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Original Article

Association between PON1 L55M polymorphism and ischemic stroke: a systematic review and meta-analysis

Peng Shao[1*], Da-Jun Qu[2*], Rui-Ying Song[3], Ming-Lu Chen[4], Li-Hua Wang[5]

[1]Department of Rehabilitation Medicine, Yantaishan Hospital, Yantai 264000, China; [2]Department of Drug Purchase, Haiyang People's Hospital, Haiyang 265100, China; [3]Department of Otolaryngology, Yuhuangding Hospital Affiliated to Qingdao University, Yantai 264000, China; [4]Department of Nuclear Radiology, Shandong Province Tumor Hospital, Jinnan 250021, China; [5]Department of Pediatrics, Haiyang People's Hospital, Haiyang 265100, China. [*]Equal contributors.

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Abstract: Objective: The present study aims to evaluate the relation between PON1 L55M polymorphism and ischemic stroke by a meta-analysis method. Methods: English and Chinese databases were retrieved to find qualified studies; a random or fixed effects model was used to merge the odds ratio (OR); Q test was used to assess the heterogeneity among studies, and Egger's test and funnel plot were used for the assessment of publication bias. Results: 14 studies were included in the meta-analysis; in total populations, there was no association between PON1 gene L55M polymorphism and ischemic stroke in additive, dominant, and recessive model, respectively. Furthermore, we did not found associations between L55M and ischemic stroke in Asian or Caucasian population. Conclusion: Available evidences suggested that L55M polymorphism had no effect on the risk of ischemic stroke. However, this conclusion needs further validation by larger sample and well-designed studies.

Keywords: Paraoxonase, PON, ischemic stroke, infarction, systematic review, meta-analysis

Introduction

Stroke is the second common cause of death and a major cause of disability [1] in the world. The survey in 2008 found that cerebrovascular disease had become the most common cause of death for Chinese residents [2]. Most strokes are ischemic strokes (IS); in developed countries, IS accounts for 67.3%~80.5% [3]; in China, it is about 43.7%~78.9% [3]. Most IS are caused by the arterial atherosclerosis [4, 5]. Therefore, the atherosclerosis-related gene mutations play important roles in the pathophysiology of IS [6-8]. Paraoxonase (PON) can prevent low-density lipoprotein (LDL) from oxidation and maintain the function of high-density lipoprotein (HDL) [9] to prevent the development of atherosclerosis. However, PON gene has a variety of polymorphisms, which explain the inter-individual differences in the concentration and activity of PON enzyme [9-13]. Many studies have found that PON1 L55M polymorphism was related to IS [14-16]. However, the results were inconsistent. In the present study, we conducted a systematic review and meta-analysis to clarify the relation between PON1 L55M polymorphism and IS.

Materials and methods

Inclusion of studies

Different combinations of "paraoxonase", "PON", "gene", "polymorphism", "genetic variation", "stroke", "cerebral vascular", "cerebral" and "brain infarction" were used as keywords to comprehensively search in the databases of from PubMed, EMBASE, ISI Web of Science, Wanfang database in China, and Chinese National Knowledge Infrastructure (CNKI) database. All studies related to the correlation between PON1 L55M polymorphism and stroke had been carefully evaluated. References of relevant studies, reviews, abstracts of related conferences had been retrieved to identify possible eligible studies. For duplicate publications, only the most recent or most complete study was included. The sources of control populations were unre-

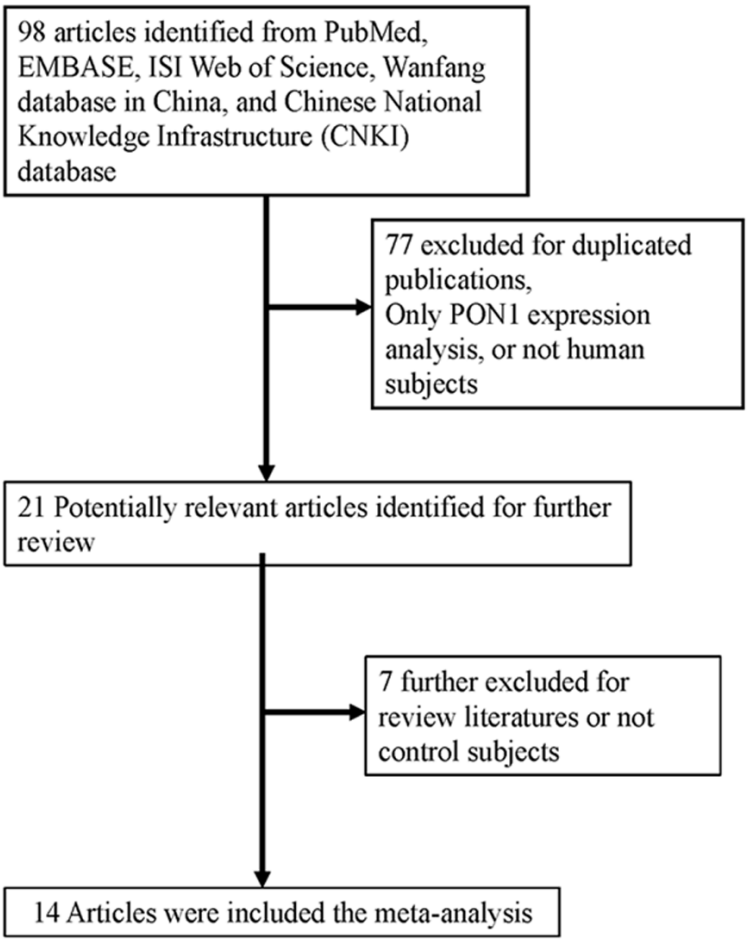

Figure 1. Flow chart of literatures identified.

stricted; the studies with genotype distributions which did not meet HWE were excluded. Studies that met the following criteria were included in the Meta-analysis: 1) population-based case-control studies, nested case-control studies or cohort studies exploring the correlation between PON1L55M genetic polymorphism and IS; 2) the IS diagnosis criteria have been widely accepted; 3) the controls were unrelated individuals, without any vascular diseases after detection; 4) allele and genotype frequencies were described in detail in control group and case group; 5) genotype distributions of control populations met HWE.

Data extraction

The following information was extracted for included studies: 1) Authors, national and ethnic backgrounds of subjects, published year; 2) the total number of subjects included in the study; definitions and characteristics of subjects in case and control groups; 3) distribution of allele and genotypes in case and control groups; 4) sample sources and methods of genetic analysis, IS subtypes and interactions of gene-gene and gene-environment. If gene frequencies were not given, they should be calculated. For literatures with different ethnic subjects, each race should be separated for data extraction. If the above information was incomplete, we contacted the corresponding author to obtain.

Statistical methods

The Review Manager 5.0 provided by Cochrane Library was used to perform meta-analysis. A random-effects model and fixed-effects model were used to merge the OR value and 95% confidence intervals (95% CI); Q test was used to assess the homogeneity among studies. I^2 was used to measure the degree of heterogeneity. If there was heterogeneity among studies, the random-effects model was used to merge the OR value. Chi-square test was used to verify HWE. $P<0.05$ was considered statistically significant. Meta-analysis of the correlation between genetic polymorphism of PON1 L55M and the risk of IS was based on following models: 1) additive model; 2) recessive model; 3) dominant model. Publication bias was assessed using a funnel plot, and $P<0.10$ was considered being biased. Because PON1 polymorphisms showed strong racial differences [17], different ethnic groups were also analyzed separately [18].

Results

The included studies and their characteristics

As shown in **Figure 1**, by searching, we initially selected 98 studies which may meet the criteria; after reading the full text, 14 studies (6374 patients and 12150 controls) were included in the analysis [19-32]; the subjects of eight studies were the Caucasian populations [20-22, 24,

Table 1. Characteristics of included studies

							Genotype						Allele			
							Case			Control			Case		Control	
Authors	Year	ethnicity	case	control	H-WE	Genotyping methods	LL	LM	MM	LL	LM	MM	L	M	L	M
Shin et al	2008	Asian	350	242	YES	Light cycler melting curve	317	33	0	215	27	0	667	33	457	27
Can Demirdogen	2008	Caucasian	108	78	YES	PCR-RFLP	54	41	13	34	30	14	149	67	98	58
Schiavon	2007	Caucasian	126	92	YES	PCR-RFLP	55	61	10	43	39	10	171	81	125	59
Slowik	2007	Caucasian	548	685	YES	PCR-RFLP	55	66	15	96	114	26	176	96	306	166
Huang	2006	Asian	153	153	YES	PCR-RFLP	148	5	0	143	10	0	301	5	296	10
Aydin	2006	Caucasian	65	84	YES	PCR-RFLP	12	42	11	20	29	35	66	64	69	99
Ranade	2005	Caucasian	81	2635	YES	PCR-RFLP	31	45	5	1015	1199	321	107	55	3229	1841
Ueno	2003	Asian	112	106	YES	PCR-RFLP	93	16	3	98	8	0	202	22	204	8
Voetsch	2002	Mixed	118	118	YES	PCR-RFLP	53	55	10	56	48	14	161	75	160	76
Imai	2000	Asian	231	431	YES	PCR-RFLP	203	31	1	371	55	5	437	33	797	65
Moghtaderi	2011	Caucasian	37	53	YES	TPARMS-PCR	17	15	5	27	19	7	49	25	73	33
Pasdar	2006	Caucasian	397	405	YES	DASH	-	-	-	-	-	-	508	286	510	300
Wang	2009	Caucasian	3550	6560	YES	Multilocus PCR	-	-	-	-	-	-	-	-	-	-
Zhang	2013	Asian	498	508	YES	Sequenom Mass ARRAY platform	-	-	-	-	-	-	-	-	-	-

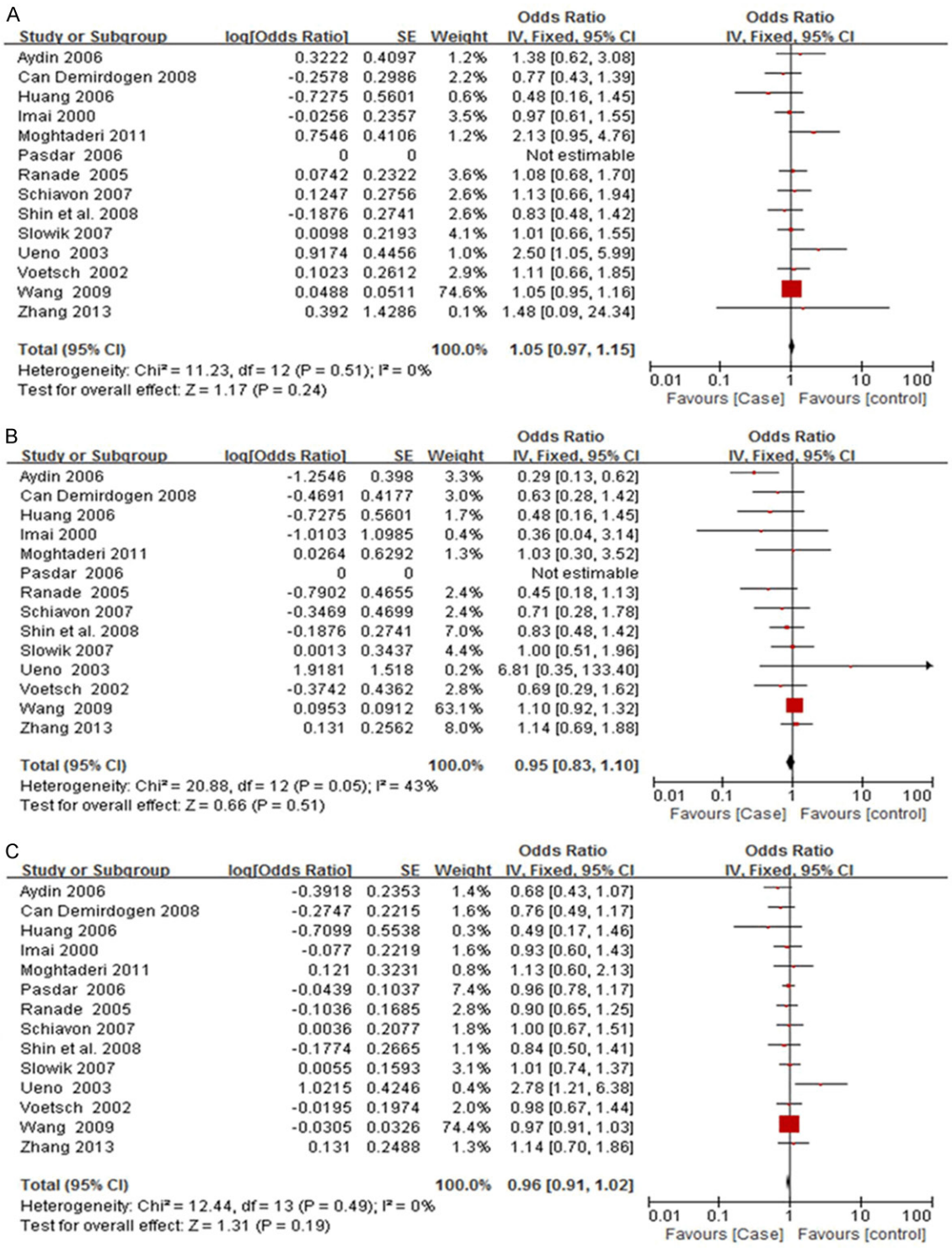

Figure 2. Forest plot of IS and PON1 L55M polymorphism in total population, the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI. In this analysis, Fixed-effects model was used. A: Additive model; B: Dominant model; C: Recessive model.

25, 29-31], and that of five studies were Asian populations [19, 23, 26, 27, 32]; one study involving mixed ethnicity [28]. The features of included studies were shown in **Table 1**.

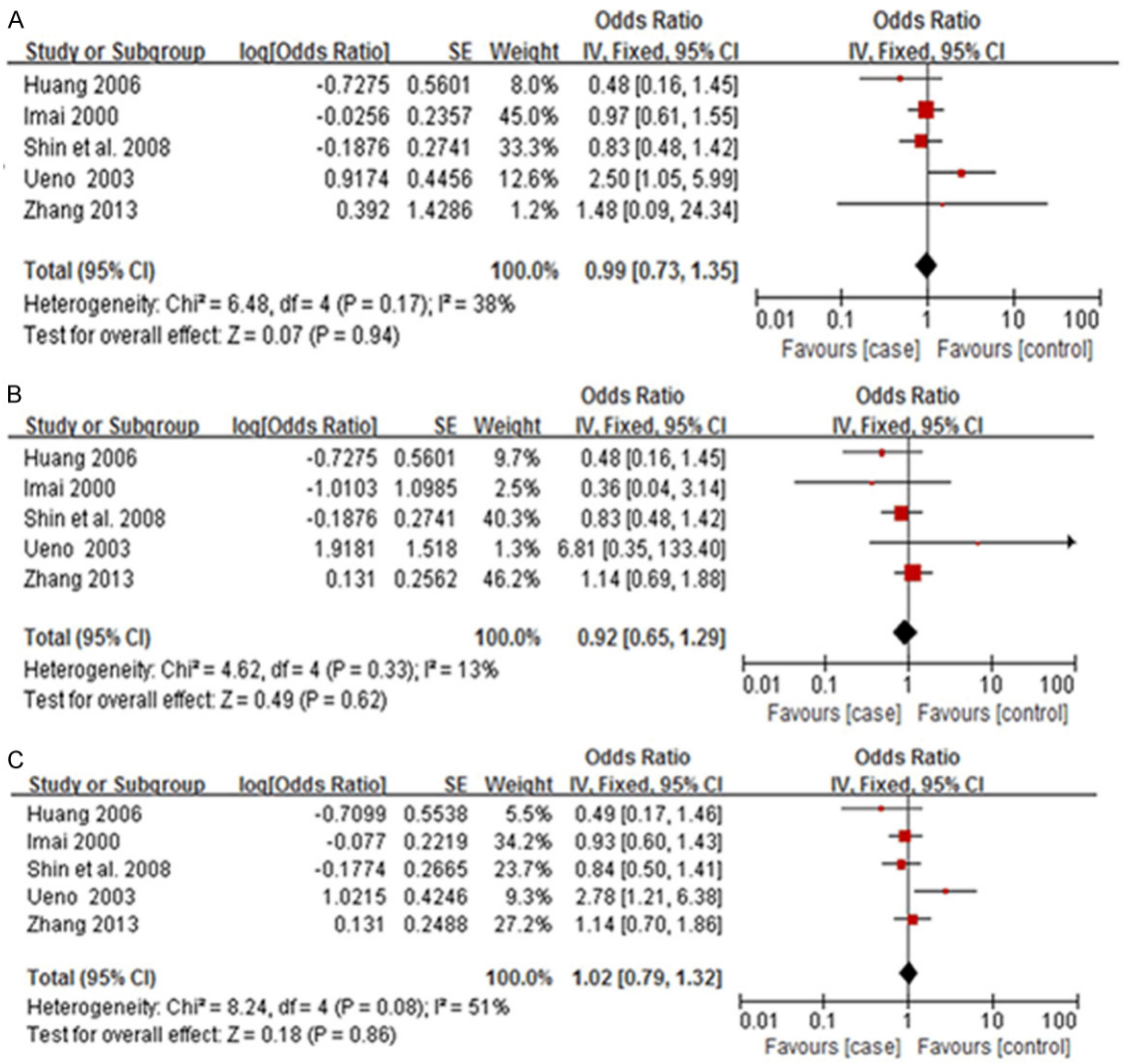

Figure 3. Forest plot of IS and PON1 L55M polymorphism in Asian population, the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI. In this analysis, Fixed-effects model was used. A: Additive model; B: Dominant model; C: Recessive model.

Association between PON1 L55M polymorphism and IS

In total population, we did not found association between L55M polymorphism and IS in additive (OR=1.05, 95% CI: 0.97-1.15; P=0.24), dominant (OR=0.95, 95% CI: 0.83-1.10; P=0.51), and recessive model (OR=0.96, 95% CI: 0.91-1.02; P=0.19), respectively (**Figure 2**).

In Asian population, we also did not found association between L55M polymorphism and IS in additive (OR=0.99, 95% CI: 0.73-1.35; P=0.94), dominant (OR=0.92, 95% CI: 0.65-1.29; P=0.62), and recessive model (OR=1.02, 95% CI: 0.79-1.32; P=0.86), respectively (**Figure 3**).

In Caucasian population, we also did not found association between L55M polymorphism and IS in additive (OR=1.06, 95% CI: 0.96-1.16; P=0.24), dominant (OR=0.71, 95% CI: 0.47-1.08; P=0.11), and recessive model (OR=0.96, 95% CI: 0.91-1.02; P=0.17), respectively (**Figure 4**).

In sensitivity analysis, all analyses showed that both in the total population and sub-ethnic populations, the results were similar to the foregoing analysis. Funnel plots and Egger tests also showed no publication bias (**Figure 5**, P=0.545, Egger'S test).

Discussion

Our analysis did not find association between PON1 gene L55M polymorphism and IS. Sen-

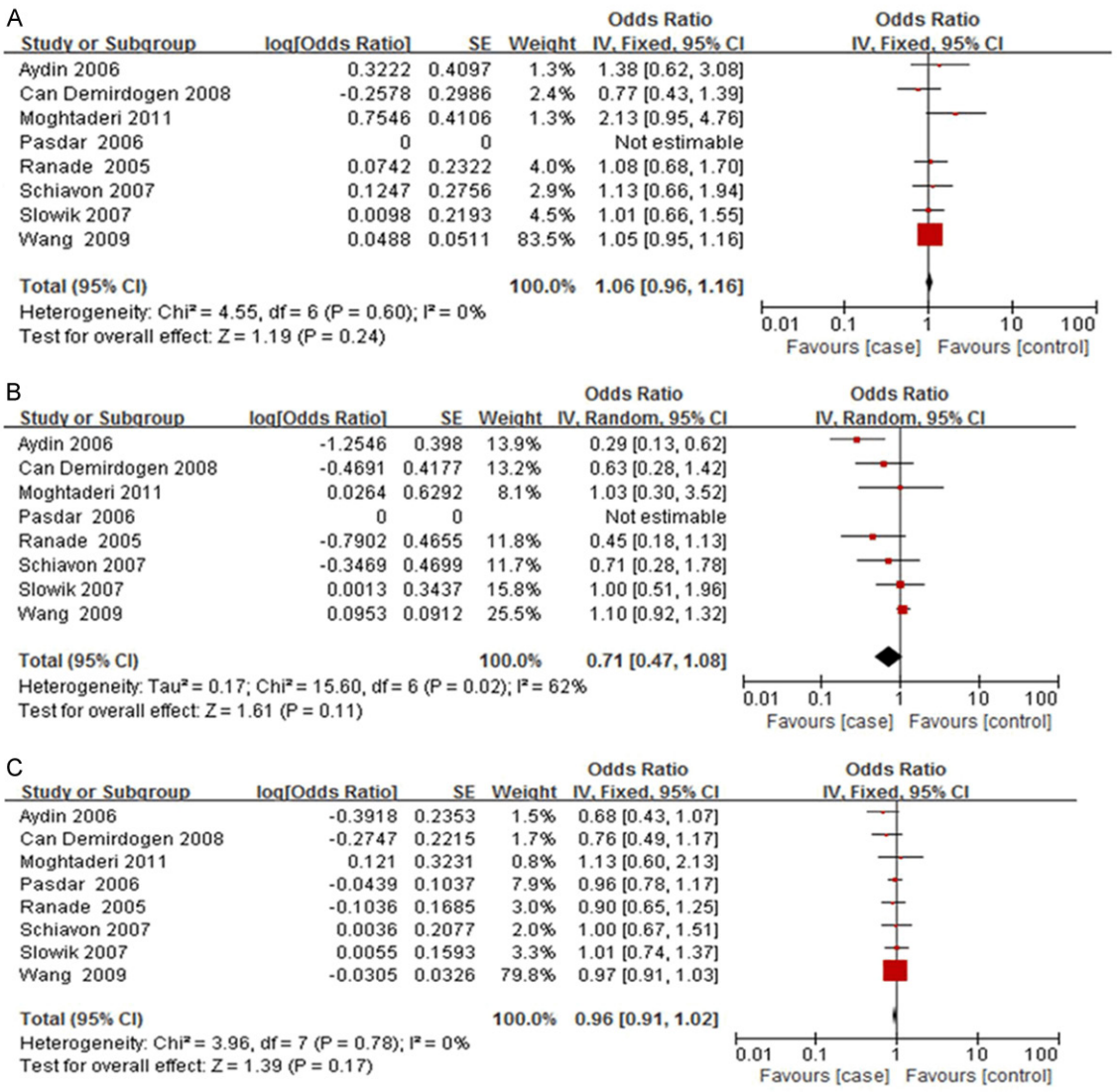

Figure 4. Forest plot of IS and PON1 L55M polymorphism in caucasian population, the horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI. In this analysis, Fixed-effects model was used. A: Additive model; B: Dominant model; C: Recessive model.

sitivity analysis which excluded specifically studies also confirmed the stability and reliability of the results.

Previous studies indicated that L55M genetic polymorphism may be associated with CAD and cerebrovascular disease [33]. And the L55M polymorphism was also reported to be associated with atherosclerosis [33], which is the main pathogenesis of IS. Therefore, the L55M polymorphic gene may also be involved in the risk of IS. However, in the present study, we did not found association between L55M and IS. Despite this, due to the following reasons, the conclusions need to be carefully explained at present. Firstly, the sample size which was included in this study was still small. Zondervan [34] suggested that in a genetic case-control study, if predicted OR value was 1.3 and the statistical power reached up to 80%, the sample size must reach up to 2,000 to 10,000. Secondly, the ethnic differences in individual studies will also affect the results. For example, the study from Brazil, besides Caucasians, Asian and African subjects also were included in the study; Finally, the present study may be affect by other traditional risk factors(age, sex), genotyping error, diagnostic cri-

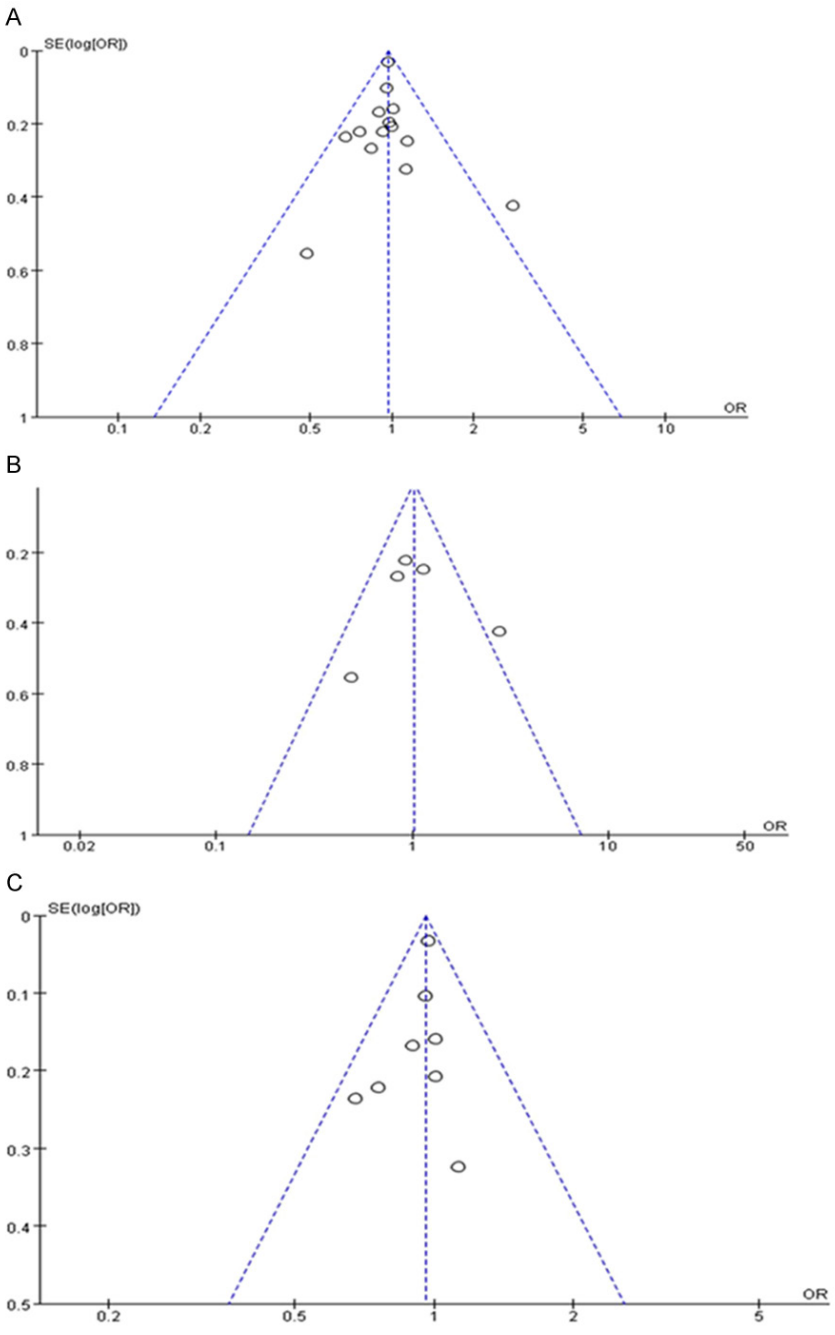

Figure 5. Begg's funnel plot for publication bias tests. Each point represents a separate study for the indicated association. Log or represents natural logarithm of OR. Vertical line represents the mean effects size. A: Total; B: Asian; C: Caucasian.

teria of IS and publication bias and other factors were likely to undermine the reliability of the analysis.

There are several limitations in the present study. First of all, for a population-based observational study by meta-analysis method may only draw estimated conclusion which was affected by a number of confounding factors. For example, one of the studies included the subjects with the age of <45 [27], and population in the control varied greatly in some individual studies. In addition, the definition of race also had different standards,whichmayaffect our results; secondly, due to a smaller number of studies were included in this meta-analysis, the results may be affected by random errors, publication bias and other factors. Finally, there may be a language bias in our study. In the meta-analysis, we only included studies published in English and Chinese language and the articles published in other languages was not included.

Conclusion

The present study indicated that PON L55M gene polymorphism was not associated with the risk of IS. However, a larger sample-size case-control study with improvement on methodologies was expected in the future.

Disclosure of conflict of interest

None.

Address correspondence to: Li-Hua Wang, Department of Pediatrics, Haiyang People's Hospital, No. 73 Haiyang Road, Haiyang 265100, China. Tel: +86 15053543312; Fax: +86 0535-3226395; E-mail: wanglihua113@126.com

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