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Original Article

Association between gene polymorphisms on chromosome 7 and the risk of ischemic stroke: a meta-analysis

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Abstract: Background: Ischemic stroke (IS) caused by thrombotic or the decrease of cerebral blood flow is one of the most prevalent health problems over the world. The cause of IS has not been clarified yet, but many risk factors have been confirmed to be associated with the pathogenesis and prognosis of IS. In this study we conducted a meta-analysis on studies concerning *Interleukin 6 (IL-6), NOS3, PON* and *SERPINE1* polymorphisms and IS susceptibility. Methods: PubMed, Medline, and Embase databases were searched for relevant articles. The pooled odds ratios (ORs) with their corresponding 95% confidence intervals (95% CIs) under five genetic models were calculated to evaluated the relations between 4 candidate genes and the risk of IS. The heterogeneity among studies was assessed by chi-square test and the statistic of I^2. Subgroup analyses were performed based on ethnicity and all statistical tests were conducted by R 3.1.2 software. Result: A total of 149 published studies were selected, which consisted of 33,758 IS cases and 56,298 control subjects. For *NOS3* gene, rs1799983 and rs61722009 increased the susceptibility to IS while rs662 of *PON1* gene and rs12026 of *PON2* gene decreased the risk of IS. No significant association was detected between rs7493 of *PON2*, rs854560 of *PON1* and IS risk. Conclusion: This meta-analysis demonstrated that the *NOS3* gene rs1799983 and rs61722009 polymorphisms, the *PON1* gene rs662 polymorphism, and the *PON2* gene rs12026 polymorphism might be associated with ischemic stroke overall.

Keywords: Ischemic stroke, *Interleukin 6 (IL-6)*, *NOS3*, *PON*, *SERPINE1*, meta analysis

Introduction

Stroke ranks first among reasons for disability and ranks second among causes for mortality globally [1]. A substantial increased incidence rate was detected from 1990 to 2013 for younger adults worldwide, although the mortality rate was declined [2]. Ischemic stroke (IS) accounts for up to 79% of the stroke cases in China [3]. In addition, there are almost no effective treatments for IS patients apart from thrombolysis with the utilization of recombinant tissue-type plasminogen activator (rtPA) [4]. Therefore, it is important and urgent to prevent the occurrence of IS through the alteration of risk factors.

Current researches show that IS is caused by thrombotic or the decrease in cerebral blood flow [5, 6]. However, the etiology of IS has not been fully illuminated. There are some factors are recognized, such as physical activity, smoking, diabetes, obesity, atrial fibrillation and high blood pressure [7, 8]. However, it does not explain all of the IS etiology. In recent years, a large number of gene polymorphisms were researched. Some stroke susceptibility gene (like *Interleukin-6*, *NOS3*, *PON*, *SERPINE1*) polymorphisms on chromosome 7 have attracted our attention.

The *IL-6* gene is located on chromosome 7p21. Interleukin-6 (IL-6) is a proinflammatory and immunoregulatory protein, which plays an important role in the inflammatory response. And an increased level of IL-6 has been reported to be associated with a worse prognosis in IS patients [9, 10]. The NOS3 gene is located on chromosome 7q35-36. And nitric oxide generated from NO synthase (NOS) has a significant effect on vascular wall [11]. The PON1 and PON2 genes map to chromosome 7q21.3. It

was known that the oxidized low-density lipoprotein (LDL) could increase atherosclerosis, and high-density lipoprotein (HDL) is regarded as one of the most important protective factors against arteriosclerosis due to its active participation in the reverse transportation of cholesterol and its ability to prevent lipid peroxidation. Paraoxonase (PON) is a unique family of calcium-dependent hydrolases, which preserves the function of HDL and protects LDL from oxidation [12, 13]. The SERPINE1 or PAI-1 gene is located in chromosome 7q22.1. Plasminogen activator inhibitors (PAIs) play a role in the regulation of plasminogen activators that convert plasminogen into plasmin.

At present, many studies were aimed to investigate the association between this polymorphism and IS, but showed contradictory results. Therefore, to evaluate the association between the gene polymorphisms on chromosome 7 (*Interleukin 6*, *NOS3*, *PON* and *SERPINE1*) and IS, we performed this meta-analysis, which had a more powerful statistical power and could draw a more responsible conclusion.

Materials and methods

Search strategy and study selection

A literature search for eligible articles was carried out in the following electronic databases: PubMed, Medline and Embase (updated to September 12, 2015). The searching strategy consisted of the following key words and their corresponding synonyms: ("IL-6" OR "Interleukin-6") AND ("endothelial nitric oxide synthase" OR "NOS3"OR "eNOS") AND ("paraoxonase" OR "PON") AND ("plasminogen activator inhibitor-1" OR "PAI-1" OR "SERPINE1") AND ("ischaemic stroke" OR "cerebral infarction" OR "IS") AND ("genetic polymorphism" OR "single nucleotide polymorphisms" OR "SNP"). Furthermore, the process of literature search was conducted without any language restriction and only studies on human subjects were considered to be eligible. Besides that, all eligible articles were extensively reviewed in order to ensure the completeness of the studies to be included in the meta-analysis. This meta-analysis was carried out according to guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [14].

Inclusion and exclusion criteria

The following inclusion criteria was set to determine whether studies should be included in the meta-analysis: (1) Case-control studies investigating associations between the four genetic polymorphisms on chromosome 7 and IS susceptibility; (2) All patients in the study must be diagnosed with IS by consistent criteria; (3) Studies must contain full text for review; (4) There were adequate data for calculating odds ratios (ORs) and the corresponding 95% confidence intervals (95% CIs); (5) Human studies was selected. The followings studies were excluded: (1) duplicated publication of the same research; (2) non case-control studies or studies contained data that did not conform to the Weinberg Hardy equilibrium; (3) studies without sufficient data for assessment (4) meta-analyses, editorials or other articles that did not involve primary studies. If overlapping case-control data was contained in multiple studies, then the latest study with the largest sample size was selected in our meta-analysis.

Data extraction

Data were carefully extracted from all qualified studies by two independent reviewers and any disagreement between them was resolved by discussion. The following relevant information was extracted from all included studies: name of the first author, publication date, original country that the study involved, ethnicity (Caucasian, Asian, African), number of cases and controls, characteristics of subjects, genetic variants involved, methods for genotyping, distributions of genotypes, results of Hardy-Weinberg equilibrium (HWE) testing, IS subtype (if reported). In addition, genotype frequencies were calculated in the case that allelic frequencies were given by studies. When different ethnic groups were contained in the included studies, then data were separately extracted.

Quality assessment

The methodological quality of the eligible studies for the four genes (*Interleukin 6, NOS, PON, SERPINE1*) was independently evaluated according to the Newcastle-Ottawa Scale (NOS) [15]. Three main aspects of the study were assessed (selection, comparability, and exposure) by the NOS which consisted of 9 core

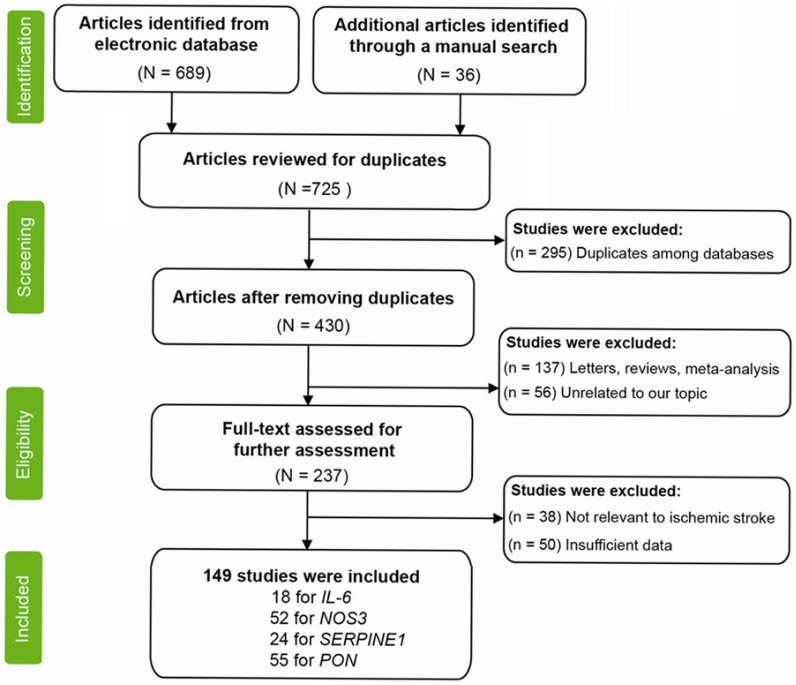

Figure 1. Literature selection flow chart.

assessment questions. Each satisfactory answer received one score and each study had a maximum score of 9. Studies with at least 6 scores were considered to be of high quality [16].

Statistical analysis

Our meta-analysis was complied with a standard which specifies that each polymorphism should contain at least 3 studies. The Chi-squared test was used to assess whether genotype frequency distributions of the control group were complied with HWE [17]. The associations between four candidate gene (*Interleukin 6, NOS3, PON*, *SERPINE1*) polymorphisms and the susceptibility to IS were evaluated by the pooled odds ratios (ORs) along with their corresponding 95% confidence intervals (95% CIs) under five genetic models (allelic, dominant, recessive, homozygous, heterozygous). The random-effects model or the fixed-effect model was adopted to calculate the pooled ORs and their corresponding 95% CI. Potential between-study heterogeneity among studies was evaluated by the chi-square test and the statistic of I^2 [18-21]. If *P*-value < 0.05 and I^2 > 50%, then significant heterogeneity was suggested. As a result of this, a pooled OR was estimated by the random-effects model due to the presence of significant heterogeneity [22], otherwise the fixed-effect model was adopted in the meta-analysis [23]. Subgroup analyses were performed by ethnicity (Caucasian, Asian, and African). Besides that, significant publication bias was detected by the funnel plot and a *P*-value < 0.05 indicated significant publication bias [24]. All statistical analyses were conducted by R software (version 3.1.2) and the significant level was set at two-sided *P* < 0.05.

Results

Included studies and quality assessment

The initial searching strategy identified 725 studies of which 295 duplicated publications were excluded. As a result of this, 430 research studies were subject to the review of titles and abstracts. We further removed 193 studies which included 137 reviews, letters and meta-analyses together with 56 irrelevant studies. As a result, a total of 101 articles which contained 149 studies were included by full-text review after the exclusion of 38 unrelated studies and 50 studies without sufficient data. The detailed information of the included studies was listed in Table S1 and the entire article retrieval and selection process was presented in **Figure 1**.

As suggested by Table S2, our meta-analysis incorporated a total of 149 case-control studies with 33,758 IS cases and 56,298 non-cases. These studies covered four genes including ten gene polymorphisms and their detailed characteristics were presented in Table S2. The case group contained patients with IS confirmed by CT and/or MRI. Genotype distributions of the control group were all complied with HWE and the NOS quality assessment suggested that all 149 studies scored more than 6 and therefore they were considered to be of high quality.

Table 1. Meta analysis of ten polymorphisms and ischemic stroke susceptibility

Gene	SNP	Genetic model[1]	OR [95% CI][2]	P_{OR}[3]	Tau[2]	I^2	P_{HET}[4]	Ethnicity			$P_{publication\ bias}$
								Caucasian	Asian	African	
SERPINE1	rs1799889	**5G** vs. 4G	0.88 [0.77, 1.00]	0.074	0.118	84.43%	0.000	0.99 [0.89, 1.10]	**0.70 [0.54, 0.91]***	1.37 [0.96, 1.94]	0.137
		5G5G vs. 4G4G	0.82 [0.65, 1.04]	0.117	0.294	76.37%	0.000	0.97 [0.79, 1.19]	**0.56 [0.34, 0.92]***	1.97 [0.95, 4.07]	0.227
		5G5G+4G **5G** vs. 4G4G	0.81 [0.67, 1.00]	0.067	0.267	83.90%	0.000	1.01 [0.84, 1.22]	**0.54 [0.36, 0.80]***	**1.87 [1.03, 3.42]***	0.119
		5G5G vs. 4G4G +4G**5G**	0.91 [0.79, 1.05]	0.168	0.013	15.85%	0.014	0.95 [0.84, 1.08]	0.80 [0.58, 1.12]	1.29 [0.73, 2.28]	0.580
		4G**5G** vs. 4G4G	0.82 [0.67, 1.00]	0.063	0.221	79.28%	0.000	0.95 [0.84, 1.08]	0.80 [0.58, 1.12]	1.29 [0.73, 2.28]	0.137
IL6	rs1800795	**C** vs. G	0.87 [0.70, 1.09]	0.263	0.212	87.83%	0.000	0.80 [0.61, 1.04]	1.22 [0.99, 1.49]	-	0.674
		CC vs. GG	0.70 [0.43, 1.14]	0.163	0.794	84.78%	0.000	0.65 [0.38, 1.12]	1.41 [0.95, 2.11]	-	0.675
		CC+G**C** vs. GG	0.86 [0.68, 1.10]	0.270	0.241	80.85%	0.000	0.77 [0.58, 1.03]	**1.27 [1.00, 1.61]***	-	0.361
		CC vs. GG+G**C**	0.76 [0.51, 1.14]	0.191	0.506	80.87%	0.000	0.72 [0.46, 1.13]	1.32 [0.90, 1.94]	-	0.746
		G**C** vs.GG	0.92 [0.77, 1.11]	0.394	0.088	57.92%	0.002	0.72 [0.46, 1.13]	1.32 [0.90, 1.94]	-	0.295
NOS3	rs1799983	**T** vs. G	**1.32 [1.10, 1.57]***	0.004	0.125	84.92%	0.000	1.00 [0.84, 1.19]	**1.54 [1.18, 2.01]***	**1.97 [1.59, 2.43]***	0.342
		TT vs. GG	**1.64 [1.11, 2.43]***	0.019	0.467	76.66%	0.000	1.09 [0.79, 1.51]	**2.13 [1.00, 4.54]***	**3.48 [2.19, 5.51]***	0.477
		TT+GT vs. GG	**1.38 [1.09, 1.74]***	0.021	0.287	88.88%	0.000	0.94 [0.72, 1.23]	**1.71 [1.20, 2.42]***	**2.51 [1.86, 3.39]***	0.392
		TT vs. GG+GT	**1.43 [1.05, 1.94]***	0.036	0.254	66.80%	0.001	1.12 [0.87, 1.43]	1.63 [0.84, 3.19]	**2.24 [1.16, 3.42]***	0.489
		GT vs.GG	**1.31 [1.04, 1.66]***	0.060	0.298	88.39%	0.000	1.12 [0.87, 1.43]	1.63 [0.84, 3.19]	**2.24 [1.46, 3.42]***	0.525
	rs2070744	**T** vs. C	0.96 [0.88, 1.05]	0.453	0.016	34.89%	0.089	**1.18 [1.01, 1.38]***	0.91 [0.81, 1.03]	**0.77 [0.62, 0.97]***	0.509
		TT vs. CC	0.75 [0.48, 1.16]	0.212	0.311	53.35%	0.020	1.38 [0.96, 1.99]	**0.51 [0.28, 0.93]***	0.60 [0.36, 1.00]	0.425
		TT+C**T** vs. CC	0.72 [0.48, 1.10]	0.143	0.267	51.10%	0.026	1.28 [0.91, 1.79]	**0.49 [0.27, 0.91]***	0.65 [0.40, 1.07]	0.333
		TT vs. CC+C**T**	0.98 [0.89, 1.09]	0.853	0.026	37.82%	0.059	1.22 [0.99, 1.51]	0.95 [0.84, 1.09]	0.76 [0.57, 1.01]	0.892
		CT vs.CC	0.67 [0.43, 1.06]	0.102	0.351	55.50%	0.015	1.28 [0.92, 1.77]	0.95 [0.82, 1.10]	0.76 [0.57, 1.01]	0.356
	rs61722009	**4a** vs. 4b	1.11 [0.90, 1.38]	0.299	0.120	71.72%	0.000	0.93 [0.60, 1.43]	1.16 [0.89, 1.53]	1.23 [0.93, 1.63]	0.127
		4a4a vs. 4b4b	**2.23 [1.61, 3.10]***	0.037	0.407	40.22%	0.104	0.59 [0.19, 1.79]	**2.88 [1.87, 4.44]***	1.71 [0.72, 4.01]	0.200
		4a4a +4b**4a** vs. 4b4b	1.09 [0.88, 1.36]	0.403	0.116	65.97%	0.000	0.94 [0.58, 1.52]	1.13 [0.85, 1.49]	1.21 [0.88, 1.68]	0.133
		4a4a vs. 4b4b+4b**4a**	**2.07 [1.49, 2.88]***	0.036	0.306	33.96%	0.177	0.60 [0.20, 1.82]	**2.54 [1.66, 3.89]***	1.64 [0.70, 3.85]	0.280
		4b**4a** vs. 4b4b	1.06 [0.87, 1.28]	0.566	0.076	54.27%	0.004	0.60 [0.17, 2.11]	**2.46 [1.35, 4.48]***	1.64 [0.70, 3.85]	0.144
	rs1800779	**A** vs. G	0.90 [0.52, 1.57]	0.705	0.194	82.82%	0.003	1.56 [1.06, 2.29]*	**0.68 [0.51, 0.90]***	-	0.901
		AA vs. GG	0.72 [0.24, 2.14]	0.550	0.577	66.68%	0.042	1.85 [0.80, 4.28]	**0.41 [0.18, 0.93]***	-	0.159
		AA+G**A** vs. GG	0.80 [0.46, 1.39]	0.438	0.301	51.82%	0.124	1.44 [0.64, 3.25]	**0.44 [0.19, 0.99]***	-	0.063
		AA vs. GG+G**A**	0.95 [0.51, 1.77]	0.875	0.251	81.49%	0.005	**1.82 [1.11, 2.97]***	**0.69 [0.50, 0.95]***	-	0.616
		G**A** vs.GG	0.74 [0.41, 1.35]	0.345	0.000	0.00%	0.603	0.94 [0.86, 1.04]	1.03 [0.82, 1.30]	-	0.137
PON1	rs662	**A** vs. G	**0.85 [0.79, 0.92]***	0.000	0.020	49.28%	0.002	1.01 [0.93, 1.09]	**0.78 [0.71, 0.85]***	-	0.150
		AA vs. GG	**0.73 [0.60, 0.88]***	0.002	0.153	58.86%	0.000	0.98 [0.80, 1.22]	**0.62 [0.48, 0.79]***	-	0.135
		AA+G**A** vs. GG	**0.85 [0.76, 0.96]***	0.006	0.032	37.47%	0.020	**1.00 [0.70, 0.92]***	**0.80 [0.70, 0.92]***	-	0.412
		AA vs. GG+G**A**	**0.82 [0.72, 0.94]***	0.004	0.068	55.75%	0.000	1.01 [0.90, 1.15]	**0.69 [0.57, 0.83]***	-	0.110
		G**A** vs.GG	**0.90 [0.83, 0.98]***	0.036	0.008	12.04%	0.164	1.02 [0.91, 1.13]	**0.71 [0.63, 0.81]***	-	0.572
	rs854560	**T** vs. A	1.04 [0.95, 1.14]	0.349	0.000	0.00%	0.341	1.06 [0.96, 1.17]	0.97 [0.77, 1.22]	-	0.882
		TT vs. AA	1.12 [0.91, 1.37]	0.293	0.016	8.68%	0.651	1.16 [0.94, 1.44]	0.68 [0.28, 1.69]	-	0.888

		TT+**AT** vs. AA	1.09 [0.93, 1.28]	0.280	0.000	0.00%	0.768	1.11 [0.94, 1.32]	0.67 [0.27, 1.63]	-	0.850
		TT vs. AA+**AT**	1.03 [0.90, 1.17]	0.609	0.000	0.01%	0.485	1.05 [0.90, 1.22]	0.99 [0.77, 1.28]	-	0.749
		AT vs. AA	1.08 [0.90, 1.28]	0.415	0.000	0.00%	0.859	1.05 [0.90, 1.22]	0.99 [0.77, 1.28]	-	0.696
PON2	rs7493	**G** vs. C	1.06 [0.93, 1.21]	0.344	0.012	39.77%	0.045	1.06 [0.95, 1.19]	1.08 [0.82, 1.42]	-	0.899
		GG vs. CC	1.06 [0.73, 1.52]	0.809	0.084	36.04%	0.050	0.98 [0.65, 1.48]	1.23 [0.59, 2.56]	-	0.252
		G**G**+**GC** vs. CC	1.09 [0.90, 1.32]	0.392	0.046	55.72%	0.038	1.13 [0.96, 1.35]	1.04 [0.71, 1.54]	-	0.953
		GG vs. CC+C**G**	1.03 [0.87, 1.22]	0.823	0.005	6.52%	0.109	0.98 [0.79, 1.20]	1.14 [0.85, 1.51]	-	0.939
		C**G** vs.CC	1.12 [1.00, 1.27]	0.332	0.032	44.75%	0.065	0.98 [0.79, 1.20]	1.14 [0.85, 1.51]	-	0.614
	rs12026	**G** vs. C	**0.85 [0.75, 0.97]***	0.092	0.000	0.00%	0.745	**0.85 [0.73, 0.98]***	0.89 [0.67, 1.19]	-	0.656
		GG vs. CC	0.69 [0.46, 1.02]	0.063	0.000	0.00%	0.658	0.66 [0.43, 1.03]	0.80 [0.33, 1.99]	-	0.841
		GG+**GC** vs. CC	**0.85 [0.73, 0.99]***	0.193	0.000	0.00%	0.838	0.84 [0.71, 1.00]	0.87 [0.62, 1.23]	-	0.376
		GG vs. CC+C**G**	0.68 [0.46, 1.01]	0.081	0.000	0.00%	0.674	0.65 [0.42, 1.00]	0.84 [0.34, 2.06]	-	0.782
		C**G** vs.CC	0.93 [0.79, 1.09]	0.366	0.000	0.00%	0.899	0.65 [0.42, 1.00]	0.84 [0.34, 2.06]	-	0.179

1. Bold letters: mutation allele. 2. Pooled odds ratios and 95% confidence intervals. 3. OR: odds ratio. 4. HET: heterogeneity. 5. *Indicates statistically significant correlations.

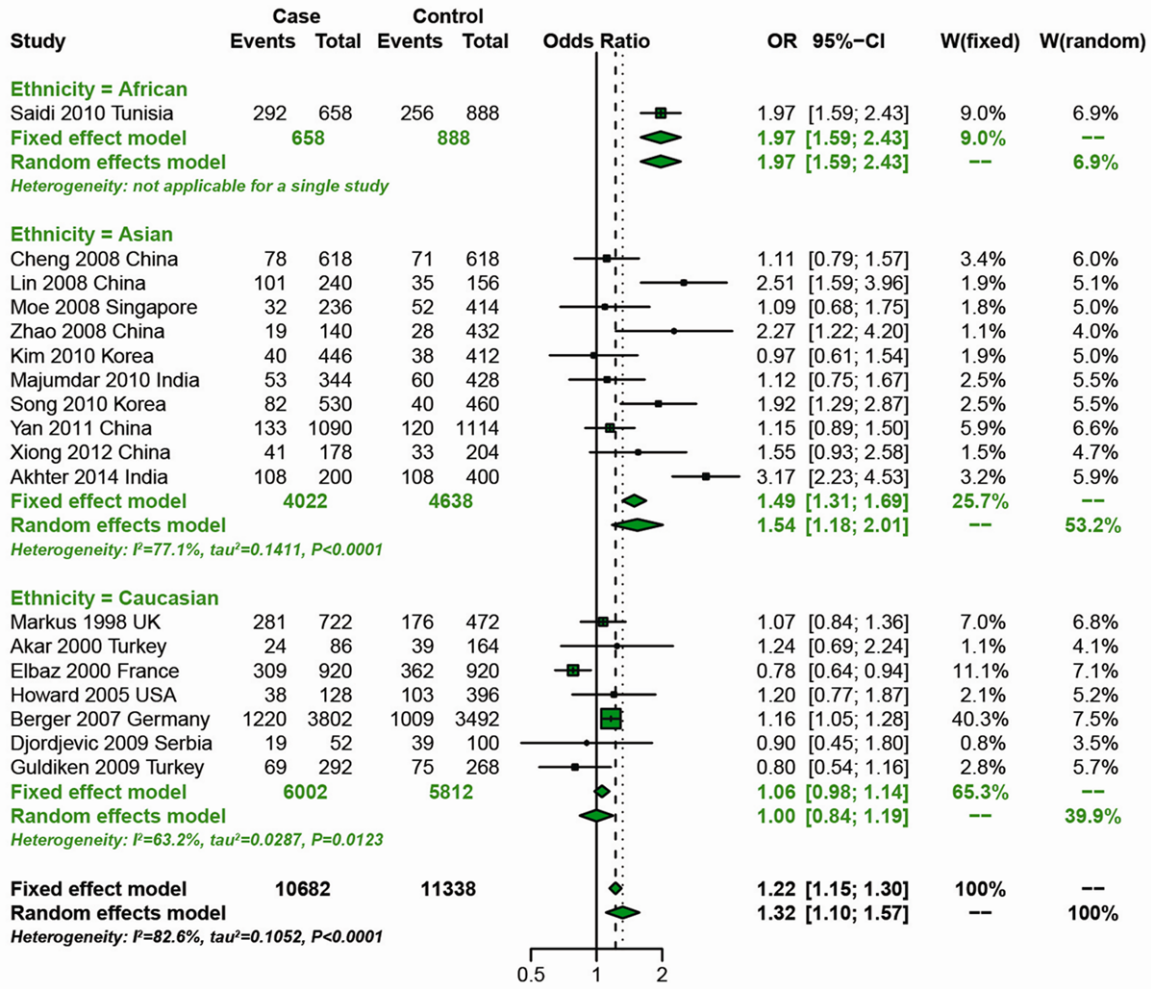

Figure 2. Forest plot of rs1799983 in *NOS3* gene under allelic model.

Summary results from meta-analysis

Table 1 suggested that four of the ten gene polymorphisms were significantly associated with an altered risk of IS under five models (dominant, recessive, homozygous, heterozygous, allelic). The T allele of rs1799983 was significant associated with an increased risk of IS under the five genetic models (dominant: OR = 1.38, 95% CI = 1.09-1.74; recessive: OR = 1.43, 95% CI = 1.05-1.94; homozygous: OR = 1.64, 95% CI = 1.11-2.43; heterogeneity: OR = 1.31, 95% CI = 1.04-1.66; allelic: OR = 1.32, 95% CI = 1.10-1.57) (**Figure 2**). Furthermore, the intron 4 VNTR polymorphism of *NOS3* (rs61722009) was significantly associated with a 123% increase in the risk of IS under the homozygous model (**Figure 3**, OR = 2.23, 95% CI = 1.61-3.10, *P* = 0.037). Apart from that, the G allele of rs662 was significantly associated with a decreased risk of IS under the allelic model (**Figure 4**, OR = 0.85, 95% CI = 0.79-0.92, *P* = 0.02). The rs12026 C polymorphism site was significantly associated with an increased risk of IS compared to G under the allelic model (**Figure 5**, OR = 2.23, 95% CI = 1.61-3.10, *P* = 0.0037). The overall analyses also indicated that rs1799889, rs1800795, rs2070744, rs1800779, rs854560 and rs7493 polymorphism did not have significant association with the risk of IS under the allelic model (Figures S1, S2, S3, S4, S5, S6, rs1799889: OR = 0.88, 95% CI = 0.77-1.00, rs1800795: OR = 0.87, 95% CI = 0.70-1.09, rs2070744: OR = 0.96, 95% CI = 0.88-1.05, rs1800779: OR = 0.96, 95% CI = 0.88-1.05, rs854560: OR = 1.04, 95% CI = 0.9-1.14, rs7493: OR = 1.06, 95% CI = 0.93-1.21).

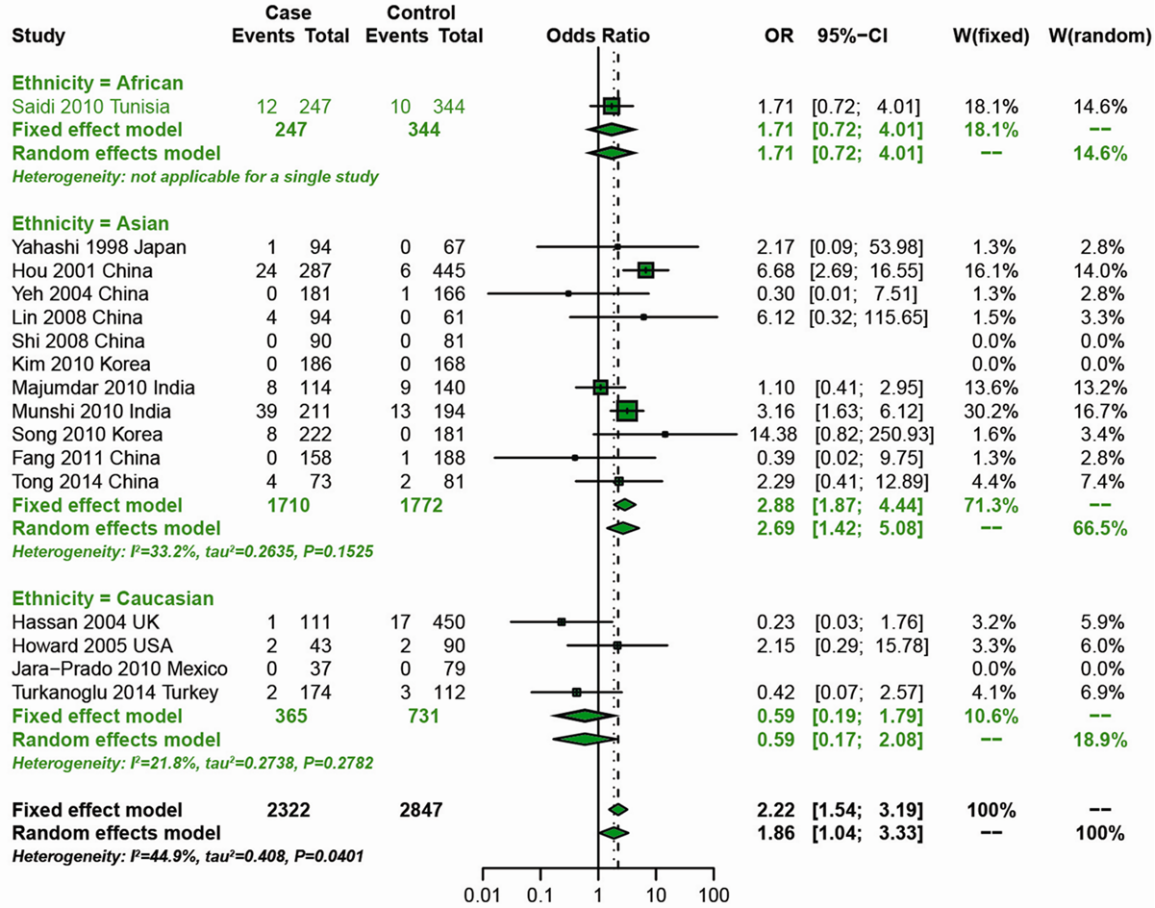

Figure 3. Forest plot of rs61722009 in *NOS3* gene under homozygote model.

Subgroup analyses

As suggested by subgroup analyses based on ethnicity (Caucasian, Asian, African), for *SERPINE1*, 5G was a protective factor in Asian (OR, 95% CI: 0.70, 0.54-0.91), while it was associated with an increased risk of IS in African (OR, 95% CI: 1.87, 1.03-3.42). For *IL6*, the C allele was a risk factor in Asian (OR, 95% CI: 1.27, 1.00-1.61). For *NOS3*, the T allele of rs1799983 was significantly associated with an increased risk of IS in both Asian and African (OR, 95% CI: 1.54, 1.18-2.01; OR, 95% CI: 1.97, 1.59-2.43). Moreover, the T allele of rs2070744 was associated with an increased risk of IS in Caucasian (OR, 95% CI: 1.18, 1.01-1.38), whereas it was significantly associated with a reduced risk of IS in both Asian and African (OR, 95% CI: 0.51, 0.28-0.93; OR, 95% CI: 0.77, 0.62-0.97). We also discovered that the 4a allele of rs6172009 was significantly associated with an increased risk of IS in Asian (OR, 95% CI: 2.88, 1.87-4.44). On top of that, the A allele of rs1800779 had significant association with an increased risk of IS in Caucasian (OR, 95% CI: 1.56, 1.06-2.29), whereas it was associated with a reduced risk of IS in Asian (OR, 95% CI: 0.68, 0.51-0.90). For *PON1*, the A allele of rs662 was significantly associated with a reduced risk of IS in Asian (OR, 95% CI: 0.62, 0.48-0.79) and the G allele of rs12026 for *PON2* was also associated with a 15% decrease in the risk of IS in Caucasian (OR, 95% CI: 0.85, 0.73-0.98).

Heterogeneity test and publication bias

Potential publication bias was assessed by the funnel plot. As suggested by **Table 1**; **Figures 6** and S7, there was no significant publication bias presented for all gene polymorphisms involved in our meta-analysis (all *P*-value > 0.05)

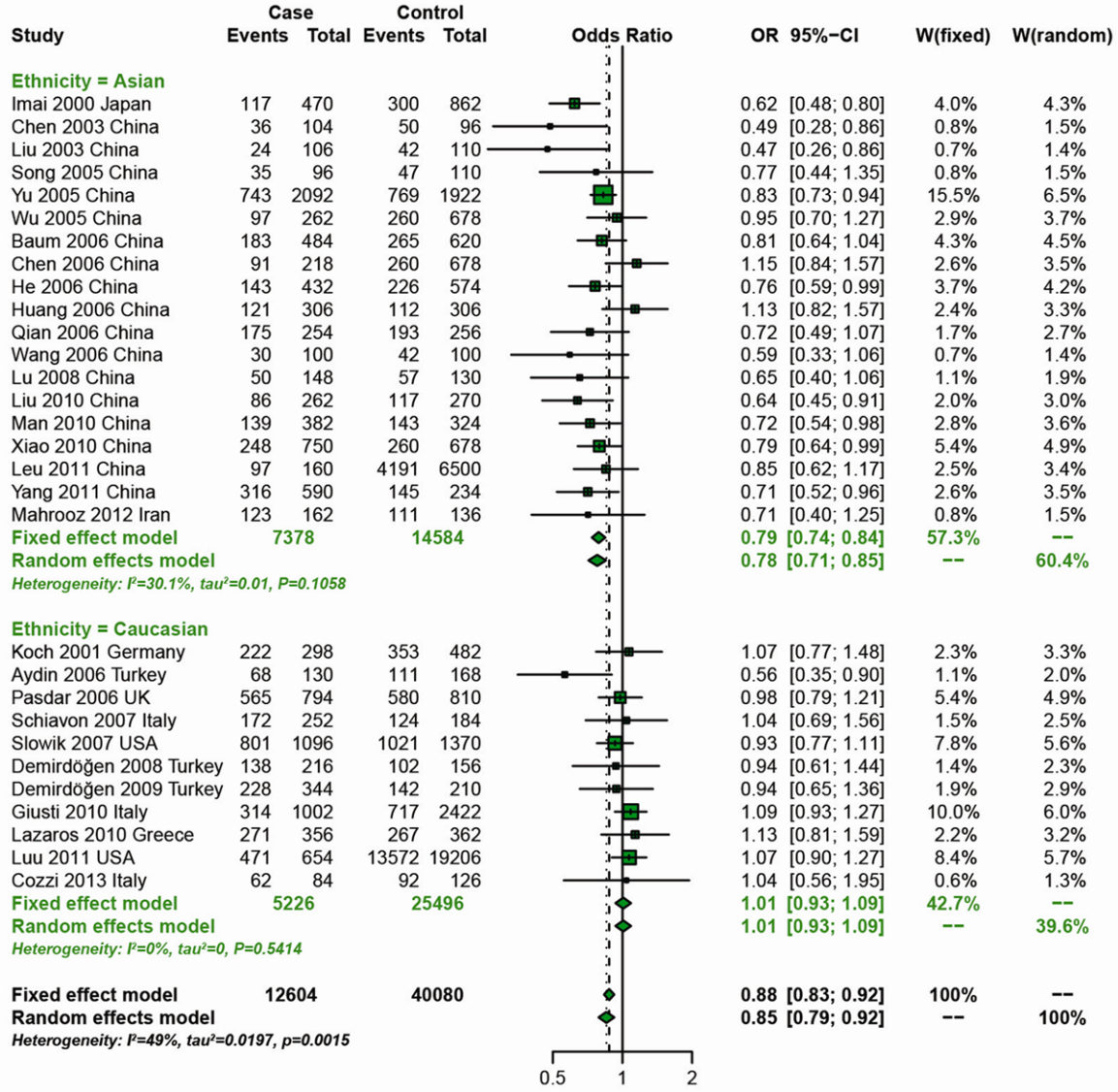

Figure 4. Forest plot of rs662 in *PON1* gene under allelic model.

Discussion

This study enabled us to discovered that IS was not associated with *PAI-1* or *SERPINE1* gene 4G/5G (rs1799889) polymorphism in the overall analysis, but associated with PAI-1 4G/5G polymorphism in Asian under the allelic and homozygous model. A meta-analysis conducted by Attia et al. [25] revealed that PAI-1 4G/5G polymorphism might be strongly associated with IS which was contrary to the results obtained from our study. This inconsistency may be attributed to the between-study heterogeneity existed in studies involving rs1799889 polymorphism and such heterogeneity might be explained by linkage disequilibrium (LD) in unknown causal allele. It is suspected that various LD patterns with the causative allele could trigger different protective and risk effects on IS development, particularly in different populations. Besides, different proportions of stroke subtypes occurred in included studies possibly accounted for some of the heterogeneity.

In this study, IS was significantly associated with *NOS3* gene G894T (rs1799983) polymorphism and 4a/b (rs61722009) polymorphism, but it had no significant association with T-786C (rs2070744) and rs1800779 polymorphisms in the overall meta-analysis. Nevertheless, sub-

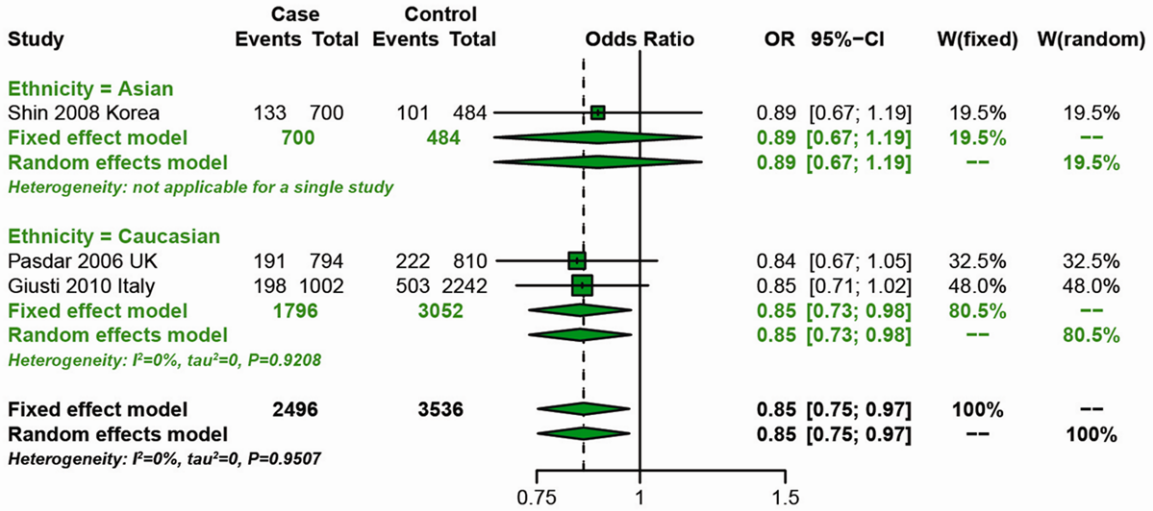

Figure 5. Forest plot of rs12026 in *PON2* gene under allelic model.

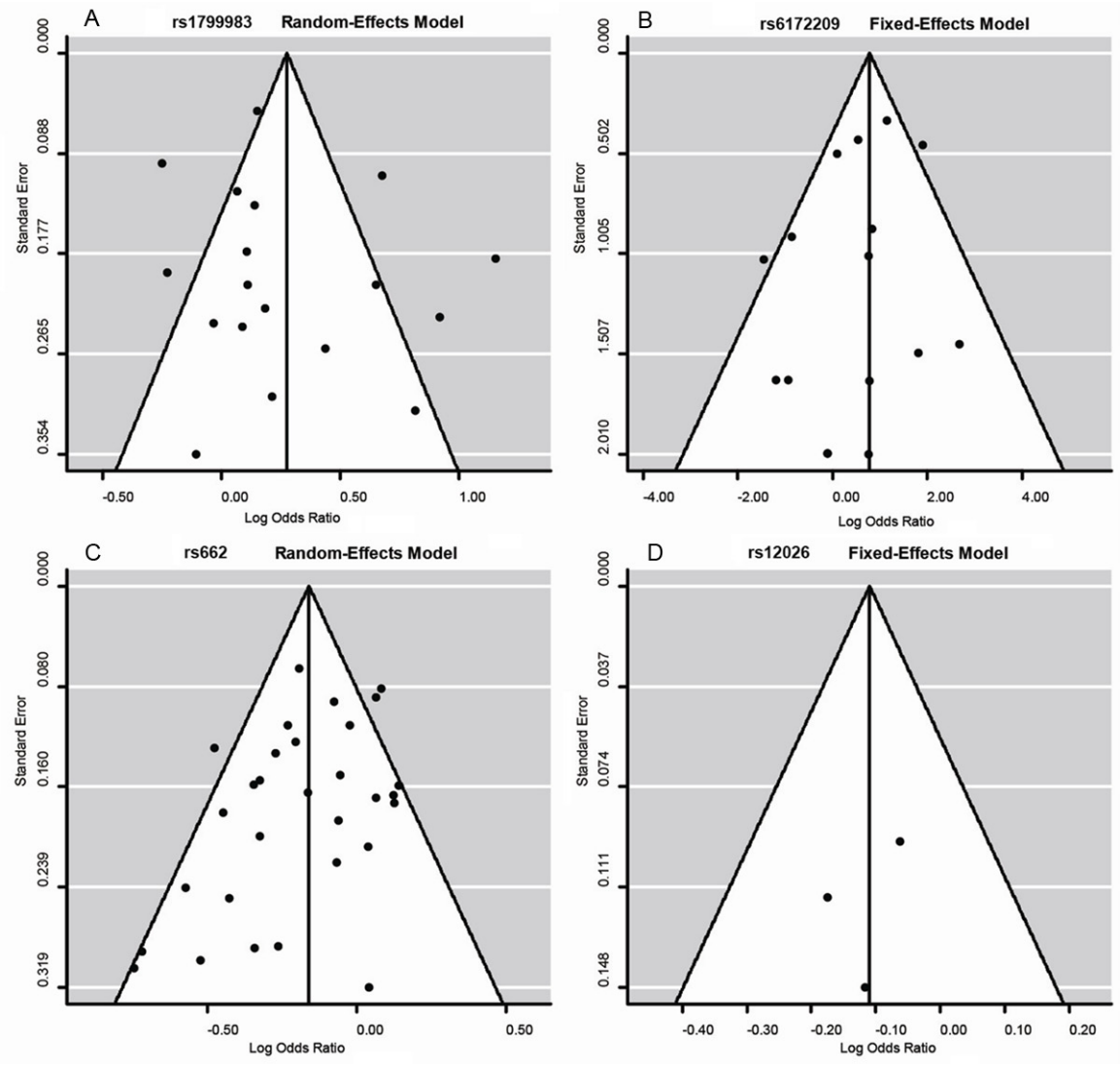

Figure 6. Funnel plots of rs1799983, rs6172209, rs662, and rs12026 under random-effects model.

group analysis by ethnicity suggested inconsistent results which might indicate an ethnicity-specific role of gene polymorphism in IS risk. For T-786C polymorphism, an increased risk was found in Caucasian under the allelic model and a decreased risk was observed in Asian under the homozygous and dominant model. For rs1800779 polymorphism, an increased risk was revealed in Caucasian under the allelic and recessive model, while a decreased risk was found in Asian under four genetic models. Subgroup analyses were not powerful enough to detect significant difference between different ethnicities due to the comparatively small sample sizes. A meta-analysis conducted by Wang et al. [26] demonstrated that IS was associated with multiple gene polymorphisms in Asian, including G894T, 4a/b, and T-786C polymorphism. Another meta-analysis also suggested the role of G894T and 4a/b polymorphism in the susceptibility to IS in Asian, whereas T-786C polymorphism was not significantly associated with IS in both Asian and Caucasian [27]. Therefore, we recommend to design and carry out future studies with large sample size in all ethnicities to justify the above conflicting results.

In this meta-analysis, a statistically significant association was found between IS and *PON1* gene *Q192R* (rs662) polymorphism in both the overall analysis and Asian under all models. The described relevance between *Q192R* polymorphism and IS was in line with the weak association between *Q192R* polymorphism and the risk of coronary artery disease (CAD) that shares some common risk factors with IS including lipid abnormality, hypertension and genetic polymorphisms [28-30]. We speculated that the associations between IS and the two atherosclerotic phenotypes are genuine which demands further investigation to clarify the potential mechanisms. It is also possible that another intermediate atherosclerotic phenotype is affected by *Q192R* polymorphism and the direct effect should be considerably larger than the moderate association between IS and CAD. Since *PON1* gene L55M (rs854560) polymorphism was reported to be correlated with atherosclerosis that was involved in the pathogenic mechanism of IS [31], the L55M polymorphism was hypothesized to be associated with IS in this study. However, we did not detect any association between IS and *L55M* polymorphism under any of the models which was consistent with other meta-analyses [32, 33].

Furthermore, IS was identified to be associated with *PON2* gene Ala148Gly (rs12026) polymorphism in the overall and Caucasian under the allelic model, but it had no significant association with *PON2* gene Ser311Cys (rs7493) polymorphism. This study revealed a weak relationship between Ala148Gly polymorphism and IS. A decreased risk of IS was observed under the allelic and dominant model. However, the result must be interpreted with discretion due to limited statistical power. Previous meta-analysis [34] revealed that Ser311Cys polymorphism was not associated with IS which was consistent with our result. In this study, IS was not significantly associated with *IL-6* gene -174G/C (rs1800795) under the five models which was consistent with other meta-analysis [35].

This meta-analysis might encounter some limitations as follows. First, the overall evaluation was conducted without adjustment according to several potentially confounders. A more precise evaluation may require all raw data from individual studies. Second, a high degree of heterogeneity was seen in the present study. The potential sources of heterogeneity may be explained by some factors like clinical characteristics including drinking, smoking, diabetes, high blood pressure and lipid abnormality. Third, the number of cases and controls in our study were relatively small, especially for the rs1800779 and rs12026 polymorphisms. Fourth, since few studies were performed on African, the above conclusion may not be application to other ethnicity.

In summary, this meta-analysis demonstrated that the *NOS3* gene rs1799983 and rs61722009 polymorphisms, the *PON1* gene rs662 polymorphism and the *PON2* gene rs12026 polymorphism might be associated with ischemic stroke. Apart from that, the *SERPINE1* gene rs1799889 polymorphism and the *NOS3* gene rs2070744 polymorphism might be considered as protective factors for IS in Asian. No significant associations were identified regarding to the *PON1* gene rs854560 polymorphism and *PON2* geners7493 polymorphism. More convincing evidence is demanded to draw solid conclusions with respect to the *NOS3* gene rs1800779 and *PON2* gene rs12026 polymorphism.

Disclosure of conflict of interest

None.

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Table S2. Main characteristic of included studies

Gene	SNP	Author	Year	Country	Ethnicity	Case	Control	Case genotype			Control genotype			NOS Score
								WW	WM	MM	WW	WM	MM	
SERPINE1	rs1799889	Catto	1997	UK	Caucasian	558	172	150	274	134	56	80	36	6
		Liu	1998	China	Asian	107	95	44	43	20	25	48	22	7
		Endler	2000	Austria	Caucasian	137	115	43	63	31	48	48	19	6
		Roest	2000	Netherlands	Caucasian	498	512	146	259	93	159	263	90	6
		Nowak	2001	Germany	Caucasian	198	951	65	91	42	275	473	203	7
		Zhang	2001	China	Asian	95	60	50	31	14	15	30	15	7
		Hindorff	2002	USA	Caucasian	41	385	7	24	10	115	187	83	8
		Chen	2003	China	Asian	100	150	40	46	14	58	68	24	7
		Crainich	2003	USA	Caucasian	265	753	81	143	41	200	387	166	6
		Zhang	2003	China	Asian	113	121	48	47	18	23	70	28	7
		Guan	2004	China	Asian	222	215	75	105	42	46	121	48	6
		Yeh	2004	China	Asian	213	200	79	103	31	71	102	27	7
		Yi	2004	China	Asian	52	57	20	22	10	28	27	2	6
		Jood	2005	USA	Caucasian	600	600	162	307	131	186	280	134	8
		Tang	2005	China	Asian	122	50	66	35	21	13	26	11	6
		Wiklund	2005	Sweden	Caucasian	311	760	136	118	57	241	370	149	6
		Komitopoulou	2006	Greece	Caucasian	87	101	23	50	14	23	55	23	7
		Saidi	2006	Tunisia	African	134	118	23	74	37	33	58	27	6
		Xu	2006	China	Asian	72	77	15	29	28	5	35	37	6
		Liu	2008	China	Asian	220	140	48	114	58	43	70	27	7
		Tang	2008	China	Asian	90	30	40	34	16	6	19	5	7
		Adamski	2009	Poland	Caucasian	389	291	120	188	81	89	136	66	7
		Nakai	2009	Japan	Asian	47	47	15	22	10	2	15	30	6
		Balcerzyk	2011	Poland	Caucasian	70	133	23	35	12	47	60	26	7
IL-6	rs1800795	Flex	2002	Italy	Caucasian	84	183	44	30	10	53	80	50	6
		Pola	2002	Italy	Caucasian	119	133	56	48	15	28	58	47	6
		Revilla	2002	Spain	Caucasian	82	82	27	40	15	37	39	6	7
		Greisenegger	2003	Austria	Caucasian	214	214	81	96	37	76	108	30	7
		Pola	2003	Italy	Caucasian	119	133	56	48	15	28	58	47	6
		Balding	2004	Ireland	Caucasian	105	389	33	60	12	123	198	68	7
		Flex	2004	Italy	Caucasian	237	223	100	115	22	56	99	68	6
		Chamorro	2005	Spain	Caucasian	273	105	104	134	35	46	50	9	6
		Karahan	2005	Turkey	Caucasian	86	83	54	24	8	55	22	6	6
		Lalouschek	2006	Austria	Caucasian	404	415	143	187	74	156	192	67	6
		Banerjee	2008	India	Asian	112	212	77	35	0	156	52	4	7
		Liu	2010	China	Asian	157	163	138	19	0	153	10	0	8
		Tong	2010	China	Asian	748	748	747	1	0	743	5	0	7
		Balcerzyk	2012	Poland	Caucasian	80	138	21	43	16	40	76	22	7
		Titov	2012	Russia	Caucasian	200	140	73	113	14	44	71	25	7
		Chakraborty	2013	India	Asian	100	120	57	35	8	73	39	8	6
		Xuan	2014	China	Asian	430	461	205	170	55	246	171	44	7
		Bazina	2015	Croatia	Caucasian	114	187	39	53	22	63	98	26	7
NOS3	rs1799983	Markus	1998	UK	Caucasian	361	236	127	187	47	96	104	36	6
		Akar	2000	Turkey	Caucasian	43	82	24	14	5	46	33	3	6
		Elbaz	2000	France	Caucasian	460	460	212	187	61	163	232	65	7
		Howard	2005	USA	Caucasian	64	198	33	24	7	109	75	14	6
		Berger	2007	Germany	Caucasian	1901	1746	869	844	188	875	733	138	6
		Cheng	2008	China	Asian	309	309	235	70	4	243	61	5	6
		Lin	2008	China	Asian	120	78	25	89	6	49	23	6	6
		Moe	2008	Singapore	Asian	118	207	89	26	3	160	42	5	7
		Zhao	2008	China	Asian	70	216	53	15	2	190	24	2	6
		Djordjevic	2009	Serbia	Caucasian	26	50	13	7	6	18	25	7	6
		Guldiken	2009	Turkey	Caucasian	146	134	82	59	5	66	61	7	7
		Kim	2010	Korea	Asian	223	206	184	38	1	168	38	0	7

		Majumdar	2010	India	Asian	172	214	124	43	5	159	50	5	7
		Saidi	2010	Tunisia	African	329	444	98	170	61	229	174	41	6
		Song	2010	Korea	Asian	265	230	185	78	2	190	40	0	6
		Yan	2011	China	Asian	545	557	417	123	5	446	102	9	7
		Xiong	2012	China	Asian	89	102	59	19	11	72	27	3	5
		Akhter	2014	India	Asian	100	200	20	52	28	106	80	14	7
	rs2070744	Hassan	2004	UK	Caucasian	298	599	40	143	115	96	283	220	6
		Aagawak	2005	Japan	Asian	220	214	3	41	176	1	34	179	7
		Aagawak	2005	Korea	Asian	191	191	1	46	144	1	41	149	6
		Howard	2005	USA	Caucasian	100	192	10	31	59	24	86	82	5
		Song	2006	Korea	Asian	132	113	0	26	106	0	13	100	7
		Cheng	2008	China	Asian	309	309	11	58	240	3	56	250	7
		Moe	2008	Singapore	Asian	120	207	7	27	86	3	52	152	6
		Yamada	2008	Japan	Asian	311	971	9	46	256	10	213	748	6
		Kim	2010	Korea	Asian	223	206	0	37	186	0	35	171	6
		Majumdar	2010	India	Asian	129	129	9	50	70	5	55	69	6
		Saidi	2010	Tunisia	African	329	444	36	131	162	33	162	249	7
		Song	2010	Korea	Asian	265	232	4	43	218	0	39	193	7
		Yan	2011	China	Asian	558	557	2	122	434	10	96	451	7
		Turkanoglu	2014	Turkey	Caucasian	245	145	6	93	146	6	57	82	6
		Akhter	2014	India	Asian	100	200	7	27	66	8	72	120	5
	rs61722009	Yahashi	1998	Japan	Asian	127	91	93	33	1	67	24	0	7
		Hou	2001	China	Asian	364	516	263	77	24	439	71	6	7
		Hassan	2004	UK	Caucasian	132	595	110	21	1	433	145	17	7
		Yeh	2004	China	Asian	213	200	181	32	0	165	34	1	6
		Howard	2005	USA	Caucasian	55	120	41	12	2	88	30	2	6
		Lin	2008	China	Asian	120	78	90	26	4	61	17	0	6
		Shi	2008	China	Asian	97	99	90	7	0	81	18	0	7
		Jara-Prado	2010	Mexico	Caucasian	48	96	37	11	0	79	17	0	7
		Kim	2010	Korea	Asian	223	206	186	37	0	168	38	0	6
		Majumdar	2010	India	Asian	175	214	106	61	8	131	74	9	6
		Munshi	2010	India	Asian	357	283	172	146	39	181	89	13	5
		Saidi	2010	Tunisia	African	329	444	235	82	12	334	100	10	7
		Song	2010	Korea	Asian	265	222	214	43	8	181	41	0	7
		Fang	2011	China	Asian	191	236	158	33	0	187	48	1	7
		Tong	2014	China	Asian	100	100	69	27	4	79	19	2	6
		Turkanoglu	2014	Turkey	Caucasian	245	145	172	71	2	109	33	3	6
	rs1800779	Howard	2005	USA	Caucasian	101	186	9	32	60	23	80	83	6
		Cheng	2008	China	Asian	309	309	10	55	244	4	42	263	7
		Akhter	2014	India	Asian	100	200	6	33	61	6	58	136	7
PON1	rs662	Imai	2000	Japan	Asian	235	431	129	95	11	190	182	59	7
		Koch	2001	Germany	Caucasian	149	241	6	64	79	15	99	127	6
		Chen	2003	China	Asian	52	48	21	26	5	10	26	12	6
		Liu	2003	China	Asian	53	55	32	18	3	21	26	8	6
		Song	2005	China	Asian	48	55	17	27	4	17	29	9	7
		Yu	2005	China	Asian	1046	961	439	471	136	346	461	154	7
		Wu	2005	China	Asian	131	339	56	53	22	134	150	55	7
		Aydin	2006	Turkey	Caucasian	65	84	11	40	14	11	35	38	7
		Baum	2006	China	Asian	242	310	91	119	32	110	135	65	7
		Chen	2006	China	Asian	109	339	35	57	17	134	150	55	8
		He	2006	China	Asian	216	287	100	89	27	111	126	50	6
		Huang	2006	China	Asian	153	153	53	79	21	56	82	15	7
		Pasdar	2006	UK	Caucasian	397	405	30	169	198	36	158	211	6
		Qian	2006	China	Asian	127	128	15	49	63	5	53	70	5
		Wang	2006	China	Asian	50	50	23	24	3	16	26	8	7
		Schiavon	2007	Italy	Caucasian	126	92	12	56	58	12	36	44	7
		Slowik	2007	USA	Caucasian	548	685	48	199	301	41	267	377	7

		Demirdöğen	2008	Turkey	Caucasian	108	78	18	42	48	7	40	31	7
		Lu	2008	China	Asian	74	65	31	36	7	22	29	14	6
		Demirdöğen	2009	Turkey	Caucasian	172	105	21	74	77	9	50	46	6
		Giusti	2010	Italy	Caucasian	501	1211	241	206	54	604	497	110	6
		Lazaros	2010	Greece	Caucasian	178	181	7	71	100	8	79	94	7
		Liu	2010	China	Asian	131	135	61	54	16	45	63	27	7
		Man	2010	China	Asian	191	162	74	95	22	53	75	34	6
		Xiao	2010	China	Asian	375	339	169	164	42	134	150	55	6
		Leu	2011	China	Asian	80	3250	8	47	25	406	1497	1347	6
		Luu	2011	USA	Caucasian	327	9603	24	135	168	818	3998	4787	5
		Yang	2011	China	Asian	295	117	83	150	62	43	59	15	5
		Mahrooz	2012	Iran	Asian	81	68	4	31	46	2	21	45	7
		Cozzi	2013	Italy	Caucasian	42	63	4	14	24	4	26	33	7
	rs854560	Imai	2000	Japan	Asian	235	431	1	31	203	5	55	371	6
		Voetsch	2002	Brazil	Caucasian	118	118	10	55	53	14	48	56	7
		Ueno	2003	Japan	Asian	112	106	3	16	93	0	8	98	6
		He	2006	China	Asian	216	287	0	12	204	0	13	274	6
		Huang	2006	China	Asian	153	153	0	5	148	0	10	143	7
		Qian	2006	China	Asian	127	128	10	39	78	6	44	78	6
		Schiavon	2007	Italy	Caucasian	126	92	10	61	55	10	39	43	6
		Slowik	2007	USA	Caucasian	548	682	70	260	218	78	327	277	7
		Demirdöğen	2008	Turkey	Caucasian	108	78	13	41	54	14	30	34	7
		Shin	2008	Korea	Asian	350	242	0	33	317	0	27	215	6
		Demirdöğen	2009	Turkey	Caucasian	172	105	21	68	83	19	42	44	6
		Lazaros	2010	Greece	Caucasian	178	181	73	90	15	79	83	19	8
		Luu	2011	USA	Caucasian	267	3323	109	119	39	1444	1499	380	7
PON2	rs7493	Imai	2000	Japan	Asian	235	431	152	78	5	279	132	20	7
		Zhao	2005	China	Asian	108	123	44	54	10	75	46	2	7
		Pasdar	2006	UK	Caucasian	397	405	14	157	226	25	164	216	7
		Slowik	2007	USA	Caucasian	548	684	298	219	31	397	236	51	6
		Xu	2007	China	Asian	177	108	117	47	13	64	38	6	6
		Shin	2008	Korea	Asian	350	242	13	108	229	9	81	152	6
		Xu	2008	China	Asian	177	108	117	47	13	64	38	6	7
		Giusti	2010	Italy	Caucasian	501	1212	296	187	18	757	411	44	6
		Lazaros	2010	Greece	Caucasian	178	181	88	73	17	82	74	25	6
	rs12026	Pasdar	2006	UK	Caucasian	397	405	222	159	16	211	166	28	7
		Shin	2008	Korea	Asian	350	242	228	111	11	150	83	9	6
		Giusti	2010	Italy	Caucasian	501	1211	318	168	15	753	413	45	6

NOS: Newcastle-Ottawa Quality Assessment; W: wild allele, M: mutation allele; SNP: single nucleotide polymorphism.

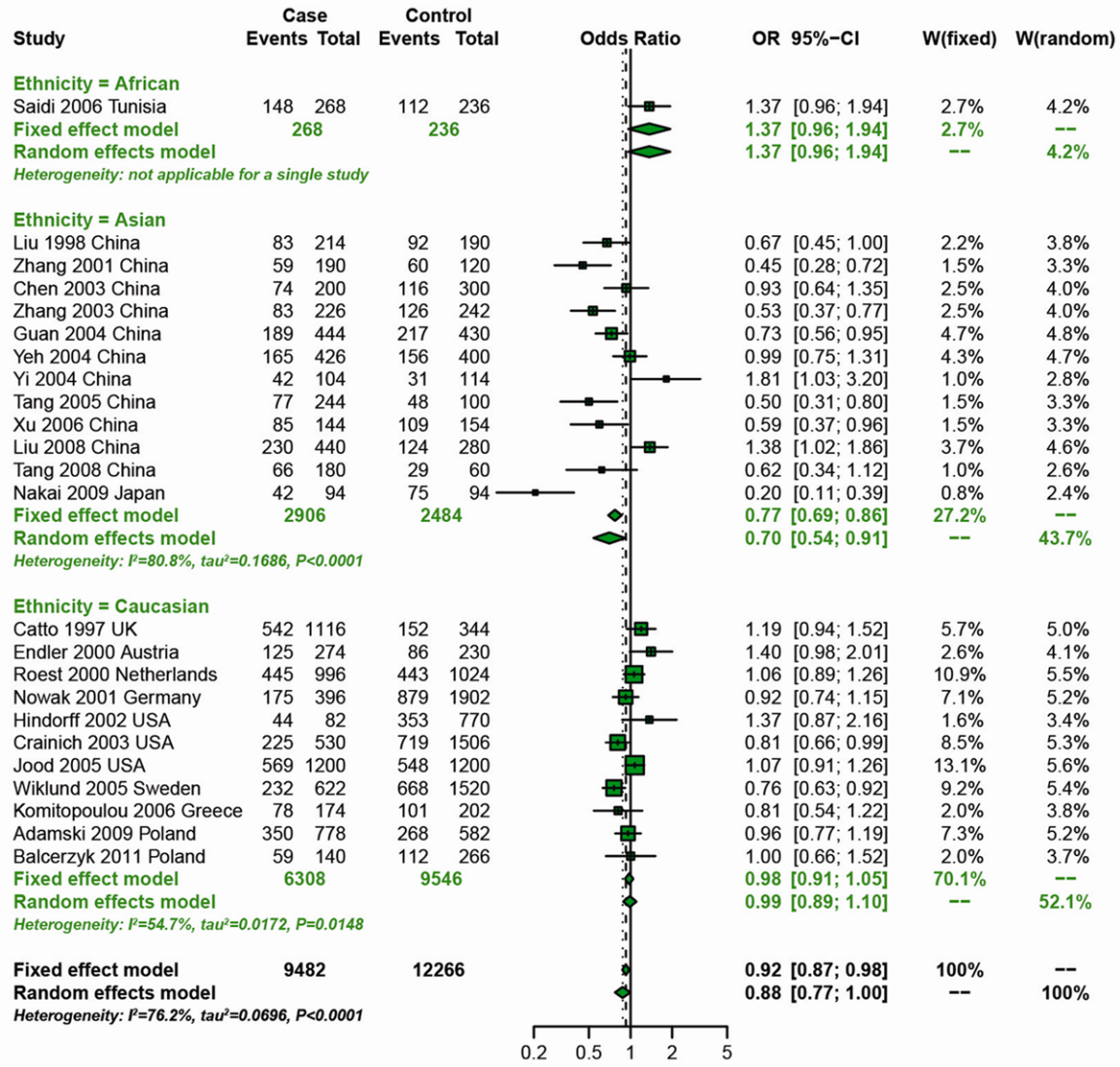

Figure S1. Forest plot of rs1799889 in *SERPINE1* gene under allelic model.

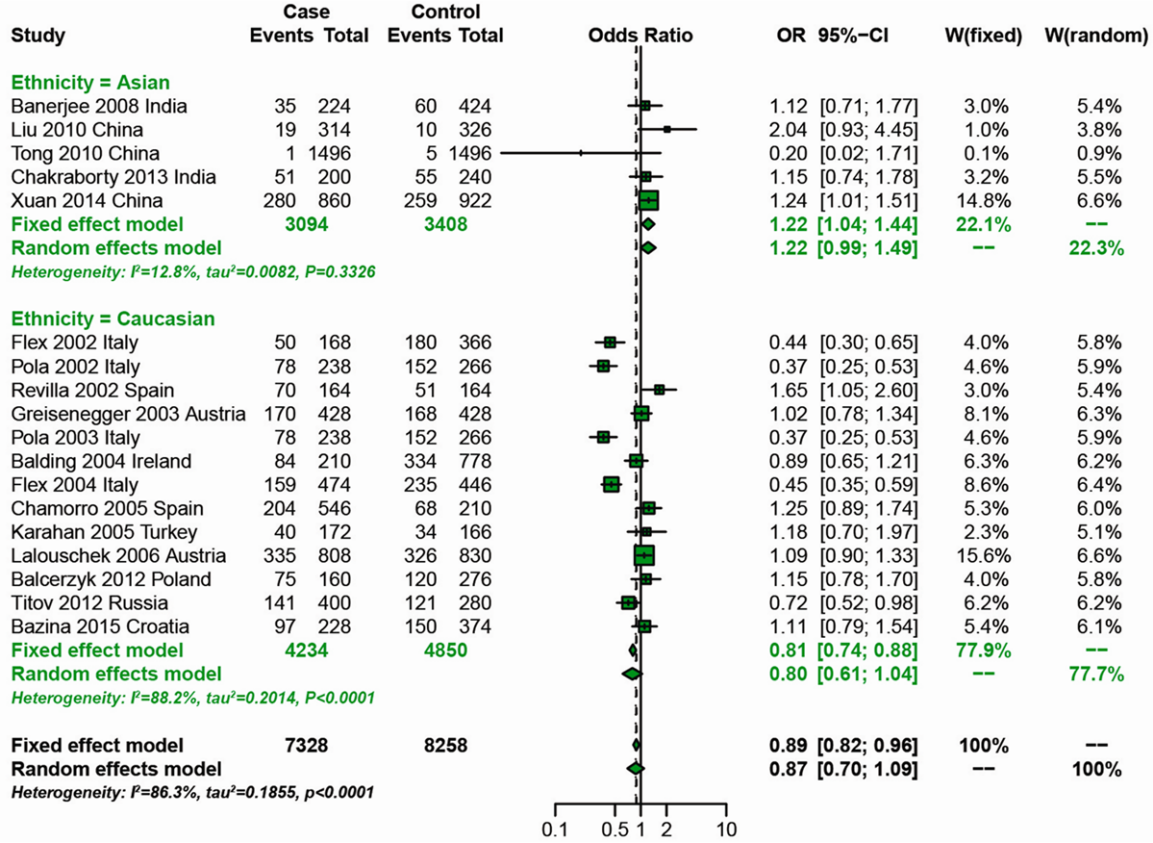

Figure S2. Forest plot of rs1800795 in *IL6* gene under allelic model.

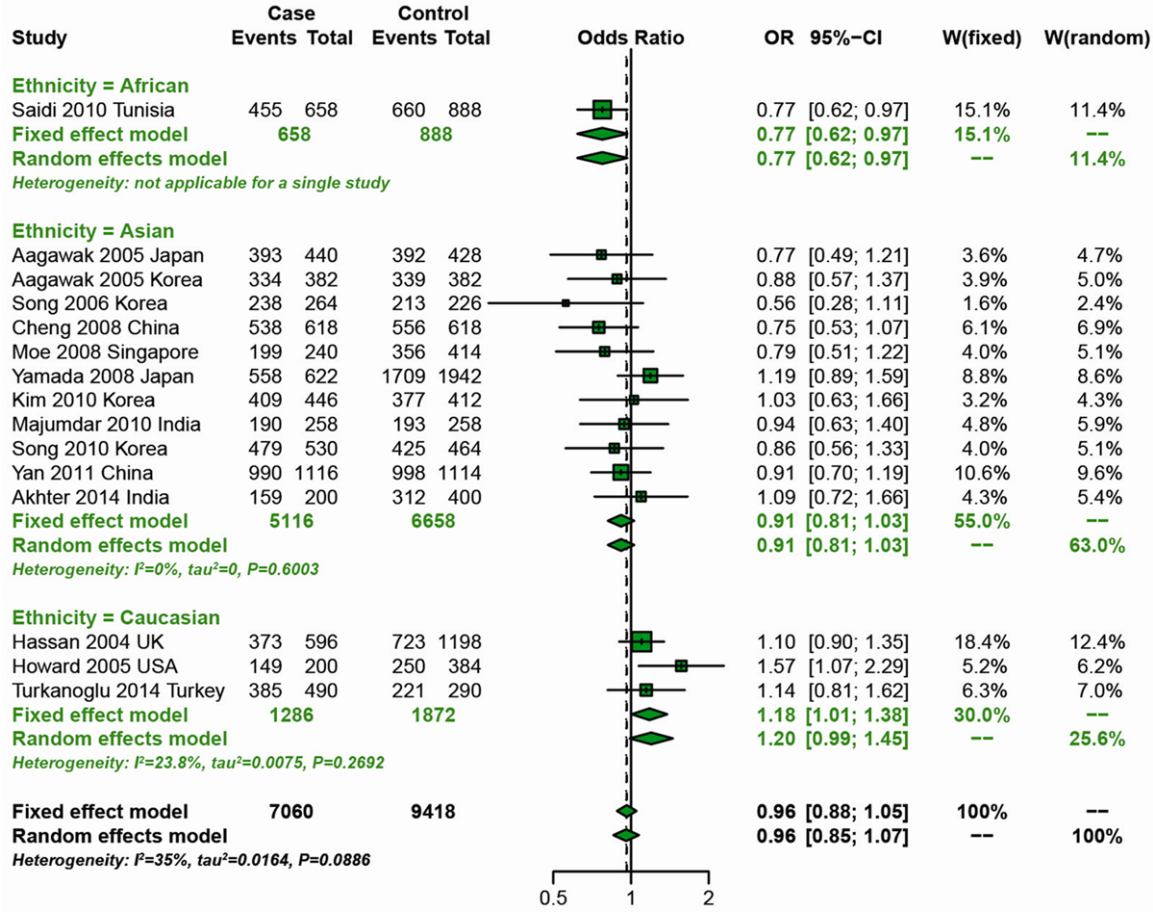

Figure S3. Forest plot of rs2070744 in *NOS3* gene under allelic model.

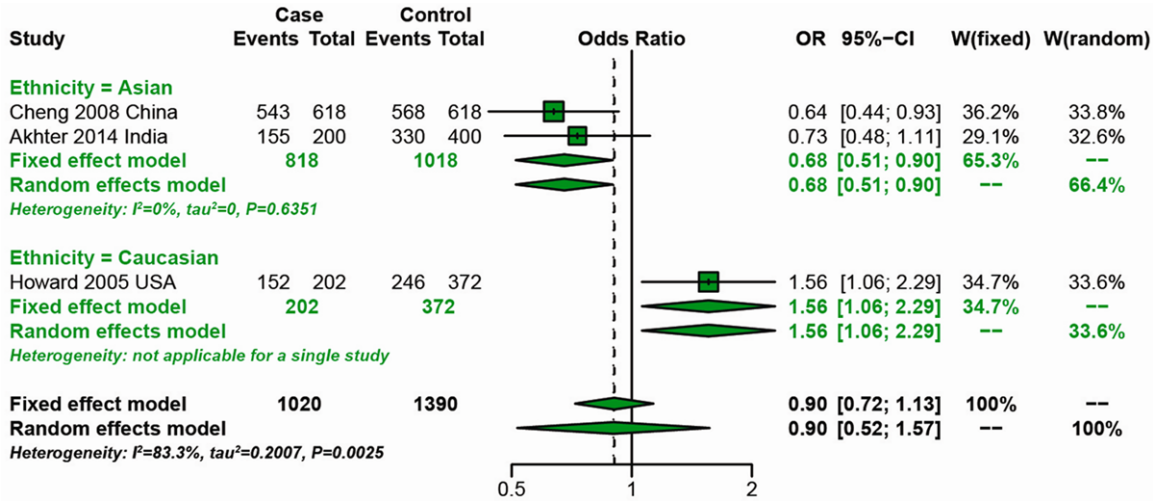

Figure S4. Forest plot of rs1800779 in *NOS3* gene under allelic model.

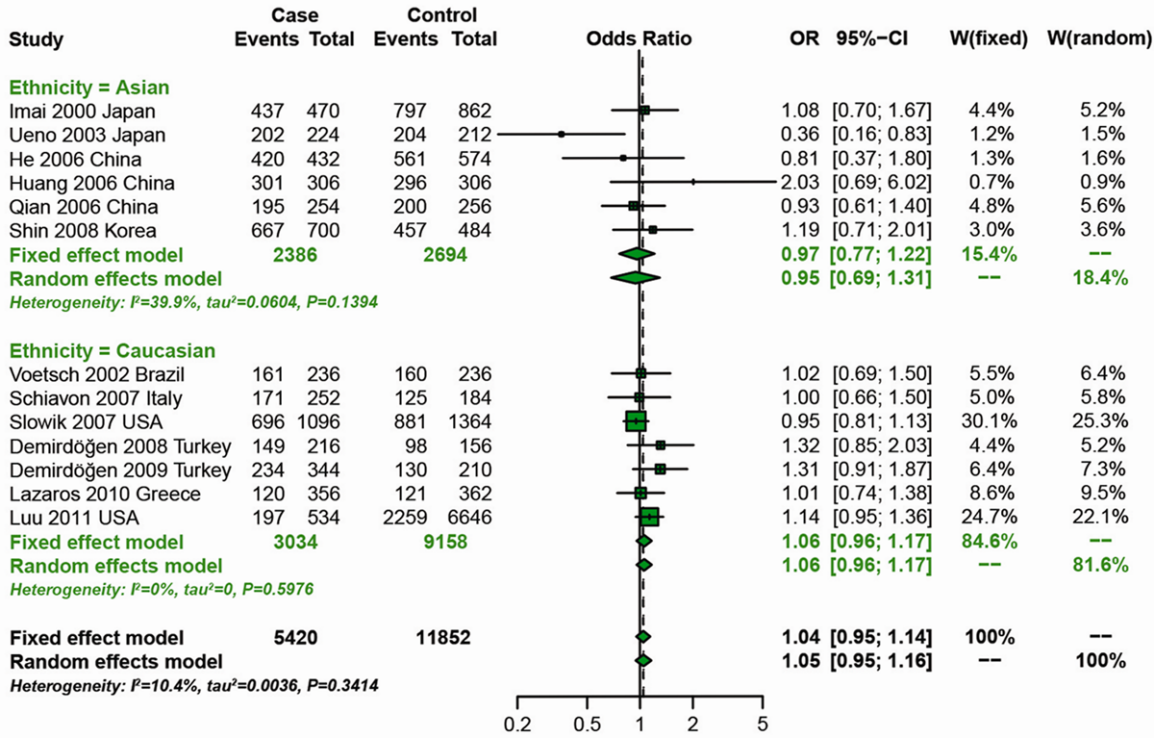

Figure S5. Forest plot of rs854560 in *PON1* gene under allelic model.

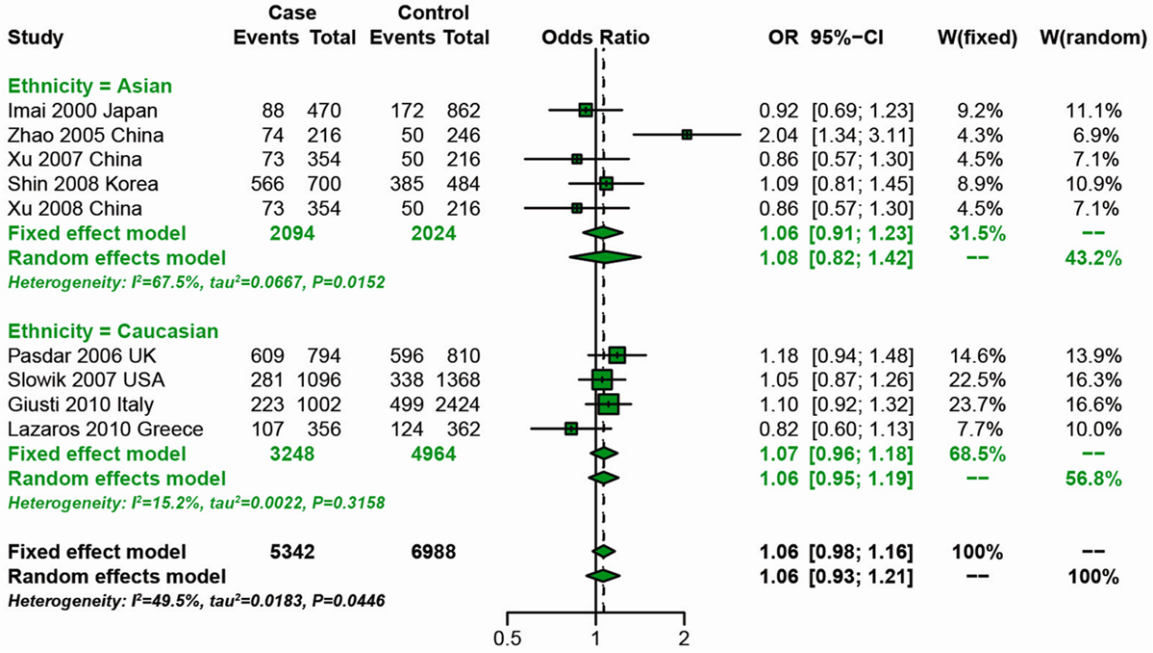

Figure S6. Forest plot of rs7493 in *PON2* gene under allelic model.

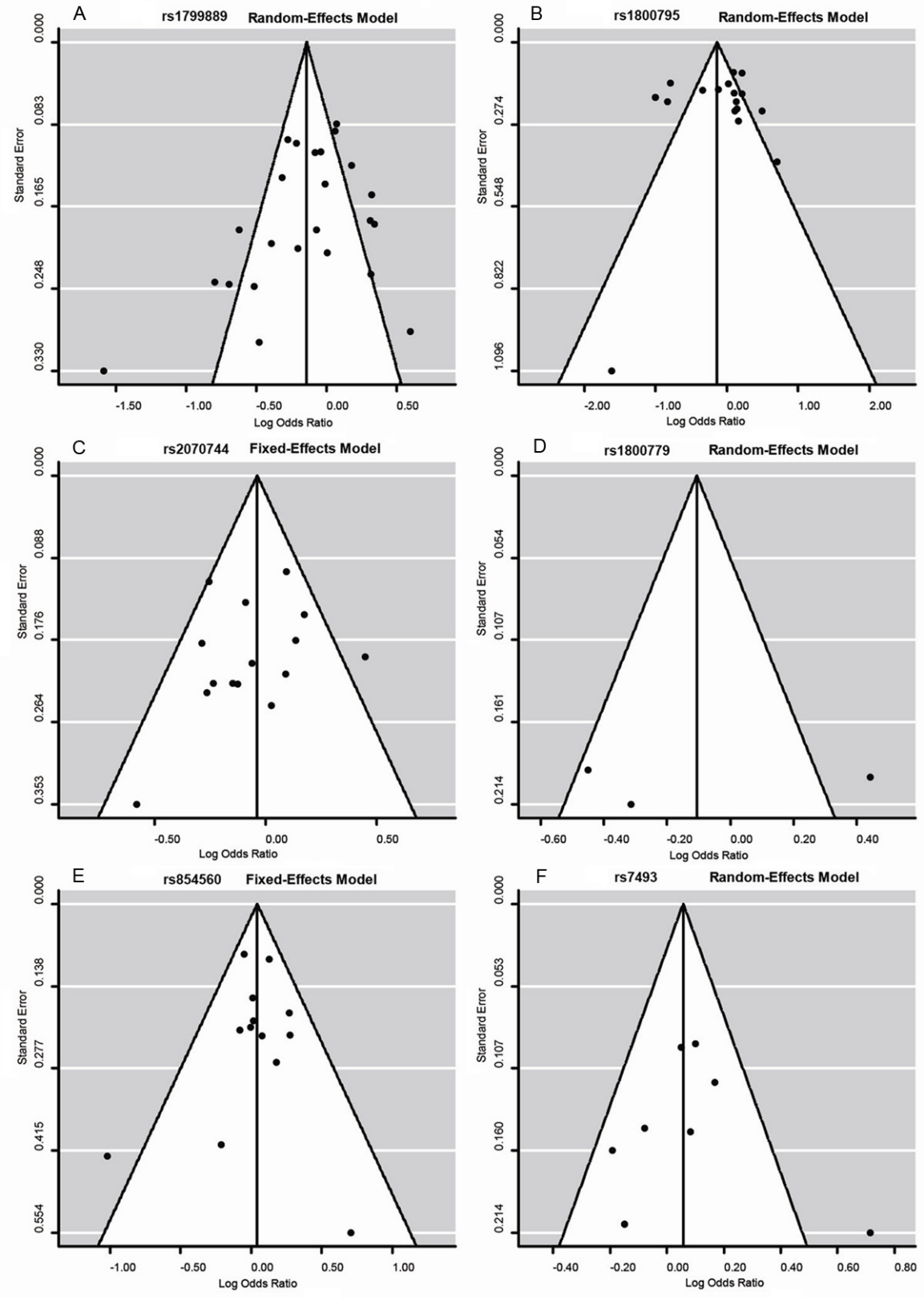

Figure S7. Funnel plots of rs1799889, rs1800795, rs2070744, rs1800779, rs854560 and rs7493 under random-effects model or fixed-effects model.