       | PCR-RFLP        | 197/200     | 197/200       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Heijmans, B.T. [14]   | 2000 | European  | CHD       | PCR             | 364/200     | 364/200       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Sen-Banerjee, S. [15] | 2000 | American  | MI        | PCR-RFLP        | 492/512     | 492/512       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Aubo, C. [48]         | 2000 | European  | MI        | PCR-RFLP        | 103/388     | 103/388       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Osei-Hyiaman, D. [49] | 2001 | Asian     | CAD       | PCR             | 201/231     | 201/231       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Mackness, B. [16]     | 2001 | European  | CHD       | PCR-RFLP        | 417/200     | 417/200       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Sentí, M. [8]         | 2001 | European  | MI        | PCR-RFLP        | 280/360     | 280/360       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Robertsohn, K.S. [50] | 2001 | European  | MI        | PCR-RFLP        | 115/269     | 115/269       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Wang, X. [20]         | 2001 | Asian     | CAD       | PCR             | 215/205     | 215/205       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Bathroom, M.C. [25]    | 2006 | European  | CAD       | PCR-RFLP        | 710/199     | 710/199       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Amendo, K. [26]       | 2006 | Asian     | MI        | PCR-RFLP        | 124/35      | 124/35        | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Baum, L. [27]         | 2006 | Asian     | CAD       | PCR             | 210/431     | 210/431       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Rios, D.I. [28]       | 2006 | African   | CAD       | PCR             | 210/431     | 210/431       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Balcerzyk, A. [29]    | 2006 | Asian     | CAD       | PCR             | 710/199     | 710/199       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Bhumichand, T. [30]   | 2006 | Asian     | CAD       | PCR             | 642/273     | 642/273       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Andrianatos, K. [31]  | 2006 | Asian     | CAD       | PCR             | 387/173     | 387/173       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Kaman, D. [32]        | 2006 | Asian     | CAD       | PCR             | 139/119     | 139/119       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Balcerzyk, A. [33]    | 2006 | Asian     | CAD       | PCR             | 144/62      | 144/62        | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Mukamal, K.J. [34]    | 2006 | American  | MI        | PCR             | 218/121     | 218/121       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Izar, M. C. [35]      | 2006 | Asian     | MI        | PCR             | 488/584     | 488/584       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Mohamed, R.H. [36]    | 2006 | Asian     | MI        | PCR             | 150/90      | 150/90        | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |
| Lakshm, M. [37]       | 2006 | Asian     | MI        | PCR             | 124/221     | 124/221       | 74/22  | 7       | 184/3 | 0.00/0.16     | 7         |

(continued)
conducted to determine whether the PON1 55M or 192R alleles are closely associated with HD; some of them have found an association between the polymorphism and the disease\cite{hernandez-diaz2016medicina,hernandez-diaz2016medicina,hernandez-diaz2016medicina} while others have not\cite{hernandez-diaz2016medicina,hernandez-diaz2016medicina}. In this study, we performed a meta-analysis which is a very useful tool to combine information from different sources, by pooling 64 case-control studies to comprehensively determine the overall strength of associations between PON1 polymorphisms (L55M and Q192R) and the susceptibility to develop heart diseases.

2. Methods

This meta-analysis was designed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA Compliant) statement. The protocol of the systematic review was registered in PROSPERO (http://www.crd.york.ac.uk/prospero/) with registration number: CRD42016043782. Ethics approval was not necessary for this study, due to only data from individual studies were analyzed.

2.1. The literature search

The search for all the studies investigating the association of the PON1 polymorphism with HD risk was conducted through a systematic computerized literature search from PubMed and EBSCO databases prior to July 2016 using the following search terms: (“paraoxonase1” or “PON1”) and (“L55M polymorphism” or “Q192R polymorphism”) and (“heart disease” or “coronary heart disease” or “coronary artery disease” or “myocardial infarction”). We also conducted a manual search to find other potential articles based on references identified in individual articles.

2.2. Inclusion and exclusion criteria

As a prerequisite, the selection of studies in our meta-analysis was abided by the predefined inclusion and exclusion criteria: the study investigated the association between the PON1 polymorphisms and heart disease; the study included patients diagnosed with any heart disease; the study used healthy subjects as controls; provided sufficient data on allele or genotype distribution in patients and controls; the study was written in English; the study had been published in peer-reviewed journals. The exclusion criteria were: studies without control population; to be comments, review articles, meta-analysis, or articles only with an abstract.

2.3. Data extraction and methodological assessment

To make sure of the accuracy of the information, data extraction was performed independently by two authors (YHD and CRP) on the basis of a standard protocol including the following elements: publication year, the first author’s surname, geographical location, design of study, total number of cases and controls, mean age, sex, genotype frequencies, and genotyping method. Any encountered discrepancies were adjudicated by a discussion until a consensus was reached. The quality of each selected study was assessed independently by the same two authors according to the Newcastle-Ottawa Scale (NOS). The study quality was evaluated based on 8 items and assigned a quality score that ranged from 0 to 9 points. The NOS criteria included three aspects selection: 0 to 4; comparability: 0 to 2; and outcome: 0 to 3. The quality of the body of evidence for each determinant was examined according to the grading of recommendations assessment, development, and evaluation (GRADE). The overall quality was determined to be high, moderate, low, or very low.
Table 1

Results of meta-analysis for PON1 polymorphisms and risk of heart diseases by sub-groups.

| Genetic model | Group | OR (95% CI) | Cochran Q test | Egger's test |
|---------------|-------|-------------|----------------|--------------|
| L55M          | Allelic | 1.01 (0.96–1.08) | 0.095 | 27 | 0.175 |
|               | Homozygote | 0.98 (0.87–1.11) | 0.197 | 18 | 0.986 |
|               | Heterozygote | 1.02 (0.95–1.09) | 0.407 | 3 | 2.422 |
|               | Dominant | 0.99 (0.88–1.11) | 0.297 | 11 | 0.721 |
|               | Recessive | 1.04 (0.97–1.10) | 0.077 | 28 | 0.091 |
|               | Allelic | 1.03 (0.92–1.15) | 0.966 | 0 | 0.698 |
|               | Homozygote | 1.05 (0.82–1.34) | 0.769 | 0 | 0.404 |
|               | Heterozygote | 1.04 (0.89–1.22) | 0.579 | 0 | 0.095 |
|               | Dominant | 1.02 (0.81–1.29) | 0.466 | 0 | 0.256 |
|               | Recessive | 1.05 (0.90–1.22) | 0.844 | 0 | 0.075 |
|               | Allelic | 1.01 (0.92–1.11) | 0.807 | 37 | 0.514 |
|               | Homozygote | 0.96 (0.78–1.18) | 0.131 | 31 | 0.708 |
|               | Heterozygote | 1.03 (0.94–1.12) | 0.688 | 0 | 0.103 |
|               | Dominant | 0.96 (0.82–1.11) | 0.413 | 2 | 0.496 |
|               | Recessive | 1.10 (0.97–1.23) | 0.068 | 0 | 0.060 |
|               | Allelic | 1.00 (0.92–1.09) | 0.806 | 0 | 0.100 |
|               | Homozygote | 0.92 (0.75–1.13) | 0.965 | 0 | 0.417 |
|               | Heterozygote | 1.03 (0.87–1.21) | 0.162 | 33 | 0.383 |
|               | Dominant | 0.99 (0.85–1.17) | 0.899 | 0 | 0.889 |
|               | Recessive | 1.02 (0.89–1.16) | 0.328 | 12 | 0.238 |
|               | Allelic | 0.99 (0.92–1.09) | 0.162 | 28 | 0.111 |
|               | Homozygote | 1.20 (0.93–1.54) | 0.122 | 0 | 0.106 |
|               | Heterozygote | 0.99 (0.84–1.18) | 0.532 | 32 | 0.255 |
|               | Dominant | 0.98 (0.90–1.07) | 0.105 | 0 | 0.232 |
|               | Recessive | 1.44 (1.33–1.56) | 0.666 | 0 | 0.274 |
|               | Allelic | 1.18 (1.03–1.35) | 0.929 | 0 | 0.577 |
|               | Homozygote | 1.33 (0.85–2.07) | 0.984 | 0 | 0.159 |
|               | Heterozygote | 1.20 (1.02–1.41) | 0.881 | 0 | 0.859 |
|               | Dominant | 1.23 (0.79–1.89) | 0.987 | 0 | 0.226 |
|               | Recessive | 1.21 (1.03–1.41) | 0.880 | 0 | 0.942 |
|               | Allelic | 0.81 (0.62–1.06) | 0.136 | 27 | 0.853 |
|               | Homozygote | 0.51 (0.26–1.01) | 0.151 | 31 | 0.175 |
|               | Heterozygote | 0.91 (0.64–1.39) | 0.881 | 16 | 0.491 |
|               | Dominant | 0.57 (0.32–1.01) | 0.237 | 29 | 0.088 |
|               | Recessive | 0.83 (0.58–1.19) | 0.116 | 0 | 0.900 |
|               | Allelic | 1.03 (0.93–1.14) | 0.505 | 0 | 0.079 |
|               | Homozygote | 1.01 (0.81–1.26) | 0.457 | 0 | 0.825 |
|               | Heterozygote | 1.01 (0.82–1.25) | 0.231 | 30 | 0.877 |
|               | Dominant | 1.05 (0.89–1.24) | 0.891 | 0 | 0.696 |
|               | Recessive | 1.03 (0.85–1.25) | 0.244 | 27 | 0.768 |
| CHD, CAD, and MI | Allelic | 0.83 (0.63–1.03) | 0.103 | 11 | 0.182 |
|               | Homozygote | 0.82 (0.64–1.01) | 0.271 | 10 | 0.209 |
|               | Heterozygote | 0.99 (0.93–1.05) | 0.206 | 14 | 0.064 |
|               | Dominant | 0.92 (0.84–1.00) | 0.064 | 24 | 0.055 |
|               | Recessive | 0.96 (0.91–1.02) | 0.196 | 15 | 0.129 |
|               | Allelic | 0.97 (0.91–1.03) | 0.535 | 0 | 0.944 |
|               | Homozygote | 0.85 (0.71–1.02) | 0.158 | 32 | 0.653 |
|               | Heterozygote | 0.97 (0.85–1.11) | 0.182 | 29 | 0.462 |
|               | Dominant | 0.93 (0.83–1.04) | 0.352 | 0 | 0.820 |
|               | Recessive | 0.98 (0.90–1.07) | 0.421 | 0 | 0.701 |
|               | Allelic | 0.91 (0.84–0.98) | 0.272 | 15 | 0.023 |
|               | Homozygote | 0.73 (0.60–0.88) | 0.119 | 25 | 0.293 |
|               | Heterozygote | 0.98 (0.89–1.09) | 0.231 | 16 | 0.111 |
|               | Dominant | 1.38 (1.22–1.56) | 0.775 | 0 | 0.229 |
|               | Recessive | 0.88 (0.79–0.99) | 0.173 | 23 | 0.045 |
|               | Allelic | 0.93 (0.86–1.00) | 0.151 | 25 | 0.520 |
|               | Homozygote | 0.75 (0.57–0.99) | 0.053 | 46 | 0.709 |
|               | Heterozygote | 0.92 (0.82–1.04) | 0.090 | 38 | 0.420 |
|               | Dominant | 0.70 (0.50–0.99) | 0.140 | 37 | 0.485 |
|               | Recessive | 0.85 (0.75–0.97) | 0.108 | 37 | 0.075 |

(continued)
patients and 11,732 healthy controls; there was no statistical evidence of association between the L55M polymorphism and an overall risk of heart disease (Table 2). In the sub-group analysis stratified by diagnostic, no association among this polymorphism and CHD, CAD, or MI was observed in all genetic models (Table 2). When performing a meta-analysis by ethnicity, higher risk was detected in European (recessive model: OR 1.44, 95%CI 1.33–1.56) and Asian populations (allelic model: OR 1.18, 95%CI 1.03–1.35; heterozygote model: OR 1.20, 95%CI 1.02–1.41; and recessive model: OR 1.21, 95%CI 1.03–1.41), but not in African or Mexican populations (Figs. 1 and 2; Table 2).

Figure 1. Results of analysis in European population for L55M polymorphism. A, B, and C showing the forest plot for genetic models: allelic, homozygote, and recessive, respectively; D, E, and F showing the funnel plot of publication biases with the genetic models above mentioned.
3.3. Association of Q192R polymorphism and the risk of heart diseases

A total of 64 studies with 19,715 patients and 33,397 controls were eligible for the pooled analysis of Q192R polymorphism. Overall, no significant association was found between the \( \text{PON1} \) gene Q192R polymorphism and heart diseases risk. The main results of meta-analysis are shown in Table 2. However, in the stratification analysis by diagnostic type, a significantly decreased risk of CAD (allelic model: OR 0.91, 95%CI 0.84–0.98; homozygote model: OR 0.73, 95%CI 0.60–0.88; and recessive model: OR 0.88, 95%CI 0.79–0.99) and MI (homozygote model: OR 0.75, 95%CI 0.57–0.99; dominant model: OR 0.70, 95%CI 0.50–0.99; and recessive model: OR 0.85, 95%CI 0.75–0.97) was identified (Figs. 3 and 4; Table 2). Moreover, in coronary artery diseases, subjects with a Q allele had a markedly increased risk of developing the disease (dominant model: OR 1.38, 95%CI 1.22–1.56). No association was observed in CHD population (Fig. 3; Table 2). In a stratified analysis by specific ethnicity, the Q192R polymorphism had a protective effect under all genetic models in Asian (allelic model: OR 0.74, 95%CI 0.67–0.83; homozygote model: OR 0.48, 95%CI 0.35–0.63; heterozygote model: OR 0.49, 95%CI 0.37–0.66; and recessive model: OR 0.69, 95%CI 0.57–0.84) and African populations under allelic, homozygote and dominant models: OR 0.67, 95%CI 0.53 to 0.84; OR 0.51, 95%CI 0.29 to 0.90; OR 0.45, 95%CI 0.30 to 0.68 (Figs. 5 and 6; Table 2). No relationship was found between the polymorphism and the disease in European or American populations (Table 2).

![Figure 2](image-url)
3.4. Test for heterogeneity and sensitivity analyses

The subgroup analysis revealed no significant heterogeneity among studies (Table 2). In the sensitivity analyses, the influence of each study on the pooled OR was checked by excluding 1 study each time. If the exclusion of any single study did not alter the significance of the final decision, it suggested that the outcomes were robust. The corresponding pooled ORs were not materially altered, confirming that our results were statistically robust.

3.5. Publication bias

Begg’s funnel plots and the Egger test were performed to evaluate the publication bias of the selected literature. The shape of the
funnel plot appeared to be symmetric (Figs. 1–6). The Egger test was then used to statistically assess funnel plot symmetry (Table 2). The results suggested no significant publication bias in all pooled studies.

4. Discussion

An increased lipid peroxidation is associated with a progression of heart diseases; however, the high-density lipoproteins (HDL) play an important role in protecting against these diseases due to their antioxidant properties. The main antioxidant enzyme carried by HDL particles is PON1.[3,7] The gene encoding human PON1 has been cloned and sequenced; then several polymorphisms in its sequence have been identified. Specifically, L55M and Q192R polymorphisms have been associated with changes in protection against lipid peroxidation and with an altered risk of heart diseases.[17] Due to the above mentioned, PON1 can be recognized as a heart disease susceptibility gene. In this study, 64 studies that had studied the correlation between PON1 polymorphisms and heart diseases were collected and the effect of the variability on heart disease risk was analyzed by meta-analysis which is a useful tool to obtain clear and reliable results, very important in clinical and medical areas.[71,72] Our study systematically assessed the association between the L55M/Q192R polymorphisms of PON1 gene and heart diseases risk in detail, based on a large sample (19,715 cases and 33,397 controls) and different gene contrast models, in the whole population as well as various subgroups. These features make this a more complete meta-analysis that previously published studies.[5,6,73] Moreover, other strength of our study is the quality of included studies which was evaluated by the NOS and GRADE scales and the results verified by the sensitivity analyses.

![Image]

Figure 4. Results of analysis in MI population for Q192R polymorphism. A, B, and C showing the forest plot for genetic models: homozygote, dominant, and recessive, respectively; D, E, and F showing the funnel plot of publication biases with the genetic models above mentioned. MI=myocardial infarction.
Overall, we found that the PON1 L55M variant genotype was significantly associated with heart diseases risk based on random effect model in European and Asian populations, which is consistent with the results of Kaman et al.,[31] Aydin et al.,[33] Agrawal et al.[3], and Zama et al.[9]. On the other hand, when analyzed by subgroups (different diagnoses) no strong association was observed; possible explanations may be: the studied populations had different dietary habits and lifestyle, and the age and gender of the patients could also influence the studies. Furthermore, several studies support these findings, showing that PON1 L55M polymorphism is not a predictor of CAD or MI.[17,18]

For the Q192R polymorphism, our meta-analysis demonstrated that individuals with the R allele have lower risk of suffering MI and CAD. Our findings are consistent with the previous results reported by Tobin et al.[22] and Sanghera et al.[7]. However, our analysis also showed that the Q allele is a risk allele for developing coronary artery disease. It can be argued that the Q allele may cause HDL-deficiency and therefore a low PON1 activity, reflecting a coexistent oxidative stress. Furthermore, it is known that HDL-deficiency states can increase the risk of MI.[8]

In the subgroup analysis performed by ethnicity, the results showed that PON1 Q192R polymorphism is associated with a low risk of heart diseases in Asian and African populations, but not among Europeans and Americans, implicating that ethnicity differences play an important role in the polymorphism effects. This single nucleotide polymorphism (SNP) could modify the oxidative function of lipoproteins and may play a role in heart diseases via a protective effect against lipoprotein oxidation.[11]

Also, this SNP is more frequent in Asian populations (between
0.30 and 0.59,\cite{1,9} while several studies have showed a no association of this polymorphism in others ethnicity groups.\cite{12,31,60}

In interpreting the results, an important limitation of our study should be considered. It would have been valuable to stratify the results according to interactions among gene–gene and gene–environment, though this was not possible, as the original data sets were not available. Despite this limitation, our meta-analyses also have some advantages: firstly, we included more studies than any previously published meta-analysis on the association between \textit{PON1} polymorphism and heart diseases risk and secondly, we investigated two different \textit{PON1} polymorphisms. In summary, we performed a comprehensive analysis indicating that the genetic susceptibility for heart diseases is associated with \textit{PON1} L55M polymorphism in European and Asian populations. As for the Q192R polymorphism, the R allele is involved in protection against heart diseases in Asian and African populations (specifically for coronary artery diseases and myocardial infarction). However, the Q allele may be a risk factor to develop CAD. Additionally, more well-studied association studies are needed to provide powerful evidence to the conclusions.

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