Association between Peroxisome Proliferator-activated Receptor Gamma Gene Polymorphisms and Atherosclerotic Diseases: A Meta-analysis of Case-control Studies

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Aim: The aim of this study was to perform a meta-analysis to investigate the association between PPARγ rs1801282/rs3856806 polymorphisms and atherosclerotic diseases.

Methods: The meta-analysis was performed by searching the PubMed, Embase and Web of Science databases from the first available year to September 10, 2013. Additionally, reference lists from the identified articles, reviews and abstracts presented at the meetings of related scientific societies were also checked. All case-control studies investigating the association between PPARγ rs1801282/rs3856806 polymorphisms and the risk of atherosclerotic disease were included. The association was assessed according to the odds ratio (OR) with a 95% confidence interval (CI). Publication bias was analyzed using Begg's funnel plot and Egger's regression test.

Results: A total of 29 studies reporting PPARγ rs1801282/rs3856806 polymorphism were included in the final meta-analysis. Neither the rs1801282 (Pro12Ala) nor rs3856806 (C161T) polymorphisms showed any significant associations with susceptibility to atherosclerotic diseases. In the meta-analysis performed to assess the association between the rs3856806 gene polymorphism and atherosclerotic disease based on ethnicity and the type of disease, significant associations were found in the Caucasian subgroup, Asian, CAD and MI subgroups.

Conclusions: The present data suggest that there is no statistical evidence of a significant association between the PPARγ gene rs1801282/rs3856806 polymorphism and the risk of atherosclerotic disease. In contrast, the rs3856806 polymorphism was associated with an increased risk in the Caucasian and MI subgroups, whereas decreased risks were noted in the Asian and CAD subgroups. Due to significant between-study heterogeneity, further studies with a larger sample size involving homogeneous AS patients and well-matched controls are required in the future.


Key words: Atherosclerotic diseases, Peroxisome proliferator activated receptor gamma, Single nucleotide polymorphism, Meta-analysis

Introduction

Atherosclerosis (AS) is the most common pathological process in the arteries, leading to ischemic heart disease, peripheral vascular disease and stroke. It is well known that AS is a quintessential complex disease caused by multiple genetic and environmental factors and even complex gene-environment interactions.

Peroxisome proliferative-activated receptor-γ (PPAR-γ) is a ligand-activated nuclear transcription factor belonging to the nuclear hormone receptor superfamily, which is expressed in adipose tissue, endothelial cells and vascular smooth muscle cells. It
has been reported that PPARγ plays a critical role in atherothrombosis\textsuperscript{1-3}. However, the antiatherogenic effect of PPARγ has also been demonstrated\textsuperscript{4-6}. Concerning the controversial role of PPARγ in the development of AS, single nucleotide polymorphisms (SNPs) of the PPARγ gene have attracted increasing attention and influence the expression or activity of PPARγ\textsuperscript{7-8}. Among these SNPs, two common polymorphisms of the PPARγ gene, rs1801282 (Pro12Ala)\textsuperscript{9} and rs3856806 (C161T, also known as C1431T)\textsuperscript{10}, have been widely studied in terms of their associations with atherosclerotic diseases\textsuperscript{11-39}. However, the conclusions are inconsistent. Moreover, controversial results from meta-analyses have been reported concerning the associations between these two SNPs and coronary heart disease\textsuperscript{40-43}. Therefore, the present study was designed to evaluate the associations between these two SNPs and AS diseases, including coronary artery disease, myocardial infarction, ischemic cerebrovascular events and peripheral arterial disease, more comprehensively.

**Materials and Methods**

**Literature Search**

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines\textsuperscript{44, 45}. All published studies on humans were collected up to September 10, 2013 by systematically searching the PubMed, Embase and ISI Web of Science databases with the following search terms: (“peroxisome proliferator-activated receptor-γ” OR “peroxisome proliferator-activated receptor-gamma” OR “rs1801282” OR “rs3856806”) AND (“polymorphism” OR “mutation” OR “variant” OR “genotype”) AND (“coronary artery disease” OR “CAD” OR “coronary heart disease” OR “CHD” OR “myocardial infarction” OR “MI” OR “ischemic cardiovascular disease” OR “ischemic cardiovascular events” OR “stroke” OR “cerebrovascular disease” OR “ischemic cerebrovascular events” OR “cerebral infarction” OR “cerebral ischemia” OR “brain infarction” OR “transient ischemic attack” OR “TIA” OR “carotid artery stenosis” OR “CAS” OR “peripheral arterial disease” OR “PAD” OR “peripheral artery occlusive disease” OR “PAOD” OR “renal artery stenosis” OR “RAS” OR “retinal artery occlusion” OR “RAO” OR “aortic aneurysm” OR “atherosclerosis”). The languages were limited to English and Chinese. The electronic search was supplemented by checking the reference lists of the identified articles, reviews and abstracts presented at the meetings of related scientific societies. Two investigators (Wang P.J. & Yin Y.W.) screened each of the titles, abstracts and full texts to determine eligibility for inclusion independently. The results were compared, and any disagreements were resolved by consensus.

**Inclusion Criteria**

The inclusion criteria were as follows: (1) studies on the relationship between PPAR-γ SNPs (rs1801282/ rs3856806) and atherosclerotic diseases; (2) studies with full text articles; (3) sufficient data for estimating the odds ratio (OR) and 95% confidence interval (CI).

**Data Extraction**

The information was extracted independently by two investigators (Wang Q.L. & Li W.Z.) according to the inclusion criteria listed above. Disagreement was resolved by consensus. If these two authors could not reach a consensus, another author (Liang D.P.) was consulted. The following data were collected from each study: first author’s name, publication date, study population (country, ethnicity) and evidence of Hardy-Weinberg equilibrium (HWE) ($p<0.05$ for HWE was considered to be significant).

**Quality Score Assessment**

Two authors (Zhou P. & Yang Z.) assessed the qualities of the included studies independently using the Newcastle-Ottawa Scale (NOS)\textsuperscript{46}. The NOS ranges from 0 (worst) to 9 (best) stars. Studies with a score of 7 stars or greater were considered to be of high quality. Disagreements were settled as described above.

**Statistical Analysis**

Crude ORs with the 95% CIs were calculated for each of four genetic models: allelic model (2 allele vs. 1 allele), additive model (2/2 vs. 1/1), dominant model (1/2 + 2/2 vs. 1/1) and recessive model (2/2 vs. 1/2 + 1/1), in which the number 2 indicates the minor allele\textsuperscript{47}. Between-study heterogeneity was assessed according to the Q-test and I\textsuperscript{2} statistic, with $p<0.10$ and I\textsuperscript{2}>50% indicating evidence of heterogeneity\textsuperscript{48, 49}. The ORs were pooled via a fixed-effects model using the Mantel-Haenszel approach, when no heterogeneity was observed among the studies\textsuperscript{50}; otherwise, a random-effects model was adopted\textsuperscript{51}. In order to clarify the source of heterogeneity, subgroup and sensitivity analyses were performed and a Galbraith plot was created. The subgroup analyses were carried out based on ethnicity (Caucasian, Asian and others), type...
A total of 1,027 potentially relevant studies were identified in the search. Based on the inclusion criteria, a total of 29 studies were included in the meta-analysis. Table 1 shows the main characteristics of the studies comprising the meta-analysis. The NOS of the studies included a range of 6 and 9. The average score was 7.17, indicating that the methodological quality was generally good. There were 22 studies evaluating the relationship between the rs1801282 gene polymorphism and atherosclerotic diseases and 11 studies reporting an association between the rs3856806 polymorphism and atherosclerotic diseases.

Results

Study Characteristics
The study selection process is detailed in Fig. 1.

Fig. 1. Flow diagram of the study selection process.
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>type</th>
<th>SNP</th>
<th>Genotypes distribution (case/control)</th>
<th>MAF case/control</th>
<th>HWE Y/N (P)</th>
<th>Score</th>
</tr>
</thead>
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<tr>
<td>Wang</td>
<td>1999</td>
<td>Australia</td>
<td>Caucasian</td>
<td>CAD</td>
<td>rs3856806</td>
<td>372/79 127/53 15/1 157/55</td>
<td>N (0.013)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Bluher</td>
<td>2002</td>
<td>Germany</td>
<td>Caucasian</td>
<td>CAD</td>
<td>rs1801282</td>
<td>174/140 23/22 4/2 31/26</td>
<td>Y (0.30)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Peng</td>
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<td>China</td>
<td>Asian</td>
<td>CAD</td>
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<td>110/99 34/54 6/4 46/62</td>
<td>Y (0.29)</td>
<td>8</td>
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<tr>
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<td>Caucasian</td>
<td>MI</td>
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<td>425/1610 92/451 6/31 104/513</td>
<td>Y (0.93)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Chao</td>
<td>2004</td>
<td>China</td>
<td>Asian</td>
<td>MI</td>
<td>rs3856806</td>
<td>63/71 64/67 19/8 102/83</td>
<td>Y (0.123)</td>
<td>8</td>
<td></td>
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<td>Tobin</td>
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<td>UK</td>
<td>Caucasian</td>
<td>MI</td>
<td>rs1801282</td>
<td>434/381 103/120 10/4 123/128</td>
<td>Y (0.10)</td>
<td>9</td>
<td></td>
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<td>Pischon</td>
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<td>Caucasian</td>
<td>CHD</td>
<td>rs1801282</td>
<td>374/793 113/184 8/10 129/204</td>
<td>Y (0.85)</td>
<td>8</td>
<td></td>
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<td>Li</td>
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<td>Asian</td>
<td>MI</td>
<td>rs1801282</td>
<td>43/588 23/36 0/2 23/40</td>
<td>Y (0.08)</td>
<td>9</td>
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<td>Caucasian</td>
<td>CAD</td>
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<td>238/114 62/36</td>
<td>-</td>
<td>NE 7</td>
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<tr>
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<td>USA</td>
<td>Caucasian</td>
<td>MI</td>
<td>rs1801282</td>
<td>425/1610 92/451 6/31 104/513</td>
<td>Y (0.93)</td>
<td>7</td>
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<tr>
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<td>Asian</td>
<td>IS</td>
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<td>128/117 6/12 0/0 6/12</td>
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<td>153/110 84/97 10/7 104/111</td>
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<td>136/107 14/10 0/0 14/10</td>
<td>Y (0.63)</td>
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<td>Ruiz-Narvaez</td>
<td>2007</td>
<td>Costa Rica</td>
<td>Caucasian</td>
<td>MI</td>
<td>rs1801282</td>
<td>1440/1470 341/310 24/25 389/360</td>
<td>Y (0.065)</td>
<td>8</td>
<td></td>
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<tr>
<td>Catalano</td>
<td>2008</td>
<td>Italy</td>
<td>Caucasian</td>
<td>PAD</td>
<td>rs1801282</td>
<td>149/170 48/30 4/1 56/32</td>
<td>Y (0.79)</td>
<td>9</td>
<td></td>
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<tr>
<td>Zafarmand</td>
<td>2008</td>
<td>The Netherland</td>
<td>Caucasian</td>
<td>Mixed</td>
<td>rs1801282</td>
<td>266/1143 61/346 4/30 69/406</td>
<td>Y (0.52)</td>
<td>8</td>
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<tr>
<td>Dallongeville</td>
<td>2009</td>
<td>France</td>
<td>Caucasian</td>
<td>CHD</td>
<td>rs1801282</td>
<td>1014/983 271/278 19/13 309/304</td>
<td>Y (0.17)</td>
<td>8</td>
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<td>Evangelisti</td>
<td>2009</td>
<td>Italy</td>
<td>Caucasian</td>
<td>CAD</td>
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<td>169/258 30/38 3/0 36/38</td>
<td>Y (0.24)</td>
<td>8</td>
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<td>Vogel</td>
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<td>Denmark</td>
<td>Caucasian</td>
<td>CAD</td>
<td>rs1801282</td>
<td>161/251 36/44 5/0 46/44</td>
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<td>8</td>
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<td>AshokKumar</td>
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<td>India</td>
<td>Asian</td>
<td>CAD</td>
<td>rs1801282</td>
<td>347/366 62/54 5/4 72/62</td>
<td>Y (0.21)</td>
<td>7</td>
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<td>Caucasian</td>
<td>CAD</td>
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<td>442/204 35/10 1/4 37/18</td>
<td>N (0.00)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Moran</td>
<td>2010</td>
<td>Australia</td>
<td>Caucasian</td>
<td>AAA</td>
<td>rs1801282</td>
<td>499/2733 161/708 12/54 185/816</td>
<td>Y (0.30)</td>
<td>8</td>
<td></td>
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<tr>
<td>Wan</td>
<td>2010</td>
<td>China</td>
<td>Asian</td>
<td>CAD</td>
<td>rs3856806</td>
<td>50/55 25/30 3/4 31/38</td>
<td>Y (0.97)</td>
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<td>Yilmaz-Aydogan</td>
<td>2011</td>
<td>Turkey</td>
<td>Asian</td>
<td>CAD</td>
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<td>176/88 26/17 0/0 26/17</td>
<td>Y (0.37)</td>
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<td>Yilmaz-Aydogan</td>
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<td>Turkey</td>
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<td>78/43 0/0 9/9 18/18</td>
<td>N (0.00)</td>
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<tr>
<td>Wang</td>
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<td>China</td>
<td>Asian</td>
<td>MI</td>
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<td>107/131 14/2 0/4 14/10</td>
<td>N (0.00)</td>
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<td>China</td>
<td>Asian</td>
<td>CAD</td>
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<td>586/595 245/341 33/72 311/485</td>
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<td>Asian</td>
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<td>133/49 85/52</td>
<td>-</td>
<td>NE 8</td>
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<td>Youssef</td>
<td>2013</td>
<td>Tunisia</td>
<td>African</td>
<td>CAD</td>
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<td>181/158 57/78 1/8 59/94</td>
<td>Y (0.66)</td>
<td>8</td>
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</tr>
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</table>

HWE: Hardy-Weinberg equilibrium, Y: yes, N: no, NE: not evaluate, P: p value of test for HWE, MAF: minor allele frequency
MI: myocardial infarction, CAD: coronary artery disease, IS: ischemic stroke, PAD: peripheral arterial disease, AAA: abdominal aortic aneurysm, CHD: coronary heart disease, Mixed: IS + MI + CAD
Table 2. Results of meta-analysis for PPARy SNPs and atherosclerotic disease

<table>
<thead>
<tr>
<th>Study group</th>
<th>Study (n)</th>
<th>Sample size (case/control)</th>
<th>Allelic model</th>
<th>Additive model</th>
<th>Dominant model</th>
<th>Recessive model</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95%CI) M</td>
<td>OR (95%CI) M</td>
<td>OR (95%CI) M</td>
<td>OR (95%CI) M</td>
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<tr>
<td>rs1801282</td>
<td>Overall</td>
<td>22</td>
<td>1.00 (0.89-1.12) R</td>
<td>1.02 (0.82-1.27) F</td>
<td>1.00 (0.88-1.13) R</td>
<td>1.02 (0.82-1.27) F</td>
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<tr>
<td>SA based on ethnicity</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Caucasian</td>
<td>14</td>
<td>8613/16467</td>
<td>1.02 (0.91-1.14) R</td>
<td>1.14 (0.90-1.43) F</td>
<td>1.00 (0.88-1.13) R</td>
<td>1.14 (0.90-1.44) F</td>
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<tr>
<td>Asian</td>
<td>7</td>
<td>1326/1590</td>
<td>1.08 (0.86-1.35) F</td>
<td>0.62 (0.30-1.27) F</td>
<td>1.10 (0.74-1.63) R</td>
<td>0.61 (0.30-1.24) F</td>
</tr>
<tr>
<td>SA based on type of diseases</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CAD</td>
<td>11</td>
<td>3515/4958</td>
<td>0.95 (0.85-1.06) F</td>
<td>0.91 (0.63-1.32) F</td>
<td>0.94 (0.83-1.05) F</td>
<td>0.93 (0.64-1.35) F</td>
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<tr>
<td>MI</td>
<td>7</td>
<td>3808/8776</td>
<td>0.93 (0.76-1.14) F</td>
<td>0.87 (0.60-1.25) F</td>
<td>0.95 (0.74-1.22) R</td>
<td>0.88 (0.61-1.28) F</td>
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<td>IS</td>
<td>2</td>
<td>183/1648</td>
<td>0.75 (0.44-1.28) F</td>
<td>1.00 (0.13-7.55) F</td>
<td>0.71 (0.40-1.26) F</td>
<td>1.03 (0.14-7.74) F</td>
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<tr>
<td>Sensitivity analysis</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>BH</td>
<td>18</td>
<td>9290/17789</td>
<td>1.01 (0.90-1.14) R</td>
<td>1.11 (0.89-1.40) F</td>
<td>0.99 (0.88-1.13) R</td>
<td>1.12 (0.89-1.41) F</td>
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<tr>
<td>BS</td>
<td>20</td>
<td>9827/18020</td>
<td>1.00 (0.88-1.12) R</td>
<td>1.01 (0.81-1.26) F</td>
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<td>1.01 (0.81-1.27) F</td>
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<tr>
<td>rs3856806</td>
<td>Overall</td>
<td>11</td>
<td>0.91 (0.75-1.11) R</td>
<td>1.14 (0.71-1.85) R</td>
<td>0.83 (0.67-1.02) R</td>
<td>1.19 (0.75-1.89) R</td>
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<tr>
<td>SA based on ethnicity</td>
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<tr>
<td>Caucasian</td>
<td>4</td>
<td>2679/5121</td>
<td>1.07 (0.84-1.37) R</td>
<td>1.72 (1.12-2.66) F</td>
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<td>1.71 (1.11-2.62) F</td>
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<tr>
<td>Asian</td>
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<td>1910/1820</td>
<td>0.80 (0.64-0.99) R</td>
<td>0.87 (0.50-1.51) R</td>
<td>0.70 (0.62-0.81) F</td>
<td>0.63 (0.47-0.84) F</td>
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<td>SA based on type of diseases</td>
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<td></td>
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<tr>
<td>CAD</td>
<td>8</td>
<td>2480/2102</td>
<td>0.78 (0.64-0.95) R</td>
<td>0.67 (0.51-0.88) F</td>
<td>0.69 (0.61-0.79) F</td>
<td>0.92 (0.54-1.57) R</td>
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<td>MI</td>
<td>1</td>
<td>146/146</td>
<td>1.35 (0.95-1.92) F</td>
<td>2.68 (1.10-6.54) F</td>
<td>1.25 (0.79-1.98) F</td>
<td>2.58 (1.09-6.10) F</td>
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<tr>
<td>Sensitivity analysis</td>
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<td></td>
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<tr>
<td>BH</td>
<td>7</td>
<td>2762/5481</td>
<td>1.12 (1.01-1.25) F</td>
<td>1.70 (1.18-2.45) F</td>
<td>1.00 (0.80-1.24) R</td>
<td>1.69 (1.17-2.42) F</td>
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<tr>
<td>BS</td>
<td>10</td>
<td>4342/6727</td>
<td>0.93 (0.75-1.15) R</td>
<td>1.18 (0.69-2.00) R</td>
<td>0.85 (0.68-1.06) R</td>
<td>1.20 (0.72-2.00) R</td>
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</tbody>
</table>

M: model, F: fixed effects model, R: random effects model, SNP: single nucleotide polymorphism, SA: Subgroup analysis, BH: based on HWE (studies without HWE were excluded), BS: based on score (studies with score ≤ 6 were excluded), CAD: coronary artery disease, MI: myocardial infarction, IS: ischemic stroke, Others: other atherosclerotic diseases.
As shown in Table 2, there was no evidence of a significant association between the rs1801282 gene polymorphism and susceptibility to atherosclerotic disease (for the allelic model: OR=1.00, 95%CI=0.89-1.12; for the additive model: OR=1.02, 95%CI=0.82-1.27; for the dominant model: OR=1.00, 95%CI=0.88-1.13; and for the recessive model: OR=1.02, 95%CI=0.82-1.27) (Fig. 2). No significant associations were found in the meta-analysis performed to assess the association between the rs1801282 gene polymorphism and atherosclerotic diseases based on ethnicity and the type of disease.

As shown in Table 2, there was no evidence of a significant association between the rs3856806 polymorphism and atherosclerotic diseases (for the allelic model: OR=0.91, 95%CI=0.75-1.11; for the additive model: OR=1.14, 95%CI=0.71-1.85; for the dominant model: OR=0.83, 95%CI=0.67-1.02; and for the recessive model: OR=1.19, 95%CI=0.75-1.89) (Fig. 3). According to the meta-analysis performed to assess the association between the rs3856806 gene polymorphism and atherosclerotic
For rs1801282, significant heterogeneity was detected in the allelic model (I² = 63.2%) and dominant model (I² = 62.8%), but not the additive model (I² = 27.4%) or recessive model (I² = 24.4%). In order to clarify the source of heterogeneity, we performed subgroup and sensitivity analyses. Heterogeneity was removed in the analyses of the Asian subgroup, CAD subgroup and IS subgroup (Table 2). We next created a Galbraith plot to graphically assess the source of the heterogeneity. Five studies17, 20, 25, 32, 39 were identified as the main contributors of heterogeneity for all genetic models. In addition, one study by Zafarmand et al.26 was identified as a contributor of heterogeneity for all allelic models, and two studies18, 36 were identi-
The PPAR γ gene spans approximately 100 kb, is located on chromosome 3p25 and contains nine exons, with exons 1-6 being the common region. The most studied SNP of PPAR γ is rs1801282 (Pro12Ala), and the next most frequently occurring PPAR γ polymorphism is rs3856806 (C161T). Many studies have explored the association between rs1801282/rs3856806 and atherosclerotic disease, with contradictory conclusions. Considering that atherosclerosis is a pathological process related to coronary artery disease, myocardial infarction, ischemic cerebrovascular events and peripheral arterial disease, we conducted the current meta-analysis to further understand the association between PPAR γ polymorphisms and the risk of atherosclerotic diseases.

For rs3856806, significant heterogeneity was present in the allelic model ($I^2 = 80.8\%$), additive model ($I^2 = 67.0\%$), dominant model ($I^2 = 77.2\%$) and recessive model ($I^2 = 65.2\%$). In order to clarify the source of heterogeneity, we performed subgroup and sensitivity analyses. Consequently, heterogeneity was partly removed in the subgroup analyses based on ethnicity and the type of disease (Table 2). We next created a Galbraith plot to graphically assess the source of the heterogeneity. As a result, five studies$^{15, 28, 32, 34, 37}$ were identified as the main contributors of heterogeneity for the allelic models, two studies$^{15, 37}$ were identified as the main contributors of heterogeneity for the additive and recessive models and four studies$^{11, 28, 32, 37}$ were identified as contributors of heterogeneity for the dominant model (Fig. 7).

**Discussion**

The PPAR γ gene spans approximately 100 kb, is located on chromosome 3p25 and contains nine exons, with exons 1-6 being the common region. The most studied SNP of PPAR γ is rs1801282 (Pro12Ala), and the next most frequently occurring PPAR γ polymorphism is rs3856806 (C161T). Many studies have explored the association between rs1801282/rs3856806 and atherosclerotic disease, with contradictory conclusions. Considering that atherosclerosis is a pathological process related to coronary artery disease, myocardial infarction, ischemic cerebrovascular events and peripheral arterial disease, we conducted the current meta-analysis to further understand the association between PPAR γ polymorphisms and the risk of atherosclerotic diseases. Overall, no significant associations were found between the PPAR γ gene rs1801282/rs3856806 polymorphism and the risk of...
diseases have been studied. In particular, the Pro allele may be associated with an increased risk of diabetic nephropathy and inflammatory bowel disease (56-58). Concerning atherosclerotic diseases, controversial conclusions from several meta-analyses have been reported (40, 41, 43). Two studies showed that the Pro-12Ala polymorphism is not associated with coronary heart disease susceptibility (40, 43), whereas another meta-analysis demonstrated that the Pro12Ala polymorphism may be a risk-conferring locus for the progression of coronary artery disease in Caucasians (41). However, the association between the Pro12Ala polymorphism and coronary heart disease is insufficient to confirm the association between the Pro12Ala polymorphism and the total risk of atherosclerotic diseases. The present study, including studies related to all types of atherosclerotic disease, showed no evidence of a significant association between the Pro12Ala polymorphism and atherosclerotic diseases when all studies were pooled in the meta-analysis. In order to conduct a more comprehensive analysis of the PPARγ gene rs1801282/rs385680 polymorphism and the risk of atherosclerotic diseases, subgroup analyses were performed. In the subgroup analyses based on ethnicity and the type of disease, significant associations were found in the Caucasian, Asian, CAD and MI subgroups in rs385680, but not rs1801282.

The rs1801282 (Pro12Ala) mutation of PPARγ is a single nucleotide polymorphism of G to C variation at position +34 in the PPARγ specific exon B (9). Consequently, the PPARγ2 protein is modified at position 12 with alanine substituting a proline residue (this SNP is also known as Pro12Ala) (9). It has been reported that this mutation may cause a conformational change in the PPARγ protein and consequently a reduced transcriptional activity (7, 55). Moreover, the associations between the above mutation and various diseases may be associated with an increased risk of diabetic nephropathy and inflammatory bowel disease (56-58). Concerning atherosclerotic diseases, controversial conclusions from several meta-analyses have been reported (40, 41, 43). Two studies showed that the Pro12Ala polymorphism is not associated with coronary heart disease susceptibility (40, 43), whereas another meta-analysis demonstrated that the Pro12Ala polymorphism may be a risk-conferring locus for the progression of coronary artery disease in Caucasians (41). However, the association between the Pro12Ala polymorphism and coronary heart disease is insufficient to confirm the association between the Pro12Ala polymorphism and the total risk of atherosclerotic diseases. The present study, including studies related to all types of atherosclerotic disease, showed no evidence of a significant association between the Pro12Ala polymorphism and atherosclerotic diseases in the overall

Fig. 5. Funnel plots of all models for rs3856806 in the overall analysis. A. allelic model (T allele vs. C allele); B. additive model (T/T vs. C/C); C. dominant model (C/T + T/T vs. C/C); and D. recessive model (T/T vs. C/T + C/C). se: standard error; OR: odds ratio.
Another frequently occurring PPARγ polymorphism is rs3856806 (C161T), which involves a silent substitution from C to T in exon 6. Among the included studies, four studies reported that the T allele protects against the risk of CAD: one study showed that the frequency of the TT genotype is significantly higher among patients with acute myocardial infarction than in controls and one study demonstrated that the TT genotype is associated with increased abdominal aortic aneurysm growth. The current study provided no evidence of a significant association between the rs3856806 polymorphism and atherosclerotic diseases. However, significant associations were found in the subgroup analysis based on ethnicity. In particular, the present results showed that the T allele increased the risk of atherosclerotic disease by 1.71- to 1.72-fold compared with the C allele in the Caucasian subgroup and T allele reduced the risk of AS by 20%-37% in the Asian subgroup. Similarly, the T allele was shown to protect against the risk of CAD, while increasing the risk of MI.

The data presented above raise the question as to the reasons for the contradictory results between the Caucasian and Asian subgroups and the different AS subtypes. A potential explanation for the difference between the Caucasian subgroup and the Asian subgroup may be ethnic differences. Genetic diversity of the C161T polymorphism plays an important role in the etiology of atherosclerosis across various ethnic populations. In addition, environmental factors play important roles in the etiology of AS. Therefore, the differences noted between the Caucasian and Asian subgroups in this study may also be due to the varied geographic distribution, linked to factors related to analysis as well as the subgroup analyses based on ethnicity and the type of disease.

Fig. 6. Galbraith plots for rs1801282 in the overall analysis. A. allelic model (Ala allele vs. Pro allele); B. additive model (Ala/Ala vs. Pro/Pro); C. dominant model (Pro/Ala + Ala/Ala vs. Pro/Pro); and D. recessive model (Ala/Ala vs. Pro/Ala + Pro/Pro). The outlier dots indicate the main contributors to heterogeneity.
found in the recessive model of rs3856806, the results regarding the association between the rs3856806 polymorphism and atherosclerotic diseases should be interpreted with caution.

Nonetheless, the results of the current meta-analysis including high-quality studies suggest that there is no statistical evidence of a significant association between the PPARγ gene rs1801282/rs3856806 polymorphism and atherosclerotic diseases. The rs3856806 polymorphism was associated with an increased risk in the Caucasian and MI subgroups, whereas a decreased risk was observed in the Asian and CAD subgroups. Nevertheless, due to significant between-study heterogeneity, further studies with a larger sample size involving a homogeneous AS patient population and well-matched controls are required in the future.

climate, diet, lifestyle and economic status. With respect to the discrepant results for the different AS subtypes, this finding may be due to the small sample size in the MI subgroup, which may have increased the probability of false-positives or -negatives. Hence, further large-scale well designed studies are required.

Several limitations of this study should be taken into consideration when interpreting the results. First, a meta-analysis is a type of retrospective study, and recall and selection bias may inevitably exist. Second, there was significant between-study heterogeneity among the included studies. Heterogeneity may affect the precision of the results, despite the use of appropriate meta-analytic techniques with a random-effects model. Further studies, in which the atherosclerotic diseases and controls are well-defined, are warranted. Third, as statistical evidence of publication bias was
Conflicts of Interest

None.

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