Association between Interleukin-6 (G174C and G572C) promoter gene polymorphisms and risk of ischaemic stroke: A meta-analysis

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KEY WORDS

Ischaemic stroke
Inflammatory gene
Single nucleotide Polymorphisms
Interleukin-6
Cytokine
Meta-analysis

ABSTRACT

Background: Interleukin-6 (IL-6), as one of the most typical pro-inflammatory and immunoregulatory cytokines, is believed to be associated with the genesis and maintenance of inflammatory response. Genetic association studies (GAS) that have investigated the association between Interleukin 6 (G174C and G572C) promoter gene polymorphisms and susceptibility to ischemic stroke (IS) which have produced contradictory and unconvincing results.

Purpose: The aim of this meta-analysis is to provide a relatively comprehensive account of the association of IL-6 (G174C and G572C) polymorphisms with susceptibility to IS.

Methods: A literature search was conducted using electronic database PubMed, Medline, and Trip database for all case-control studies investigating for association of IL-6 genetic polymorphisms with ischemic stroke published till August 30, 2014. The following combinations of main keywords were used: ('Interleukin-6' or 'IL-6') and ('ischaemic stroke or 'cerebral infarction' or 'IS') and ('genetic polymorphism' or 'single nucleotide polymorphisms' or 'SNP'). Pooled Odds ratios (ORs) and 95% confidence intervals (CIs) were determined for IL-6 gene-disease association. Meta-analysis was carried out using Revman 5.3 software.

Results: 16 case-control studies involving a total of 3,317 IS patients and 3,432 healthy controls for G174C polymorphism and 3 case-control studies with a total of 2,001 IS patients and 2,027 healthy controls for G572C IL-6 gene polymorphisms were included in a meta-analysis. For IL-6 G174C gene polymorphisms, no significant association was observed under dominant [GC + CC vs. GG: OR = 1.01, 95% CI: 0.77–1.34, P = 0. 92], recessive [CC vs. GG + GC: OR = 0.82, 95% CI: 0.40–1.70, P = 0. 59] and allelic model [C vs. G Allele: OR = 0.99, 95% CI: 0.74–1.31, P = 0. 93]. For IL-6 G572C, no significant association was observed under dominant [CC vs. GG + GC: OR = 0.99, 95% CI: 0.57–1.71, P = 0. 97], recessive [CC vs. GG + GC: OR = 0.93, 95% CI: 0.60–1.45, P = 0. 75] and allelic model [C vs. G Allele: OR = 0.95, 95% CI: 0.66–1.36, P = 0. 76].

Conclusion: This meta-analysis shows that IL-6 (G174C) and IL-6 (G572C) gene polymorphisms may not be associated with an increased susceptibility to IS. Further studies are required for confirmatory results.

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Introduction

Stroke is the third leading cause of death worldwide after Ischemic Heart Disease (IHD) and Cancer. Stroke has accounted for nearly 5.7 million deaths worldwide, 87% of these deaths occur in low and middle income countries.[1] Incidence of stroke in South Asian countries has increased by more than 100%, while this is decreased by 42% in developed European countries in last four decades.[2] Ischaemic stroke (IS) accounts for 85% of stroke and its pathophysiology are regulated by a combination of lifestyle, environmental and unclear genetic risk factors.[3] Inflammation and genetics are both prominent mechanisms in the pathogenesis of ischemic stroke.[4] Candidate genes, stroke susceptibility alleles and their association with stroke pathogenesis have been intensely studied in the last few years.[5,6]

Human Interleukin-6 (IL-6) gene is located at chromosome 7p21 which consists of 5 exons and 4 introns and synthesized as a precursor protein of 232 amino acids.[7,8] IL-6 is a pleiotropic cytokine associated with atherosclerosis and cardiovascular disease that may also be a key mediator in the inflammatory response to ischemic stroke.[9] Two functional promoter polymorphisms, G174C and G572C have been identified in the IL-6 promoter region and these two genetic variants may be associated with the increased level of IL-6.[10] The levels of IL-6 were found to be increased in both serum and cerebro-spinal fluid after ischemic stroke, and elevated IL-6 levels have been associated with greater stroke severity, larger final infarct volume, early neurological worsening, and worse functional outcome.[11–18]

Numerous studies have investigated the association of IL-6 G174C and G572C gene polymorphisms in relation to various ischaemic and atherosclerotic cardiovascular diseases. Associations have been reported between the *GG* genotype and asymptomatic carotid artery atherosclerosis,[19–22] risk of coronary heart disease,[23] peripheral arterial occlusive disease,[24] multi-infarct dementia,[25] and longer hospital and intensive care unit stay after coronary artery bypass graft surgery.[26] However, other studies have found associations between the *CC* genotype and asymptomatic carotid artery atherosclerosis and increased mortality among abdominal aortic aneurysm patients.[27] Reasons for these contradictory findings are unclear.

Inflammation and ischemic stroke are interrelated as many studies suggest that IL-6 may play a central role in the inflammatory response to cerebral ischemia.[28–43] However, although the role of IL-6 in ischemic stroke has been extensively studied, the influence of IL-6 genetic polymorphisms on stroke is not well understood. The purpose of this meta-analysis is to summarize the studies that have examined the IL-6 (G174C and

G572C) polymorphism in relation to ischemic stroke and to discuss the implications of these results for future research.

Methods

Identification of Relevant Studies

A literature search for GAS that investigated the association between the IL-6 gene polymorphisms and susceptibility to IS published before August 30, 2014 which was conducted in the following electronic databases: PubMed, Medline and trip databases. The following combinations of main keywords were used: ('Interleukin-6' or 'IL-6') and ('ischaemic stroke or 'cerebral infarction' or 'IS') and ('genetic polymorphism' or 'single nucleotide polymorphisms' or 'SNP'). The search was done without limitations on language, but only included those studies that were conducted on human subjects. All references in eligible articles were extensively reviewed to identify additional published articles.

Inclusion and Exclusion Criteria

To be included in the analysis, eligible studies had to meet the following criteria: (a) case-control studies on the association between the IL-6 gene polymorphisms and susceptibility to IS; (b) all patients in the candidate studies meet the diagnostic criteria for IS; (c) studies with sufficient available data to calculate Odds Ratios (ORs) with corresponding 95% Confidence intervals (CIs). The major reason for excluding studies were: (i) not case-control study; (ii) duplicates publications with overlapping subjects from the same study; and (iii) no available data reported. For multiple studies using overlapping cases or controls, the most recent study with the largest sample size was included in the meta-analysis. This metaanalysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines with only slight modification, and did not require ethics board approval.[44]

Data Extraction

According to the PRISMA guidelines, two investigators independently PK and AKY checked each full-text report for eligibility and extracted the following data from eligible studies: surname of first author, year of publication, country of origin, ethnicity, number of case and control, age, sex ratio, genotyping method, allele and genotype frequency etc. Disagreements were solved by discussion between all authors until consensus was reached.

Quality Assessment

Newcastle-Ottawa Scale (NOS) criteria[45] were used to assess the qualities of all included studies. The NOS criteria use a ''star'' rating system to judge methodological quality based on three aspects of a study: selection, comparability, and exposure. Scores range from 0 stars (worst) to 9 stars (best), with a score of 5 or higher indicating a moderate-high methodological quality. Two authors independently assessed the quality of included studies. Discrepancies over quality scores were resolved by discussion with all authors and subsequent consensus.

Statistical Analysis

Genotype distributions in the controls were tested for conformation to Hardy-Weinberg equilibrium (HWE) using the chi-square test. HWE in the controls was tested by comparing the expected and observed genotype frequencies using the Pearson chi-square test for goodness of fit. The association between the IL-6 gene polymorphisms and susceptibility to IS was assessed by the pooled odds ratios (ORs) with their corresponding 95% confidence intervals (95%CIs) under three genetic models, including dominant, recessive and allelic model. Taking into consideration possible between-study heterogeneity, a statistical test for heterogeneity was first conducted using Cochran's Q statistic and the I^2 metric. We considered the presence of significant heterogeneity at the 10% level of significance and values of I^2 exceeding 50% as an indicator of significant heterogeneity. When no heterogeneity was found with P.0.10 or $I^2 < 50\%$, a fixed-effects model was used to estimate the pooled ORs and 95%CIs. Otherwise, a random-effects model was applied. In addition to an overall comparison, stratified analyses, based on ethnicity, source of control, HWE status, and genotyping method where applicable, were also performed to explore possible explanations of between-study heterogeneity and to investigate whether overall reported associations were present in subgroups. Begg's funnel plot was used to assess the potential for publication bias.

Results

Figure-1 represents a flow diagram of retrieved and excluded studies with their reasons for exclusion. A total of 285 relevant papers were identified using the pre-specified search strategy. In accordance with the inclusion criteria, 16 case-control studies were included for IL-6 G174C with a total of 3317 IS patients and 3482 healthy controls and 3 case control studies for IL-6 G572C with a total of 1814 IS patients and 3219 healthy controls in this meta-analysis. For IL-6 G174C, studies were conducted in two major ethnic populations, with nine including Asians and seven as Caucasians. The publication duration of included studies ranged from 2002 to 2014. The characteristics and methodological quality of all included studies are summarized in Table-1.

Association between the IL-6 G174C Polymorphism and Susceptibility to IS

Sixteen case-control studies[28–38] investigated the relationship between G174C and susceptibility to IS with a total of 3317 IS patients and 3432 healthy controls. Since between-study heterogeneity obviously existed ($P<0.10$ and $I^2 >50\%$ under all genetic models), the random-effect model was used. As shown in Figure-2, no significant association was found under dominant

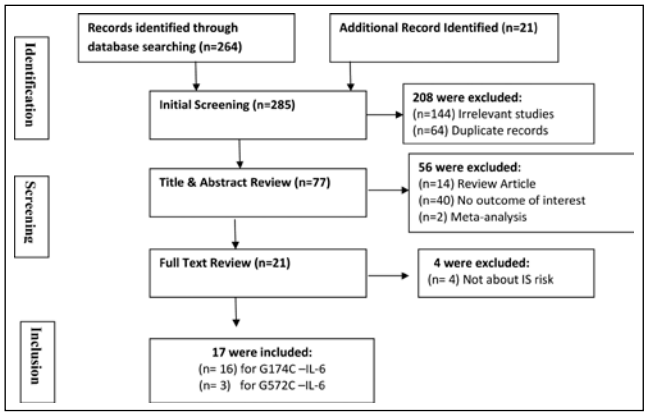


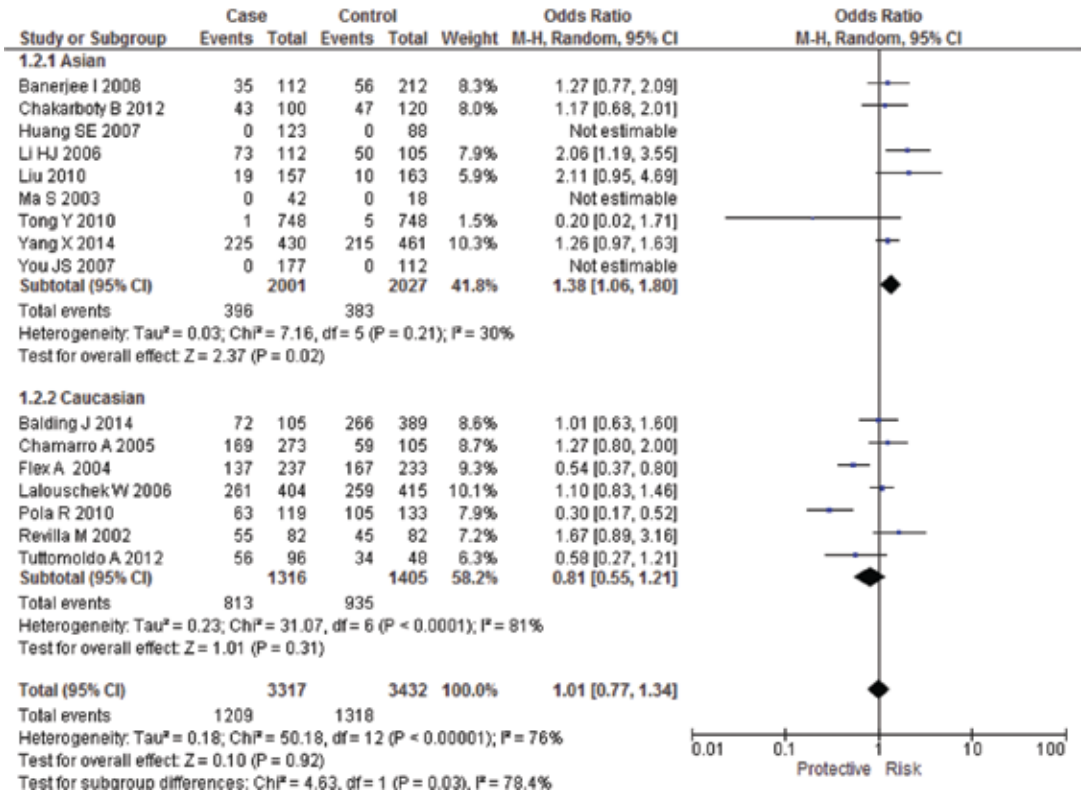
Fig. 1: Flow diagram of the selection of studies and specific reasons for exclusion from the present meta-analysis.

Table 1: Characteristic of studies included in the meta-analysis of the association of IL-6 G174C and G572C gene polymorphism with the risk of ischemic stroke

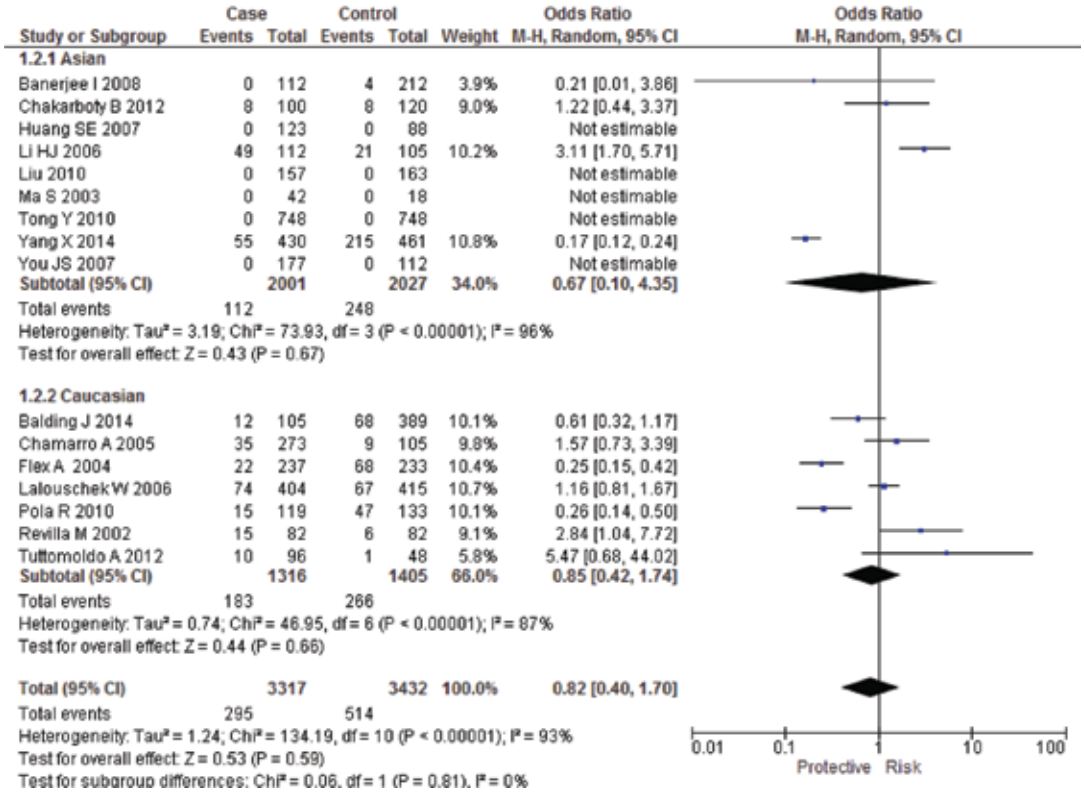
S.No	Year	Author	Origin	Ethnicity	Cases/ controls	HWE	Matching criteria	Genotyping Method	Variants	M/F	Age [Mean ± S.D]	NOS Star	Source of control
1.	2010	Tong *et al.*	China	Asian	748/748	Yes	Age + Sex	Taqman Sequencing	G174C	431/317	61.52 ± 9.68	8/9	PB
									G572C	431/317	60.61 ± 9.11		
2.	2005	Lalouschek et *al.*	Austria	Caucasian	404/415	Yes	Smoking	Multiplex PCR	G174C	257/147	53 (49–57)	8/9	PB
										253/162	49 (43–56)		
3.	2004	Flex *et al.*	Italy	Caucasian	237/223	Yes	Age + Sex	PCR-RFLP	G174C	132/105	76.2 ± 9.4	6/9	HB
										107/116	76.1 ± 6.8		
4	2012	Tuttolomondo *et al.*	Italy	Caucasian	96/48	No	Age	PCR-RFLP	G174C	45/51	71.9 ± 9.75	7/9	HB
										16/32	71.4 ± 7.45		
5.	2008	Banerjee *et al.*	India	Asian	112/212	Yes	Age + Sex	PCR-RFLP	G174C	72/40	58.6 ± 14.2	7/9	HB
										143/69	57.4 ± 8.8		
6.	2012	Chakraborty *et al.*	India	Asian	100/120	Yes	Age + Sex	PCR-RFLP	G174C	69/31	54.0 ± 10.9	8/9	PB
										83/37	52.5 ± 9.8		
7.	2002	Revilla *et al.*	Spain	Caucasian	82/82	Yes	Age + Sex	PCR-RFLP	G174C	60/22	64.9 ± 9.5	7/9	HB
										55/27	64.8 ± 9.1		
8.	2003	Ma *et al.*	China	Asian	42/18	Yes	–	–	G174C			8/9	PB
9.	2004	Balding *et al.*	Ireland	Caucasian	105/389	Yes	Sex	PCR-RFLP	G174C	63/32	69 (35–99)	7/9	PB
										226/163	37.1 (18–65)		
10.	2005	Chamorro *et al.*	Spain	Caucasian	273/105	Yes	Sex + Same area	PCR-RFLP	G174C	191/82	67.0 ± 10	6/9	HB
										62/43	64.0 ± 10		
11.	2006	Li *et al.*	China	Asian	112/105	No	NA	PCR-RFLP	G174C	NA	NA	8/9	PB
12.	2010	Liu *et al.*	China	Asian	157/163	Yes	NA	PCR-RFLP	G174C	NA	NA	8/9	PB
13.	2007	Huang *et al.*	China	Asian	123/88	Yes	NA	PCR-RFLP	G174C	NA	NA	8/9	PB
14.	2007	You *et al.*	China	Asian	177/112	Yes	NA	PCR-RFLP	G174C	NA	NA	7/9	PB
15.	2014	Xuan *et al.*	China	Asian	430/461	Yes	Age	Taqman Sequencing	G174C	261/169	45.4 ± 9.5	6/9	HB
									G572C	253/208	44.8 ± 10.1		
16.	2002	Pola *et al.*	Italy	Caucasian	119/133	Yes	Age + Sex	PCR-RFLP	G174C	57/62	76.8 ± 8.4	7/9	HB
										62/71	76.2 ± 7.1		
17.	2006	Yamada *et al.*	Japan	Asian	636/2010	Yes	Smoking + BMI	PCR-SSCP	G572C	372/264	67.2 ± 11.1	7/9	HB
										844/1166	63.0 ± 11.4		

M = Male; F = Female; S.D = Standard Deviation; HWE = Hardy Weinberg Equilibrium; NOS = Newcastle Ottawa Scale; PB = Population Based; HB = Hospital based, PCR-RFLP-Polymerase Chain Reaction-Restriction Fragment Length Polymorphism, RT-PCR-Real Time-Polymerase Chain Reaction.

A. Dominant Model IL-6 G174C



B. Recessive Model IL-6 G174C



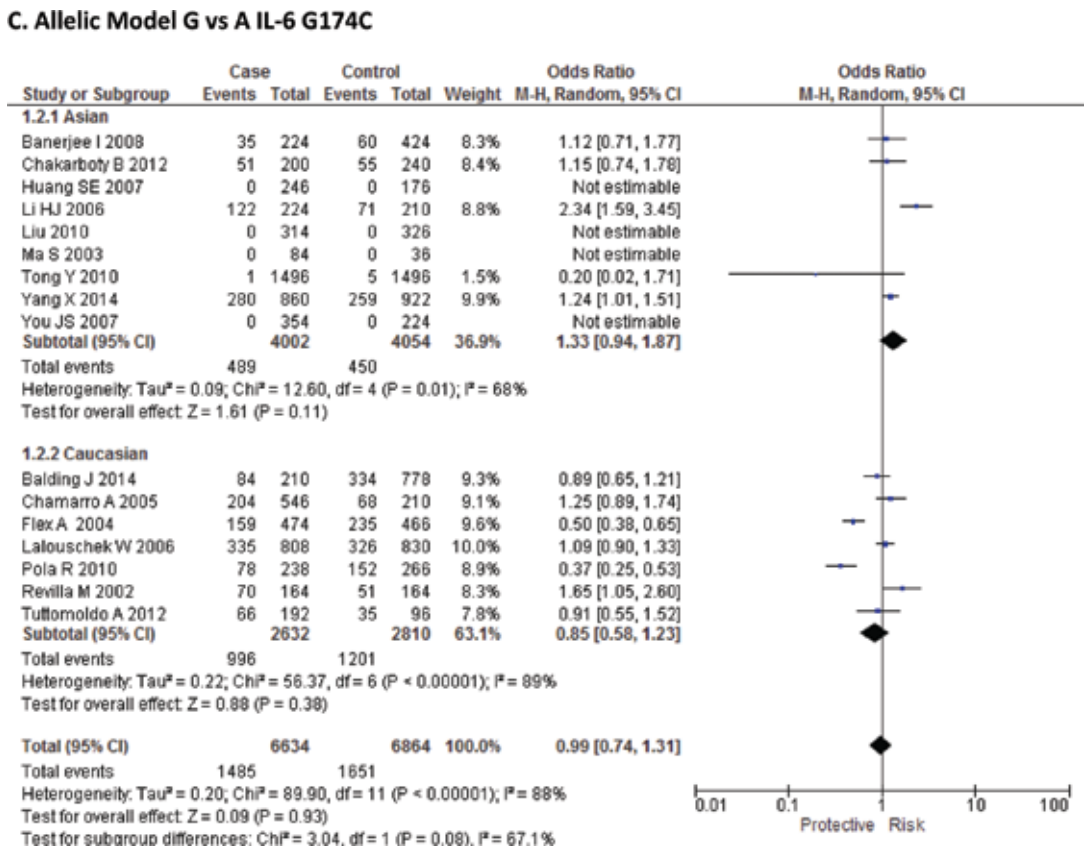


Fig. 2: Forest plots for association between IL-6 G174C polymorphism and IS risk in **(A)** Dominant model (CC + GC vs. GG); **(B)** Recessive model (CC vs. GG + GC); **(C)** Allelic Model [C allele vs. G allele] based on ethnic studies.

[GC + CC vs. GG: OR = 1.01, 95% CI: 0.77–1.34, P = 0. 92], recessive [CC vs. GG + GC: OR = 1.02, 95% CI: 0.58–1.78, P = 0. 95] and allelic model [C vs. G Allele: OR = 0.99, 95% CI: 0.74–1.31, P = 0. 93]. Based on an ethnicity stratification analysis, a significant association was observed under a dominant model [GC + CC vs. GG: OR = 1.34, 95% CI: 1.10–1.62, P = 0. 003] in Asians, but not in Caucasians [GC + CC vs. GG: OR = 0.81, 95% CI: 0.55–1.21, P = 0. 31] studies (Figure-3).

Begg's funnel plots were used to assess the potential publication bias of included Asian studies under a dominant model for IL-6 G174C SNPs. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Figure-4).

Association between the IL-6 G572C Polymorphism and Susceptibility to IS

Three case-control studies had investigated the relationship between G572C[28,30,41] and susceptibility to IS with a total of 1814 IS patients and 3219 healthy controls. Since between-study heterogeneity obviously existed (P<0.10 and I^2 >50% under all genetic models), the random-effects model was used. Overall, the IL-6 G572C polymorphism was not significantly associated with the susceptibility of IS under dominant [GC + CC vs. GG: OR = 0.99, 95% CI: 0.57–1.71, P = 0. 97], recessive [CC vs. GG + GC: OR = 0.93, 95% CI: 0.60–1.45, P = 0. 75] and allelic model [C vs. G Allele: OR = 0.95, 95% CI: 0.66–1.36, P = 0. 76] (Figure-5).

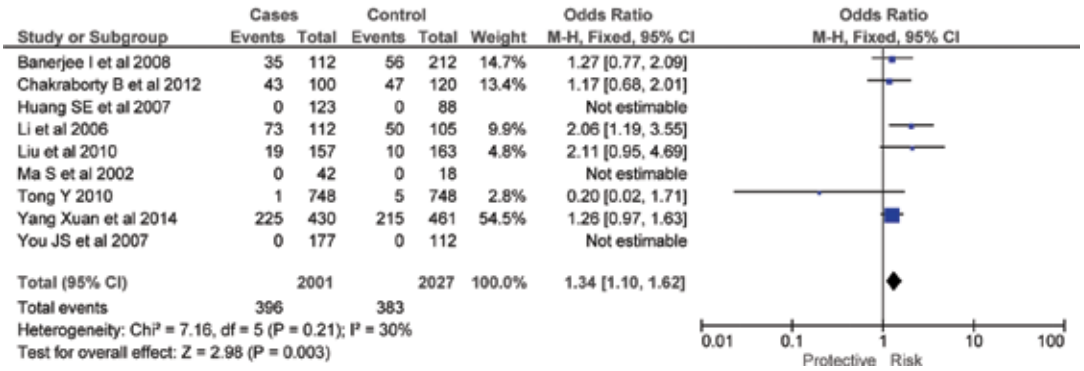
Discussion

This study was designed to advance the understanding of association between the IL-6 G174C and G572C gene polymorphism and risk of ischaemic stroke. In this meta-analysis, 17 studies (16 studies for G174C, 3 studies for G572C) on IL-6 polymorphisms were performed to provide the most comprehensive assessment of the association between the polymorphisms and IS risk. Our data did not support a genetic association between the polymorphisms and IS risk in populations.

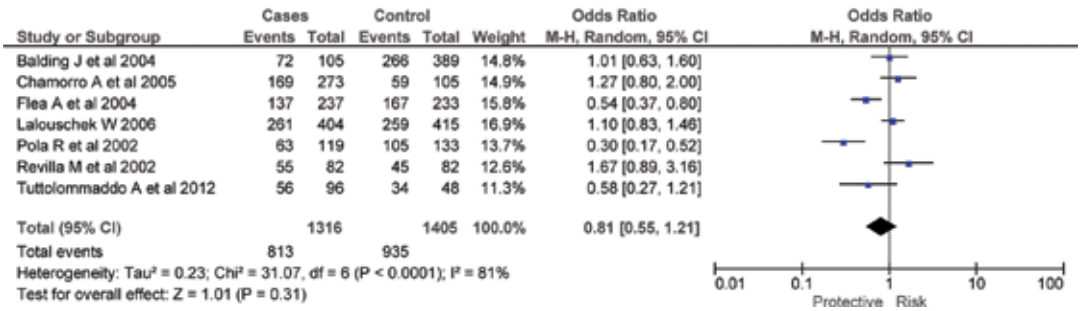
This meta-analysis must be interpreted with caution because of certain limitations. First, the outcomes were based on individual unadjusted ORs, whereas a more precise evaluation should be adjusted by potentially suspected factors, including age, gender, smoking status, and environmental factors. Second, these estimations were obtained by pooling the studies with regard to heterogeneity. However, heterogeneity provided the opportunity to identify factors that modified the genotype. Our meta analysis show heterogeneity except in dominant model of quality studies and some of the factors identified are age, sex, quality of studies and risk factors for ischaemic stroke which could not be stratified in our metaanalysis due to lack of raw data in studies. Pooling studies with different results lead to a high degree of heterogeneity, but might result in hazardous or invalid estimates. Finally, we cannot exclude the possibility that the results were biased because of undetected stratification in the original case–control samples.

A. Dominant Model IL-6 G174C

1. Asian Population

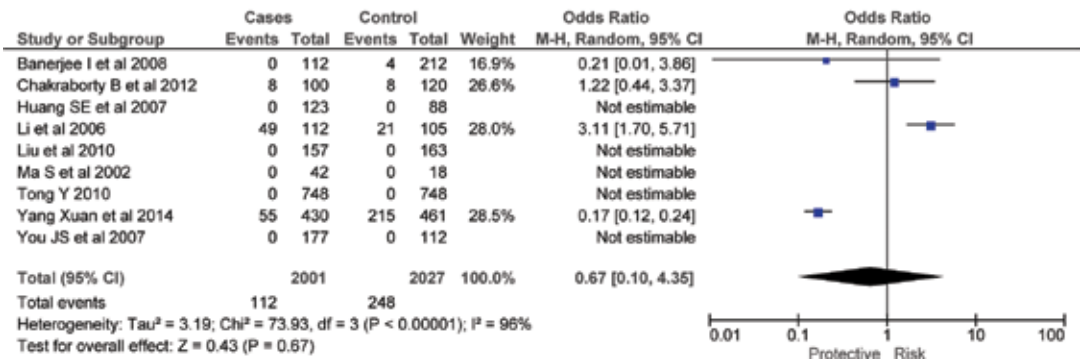


2. Caucasian Population

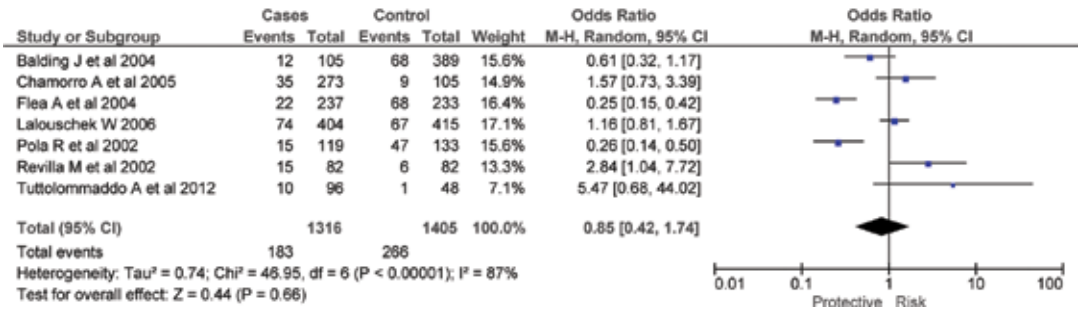


B. Recessive Model IL-6 G174C

1. Asian Population



2. Caucasian Population



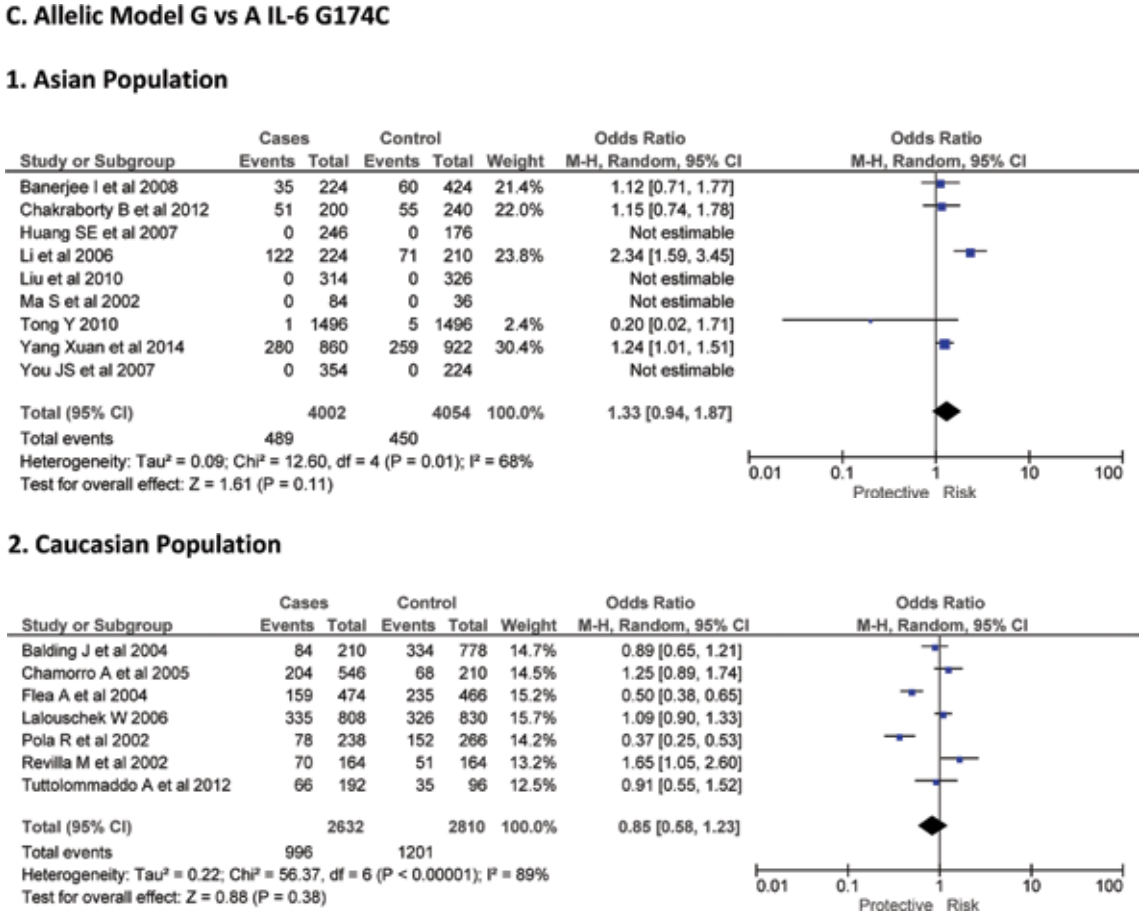


Fig. 3: Forest plots for association between IL-6 174 G/C polymorphism and IS risk in **(A)** Dominant model (CC + GC vs. GG); **(B)** Recessive model (CC vs. GG + GC); **(C)** Allelic Model [C allele vs. G allele] based on ethnic studies.

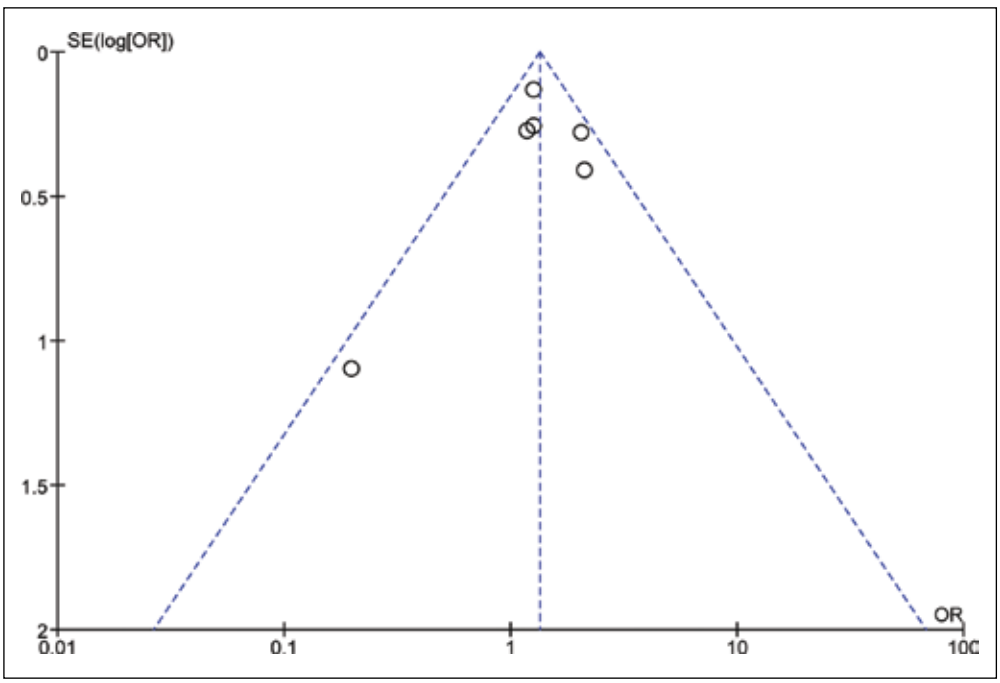


Fig. 4: Begg's Punnel Plot for Publication bias in Asian Population for IL-6 G174C.

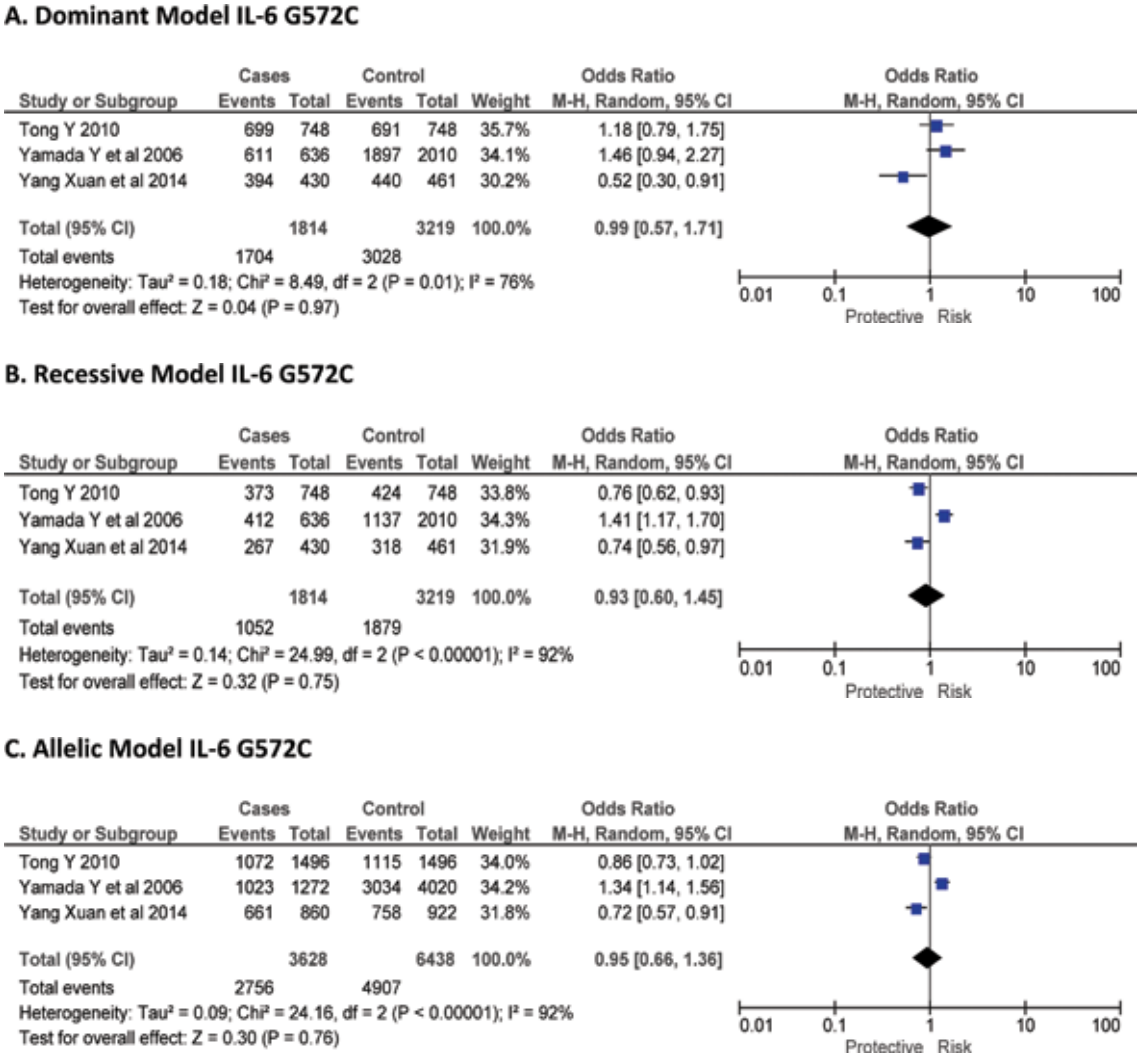


Fig. 5: Forest plots for association between IL-6 G572C polymorphism and IS risk in **(A)** Dominant model (CC + GC vs. GG); **(B)** Recessive model (CC vs. GG + GC); **(C)** Allelic Model [C allele vs. G allele].

In summary, the present meta-analyses did not infer that Ischaemic stroke is a complex multifactorial disease, in addition to genetic factors, environmental factors also play an important role in IS aetiology. Thus, this discrepancy may also be caused by varying geographical distribution, linked to climate, diet, life- style and economic status.

In summary, the present meta-analyses did not support a prominent association of the IL-6 promoter polymorphisms (G174C and G572C) with IS risk. However, the G174C polymorphism might be associated with IS in Asian studies based on sampled studies. More convincing evidence is required to conclude about the relation between these polymorphisms and risk of IS.

Conclusion

Well designed studies are needed to investigate the association of polymorphisms in IL6 larger and various ancestry populations.

Authorship Contribution

Pradeep Kumar: Concept, data search, extraction and writing of manuscript, **Arun K Yadav:** Data search and extraction, **Amit Kumar:** Analysis, **Ram Sagar:** Data entry, **Awadh K Pandit:** Manuscript writing, **Kameshwar Prasad:** Concept and designing of manuscript.

This article complies with International Committee of Medical Journal editor's uniform requirements for manuscript.

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