

Association between rs1800795 polymorphism in the interleukin-6 gene and the risk of polycystic ovary syndrome

A meta-analysis

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Abstract

Objective: Several published articles have investigated the association between the -174 G/C (rs1800795) polymorphism in the interleukin-6 (*IL-6*) gene and the risk of polycystic ovary syndrome (PCOS). However, the results were inconsistent. In the present study, a meta-analysis was performed to resolve this inconsistency.

Methods: Eligible studies reporting an association between the *IL-6* rs1800795 polymorphism and PCOS susceptibility were included from PubMed, Embase, Web of Science, and the Cochrane Library up to December 1, 2017. The odds ratio (OR) with the 95% confidence interval (CI) was used to calculate the strength of the associations. Publication bias detection was conducted using Begg test. We used STATA 11.0 software to perform the statistical analyses.

Results: Six articles detailing case-control studies were included, reporting a total of 512 cases and 606 controls. The meta-analysis results indicated that rs1800795 was associated with decreased PCOS susceptibility in the overall population under the allelic model (G vs. C, OR=0.59, 95% CI: 0.41–0.85, $P=.005$), the homozygous model (GG vs. CC, OR=0.45, 95% CI: 0.28–0.73, $P=.001$), heterozygous model (GG vs. CG, OR=0.50, 95% CI: 0.26–0.95, $P=.036$), and the dominant model (GC+CC vs. GG, OR=0.48, 95% CI: 0.26–0.89, $P=.020$). However, a threshold P value of .05 was found under the recessive model (CC vs. GG+CG, OR=0.62, 95% CI: 0.39–1.00).

Conclusions: This meta-analysis concluded that *IL-6* rs1800795 polymorphism has a decreased association with PCOS risk among all populations studied. The results suggested that the *IL-6* rs1800795 polymorphism is a protective factor for PCOS susceptibility. Given the limited ethnic groups and sample size, further studies are required to validate the association.

Abbreviations: CI = confidence interval, HWE = Hardy-Weinberg equilibrium, *IL-6* = interleukin-6, NOS = Newcastle-Ottawa Scale, OR = Odds ratio, PCOS = polycystic ovary syndrome, SNP = single-nucleotide polymorphism.

Keywords: interleukin-6, meta-analysis, polycystic ovary syndrome, polymorphism, rs1800795

1. Introduction

Polycystic ovary syndrome (PCOS) is a common and complex gynecological endocrine disorder that affects approximately 6%

to 10% of women of their reproductive age.^[1,2] PCOS is characterized by oligoanovulation or anovulation, hyperandrogenism, hyperinsulinemia, menstrual irregularity, and consequent subfertility.^[3] PCOS is also associated with dyslipidemia, atherosclerosis, obesity, hirsutism, insulin resistance, and an increased incidence of type 2 diabetes mellitus.^[4–6] Recent studies reported that 15% to 55% of the PCOS patients were diagnosed as having nonalcoholic fatty liver disease (NAFLD). In addition, 32.7% to 44.6% of patients with PCOS suffer from metabolic syndrome. Metabolic syndrome occurs with high prevalence in PCOS patients complicated with NAFLD.^[7,8] The exact etiological mechanism of PCOS is still under debate; however, there is evidence that genetic factors play a vital role.^[9,10]

Interleukin 6 (*IL-6*), an important proinflammatory and immunomodulatory pleiotropic cytokine, plays an important role in reproductive physiology. *IL-6* is involved in various human diseases and pathophysiological processes, such as the development of atherosclerosis, ovarian steroid production, fertilization and implantation, coronary heart disease, osteoporosis, and allergic reactions.^[11–15] The *IL-6* gene is located at chromosome 7p21–24 locus with a 303 bp promoter.^[16] A common single-nucleotide polymorphism (SNP), which results in variation of G>C -174 in the promoter region of *IL-6*, has been proven to alter the gene's transcription rate.^[17] Studies involving the relationship between *IL-6* -174 G/C and PCOS susceptibility have been performed.^[18–26] However, the results remain

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inconclusive and controversial, probably because of the varied populations and limited sample sizes. Therefore, we employed a meta-analysis to investigate the relationship between *IL-6* -174 G/C (rs1800795) and PCOS susceptibility.

2. Materials and methods

2.1. Search strategy

The meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.^[27] A comprehensive strategy was carried out to search for potential publications concerning the association between *IL-6* -174 G/C (rs1800795) and PCOS susceptibility in the following databases: Web of Science, Embase, PubMed, and the Cochrane Library, from inception to December 1, 2017. The search terms included “interleukin-6,” OR “IL-6,” OR “IL6,” AND “Polycystic ovary syndrome,” OR “PCOS,” AND “polymorphism,” OR “mutations,” OR “single nucleotide polymorphism,” OR “SNP,” OR “variant,” OR “genotype,” OR “Alleles,” without any limitation imposed. Publications listed in the references were also hand-searched carefully to obtain potentially relevant articles. Disagreements concerning the inclusion of a particular study were resolved by consensus. The study protocol was approved by the ethics committee of the Hangzhou Women’s Hospital.

2.2. Inclusion and exclusion criteria

Studies were included if they met all the following criteria: research designed as a case-control study with healthy populations as controls and patients with PCOS cases; studies assessing the relationship between the *IL-6* -174 G/C (rs1800795) polymorphism and PCOS susceptibility; availability of data regarding the total number of cases and controls, number of cases and controls with G/G, G/C, and C/C genotypes; and at least 2 comparison groups (cancer group and control group). Studies were excluded if: the studies had no control group, or were case reports, review articles, or comments; the studies did not disclose the raw data regarding the *IL-6* -174 G/C (rs1800795) polymorphism; and animal studies.

2.3. Data extraction

Two experienced investigators independently extracted the data according to a preset data extraction form. The following information was extracted: first author’s surname; country in which the study was performed; publication year; nation or ethnicity; genotyping method; total number in the case and control groups, as well as the number of cases and controls with G/G, G/C, and C/C genotypes; and the *P* value used to calculate the Hardy-Weinberg equilibrium (HWE).

2.4. Quality assessment

Two authors independently performed a quality assessment of each study based on the 9-star Newcastle-Ottawa Scale (NOS),^[28] which is a widely used rating system to assessing the quality of observational studies in a meta-analysis. The NOS involves 3 broad aspects: case and control selection, comparability, and exposure. Each aspect consists of 4, 2, and 3 items respectively. This scale contains 9 items and each item scores a value of 1. An NOS score of 6 stars or above would indicate a high-quality study.

2.5. Statistical analysis

The association strength between *IL-6* -174 G/C (rs1800795) polymorphism and PCOS susceptibility was assessed by calculating the pooled odds ratio (OR) along with the 95% confidence interval (CI). The pooled ORs were measured using the *Z* test. The HWE for each SNP was tested using the χ^2 test. The ORs were combined using either the random-effects model or the fixed-effects model, as previously described.^[29,30] A *P* value <.05 was regarded as a statistically significant difference. Heterogeneity across the studies was determined using the *Q* test and the *I*² statistical tests, with *I*² <50% indicating little difference. To explore the influence of a single study on the overall results, sensitivity analysis was also performed to test the stability of the results under all genetic models. We used Begg funnel plot test to assess possible publication bias, with *P* <.05 being considered to present statistical significance. All statistical analyses were conducted with STATA 11.0 software (StataCorp, College Station, TX).

3. Results

3.1. Characteristics of the included studies

The initial search of electronic databases yielded 47 references. The flow chart of the study selection process is shown in Figure 1. Finally, 6 original articles were identified that met the inclusion criteria for the meta-analysis. The detailed characteristics of the 6 included studies are shown in Table 1.^[21–26] Four studies were performed in Turkey,^[21–23,25] one in Austria,^[26] and another in India.^[24] The frequencies of each genotype and allele, with their HWE values, are presented in Table 2. The analyzed SNP was within the HWE in 3 studies,^[23,25,26] whereas in the other 3 studies, the polymorphism was not consistent with the HWE.^[21,22,24] The NOS results indicated that the studies had scores ranging from 6 to 8, with an average of 6.33, which indicated that the methodological quality of the 6 selected studies was generally reliable (Table 1).

3.2. Meta-analysis results

The 6 studies involved a total of 512 patients with PCOS and 606 controls. Overall, there was a decreased association between rs1800795 and PCOS susceptibility in the overall population under the allelic model (G vs. C, OR=0.59, 95% CI: 0.41–0.85, *P*=.005), the homozygous model (GG vs. CC, OR=0.45, 95% CI: 0.28–0.73, *P*=.001), the heterozygous model (GG vs. CG, OR=0.50, 95% CI: 0.26–0.95, *P*=.036), and the dominant model (GC + CC vs. GG, OR=0.48, 95% CI: 0.26–0.89, *P*=.020). However, a threshold *P* value of .05 was found under the recessive model (CC vs. GG + CG, OR=0.62, 95% CI: 0.39–1.00). The main results of the meta-analysis were listed in Table 3. The forest plot of the pooled ORs of the association of rs1800795 with PCOS susceptibility under the homozygous model is shown in Figure 2.

3.3. Subgroup analysis

Subgroup analysis was available for the genotyping method, ethnicity, NOS score, and whether the selected studies conformed to the HWE. The results of subgroup analysis of the association of rs1800795 and PCOS susceptibility under the 5 models are shown in Table 4. However, some findings should be interpreted with caution because of the limited studies in certain subgroup.

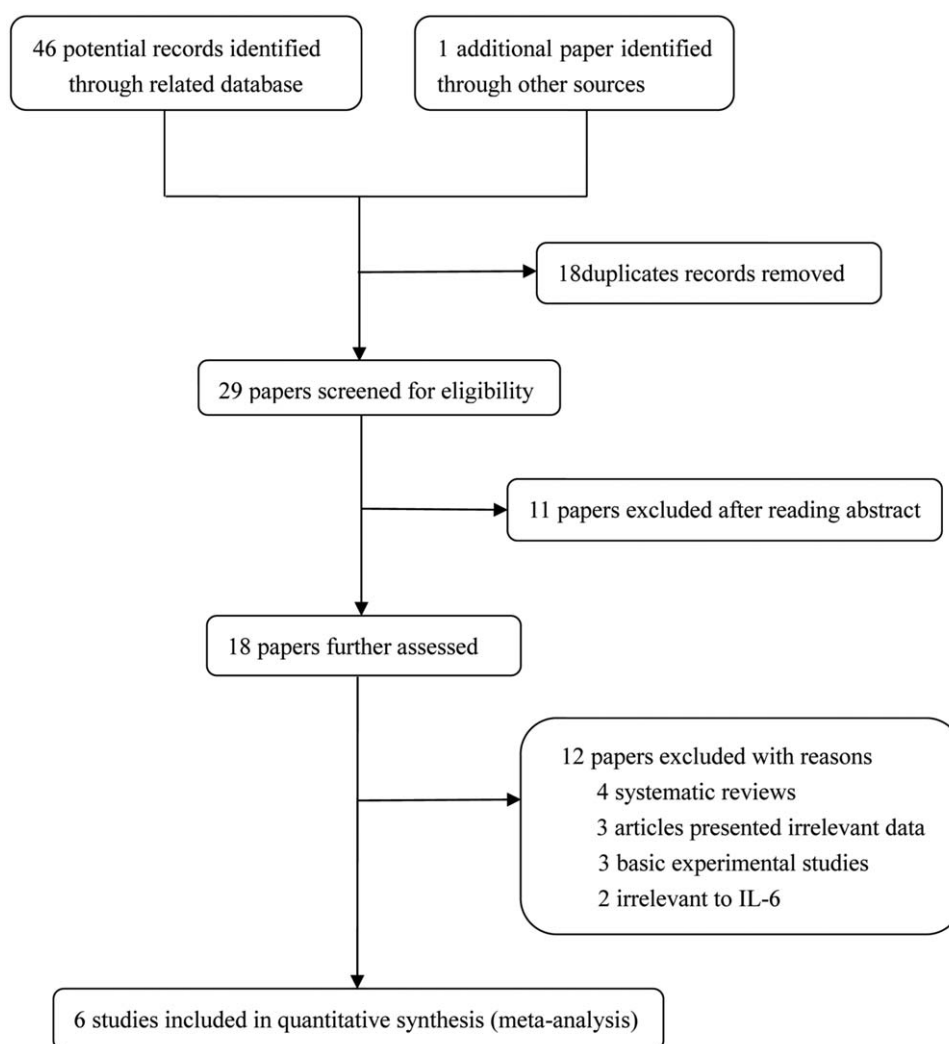


Figure 1. The detailed procedures for the literature search.

3.4. Sensitivity analysis

Sequential omission of each single study was used to perform sensitivity analysis in the 5 models. The pooled ORs and 95% CIs showed no material differences, indicating that the pooled results of the meta-analysis were robust and reliable. Sensitivity analysis of the association between rs1800795 and PCOS susceptibility under the recessive model is shown Figure 3.

3.5. Publication bias

We estimated the potential publication bias using a Begg funnel plot test. No obvious publication bias was found for the association between rs1800795 and PCOS susceptibility under any models. Publication bias under the dominant model suggested that the result is statistically robust ($P = .531$, Fig. 4).

4. Discussion

PCOS is a common endocrine disorder disease involving multiple genetic and epigenetic alterations. Cytokine genes polymorphisms may play an important role in the etiology of PCOS.^[25] As a common multifunctional cytokines, *IL-6*, has been proven to influence the processes of fertilization,

implantation, and ovulation, which are also affected in women with PCOS.^[31] Many genetic studies have been performed to investigate the associations between *IL-6* rs1800795 polymorphism and PCOS risk; however, the results were inconclusive.^[21–26]

A single study lacks sufficient statistical power to confirm the relationship between rs1800795 and the risk of PCOS because of the small sample size. To explore the uncertain association between these 2 entities, we performed a meta-analysis in a large sample size (512 patients with PCOS and 606 controls) to verify the associations between PCOS susceptibility and the *IL-6* -174 G/C (rs1800795) functional polymorphism. The results demonstrated that *IL-6* rs1800795 was associated with a decreased risk of PCOS among all populations studied. The results suggested that the *IL-6* rs1800795 polymorphism is a protective factor for PCOS susceptibility.

A previous meta-analysis with only 4 studies, containing 351 cases and 464 control participants, failed to confirm an association between these 2 entities because of the small sample size.^[20] In addition, they failed to show a correlation between *IL-6* rs1800795 polymorphism and PCOS susceptibility in subgroup analysis among the studies that conformed to the HWE under the allele model, recessive model, and dominant model. However, in

Table 1

Characteristics of the studies included in the meta-analysis.

First author	Year	Country	Ethnicity	Genotyping method	Number (case/control)	HWE	NOS score
Walch et al ^[26]	2004	Austria	Whites	Sequencing	62/94	0.0678	6
Erdogan et al ^[21]	2008	Turkey	Whites	PCR-RFLP	85/115	0.0009	6
Erdogan et al ^[22]	2009	Turkey	Whites	PCR-RFLP	88/119	0.0012	6
Vural et al ^[25]	2010	Turkey	Whites	PCR-RFLP	97/95	0.5364	8
Tumu et al ^[24]	2013	India	Asians	Sequencing	104/156	0.0242	6
Eser et al ^[23]	2016	Turkey	Whites	PCR-RFLP	76/27	0.7725	6

HWE = hardy-weinberg equilibrium, NOS = Newcastle-Ottawa Scale, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

Table 2

Polymorphisms genotype distribution and allele frequency in cases and controls.

First author	Genotype (N)								Allele frequency (N)			
	Case				Control				Case		Control	
	Total	GG	GC	CC	Total	GG	GC	CC	G	C	G	C
rs1800795 (G>C)												
Walch et al ^[26]	62	24	30	8	94	43	35	16	78	46	121	67
Erdogan et al ^[21]	85	56	25	4	115	31	73	11	137	33	135	95
Erdogan et al ^[22]	88	57	26	5	119	32	75	12	140	36	139	99
Vural et al ^[25]	97	59	34	4	95	46	42	7	152	42	134	56
Tumu et al ^[24]	104	69	31	4	156	77	73	6	169	39	227	85
Eser et al ^[23]	76	32	39	5	27	11	13	3	103	49	35	19

Table 3

Meta-analysis of the association between IL-6 rs1800795 polymorphism and PCOS susceptibility.

SNP	Association results			Heterogeneity		Model
	OR (95% CI)	$P_{(z-t)}$	$P_{(Q-t)}$	I^2 (%)		
G vs. C	0.59 (0.41–0.85)	.005	.003	71.6	Random-effects	
GG vs. CC	0.45 (0.28–0.73)	.001	.360	8.8	Fixed-effects	
GG vs. CG	0.50 (0.26–0.95)	.036	<.001	83.5	Random-effects	
CC vs. GG + CG	0.62 (0.39–1.00)	.050	.964	0	Random-effects	
GC + CC vs. GG	0.48 (0.26–0.89)	.020	<.001	82.9	Random-effects	

CI = confidence interval, OR = odds ratios, PCOS = polycystic ovary syndrome, SNP = single-nucleotide polymorphism. $P_{(z-t)}$ value for association test, $P_{(Q-t)}$ value for heterogeneity test

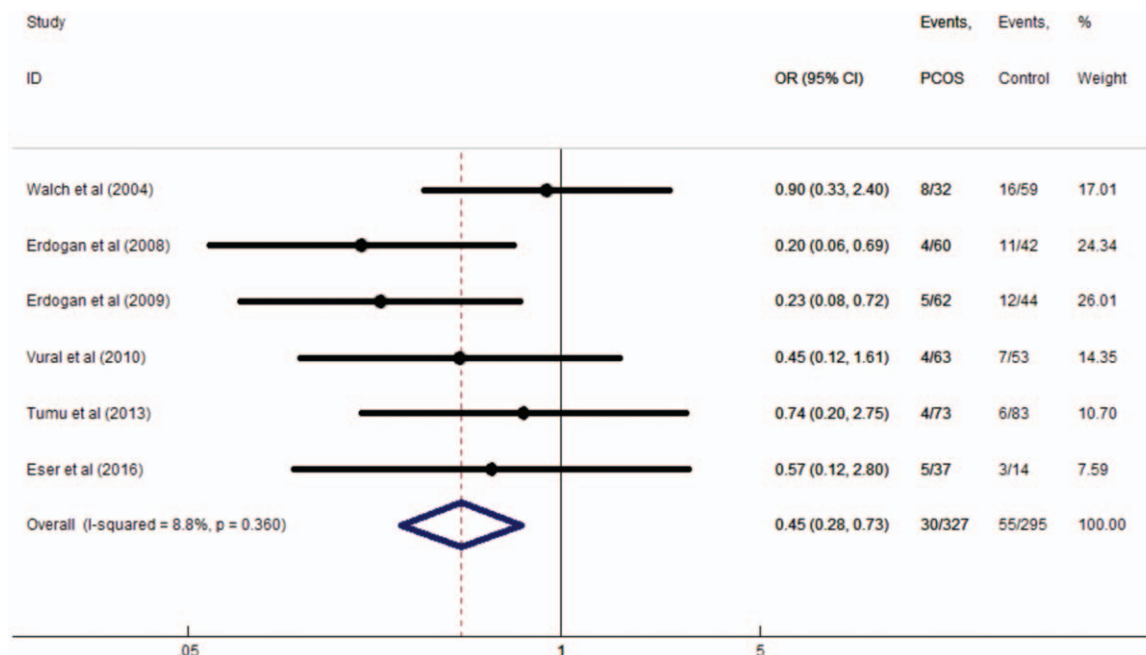


Figure 2. The forest plot of pooled odds ratios of the association of IL-6 rs1800795 polymorphism with polycystic ovary syndrome susceptibility under the homozygous model.

Table 4**Subgroup analysis of the association of rs1800795 polymorphism and PCOS susceptibility under 5 models.**

Subgroup analysis	N	OR	95% CI	$P_{(Z-t)}$	I^2 (%)	$P_{(Q-t)}$	Model
G vs. C							
Asians	1	0.62	0.40–0.95	.027	—	—	—
Whites	5	0.59	0.37–0.93	.024	77.2	.002	Random-effect
PCR-RFLP	4	0.5	0.33–0.76	.001	65.6	.033	Random-effect
Sequencing	2	0.8	0.47–1.37	.422	64.8	.092	Random-effect
HWE	3	0.43	0.29–0.62	<.001	52.8	.12	Random-effect
Non-HWE	3	0.84	0.63–1.13	.261	1	.364	Fixed-effect
NOS score=6	5	0.58	0.37–0.91	.017	76.8	.002	Random-effect
NOS score=8	1	0.66	0.42–1.05	.08	—	—	—
GG vs. CC							
Asians	1	0.74	0.20–2.75	.657	—	—	—
Whites	5	0.41	0.24–0.70	.001	17.4	.304	Fixed-effect
PCR-RFLP	4	0.3	0.16–0.56	<.001	0	.661	Fixed-effect
Sequencing	2	0.84	0.38–1.84	.658	0	.824	Fixed-effect
HWE	3	0.31	0.16–0.62	.001	18.1	.295	Fixed-effect
Non-HWE	3	0.67	0.33–1.35	.258	0	.685	Fixed-effect
NOS score=6	5	0.45	0.27–0.76	.003	27	.241	Fixed-effect
NOS score=8	1	0.45	0.12–1.61	—	—	—	—
GG vs. CG							
Asians	1	0.47	0.28–0.81	—	—	—	—
Whites	5	0.51	0.22–1.17	.11	86.8	<.001	Random-effect
PCR-RFLP	4	0.38	0.17–0.83	.015	81.3	<.001	Random-effect
Sequencing	2	0.83	0.26–2.64	.015	85.5	.009	Random-effect
HWE	3	0.26	0.14–0.49	<.001	69.5	.038	Random-effect
Non-HWE	3	0.97	0.55–1.71	.917	45.4	.16	Fixed-effect
NOS score=6	5	0.47	0.35–1.14	.067	86.2	<.001	Random-effect
NOS score=8	1	0.63	0.35–1.14	—	—	—	—
CC vs. GG+CG							
Asians	1	1	0.28–3.63	—	—	—	—
Whites	5	0.58	0.35–0.96	.035	0	.984	Fixed-effect
PCR-RFLP	4	0.52	0.28–0.96	.037	0	.997	Fixed-effect
Sequencing	2	0.8	0.38–1.70	.567	0	.687	Fixed-effect
HWE	3	0.6	0.31–1.18	.14	0	.665	Fixed-effect
Non-HWE	3	0.64	0.33–1.24	.185	0	.922	Fixed-effect
NOS score=6	5	0.63	0.38–1.06	.079	0	.92	Fixed-effect
NOS score=8	1	0.54	0.15–1.91	—	—	—	—
GC+CC vs. GG							
Asians	1	0.49	0.30–0.83	—	—	—	—
Whites	5	0.48	0.22–1.06	.068	86.2	<.001	Random-effect
PCR-RFLP	4	0.37	0.18–0.77	.008	80.5	.002	Random-effect
Sequencing	2	0.8	0.3–2.1	.644	81.8	.019	Random-effect
HWE	3	0.27	0.14–0.51	<.001	73.1	.024	Random-effect
Non-HWE	3	0.89	0.54–1.48	.65	38.2	.198	Fixed-effect
NOS score=6	5	0.46	0.22–0.98	.044	85.7	<.001	Random-effect
NOS score=8	1	0.6	0.34–1.07	—	—	—	—

CI=confidence intervals, HWE=Hardy-Weinberg equilibrium, N=the number of studies, NOS=Newcastle-Ottawa Scale, OR=odds ratios, PCOS=Polycystic ovary syndrome, PCR=polymerase chain reaction, RFLP=restriction fragment length polymorphism.

$P_{(Z-t)}$ value for association test, $P_{(Q-t)}$ value for heterogeneity test

our study, we found a statistically significant correlation among studies that conformed to the HWE under the allele model and dominant model. Another meta-analysis found positive associations between the *IL-6* rs1800795 polymorphisms and the risk of PCOS under the allelic model, homozygous model, heterozygous model, and dominant model; however, the results were inaccurate because some original data were wrong when they were extracted from the included studies.^[19] For example, the number of G/C genotypes in healthy women was 35, whereas in the study mentioned above, the corresponding number was 25.^[19] The number of C/C genotypes in patients with PCOS was 56, whereas in the study mentioned above, the number was 36.^[19] We believed that these mistakes made the results unreliable. Considering the relative small sample size, no definite

consensus could be reached. The objective of the present study was to present accurate evidence for the association between *IL-6* rs1800795 polymorphisms and PCOS risk. The results suggested that *IL-6* polymorphism rs1800795 likely has a protective effect against PCOS, even though the *P* value under the recessive model was marginal. One possible reason for this association is that the C allele results in the reduction of *IL-6* production, which helps to normalize ovarian function.^[18]

However, some limitations should be considered in interpreting the results. First, only 6 studies were included in our meta-analysis, which limited further analyses because certain original data were unavailable. Second, because of the limited studies in certain subgroups, some conclusions should be interpreted with caution in the subgroup analysis. In addition, we were unable to

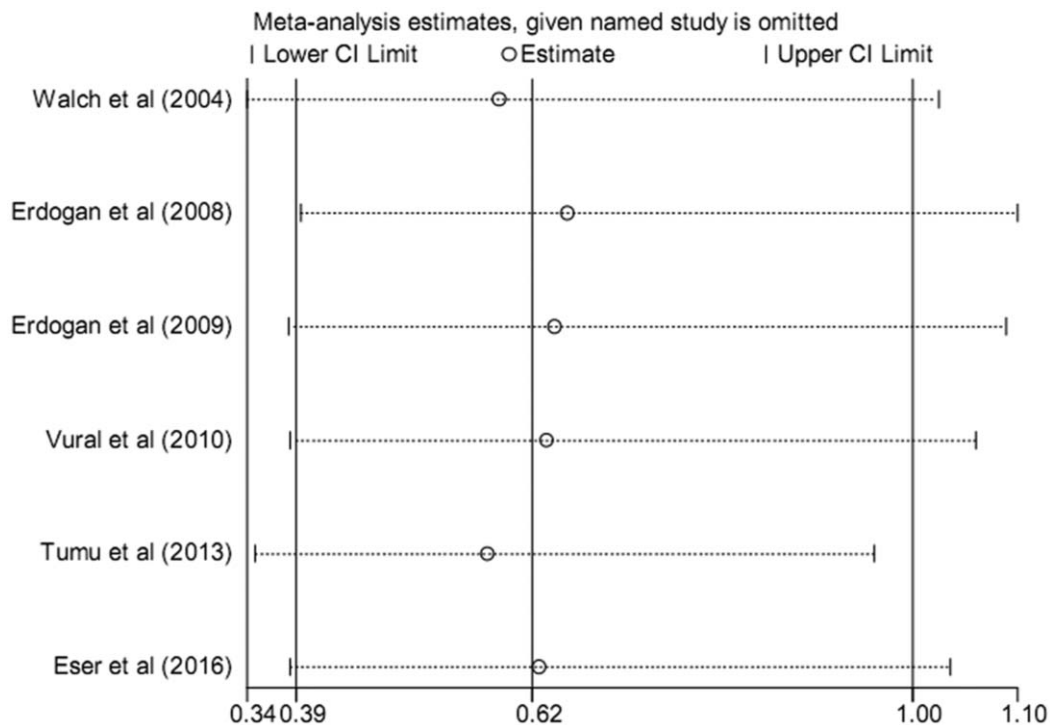


Figure 3. Sensitivity analysis of the association between *IL-6* rs1800795 polymorphism and the risk of polycystic ovary syndrome under the recessive model.

adjust for potential confounding effects such as environmental factors, lifestyle, sex, medication consumption, and other exposure factors because of the limited data. Third, 3 studies did not conform to the HWE, even though the combined ORs were not materially affected in the sensitivity analysis. Furthermore, Begg funnel plot showed no potential publication bias; however, 3 of the 6 studies are outliers. Deviation from an asymmetric distribution of the funnel plot can still indicate publication bias. We failed to verify the results at the level of molecular mechanism. Data from large sample size multicenter epidemiological studies are still needed to clarify the associations.

5. Conclusion

In summary, our meta-analysis based on 6 case-control studies concluded that *IL-6* -174G/C (rs1800795) polymorphism was

associated with PCOS susceptibility. The rs1800795 polymorphism is a protective factor for PCOS susceptibility. Given the limited number of ethnic groups and sample size, more evidence from larger epidemiological studies is needed to validate these results.

Author contributions

Linjie Chen designed this study; Zhifen Zhang and Jian Huang collected and collated data; Minjuan Jin and Zhifen Zhang extracted and confirmed the data; Linjie Chen and Minjuan Jin analyzed data; Linjie Chen wrote the manuscript; Zhifen Zhang and Minjuan Jin edited the manuscript.

Author contributions

Conceptualization: Linjie Chen, Minjuan Jin.

Formal analysis: Zhifen Zhang, Minjuan Jin.

Investigation: Zhifen Zhang.

Resources: Jian Huang.

Software: Zhifen Zhang, Jian Huang.

Supervision: Jian Huang.

Validation: Jian Huang.

Writing – original draft: Linjie Chen, Minjuan Jin.

Writing – review & editing: Zhifen Zhang, Minjuan Jin.

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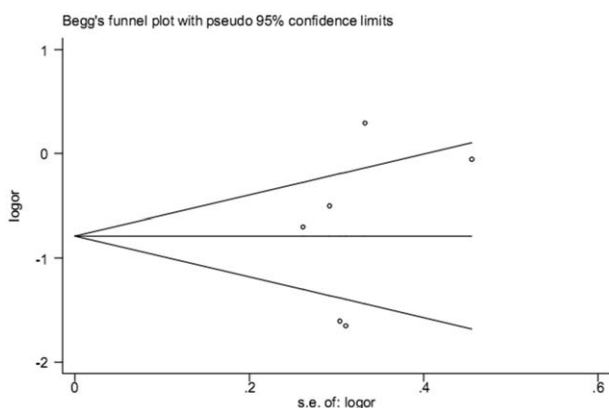


Figure 4. Publication bias detection between *IL-6* rs1800795 polymorphism and polycystic ovary syndrome susceptibility under the dominant model.

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