




Association of the IL-6 -174G > C (rs1800795) Polymorphism with Adolescent Idiopathic Scoliosis: Evidence from a Case-Control Study and Meta-Analysis

Associação do polimorfismo IL-6 -174G > C (rs1800795) com escoliose idiopática da adolescência: Evidências de um estudo de caso-controle e metanálise

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Abstract

Recent epidemiological studies have identified that the -174G > C (rs1800795) polymorphism in the promoter region of the interleukin-6 (*IL-6*) gene is associated with the risk of developing adolescent idiopathic scoliosis (AIS), but they presented inconsistent and controversial results. Thus, we performed a case-control study and meta-analysis to derive a more precise estimation of the relationship between the IL-6 -174G > C polymorphism and the risk of developing AIS. A total of 80 patients with AIS and 80 matched healthy control subjects were genotyped using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. In addition, all eligible studies published up to June 2018 were identified through a search in the PubMed, EMBASE, Google Scholar, and China National Knowledge Infrastructure (CNKI) databases. We calculated the odds ratios (ORs) and 95% confidence intervals (95% CIs) to assess the association. A total of 10 eligible studies comprising 1,695 AIS cases and 2,097 healthy controls were included in the meta-analysis. The pooled data suggested a significant association between the IL-6 -174G > C polymorphism and the susceptibility to develop AIS, which was demonstrated under 4 genetic models, that is, the allelic (C versus G; OR = 0.671; 95%CI: 0.457–0.985; $p = 0.042$), heterozygous (CG versus GG; OR = 0.734; 95%CI: 0.554–0.973; $p = 0.032$), dominant (CC + CG versus GG; OR = 0.660; 95%CI: 0.440–0.990; $p = 0.044$) and recessive models (CC versus CG + GG; OR = 0.506; 95%CI: 0.264–0.970; $p = 0.040$). The stratification analysis by ethnicity

Keywords

- ▶ idiopathic scoliosis
- ▶ interleukin-6
- ▶ polymorphism
- ▶ association
- ▶ meta-analysis

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revealed an increased risk of developing AIS in Caucasians, but not in Asians. The present meta-analysis, which is inconsistent with the previous meta-analysis, suggests that the IL-6 -174G > C polymorphism may increase the individual susceptibility to develop AIS, especially in Caucasians, and it could serve as a biomarker to predict the population at high risk of developing AIS.

Resumo

Estudos epidemiológicos recentes identificaram que o polimorfismo -174G > C (rs1800795) na região promotora do gene interleucina-6 (*IL-6*) está associado ao risco de desenvolver escoliose idiopática da adolescência (EIA), mas apresentaram resultados inconsistentes e controversos. Assim, realizamos um estudo de caso-controle e metanálise para obter uma estimativa mais precisa da relação entre o polimorfismo IL-6 -174G > C e o risco de desenvolver EIA. Um total de 80 pacientes com EIA e 80 controles saudáveis pareados foram genotipados usando o ensaio de reação em cadeia de polimerase de polimorfismos de comprimento de fragmentos de restrição (RCP-PCR). Além disso, todos os estudos elegíveis publicados até junho de 2018 foram identificados por meio de uma pesquisa nas bases de dados PubMed, EMBASE, Google Scholar e China National Knowledge Infrastructure (CNKI). Calculamos as razões de probabilidades (RPs) e os intervalos de confiança de 95% (ICs95%) para avaliar a associação. Um total de 10 estudos elegíveis compreendendo 1.695 casos de EIA e 2.097 controles saudáveis foram incluídos na metanálise. Os dados agrupados sugeriram uma associação significativa entre o polimorfismo IL-6 -174G > C e a suscetibilidade a desenvolver EIA que foi demonstrada em quatro modelos genéticos, ou seja, alélico (C versus G; RP = 0,671; IC95%: 0,457–0,985; $p = 0,042$), heterozigótico (GC versus GG; RP = 0,734; IC95%: 0,554–0,973; $p = 0,032$), dominante (CC + GC versus GG; RP = 0,660; IC95%: 0,440–0,990; $p = 0,044$) e recessivo (CC versus CG + GG; RP = 0,506; IC95%: 0,264–0,970; $p = 0,040$). A análise de estratificação por etnia revelou um aumento do risco de desenvolver EIA em caucasianos, mas não em asiáticos. Esta metanálise, que é inconsistente com relação à metanálise anterior, sugere que o polimorfismo IL-6 -174G > C pode aumentar a suscetibilidade individual para desenvolver EIA, especialmente em caucasianos, e pode servir como um biomarcador para prever a população com alto risco de desenvolver EIA.

Palavras-chave

- ▶ escoliose idiopática
- ▶ interleucina-6
- ▶ polimorfismo
- ▶ associação
- ▶ metanálise

Introduction

Idiopathic scoliosis (IS) is the most common type of musculoskeletal deformity, affecting ~3% of children and adolescents.^{1,2} Scoliosis refers to a deviation of the spine greater than 10 degrees in the coronal plane, which is most often discovered through school-screening programs or by the parents.^{1,3} The progression of IS occurs in three dimensions, with the spine simultaneously curving toward the arms and ~10% progress to a moderate or severe curve.^{4,5} There is a high variability in the clinical manifestation or phenotype of IS, which can manifest in infants (0–3 years) and children (4–9 years), but most cases occur among the adolescent population (≥ 10 years) of otherwise healthy children, with onset between (or around) puberty and skeletal maturity.^{6–8}

Adolescent idiopathic scoliosis (AIS) is prevalent in 1% to 3% of adolescents aged between 10 and 16 years.⁶ The inheritance pattern of AIS is unclear because many factors, including genetic and environmental factors, the exposome, and their combined interactions are involved.^{2,8} Genetic

association studies on AIS that have been performed in recent years, particularly linkage studies, genome-wide association studies (GWAS) and epigenetic studies, have identified several genetic loci such as *LBX1*, *GPRI26*, *SR1*, *ESR2*, *MATN1*, *POC5*, *IGF1* and *VDR* that are associated with the susceptibility to develop AIS.^{2,9–11} These studies have shown that some of these loci likely contribute to the susceptibility to develop AIS, while others could play a critical role in determining the severity of the spinal curvature and/or whether the curve is stable or progressive.⁹

Interleukin-6 (*IL-6*) is a pro-inflammatory cytokine and an anti-inflammatory myokine, which is promptly and transiently produced as a reaction to immune responses, inflammatory reactions, and hematopoiesis.¹² The human *IL-6* gene is located on chromosome 7p21–24, with an upstream promoter containing 303 bp, consisting of 5 exons, and with a length of 5 kb.^{13–15} Recently, the -174G > C (rs1800795) polymorphism in the promoter region of *IL-6* was investigated in the pathogenesis of AIS, but the results were controversial; this may be due to small sample sizes

and ethnic differences. Therefore, we performed a case-control study in Iranian AIS patients and a meta-analysis to further estimate the overall risk of developing AIS caused by the IL-6 -174G > C polymorphism.

Materials and Methods

Case-Control Study

Study Population

All subjects provided informed consent before the beginning of the study, which was approved by the Clinical Research Ethics Committee of our institution. In total, 80 consecutive AIS patients who visited 7 orthopedics clinics in 6 cities between April 2014 and September 2017 were retrospectively recruited to the present study. All of the patients underwent radiological examinations using standing postero-anterior (PA) radiographs. A total of 80 healthy matched subjects (the control group) were randomly selected from the general population after confirming the absence of any evidence of scoliosis, curvature of the spine, or other orthopedic conditions according to radiographic criteria.

Genotyping

For the genotype analysis, peripheral blood samples from all patients and controls were collected, and the genomic DNA from each sample was obtained using a commercial kit (Cinnagen, Tehran, Iran). The IL-6 -174G > C (rs1800795) polymorphism was genotyped using the polymerase chain reaction-restriction fragments length polymorphism (PCR-RFLP) technique. To investigate the IL-6 -174G > C (rs1800795) polymorphism, we used the primers 5'-TGACTT-CAGCTTACTCTTTGT-3' and reverse 5'-CTGATTGGAACCTTAT-TAAG-3'. The PCR products were digested with the *Streptococcus faecalis* ND547 (SfaNI) restriction enzyme at 37°C overnight, and then analyzed by electrophoresis in 2.0% agarose gel stained with ethidium bromide. The digested PCR products generated fragments as follows: homozygous wild (GG), 3 bands consisting of 140 bp and 58 bp; heterozygous genotype (GC), 198 bp, 140 bp and 58 bp; and homozygous mutant genotype (CC), one 198-bp band.

Statistical Analysis

The differences in the distribution of genotypes and alleles among the AIS patients and control subjects were evaluated with the Chi-squared (χ^2) test. The Hardy-Weinberg equilibrium (HWE) was computed with the goodness-of-fit χ^2 test in our control group. All statistical analysis was estimated using the International Business Machines Statistical Package for the Social Sciences (IBM SPSS, IBM Corp., Armonk, NY, US) software, version 20.0. Values of $p < 0.05$ were two-tailed, and were considered suggestive of association.

Meta-Analysis

Search Strategy

To identify all publications that evaluated the association of the IL-6 -174G > C (rs1800795) polymorphism with AIS, we

performed a comprehensive electronic search in the PubMed, EMBASE, China National Knowledge Infrastructure (CNKI) and other Chinese Biomedicine databases up to June 15, 2018. The combination of the following MeSH terms and keywords was used: (*adolescent idiopathic scoliosis* OR *scoliosis* OR *AIS*) AND (*interleukin-6* OR *IL-6* OR *-174G > C* OR *rs1800795*) AND (*SNPs* OR *polymorphism* OR *genotype* OR *allele* OR *variation*). The search was limited to published studies in humans. In addition, the reference lists of the eligible case-control studies and related reviews were manually searched to found more potential sources.

Inclusion Criteria

The following inclusion criteria were used to select articles for the meta-analysis: 1) case-control or cohort studies; 2) studies evaluating the association of the IL-6 -174 G > C polymorphism with AIS; 3) studies with sufficient data to examine an odds ratio (OR) with a 95% confidence interval (95%CI). Additionally, the following exclusion criteria were used: 1) studies that were not case-control or cohort studies; 2) studies with cases only or no controls; 3) studies with insufficient data reported; 4) abstracts, comments, case reports, letters, reviews, meta-analysis; and (5) duplicates of previous publications.

Data Extraction

Two authors carefully extracted data from all eligible studies independently according to the aforementioned inclusion criteria. Disagreements were resolved by discussion between the two investigators, or a third investigator was consulted to resolve the dispute, and a final decision was made by the majority of votes. For each included study, the following information was collected: first author, year of publication, country, ethnicity, number of cases and controls, genotyping methods, and evidence of HWE.

Statistical Analysis

The strength of the association of the IL-6 -174 G > C polymorphism with AIS was assessed using ORs with the corresponding 95%CIs. The significance of the pooled ORs was assessed by the Z test, in which values of $p < 0.05$ were considered significant. The risks (ORs) of developing AIS associated with the IL-6 -174 G > C polymorphism were estimated for each study under five genetic models: the allelic (C versus G), the homozygous (CC versus GG), the heterozygous (CC versus GC), the dominant (CC + GC versus GG), and the recessive models (CC versus GG + GC). The Q-statistic and the I^2 statistic were used to assess the heterogeneity among studies. In addition, we used the I^2 statistics to quantify the heterogeneity among the studies, which ranges from 0% to 100% and represents the proportion of variability among the studies that is attributable to heterogeneity rather than chance. Values of $p < 0.05$ on the Q-statistic indicated the presence of heterogeneity among the studies, so the pooled OR estimate of each study was calculated using the random-effects model (the DerSimonian and Laird method). Otherwise, the fixed-effects model (the Mantel-Haenszel method) was used. For each study,

we examined whether the genotype distribution in the control groups was in agreement with the HWE using the χ^2 test. One-way sensitivity analysis, by which a single study in the meta-analysis was omitted each time to reflect the influence of the individual dataset for the pooled OR, was performed to assess the stability of the results. To detect the presence of potential publication bias, visual inspection of Begg funnel plot symmetry and Egger linear regression were used. All statistical tests were performed using the Comprehensive Meta-Analysis (CMA, Biostat, Englewood, NJ, US) software, version 2.0. All *p*-values in the meta-analysis were two-sided, and values < 0.05 were considered significant.

Results

Case-Control Study

► **Table 1** presents the allele and genotype frequency distribution of the IL-6 -174G > C polymorphism in AIS cases and control subjects. The IL-6 -174G > C polymorphism genotype distributions in the control group was within the HWE (*p* = 0.818). The frequencies of the IL-6 -174G > C polymorphism genotypes (GG, GC and CC) were of 92.50%, 6.25% and 1.25% for AIS patients, and of 95.0%, 5.0% and 0.0% for the control subjects respectively. We failed to find a statistically significant association between the IL-6 -174G > C polymorphism and the risk of developing AIS in the present study.

Meta-Analysis

Eligible Studies

A flowchart describing the study selection process is presented in ► **Fig. 1**. Following the deletion of duplicate and irrelevant articles, a total of 10 case-control studies^{14,16-23} including 1,695 AIS cases and 2,097 controls were selected for the meta-analysis. The characteristics of the eligible studies are presented in ► **Table 2**. Of the 10 case-control studies, 6^{16,17,21-23} were conducted among Asian popula-

tions (1,331 AIS cases and 1,324 controls) and 4^{14,18-20} were performed with Caucasian populations (364 AIS cases and 773 controls). In total, three genotyping techniques were used in the included studies: PCR-RFLP, TaqMan and direct sequencing (DS). All of the studies indicated that the distribution of genotypes in the controls was consistent with the HWE, except for two studies (► **Table 2**).

Quantitative Synthesis of Data

► **Table 3** summarizes the main results of the IL-6 -174G > C polymorphism meta-analysis and of the heterogeneity test. The pooled data suggested a significant association between the IL-6 -174G > C polymorphism and the susceptibility to develop AIS under 4 genetic models: the allelic (C versus G: OR = 0.671; 95%CI: 0.457-0.985; *p* = 0.042; ► **Fig. 2A**), the heterozygous (CG versus GG: OR = 0.734; 95%CI: 0.554-0.973; *p* = 0.032), the dominant (CC + CG versus GG: OR = 0.660; 95%CI: 0.440-0.990; *p* = 0.044; ► **Fig. 2B**) and the recessive models (CC versus CG + GG: OR = 0.506; 95%CI: 0.264-0.970; *p* = 0.040).

► **Table 3** also lists the results of the stratified analyses by ethnicity, in which a significant association between the IL-6 -174G > C polymorphism and the risk of developing AIS was found among Caucasians in 3 genetic models: the allelic (C versus G: OR = 0.552; 95%CI: 0.318-0.959; *p* = 0.035), the homozygous (CC versus GG: OR = 0.329; 95%CI: 0.114-0.951; *p* = 0.040), and the recessive models (CC versus CG + GG: OR = 0.408, 95%CI: 0.180-0.925; *p* = 0.032); this association was not found among Asian populations. In addition, we performed a pooled analysis in the Chinese population, but the results showed that there was no statistically significant association between the IL-6 -174G > C polymorphism and the risk of developing AIS in that population (► **Table 2**).

Heterogeneity Test

► **Table 3** summarizes the main result of the heterogeneity (H) among studies. A significant heterogeneity was detected under 4 genetic models: the allelic (C versus G: $I^2 = 73.65$; p_H

Table 1 Distribution of genotype and allele frequencies in AIS cases and controls

	Cases (n = 80)	Controls (n = 80)	OR (95%CI)	p-value
IL-6 -174 G > C				
Genotypes				
GG	74 (92.50)	76 (95.0)	Reference	
CG	5 (6.25)	4 (5.0)	1.267(0.327-4.900)	0.732
CC	1 (1.25)	0 (0.00)	3.038(0.122-75.693)	0.498
Allele				
G	153 (95.62)	156 (97.50)	Reference	
C	7 (4.38)	4 (2.50)	1.784(0.512-6.219)	0.363
Genetic models				
Dominant (CC + CG versus GG)			1.541(0.418-5.681)	0.516
Recessive (CC versus CG + GG)			3.038(0.122-75.693)	0.498

Abbreviations: 95%CI, 95% confidence interval; AIS, adolescent idiopathic scoliosis; OR, odds ratio.

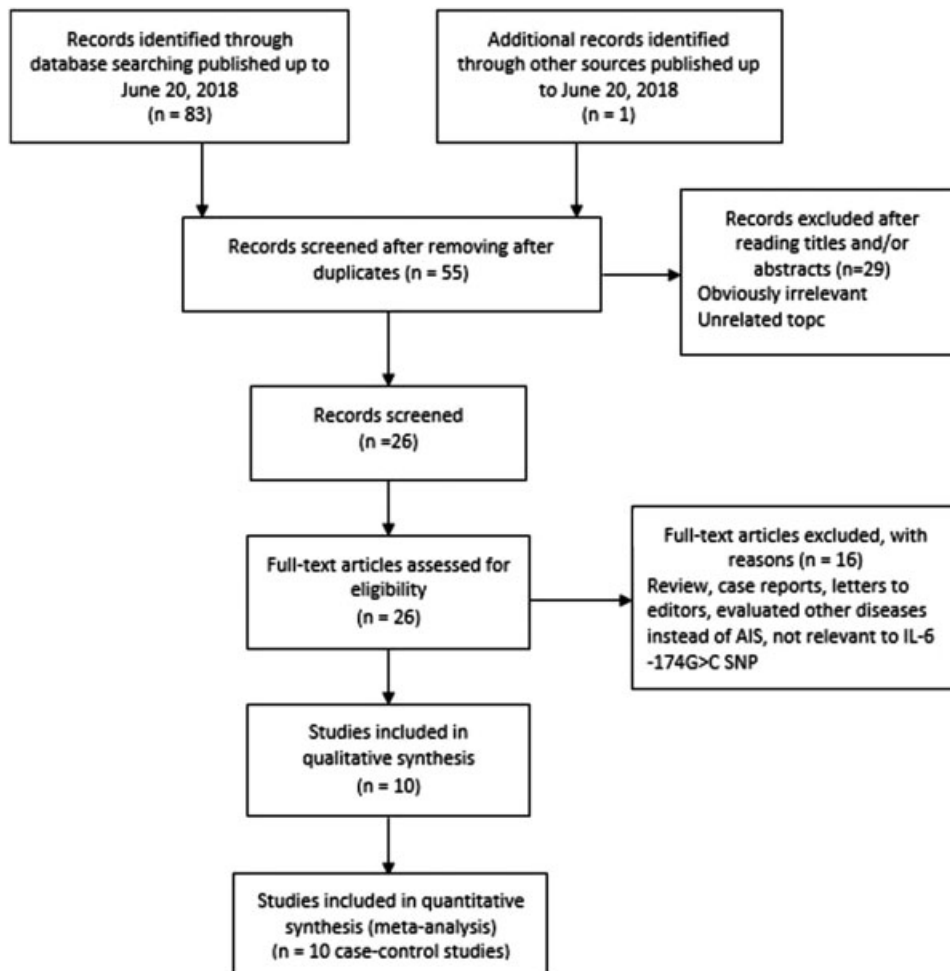


Fig. 1 Flowchart describing the selection of individual studies for the meta-analysis.

≤ 0.001), the heterozygous (CG versus GG: $I^2 = 77.57$; $p_H \leq 0.001$), the dominant (CC + CG versus GG: $I^2 = 61.46$; $p_H = 0.008$) and the recessive models (CC versus CG + GG: $I^2 = 67.97$; $p_H = 0.008$). Hence, we explored the possible sources of heterogeneity by stratified analysis by ethnicity. The results showed that studies in Asian populations were a source of substantial heterogeneity. Additionally, removing those studies that deviated from the HWE did not significantly change the substantial heterogeneity among the studies (data not shown), which indicated that the models were robust.

Sensitivity Analysis

A sensitivity analysis was performed to explore the impact of an individual study on the pooled ORs. The results revealed that no individual study significantly affected the pooled OR, indicating that our results were statistically robust. However, after excluding the two case-control studies that were not in agreement with the HWE, making the sample a poor representation, the corresponding pooled ORs were materially altered under all genetic models: the allelic (C versus G: OR = 0.713; 95%CI: 0.400–1.271; $p = 0.251$), the heterozygous (CG versus GG: OR = 0.745; 95%CI: 0.553–1.005; $p = 0.054$), the dominant (CC + CG versus GG: OR = 0.701;

95%CI: 0.377–1.302; $p = 0.261$) and the recessive models (CC versus CG + GG: OR = 0.490; 95%CI: 0.170–1.409; $p = 0.186$).

Publication Bias

A Begg funnel plot and the Egger test were performed to assess the publication bias of the included studies. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry under all genetic models: the allelic (C versus G: $p_{Begg} = 0.754$ and $p_{Egger} = 0.909$; ► **Fig. 3A**), the homozygous (CC versus GG: $p_{Begg} = 1.000$ and $p_{Egger} = 0.792$), the heterozygous (CG versus GG: $p_{Begg} = 0.754$ and $p_{Egger} = 0.834$), the dominant (CC + CG versus GG: $p_{Begg} = 1.000$ and $p_{Egger} = 0.786$; ► **Fig. 3B**) and the recessive models (CC versus CG + GG: $p_{Begg} = 1.000$ and $p_{Egger} = 0.727$). The Egger test did not show any significant statistical evidence of publication bias, which indicated a low risk of it in the present meta-analysis.

Minor Allele Frequency

The minor allele frequency (MAF) of the IL-6 -174G > C polymorphism in the healthy controls in Asians and Caucasians are presented in ► **Table 2**. The geographical frequencies of the IL-6 -174C allele were of 10.45% (0.00–20.9%) in Asians and of 47.35% (42.80–51.90%) in Caucasians respectively (► **Table 2**).

Table 2 Characteristics of the studies included in the meta-analysis

Autor/Ano	Author (year)	Country (ethnicity)	Genotyping technique	Case/Control	Cases			Controls			MAFs	HWE			
					Genotypes			Genotypes					Allele		
					GG	CG	CC	GG	CG	CC			G	G	C
Aulisa et al ¹⁴ (2007)	Aulisa et al ¹⁴ (2007)	Italy (Caucasian)	PCR-RFLP	53/206	28	22	3	28	78	28	198	214	0.073		
Lee et al ¹⁶ (2010)	Lee et al ¹⁶ (2010)	Korea (Asian)	TaqMan	198/120	197	1	0	1	395	1	239	1	0.963		
Liu et al ¹⁷ (2010)	Liu et al ¹⁷ (2010)	China (Asian)	PCR-RFLP	487/494	487	0	0	0	974	0	988	0	NA		
Mórocz et al ¹⁸ (2011)	Mórocz et al ¹⁸ (2011)	Hungary (Caucasian)	PCR-RFLP	126/197	34	67	25	117	135	117	225	169	0.943		
Nikolova et al ¹⁹ (2015)	Nikolova et al ¹⁹ (2015)	Bulgaria (Caucasian)	PCR-RFLP	80/160	42	29	9	47	113	47	174	146	0.005		
Nikolova et al ²⁰ (2016)	Nikolova et al ²⁰ (2016)	Bulgaria (Caucasian)	PCR-RFLP	105/210	54	40	11	62	148	62	220	200	0.136		
Sui et al ²¹ (2017)	Sui et al ²¹ (2017)	China (Asian)	PCR-RFLP	200/200	195	5	0	5	395	5	396	4	0.886		
Lee et al ²² (2018)	Lee et al ²² (2018)	China (Asian)	DS	184/220	183	1	0	1	367	1	438	2	0.946		
Gao et al ²³ (2018)	Gao et al ²³ (2018)	China (Asian)	PCR-RFLP	182/210	128	44	10	64	298	64	332	88	0.046		
P	Present study	Iran (Asian)	PCR-RFLP	80/80	74	5	1	7	153	7	156	4	0.818		

Abbreviations: DS, direct sequencing; HWE, Hardy-Weinberg equilibrium; MAFs, minor allele frequencies; NA, not available; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism.

Table 3 Results of the association of the IL-6 -174 G > C polymorphism with the risk of developing AIS

Subgroup	Genetic model	Type of model	Heterogeneity (H)		Odds Ratio				Publication Bias	
			I ² (%)	p _H	OR	95%CI	Z test	p _{OR}	p _{Begg}	p _{Egger}
Overall	C versus G	Random	73.65	≤ 0.001	0.671	0.457–0.985	–2.035	0.042	0.754	0.909
	CC versus GG	Random	77.57	≤ 0.001	0.439	0.439–0.192	–1.951	0.051	1.000	0.792
	CG versus GG	Fixed	22.24	0.245	0.734	0.554–0.973	–2.150	0.032	0.754	0.834
	CC + CG versus GG	Random	61.46	0.008	0.660	0.440–0.990	–2.010	0.044	1.000	0.786
	CC versus CG + GG	Random	67.97	0.008	0.506	0.264–0.970	–2.052	0.040	1.000	0.727
By ethnicity										
Asian	C versus G	Fixed	0.00	0.816	0.865	0.624–1.201	–0.866	0.386	1.000	0.552
	CC versus GG	Fixed	0.00	0.409	0.831	0.366–1.885	–0.443	0.658	NA	NA
	CG versus GG	Fixed	0.00	0.915	0.840	0.562–1.256	–0.851	0.395	0.806	0.642
	CC + CG versus GG	Fixed	0.00	0.873	0.845	0.578–1.234	–0.872	0.383	1.000	0.571
	CC versus CG + GG	Fixed	0.00	0.437	0.885	0.394–1.989	–0.296	0.767	NA	NA
Caucasian	C versus G	Random	88.10	≤0.001	0.552	0.318–0.959	–2.110	0.035	0.308	0.173
	CC versus GG	Random	84.71	≤0.001	0.329	0.114–0.951	–2.053	0.040	0.308	0.204
	CG versus GG	Random	65.43	0.034	0.670	0.413–1.086	–1.626	0.104	1.000	0.519
	CC + CG versus GG	Random	81.71	0.001	0.541	0.290–1.008	–1.935	0.053	0.734	0.490
	CC versus CG + GG	Random	77.97	0.003	0.408	0.180–0.925	–2.146	0.032	0.308	0.114
Asian (Chinese)	C versus G	Fixed	0.00	0.790	0.824	0.585–1.160	–1.109	0.267	1.000	0.799
	CC versus GG	Fixed	0.00	1.000	0.759	0.325–1.770	–0.639	0.523	NA	NA
	CG versus GG	Fixed	0.00	0.775	0.811	0.530–1.243	–0.961	0.337	1.000	0.797
	CC + CG versus GG	Fixed	0.00	0.771	0.804	0.539–1.199	–1.069	0.285	1.000	0.780
	CC versus CG + GG	Fixed	0.00	1.000	0.814	0.352–1.880	–0.482	0.630	NA	NA

Abbreviations: 95%CI, 95% confidence interval; AIS, adolescent idiopathic scoliosis; NA, not available; OR, odds ratio.

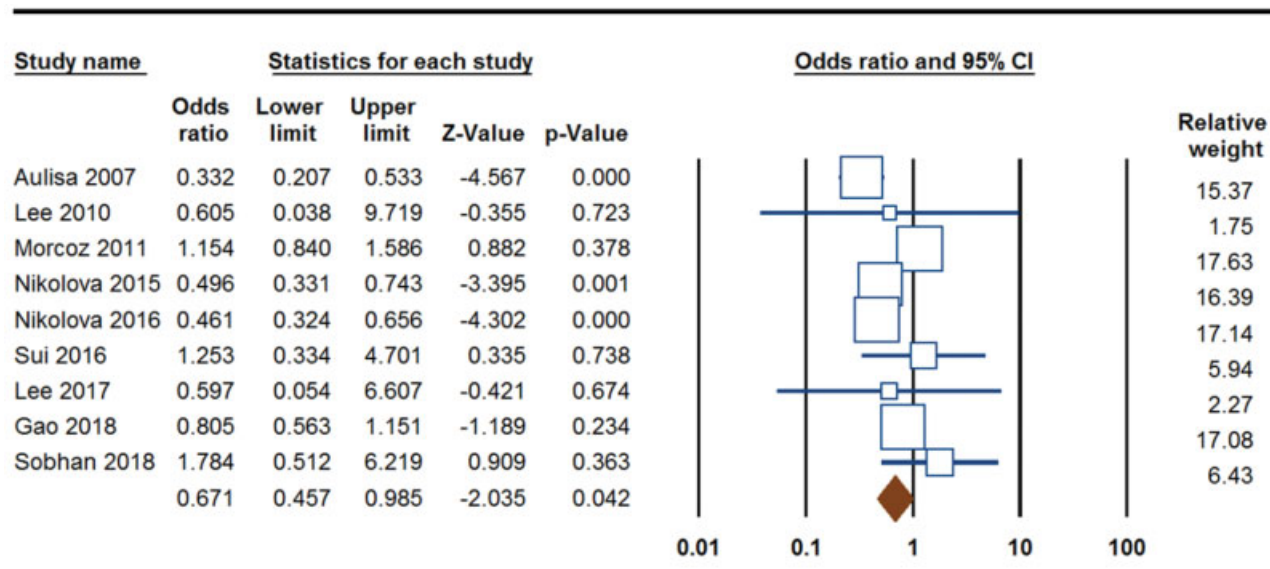
Discussion

Genetic and epigenetics factors are believed to play an important role in the etiology of AIS.^{2,24} However, the relationship between environmental risk factors and AIS may be highly complicated, and extensive research is required to ascertain how exactly do the environmental factors impact the individual susceptibility to develop AIS.^{1,2}

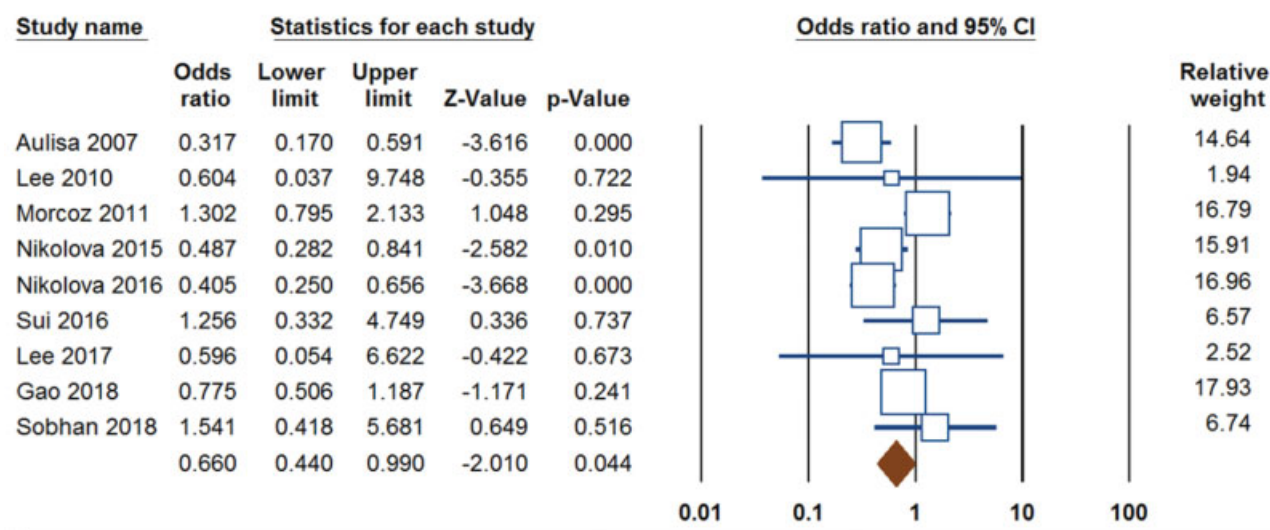
Several association studies have investigated the association between the IL-6 -174G > C polymorphism and the risk of developing AIS. After pooling the data from 10 eligible studies with 1,695 cases and 2,097 controls, we found that the association between the IL-6 -174G > C polymorphism and the risk of developing AIS is statistically significant in the overall population. Further stratified analyses by ethnicity demonstrated a significant association between the IL-6 -174G > C polymorphism and the risk of developing AIS among Caucasians, but not among Asians. The inconsistent outcome among Asians on the subgroup analysis with overall ORs might be due to genetic diversity in different ethnicities. The results of the present meta-analysis were inconsistent with those of the previous meta-analysis by Zhao et al¹⁵, which was based on five case-

control studies with 944 cases and 1,177 controls. In 2016, Zhao et al¹⁵ performed a meta-analysis to evaluate the association between the IL-6 -174G > C polymorphism and the risk of developing AIS. Their results suggested that the IL-6 -174G > C polymorphism does not have significant influence on the individual susceptibility to develop AIS.¹⁵ However, their meta-analysis had a smaller sample, and failed to confirm a significant association. Therefore, our meta-analysis with a larger sample provided a precise result regarding the association of the IL-6 -174G > C polymorphism with the risk of developing AIS.

Heterogeneity is a potential problem that should be addressed, for it might affect the results of a meta-analysis.^{25,26} The significant heterogeneity among studies could be attributable to differences in several factors, such as differences in ethnicity, sample sizes, genotyping techniques, and diversity in design and performance of the studies.^{27–30} However, in spite of the small number of studies included in present meta-analysis, a relatively large heterogeneity was observed under four genetic models in the overall population. Thus, we conducted a subgroup analysis by ethnicity to explore the sources of heterogeneity. However, after stratifying by ethnicity, no significant



A



B

Fig. 2 Forest plots of the IL-6 -174G > C polymorphism with the risk of developing AIS. (A) Allele model (C versus G); (B) dominant model (CC + CG versus GG). A random-effects model was used.

heterogeneity was observed among the Asian population, but there still was heterogeneity among the Caucasian population. Therefore, we can be presumed that the relatively large heterogeneity mainly results from different ethnic backgrounds.

The present meta-analysis has several limitations. First, given that only studies published in English and Chinese were included, there may be publication bias, although our results showed no significance. Second, because the included studies were conducted among Asians and Caucasians, the results must be interpreted carefully. Further studies concerning populations from other areas, such as Africa and North America, are required to diminish the biases produced by ethnic variation. Third, the present analyses were based on unadjusted estimates because most

studies did not provide adjusted data. More precise analyses including individual data, lifestyle factors, and environmental factors, should be conducted if possible. Finally, genetics, the environment, and the exposome are believed to play an important role in the pathophysiology of AIS, but the current meta-analysis could not assess the gene-gene and gene-environment interactions due to the limited information provided by the included studies.

In summary, the results of the meta-analysis, which are inconsistent with those of the previous meta-analysis by Zhao et al¹⁵, indicate that the IL-6 -174G > C polymorphism is associated with the risk of developing AIS, especially among Caucasians. In addition, our case-control study indicated that the IL-6 -174G > C polymorphism was not associated with the risk of developing AIS among the Iranian population.

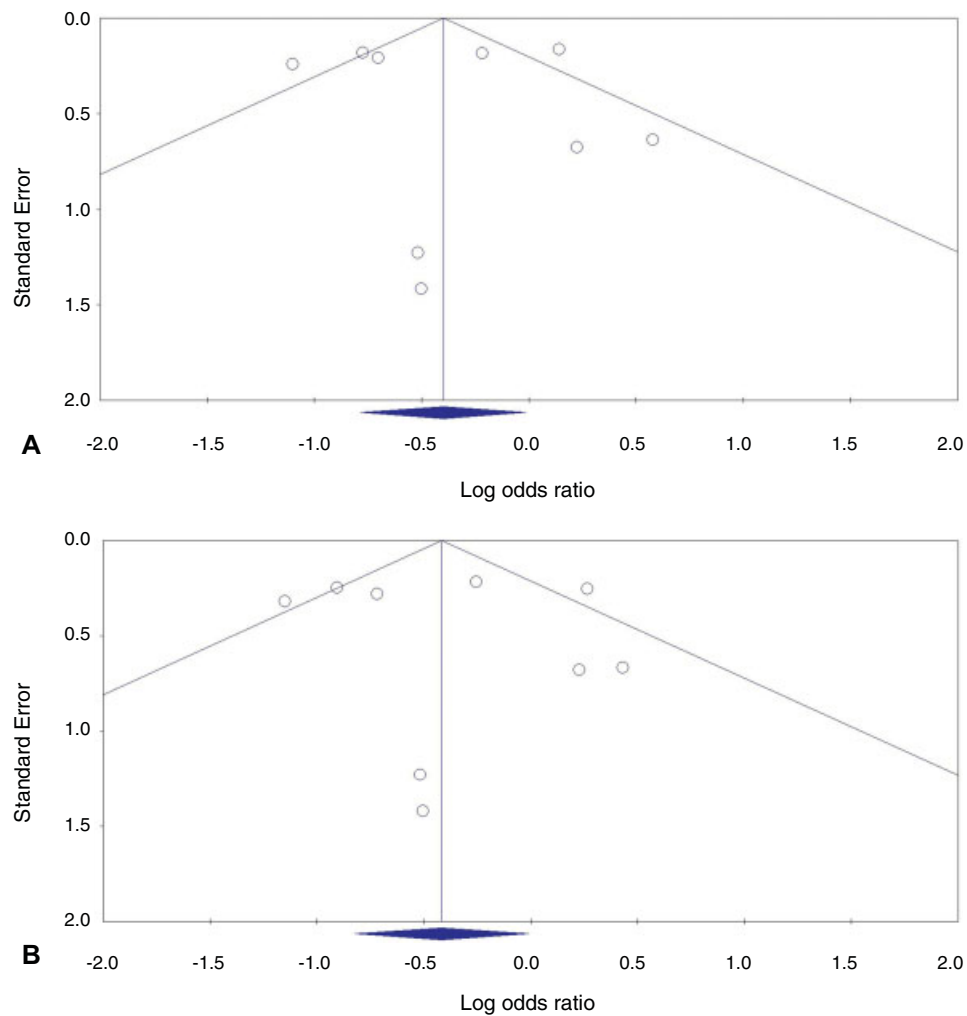


Fig. 3 Funnel plot for the detection of publication bias regarding the association of the IL-6 -174 G > C polymorphism with the risk of developing AIS. (A) Allele model (C versus G); (B) dominant model (CC + CG versus GG). A random-effects model was used.

Conflict of Interests

The authors have no conflict of interests to declare.

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