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META-ANALYSIS

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Promoter Polymorphism (-174, G/C) of Interleukin-6 and Arterial Thromboembolic Events: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Ischemic stroke and myocardial infarction are fatal diseases and are among the top 10 causes of death in Korea, including arterial thromboembolic events. Many previous studies have described the function of interleukin-6 (IL-6) in arterial thromboembolic events and the association between promoter single-nucleotide polymorphism (SNP) (rs1800795; -174, G/C) of the *IL-6* gene. However, these results were controversial. Therefore, we performed a meta-analysis to more precisely assess the association between the SNP of the *IL-6* gene and susceptibility to arterial thromboembolic events.

Material/Methods: We used PubMed, Embase, Google Scholar, and Korean Studies Information Service System (KISS) electronic databases. Comprehensive Meta-analysis software (Corporation, NJ) was used to evaluate the relationship between rs1800795 SNP of *IL-6* gene and risk of arterial thromboembolic events. Odds ratio (OR), 95% confidence interval (CI), and *P* value were also calculated. The 13 eligible studies were analyzed in the meta-analysis.

Results: The present meta-analysis found that rs1800795 SNP of *IL-6* gene is not significantly associated with susceptibility to arterial thromboembolic events (C allele *vs.* G allele, OR=1.04, 95% CI=0.91–1.19, *P*=0.619; CC *vs.* CG+GG, OR=1.09, 95% CI=0.91–1.31, *P*=0.364; CC+CG *vs.* GG, OR=0.97, 95% CI=0.78–1.21, *P*=0.763, respectively), and the SNP of *IL-6* gene also did not show any significant association with ischemic stroke or myocardial infarction (*P*>0.05 in each model).

Conclusions: We found that rs1800795 SNP of *IL-6* gene was not related to arterial thromboembolic events. However, further study will be needed to confirm these results.

MeSH Keywords: Interleukin-6 • Meta-Analysis • Polymorphism, Genetic

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Background

Arterial thromboembolic events may be caused by arterial thrombosis, which is the formation of a thrombus within an artery. Arterial thrombosis is closely related to arterial diseases such as ischemic stroke and myocardial infarction [1]. According to the American Heart Association, stroke is a fatal cerebrovascular disease and the leading cause of death and disability in the United States. In Korea, stroke is the second most common cause of death, and in 2014 it accounted for 50.3 deaths per 100 000 people aged over 65 years, according to Statistics Korea [2]. The age-standardized incidence of ischemic stroke in the population of people aged 35–74 years has been increasing annually, and ischemic stroke accounted for 76% of all cases of strokes in 2009, with a 90-day mortality rate of 3–7% [3]. Statistics Korea also reported 19.6 deaths due to myocardial infarction per 100 000 people in Korea in 2012 (*http://kostat.go.kr*).

Many pro-inflammatory cytokines are known to be involved in the risk of myocardial infarction and stroke. Cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) could play important roles in stroke and have been detected in the cerebrospinal fluid of patients with stroke [4]. Several studies have suggested that plasma levels of TNF-α and IL-6 are associated with patient prognosis following ischemic stroke [5]. Associations between IL-6 and atherosclerosis and cardiovascular disease have also been previously reported [6]. Additionally, previous epidemiological data have shown that IL-6 is associated with clinical and subclinical cardiovascular diseases [7]. IL-6 plays a major role in the synthesis of human acute-phase protein, and plasma IL-6 levels are elevated in patients with acute myocardial infarction [8]. A previous *in vivo* study found that IL-lβ stimulates myocardial injury after IL-6 is induced in endothelial cells and fibroblasts [9]. IL-6 induces a prothrombotic state by increasing expression of tissue factor, activation of endothelial cells, and increasing platelet production, and by reducing the levels of inhibitors of hemostasis [10].

IL-6 gene is located at 7p21 and encodes a cytokine that plays a role in inflammation and B cell maturation (*http://www.ncbi.nlm.nih.gov*). Two single-nucleotide polymorphisms (SNPs), -174, G/C SNP and -572, G/C SNP have been identified in the promoter region of the *IL-6* gene, which might have an effect on IL-6 transcription and plasma IL-6 levels [11–13]. The rs1800795 polymorphism has been examined in many previous studies. An association between *Helicobacter pylori* infection and decreased high-density lipoprotein (HDL) levels could be transmitted through its genotype of the *IL-6* gene [14]. In patients with type 2 diabetes, rs1800795 SNP of the *IL-6* gene is significantly related to increased risk of cardiovascular disease [15]. In addition, rs1800795 SNP of the *IL-6* gene is related with autoimmune diseases such as systemic lupus erythematosus [16], systemic sclerosis [17], and autoimmune thyroid disease [18].

Although several previous studies have investigated the association between rs1800795 polymorphism and ischemic stroke or myocardial infarction risk, these results remain controversial. As the evidence suggests that IL-6 plays a major role in thromboembolic mechanisms, the aim of this meta-analysis was to evaluate the association between rs1800795 polymorphism (-174, G/C) of the *IL-6* gene and arterial thromboembolic events.

Material and Methods

Search strategy

For the meta-analysis, we searched for published studies that considered the relationship between arterial thromboembolic events and polymorphism of the *IL-6* gene. To identify all eligible studies that investigated the association between -176, G/C SNP of the *IL-6* gene and susceptibility of arterial thromboembolic events, we performed a literature search in PubMed, Embase, Google Scholar, and Korean Studies Information Service System (KISS) electronic databases until January 1, 2016. The search terms were; "interleukin-6", "IL-6", or "IL6", AND "polymorphism", "polymorphisms", or "variant" AND "rs1800795", or"-174" AND "ischemic stroke", "myocardial infarction". We also searched previous meta-analyses of *IL-6* gene polymorphism (-174, G/C polymorphism) and ischemic stroke or myocardial infarction.

Inclusion criteria

Studies were included if they met the following criteria: (1) evaluated the association between the *IL-6* polymorphism (-174, G/C) and ischemic stroke or myocardial infarction; (2) study design using the methodology of a case-control study; (3) complete distribution of polymorphism (-174, G/C) of the *IL-6* gene in the disease group and the control group to determine odds ratio (OR), 95% confidence interval (CI), and *P* value; (4) only studies in white populations were included, and studies of Asian populations were excluded.

Data extraction

Two investigators independently searched titles and abstracts in articles. Irrelevant and incompatible studies were excluded. The investigators extracted data and reached consensus on all of the items. If the investigators generated different results, they checked the data again and had a discussion to come to an agreement. The following information were extracted from each study: (1) first author's name; (2) year of publication; (3) country; (4) number of cases and controls; (5) genotype frequency of *IL-6* gene polymorphism (-174, C/G).

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Table 1. Information of eligible studies included in the meta-analysis.

Study	Country	Disease	Case/control (n)	Case			Control			Case		Control		HWE in Control
				C/C	C/G	G/G	C/C	C/G	G/G	C	G	C	G	
Revilla et al. (2002)	Spain	IS	82/82	15	40	27	6	39	37	70	94	51	113	0.32
Balding et al. (2004)	Ireland	IS	105/389	12	60	33	68	198	123	84	126	334	444	0.45
Flex et al. (2004)	Italy	IS	237/223	22	115	100	68	99	56	159	315	235	211	0.10
Chamorro et al. (2005)	Spain	IS	273/105	35	134	104	9	50	46	204	342	68	142	0.37
Lalouschek et al. (2006)	Austria	IS	404/415	74	187	143	67	192	156	335	473	326	504	0.54
Bazina et al. (2015)	Croatia	IS	114/187	22	53	39	26	98	63	97	131	150	224	0.21
Georges et al. (2001)	France	MI	614/672	104	340	170	105	336	231	548	680	546	798	0.35
Nauck et al. (2002)	Germany	MI	2575/729	261	668	436	144	355	230	1190	1540	643	815	0.74
Licastro et al. (2004)	Italy	MI	138/97	15	88	35	7	44	46	118	158	58	136	0.42
Lieb et al. (2004)	Germany	MI	1322/1023	244	627	451	193	499	331	1115	1529	885	1161	0.84
Kelberman et al. (2004)	UK	MI	507/561	61	219	227	81	240	240	341	673	402	720	0.10
Chiappelli et al. (2005)	Italy	MI	138/204	21	112	71	24	106	127	154	254	154	360	0.78
Bennermo et al. (2011)	Sweden	MI	356/378	87	150	119	93	176	109	324	388	362	394	0.19

IS – ischemic stroke; MI – myocardial infarction; HWE – Hardy-Weinberg equilibrium.

Statistical analysis

Comprehensive meta-analysis software (Corporation, NJ) was used to perform the meta-analysis. The pooled OR, 95% CI, and *P* value were used to measure associations between susceptibility of arterial thromboembolic events and IL-6 polymorphism (-174, G/C). Firstly, we calculated the heterogeneity of studies. Heterogeneity among studies was assessed using the Q statistic and I^2 test. When the result of the Q test was $P<0.05$ or I^2 statistic was >50%, the random-effects Mantel-Haenszel method was used to determine if there was significant heterogeneity between studies. When the result of the Q test was $P>0.05$ or I^2 statistic was <50%, the fixed-effects Mantel-Haenszel method was used.

For meta-analysis of *IL-6* gene polymorphism (-174, C/G), the pooled ORs, 95% CI, and p value were calculated using combination of genotype. We first estimated the risks of "C allele *vs*. G allele", "C/C genotype+C/G genotype *vs*. G/G genotype", and "C/C genotype *vs*. C/G genotype+G/G genotype" on arterial thromboembolic events, assuming dominant and recessive effects of the variant C allele, respectively. Subgroup analyses were carried out by ischemic stroke or myocardial infarction. The $P<0.05$ was regarded as a statistically significant association.

Results

Study characteristics

To assess the association between polymorphism (-174, G/C) of *IL-6* gene and susceptibility to arterial thromboembolic events, related studies were retrieved based on the search strategy. First, we searched related studies on arterial thromboembolic events including ischemic stroke and myocardial infarction. Our meta-analysis was limited to case-control design with promoter polymorphism (-174, G/C) of the *IL-6* gene and ischemic stroke or myocardial infarction in white populations. Although 6 articles were studied with polymorphism (-174, G/C) of *IL-6* gene and susceptibility of ischemic stroke or myocardial infarction in Asian populations [19–24], the articles were excluded in the meta-analysis. Finally, 13 eligible articles were selected [25–37]. The characteristics of these 13 eligible studies are summarized in Table 1. The 13 studies consisted of 6 articles on ischemic stroke and 7 articles on myocardial infarction.

Quantitative synthesis for arterial thromboembolic events

Table 2 and Figure 1 shows overall results between *IL-6* gene polymorphism (-174, G/C) and susceptibility to arterial thromboembolic events. We analyzed whether risk of the C allele and combined genotype of the SNP were related with susceptibility of arterial thromboembolic events. The results of the Q test were *P* value or *I2*statistic in analysis of C allele *vs*. G allele, CC

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Table 2. Overall analysis between interleukin-6 polymorphism (-174, G/C) and susceptibility of arterial thromboembolic events.

	Comparison	Heterogeneity		Model	Association test		Publication bias
		P	I^2		OR (95% CI)	*P*	Egger's test *P*
IS+MI	C *vs.* G	<0.001	80.941	Random	1.04 (0.91–1.19)	0.619	0.454
IS	C *vs.* G	<0.001	87.738	Random	0.99 (0.70–1.40)	0.930	0.642
MI	C *vs.* G	0.002	70.814	Random	1.07 (0.94–1.22)	0.319	0.090
IS+MI	CC *vs.* CG+GG	<0.001	75.820	Random	1.09 (0.91–1.31)	0.364	0.321
IS	CC *vs.* CG+GG	0.002	72.982	Random	0.99 (0.70–1.39)	0.929	0.734
MI	CC *vs.* CG+GG	<0.001	80.143	Random	1.17 (0.93–1.46)	0.187	0.080
IS+MI	CC+CG *vs.* GG	<0.001	71.398	Random	0.97 (0.78–1.21)	0.763	0.783
IS	CC+CG *vs.* GG	<0.001	86.953	Random	0.98 (0.50–1.92)	0.931	0.706
MI	CC+CG *vs.* GG	0.827	<0.001	Fixed	0.99 (0.88–1.11)	0.778	0.290

IS – ischemic stroke; MI – myocardial infarction; OR – odds ratio; CI – confidence interval.

genotype *vs.* CG genotype+GG genotype, and CC genotype+CG genotype *vs.* GG genotype were <0.05 and >50%, the random-effects Mantel-Haenszel method was used (Table 2). In analysis, the pooled ORs and *P* value in allele model and combined genotype models did not show any significant association with susceptibility of arterial thromboembolic events (C allele *vs.* G allele, OR=1.04, 95% CI=0.91–1.19, *P*=0.619; CC genotype *vs.* CG genotype+GG genotype, OR=1.09, 95% CI=0.91–1.31, *P*=0.364; CC genotype+CG genotype *vs.* GG genotype, OR=0.97, 95% CI=0.78–1.21, *P*=0.763, respectively) (Table 1, Figure 1).

We also performed subgroup analyses of ischemic stroke and myocardial infarction. However, *IL-6* gene polymorphism (-174, G/C) did not show any significant association with ischemic stroke (C allele *vs.* G allele, OR=0.99, 95% CI=0.70–1.40, *P*=0.930; CC genotype *vs.* CG genotype+GG genotype, OR=0.99, 95% CI=0.70–1.39, *P*=0.929; CC genotype+CG genotype *vs.* GG genotype, OR=0.98, 95% CI=0.50–1.92, *P*=0.931, respectively) (Table 2, Figure 2) and myocardial infarction (C allele *vs.* G allele, OR=1.07, 95% CI=0.94–1.22, *P*=0.319; CC genotype *vs.* CG genotype+GG genotype, OR=1.17, 95% CI=0.93–1.46, *P*=0.187; CC genotype+CG genotype *vs.* GG genotype, OR=0.99, 95% CI=0.88–1.11, *P*=0.778, respectively) (Table 2, Figure 3).

To assess publication bias, Begg's funnel plot was used out and Egger's test was calculated. The funnel plot was symmetrical (data not shown), suggesting that there was no publication bias. Additionally, Egger's test showed quantitative evidence for absence of publication bias (*P*>0.05 in each model, Table 2).

Discussion

According to Statistics Korea, stroke and cardiovascular diseases were among the top 10 causes of death in Korea in 2014. Among them, stroke is the number 2 cause of death (*http://kostat.go.kr*). According to the Korea National Emergency Medical Center in 2014, a total of 26 208 patients visited emergency departments due to myocardial infarction and 430 patients died. A total of 91 924 stroke patients visited emergency departments due to stroke and 451 patients died in 2013 (*http://www.nemc.or.kr*). These diseases cause death and disability, creating burdens for patients, their families, society, and the world [3].

Therefore, there have been many attempts to predict or prevent these diseases. C-reactive protein (CRP) and creatinine in serum are used to predict coronary heart disease risk [38]. Red blood cell distribution width and calcium score can be used to assess cardiovascular event risk stratification and prevention [39]. Some authors developed risk scoring system for prediction of atypical symptom presentation in acute myocardial infarction patients [40]. Increase in the systemic inflammatory marker procalcitonin is related to no-reflow after primary percutaneous coronary intervention in ST-elevation myocardial infarction patients [41]. Hemorheological abnormalities, poor glycemic control, and low HDL cholesterol are used as markers and predictors for major adverse cardiovascular events and coronary heart disease in outpatients [42]. The ankle-brachial index is useful in predicting acute ischemic stroke [43].

Recently, many studies have reported the genetic contribution to predict or prevent these diseases. Several studies showed the genetic contribution to inflammatory and hemostatic

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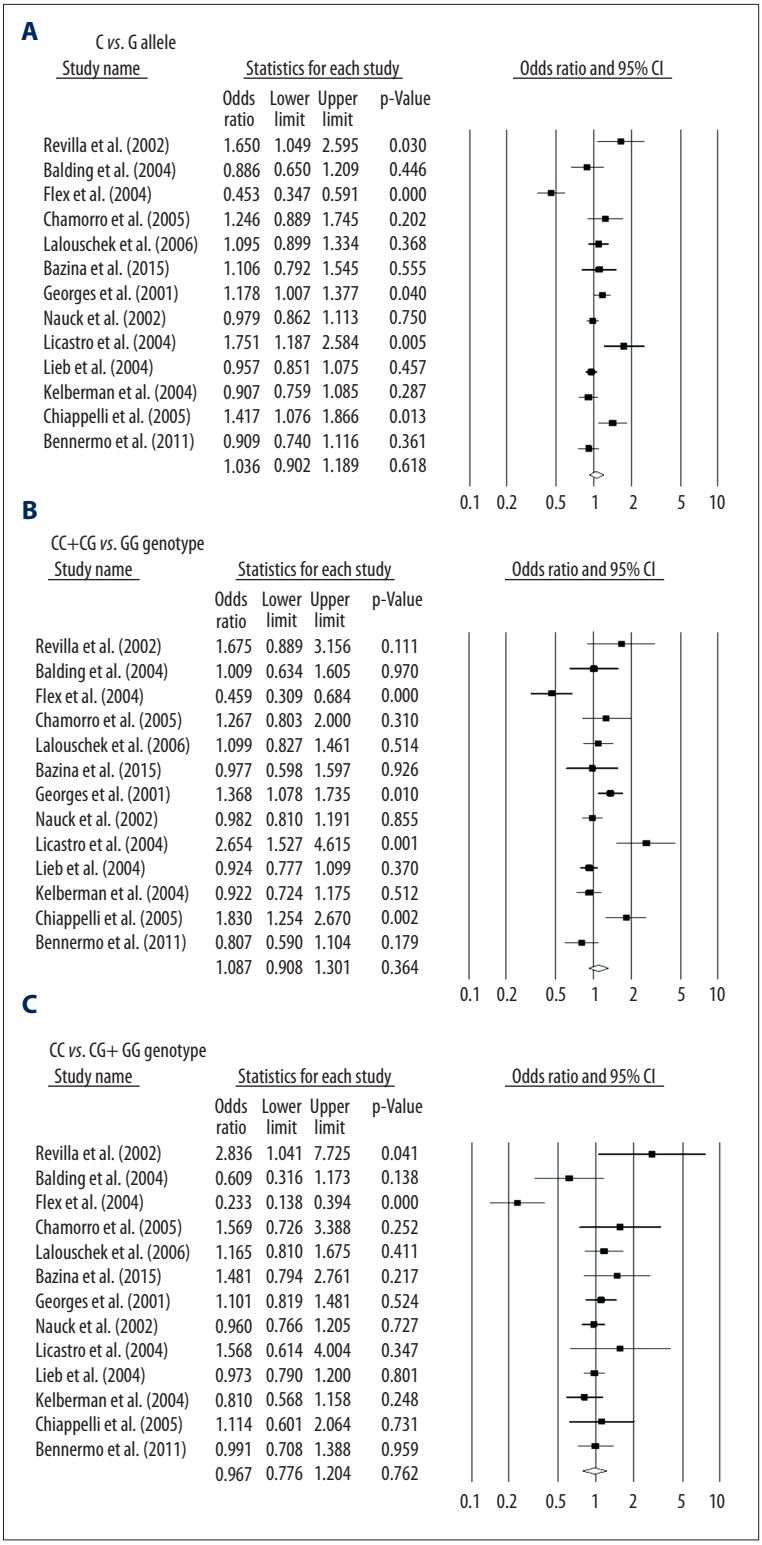

Figure 1. Interleukin-6 polymorphism (-174, G/C) and susceptibility to arterial thromboembolic events.

biomarkers in ischemic stroke patients [44]. *CYP2C19* gene polymorphisms are associated with long-term recurrent risk of ischemic stroke [45]. Peroxisome proliferator-activated receptors could be a protective factor for ischemic stroke in the Chinese Han population [46]. A previous study showed that genetic factors are associated with age at stroke onset and sex [47]. Gene-specific DNA methylation profiles and LINE-1 hypomethylation are associated with myocardial infarction

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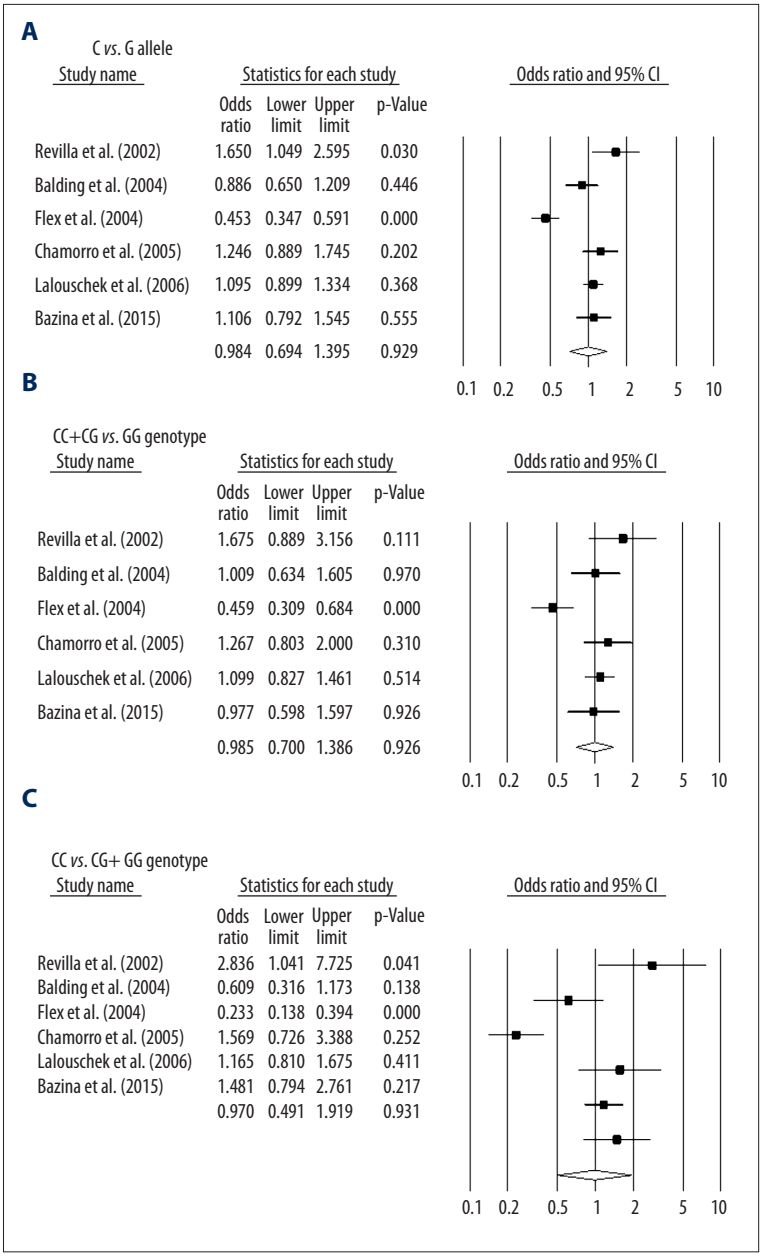

Figure 2. Interleukin-6 polymorphism (-174, G/C) and susceptibility to ischemic stroke.

risk [48]. Recently, there was an attempt to find predictors of myocardial infarction using genotype/allelic combinations by analysis of genotype frequencies of polymorphic markers [49].

Inflammatory cytokines in arterial lesions plays various roles, including plaque formation and progression and vessel thrombosis [50]. Cytokines produce adhesion molecules, matrix metalloproteinases, and reactive oxygen species and induce the expression of the messenger cytokine IL-6, which causes the release of C-reactive protein, fibrinogen, and plasminogen activator inhibitor-1. These lead to atherothrombosis, which is the proximate cause of arterial thrombosis [51]. The genotype of IL-6 is also involved in this process. The IL-6 genotype was significantly associated with thrombosis in children [52] and increased risk of ischemic stroke [53].

Therefore, we performed this meta-analysis to examine the possible association between IL-6 rs1800795 polymorphism and ischemic stroke and myocardial infarction risks. However, we found no statistically significant association between the IL-6 rs1800795 polymorphism and ischemic stroke or myocardial infarction risks in any models.

In the present study, we collected previous studies on ischemic stroke or myocardial infarction and IL-6 polymorphism and could not find any associations. Our results agree with a

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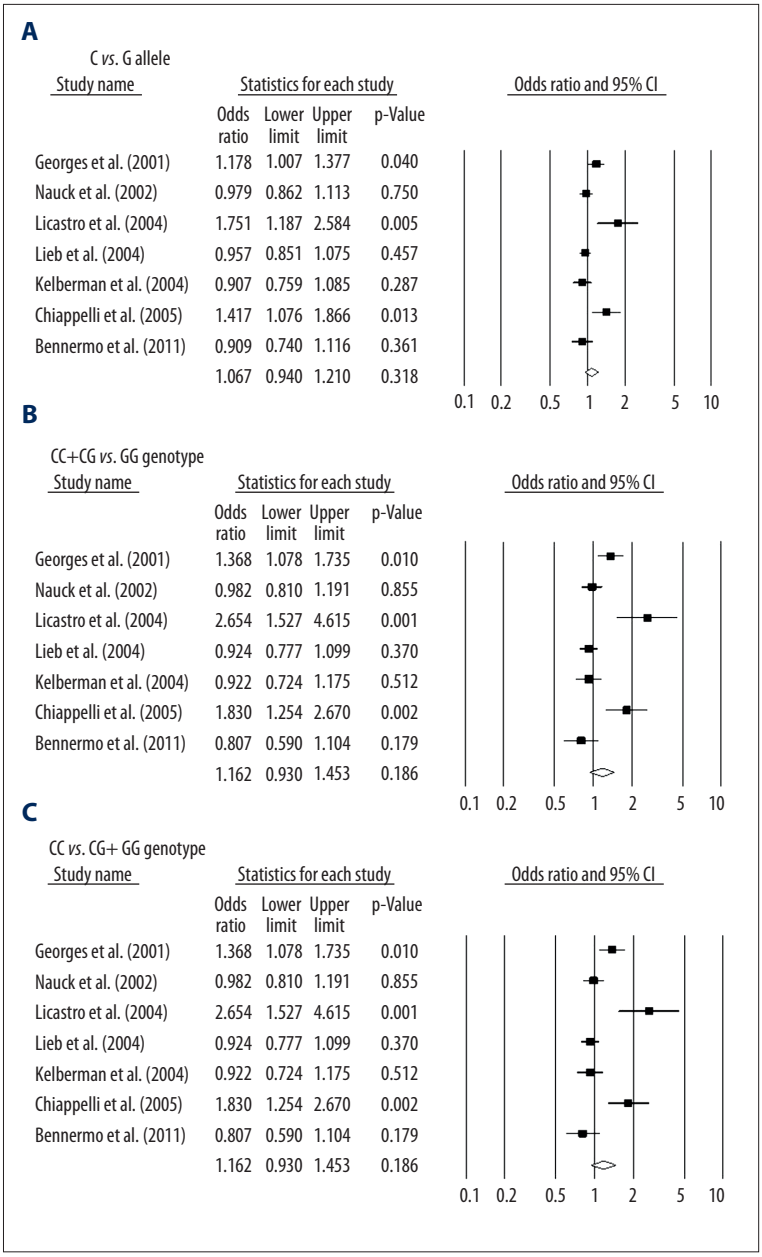

Figure 3. Interleukin-6 polymorphism (-174, G/C) and susceptibility to myocardial infarction.

previous meta-analysis in 2012, which reported a significant association between IL-6 gene -174 G/C polymorphism and myocardial infarction risk in Asians but not in whites [54]. As there were few studies on Asians, we included only studies on whites and found no association. A previous study showed that pro-inflammatory and prothrombotic polymorphisms, including IL-6, were not associated with perinatal arterial ischemic stroke [55].

Conclusions

It is clear that IL-6 plays an important role in the initiation of thrombosis, resulting in ischemic stroke or myocardial infarction. However, we could not show any statistical significance in the models. It appears that IL-6 rs1800795 is not associated with ischemic stroke or myocardial infarction risk. Further studies including clinical features are needed to clarify the possible relationship between IL-6 rs1800795 polymorphism and the development of ischemic stroke or myocardial infarction.

Conflict of interest

None.

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