Common cytokine polymorphisms and predisposition to polycystic ovary syndrome: a meta-analysis

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Abstract. The results of studies on the relationship between cytokine polymorphisms and polycystic ovary syndrome (PCOS) have been controversial. This meta-analysis was thus designed to more precisely assess the relationship between TNF-α/IL-1/IL-6/IL-10 polymorphisms and PCOS by pooling the results of published studies. A search of PubMed, Embase, Web of Science, and CNKI databases turned up 23 studies that were pooled and analyzed in this meta-analysis. The overall results showed that the distributions of TNF-α –238 G/A, TNF-α –857 C/T, and IL-1B –51 C/T polymorphisms among patients and controls differed significantly. Additionally, the distributions of TNF-α –308 G/A and IL-1B –51 C/T polymorphisms among patients and controls from Asian populations differed significantly, whereas the distributions of IL-6 –174 G/C and IL-1A –889 C/T polymorphisms among patients and controls from Caucasian populations also differed significantly. In conclusion, our meta-analysis demonstrated that TNF-α –238 G/A, TNF-α –857 C/T, and IL-1B –51 C/T polymorphisms might influence susceptibility to PCOS in the overall pooled population. Moreover, TNF-α –308 G/A and IL-1B –51 C/T polymorphisms might influence susceptibility to PCOS in Asians, whereas IL-6 –174 G/C and IL-1A –889 C/T polymorphisms might influence susceptibility to PCOS in Caucasians.

Key words: Polycystic ovary syndrome (PCOS), Tumor necrosis factor-α (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-10 (IL-10)

POLYCYSTIC OVARY SYNDROME (PCOS), characterized by polycystic ovaries, chronic anovulation, and hyperandrogenism, is the most common reproductive endocrine disorder in women of childbearing age [1, 2]. Although its definite etiologies and pathogenesis mechanisms have yet to be clarified, accumulating evidence suggests that genetic architecture greatly influences its development. Firstly, the incidence of PCOS in different populations differs significantly [3, 4], indicating that genetic background is probably one of the key factors underlying this phenomenon. Secondly, previous association studies have also detected numerous predisposing gene loci of PCOS in different populations [5, 6]. However, the etiologies and pathogenesis mechanisms of PCOS are extremely, and the precise genetic factors that contribute to the development of PCOS still need to be intensively explored.

Cytokines play vital roles in modulating immune responses and are involved in the pathogenesis of various inflammatory disorders [7, 8]. Previous studies have demonstrated that PCOS share similar properties with many chronic inflammatory disorders, and classical inflammatory mediators such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) have also been found to be elevated in patients with PCOS [9-11]. Moreover, pro-inflammatory cytokines and its associated over-activated immune responses have also been shown to be associated with higher androgen levels, and have been shown to be able to impact ovarian function and jeopardize the processes of ovulation in PCOS [12, 13]. Therefore, if a polymorphism can impact gene expression or the protein structure of cytokines, it is highly likely that it might alter inflammation status and influence predisposition to PCOS.

In the last two decades, investigators around the world have extensively explored the relationship between cytokine polymorphisms and PCOS, particularly for polymorphisms of TNF-α, interleukin-1 (IL-1), interleukin-6 (IL-6), and interleukin-10 (IL-10), yet the relationship between TNF-α/IL-1/IL-6/IL-10 polymorphisms and
PCOS still remains controversial and ambiguous. Thus, we designed this meta-analysis to obtain a more statistically reliable conclusion regarding the relationship between TNF-α/IL-1/IL-6/IL-10 polymorphisms and PCOS by pooling the results of already published studies.

**Materials and Methods**

The PRISMA guideline was followed by the authors when conducting this meta-analysis [14].

**Literature search and inclusion criteria**

Literature search of PubMed, Web of Science, Embase, and CNKI was conducted using the following terms: (Tumor necrosis factor-α or TNF-α or interleukin-10 or IL-10 or interleukin 10 or IL 10 or interleukin-6 or IL-6 or interleukin 6 or IL 6 or interleukin-1 or IL-1 or interleukin 1 or IL 1) and (polymorphism or variant or variation or mutation or SNP or genome-wide association study or genetic association study or genotype or allele) and (polycystic ovary syndrome or PCOS). The references of the articles obtained were also checked for additional related studies.

Eligible studies had to meet all three inclusion criteria: 1. formally published study evaluating relationship between TNF-α/IL-1/IL-6/IL-10 polymorphisms and PCOS; 2. provided genotypic distribution of TNF-α/IL-1/IL-6/IL-10 polymorphisms in patients with PCOS and controls; 3. the entire manuscript was available in English or Chinese. Articles were excluded when any one of the following three conditions was fulfilled: 1. studies were not concerning TNF-α/IL-1/IL-6/IL-10 polymorphisms and PCOS; 2. studies were reviews or expert comments; 3. case series only involved participants with PCOS. When duplicate reports were uncovered during literature search, only the most recent one was included for pooled meta-analysis.

**Data extraction and quality assessment**

The following five items were extracted from the studies included: 1. surname of first author; 2. year of online publication; 3. country and ethnicity of involved participants; 4. number of patients and controls; 5. genotypic distributions of TNF-α/IL-1/IL-6/IL-10 polymorphisms in patients and control subjects. The p values of Hardy-Weinberg equilibrium (HWE) were also calculated based on genotypic distributions of TNF-α/IL-1/IL-6/IL-10 polymorphisms.

Newcastle-Ottawa scale (NOS) was used to assess the quality of the studies included [15]. Its score range is from zero to nine, and the methodology quality of an article is considered to be good if it can get a score of greater than seven.

Data extraction and quality assessment of the studies included were independently performed by two authors. We wrote to the corresponding authors of eligible studies for additional data if we failed to extract the necessary information from the studies included.

**Statistical analyses**

Review Manager software was used to pool meta-analysis results. Z test was used to evaluate the relationship between TNF-α/IL-1/IL-6/IL-10 polymorphisms and predisposition to PCOS with the statistical significant threshold at 0.05. I² statistics was used to estimate heterogeneity. DerSimonian-Laird method was used to pool the results if I² is was larger than 50%. Otherwise, Mantel-Haenszel method was used to pool the results. The authors also conducted subgroup analyses by ethnicity. Stabilities of pooled results were examined by omitting one study each time and pooling the results of the other studies. Publication biases were examined by using funnel plots.

**Results**

**Characteristics of included studies**

Of the 173 articles were retrieved by the literature search, 44 were assessed for eligibility after omitting unrelated and repeated reports. Twelve reviews and nine studies with incomplete data were further excluded for a total of 23 studies finally pooled in our meta-analysis (Fig. 1). Extracted data of eligible studies are summarized in Table 1. Rotterdam criterion was used by most of the eligible studies for diagnosing PCOS, whereas Mao et al., Milner et al., Korhonen et al., Walch et al. and Kolbus et al. used NIH criterion, and Thathapudi et al. used 2006 AE-PCOS criterion.

**Meta-analyses of TNF-α polymorphisms and PCOS**

Twelve studies were eligible for estimation of relationship between TNF-α polymorphisms and PCOS. TNF-α –238 G/A (dominant comparison: OR = 1.78, p = 0.002; over-dominant comparison: OR = 0.55, p = 0.002; allele comparison: OR = 1.60, p = 0.005) and –857 C/T (dominant comparison: OR = 0.67, p = 0.004; over-dominant comparison: OR = 1.46, p = 0.007; allele comparison: OR = 0.72, p = 0.007) polymorphisms were found to be significantly associated with PCOS in overall pooled population, and –308 G/A polymorphism was also found to be significantly associated with PCOS in Asians (allele comparison: OR = 1.50, p = 0.05). The pooled meta-analyses did not reveal any significant associations for TNF-α –1,031 T/C polymorphism and PCOS (see Table 2).
Meta-analyses of IL-6 polymorphisms and PCOS

Five studies were eligible for estimation of relationship between IL-6 polymorphisms and PCOS. IL-6 –174 G/C polymorphism was found to be significantly associated with PCOS in Caucasians (recessive comparison: OR = 0.58, \( p = 0.04 \)). Nevertheless, we did not observe any other significant associations for IL-6 –174 G/C polymorphism in pooled meta-analyses (see Table 2).

Meta-analyses of IL-1 polymorphisms and PCOS

Six studies were eligible for estimation of relationship between IL-1 polymorphisms and PCOS. IL-1B –51 C/T polymorphism was found to be significantly associated with PCOS in overall pooled population (dominant comparison: \( OR = 0.70, p = 0.03 \)) and Asians (dominant comparison: OR = 0.66, \( p = 0.01 \); allele comparison: OR = 0.63, \( p = 0.001 \)). Moreover, IL-1A –889 C/T polymorphism was found to be significantly associated with PCOS in Caucasians (dominant comparison: OR = 0.56, \( p = 0.01 \); over-dominant comparison: OR = 1.71, \( p = 0.03 \); allele comparison: OR = 0.68, \( p = 0.04 \)). The pooled meta-analyses did not reveal any significant associations for IL-1B +3,953 C/T polymorphism and PCOS (see Table 2).

Meta-analyses of IL-10 polymorphisms and PCOS

Three studies were eligible for estimation of relationship between IL-10 polymorphisms and PCOS. The pooled meta-analyses did not reveal any significant associations for IL-10 polymorphisms and PCOS (see Table 2).
| First author, year | Country | Ethnicity | Diagnostic criteria | Sample size | Genotype distribution | p-value for HWE | NOS score |
|-------------------|---------|-----------|---------------------|-------------|-----------------------|----------------|-----------|
| Zhang et al. 2019 | India   | Mixed     | 2003 Rotterdam criterion | 200/200 | GG/GA/AA | 0.067 | 8 |
| Bhatnager 2019   | Iran    | Mixed     | 2003 Rotterdam criterion | 114/105 | GG/GA/AA | 0.007 | 8 |
| Kordestani 2018  | China   | Asian     | 1990 NIH criterion    | 84/72     | 104/6/2 | 0.808 | 7 |
| Wen 2013         | China   | Asian     | 2003 Rotterdam criterion | 102/96  | GG/GA/AA | 0.067 | 8 |
| Zhang et al. 2019 | India   | Mixed     | 2006 AE-PCOS criterion | 204/204 | 186/6/2 | 0.510 | 8 |
| Xie 2016         | China   | Asian     | 2003 Rotterdam criterion | 217/144  | 162/139/5 | <0.001 | 8 |
| Walch 2004       | Turkey  | Caucasian | 2003 Rotterdam criterion | 144/112  | 129/69/2 | 0.027 | 8 |
| Kolbus 2007      | Australia | Caucasian | 1990 NIH criterion    | 105/102  | 93/15/2 | 0.817 | 7 |
| Xia 2013         | China   | Asian     | 2003 Rotterdam criterion | 32/39/5  | 11/13/3 | 0.772 | 7 |
| Tumu 2013        | Turkey  | Caucasian | 2003 Rotterdam criterion | 97/95    | 146/127/2 | <0.001 | 8 |
| Vural 2010       | Turkey  | Caucasian | 2003 Rotterdam criterion | 104/156  | 162/139/5 | <0.001 | 8 |
| Yun 2011         | Turkey  | Caucasian | 2003 Rotterdam criterion | 217/144  | 162/139/5 | <0.001 | 8 |
| Kolbus 2007      | Australia | Caucasian | 1990 NIH criterion    | 105/102  | 93/15/2 | 0.817 | 7 |
| Kolbus 2007      | Egypt   | Mixed     | 2003 Rotterdam criterion | 105/102  | 93/15/2 | 0.817 | 7 |
| Talaat 2016      | Turkey  | Caucasian | 2003 Rotterdam criterion | 97/95    | 146/127/2 | <0.001 | 8 |
| Vural 2010       | Turkey  | Caucasian | 2003 Rotterdam criterion | 104/156  | 162/139/5 | <0.001 | 8 |
| Abbreviations: HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa scale; NA, Not available. |
| Polymorphisms | Population | Sample size | Dominant comparison | Recessive comparison | Over-dominant comparison | Allele comparison |
|---------------|------------|-------------|---------------------|----------------------|--------------------------|------------------|
|               |            |             | p value | OR (95%CI) | p value | OR (95%CI) | p value | OR (95%CI) | p value | OR (95%CI) |
| *TNF-α* –238 G/A | Overall     | 557/473     | 0.002   | 1.78 (1.24–2.56) | 0.97    | 0.97 (0.22–4.27) | 0.002   | 0.55 (0.38–0.80) | 0.005   | 1.60 (1.15–2.21) |
|               | Asian       | 246/168     | 0.83    | 1.12 (0.41–3.03) | NA      | NA         | 0.83    | 0.89 (0.33–2.43) | 0.83    | 1.11 (0.42–2.99) |
| *TNF-α* –308 G/A | Overall     | 1,015/997   | 0.55    | 1.07 (0.85–1.36) | 0.16    | 0.58 (0.27–1.23) | 0.89    | 0.98 (0.77–1.26) | 0.35    | 1.11 (0.90–1.37) |
|               | Asian       | 351/288     | 0.11    | 1.42 (0.92–2.21) | 0.08    | 0.24 (0.05–1.17) | 0.31    | 0.79 (0.51–1.25) | 0.05    | 1.50 (1.01–2.24) |
|               | Caucasian   | 181/203     | 0.22    | 1.34 (0.84–2.11) | 0.89    | 0.92 (0.27–3.08) | 0.22    | 0.74 (0.46–1.19) | 0.26    | 1.26 (0.84–1.88) |
| *TNF-α* –857 C/T | Overall     | 593/615     | 0.004   | 0.67 (0.51–0.88) | 0.41    | 1.53 (0.56–4.14) | 0.007   | 1.46 (1.11–1.93) | 0.007   | 0.72 (0.57–0.91) |
|               | Asian       | 351/288     | 0.17    | 1.50 (0.61–3.69) | 0.04    | 0.38 (0.15–0.97) | 0.66    | 0.81 (0.32–2.05) | 0.68    | 1.15 (0.59–2.25) |
|               | Caucasian   | 181/203     | 0.22    | 1.34 (0.84–2.11) | 0.89    | 0.92 (0.27–3.08) | 0.22    | 0.74 (0.46–1.19) | 0.26    | 1.26 (0.84–1.88) |
| *IL-6* –174 G/C | Overall     | 492/596     | 0.16    | 1.61 (0.83–3.15) | 0.05    | 0.63 (0.39–1.01) | 0.36    | 0.72 (0.36–1.45) | 0.40    | 1.25 (0.75–2.08) |
|               | Caucasian   | 388/440     | 0.38    | 1.50 (0.61–3.69) | 0.04    | 0.38 (0.05–0.97) | 0.66    | 0.81 (0.32–2.05) | 0.68    | 1.15 (0.59–2.25) |
| *IL-1A* –889 C/T | Overall     | 386/306     | 0.52    | 0.79 (0.39–1.61) | 0.43    | 1.39 (0.61–3.17) | 0.66    | 1.18 (0.57–2.44) | 0.52    | 0.86 (0.54–1.36) |
|               | Caucasian   | 181/129     | 0.01    | 0.56 (0.35–0.89) | 0.64    | 1.23 (0.52–2.91) | 0.03    | 1.71 (1.06–2.75) | 0.04    | 0.68 (0.48–0.98) |
| *IL-1B* –51 C/T | Overall     | 482/421     | 0.04    | 0.74 (0.36–0.98) | 0.12    | 1.83 (0.85–3.93) | 0.64    | 0.87 (0.48–1.58) | 0.03    | 0.70 (0.32–0.96) |
|               | Asian       | 377/319     | 0.01    | 0.66 (0.48–0.90) | 0.11    | 2.20 (0.84–5.77) | 0.71    | 0.85 (0.36–2.01) | 0.001   | 0.63 (0.47–0.83) |
| *IL-1B* +3,953 C/T | Overall    | 223/188     | 0.67    | 1.54 (0.20–11.65)| 0.14    | 2.27 (0.76–6.78) | 0.56    | 0.59 (0.10–3.57) | 0.66    | 1.53 (0.23–10.24)|
| *IL-10* –1,082 A/G | Overall | 249/250     | 0.23    | 1.26 (0.87–1.83) | 0.86    | 0.95 (0.58–1.58) | 0.30    | 0.83 (0.58–1.18) | 0.35    | 1.13 (0.87–1.46) |
|               | Caucasian   | 188/170     | 0.55    | 1.14 (0.73–1.79) | 0.62    | 0.86 (0.48–1.56) | 0.83    | 0.96 (0.63–1.45) | 0.51    | 1.11 (0.82–1.50) |
| *IL-10* –819 C/T | Overall     | 151/155     | 0.37    | 0.81 (0.52–1.28) | 0.32    | 1.99 (0.51–7.82) | 0.86    | 0.93 (0.41–2.12) | 0.13    | 0.77 (0.55–1.08) |

Abbreviations: OR, Odds ratio; CI, Confidence interval; NA, Not available.
**Sensitivity analyses**

Stabilities of pooled meta-analyses results were examined by omitting one study each time and pooling the results of the other studies. The trends of associations remained unchanged in sensitivity analyses, indicating that our pooled meta-analyses results were statistically stable.

**Publication biases**

Publication biases were examined by funnel plots. Funnel plots were overall symmetrical, suggesting that our pooled meta-analyses results were not likely to be severely influenced by publication biases.

**Discussion**

The meta-analysis results demonstrated that TNF-α −238 G/A, TNF-α −857 C/T, and IL-1B −51 C/T polymorphisms might influence susceptibility to PCOS in overall pooled population. Moreover, we found that TNF-α −308 G/A and IL-1B −51 C/T polymorphisms might influence susceptibility to PCOS in Asians, whereas IL-6 −174 G/C and IL-1A −889 C/T polymorphisms might influence susceptibility to PCOS in Caucasians. The trends of associations remained unchanged in sensitivity analyses, suggesting that our pooled meta-analysis results were quite stable statistically.

A few points need to be considered when interpreting our findings. First, previous experimental studies have demonstrated that all investigated polymorphisms are correlated with altered gene expression or protein structure of corresponding cytokines [16, 17]. Thus, it is likely that these variations might influence normal functioning of TNF-α/IL-1/IL-6/IL-10, lead to immune dysfunction, and influence predisposition to PCOS. In this meta-analysis, we did not observe any positive findings for IL-10 polymorphisms. Nevertheless, since only three studies were pooled analyzed, it is possible that our pooled meta-analysis is still not statistically sufficient to detect the real associations between IL-10 polymorphisms and PCOS, and future studies involving larger populations are still needed to get a more statistically robust finding. Second, the etiologies and pathogenesis mechanisms of PCOS are extremely sophisticated, although many literatures support the finding that inflammation and immune-regulatory genes are involved in the pathogenesis of PCOS, we also need to point out that several reports failed to find any significant association between inflammatory gene pathways and PCOS, such as Bhatt et al. [18]. Considering that PCOS is a multi-factorial disease, further association studies also need to be conducted to consider the potential influence of gene-gene interactions to more precisely measure the effects of certain gene polymorphisms on predisposition to PCOS [19]. Third, we also intended to analyze gene polymorphisms of other cytokines such as IL-4, IL-8, and IL-12 at the beginning. However, since we could not find at least two eligible studies for gene polymorphisms in these cytokines, we had to focus only on TNF-α, IL-1, IL-6 and IL-10 in this meta-analysis. Fourth, we did not set any restrictions on the investigated polymorphisms, nevertheless we noticed that previous investigators even failed to analyze some very common polymorphisms of IL-6 and IL-10 such as IL-6 −572 G/C, IL-6 −634 G/C, and IL-10 −592 C/A. In the future, we hope to analyze the associations between these IL-6 or IL-10 polymorphisms and PCOS. Fifth, since different ethnicities were involved in our overall pooled analysis, the distributions of cytokine polymorphisms varied from study to study, especially when those studies were of different ethnic groups. This suggests that the effects of cytokine polymorphisms on predisposition to PCOS may vary from population to population, and that the positive findings in one ethnic subgroup should not be generalized to broader populations.

Like all meta-analyses, a few limitations of our pooled meta-analyses should also be acknowledged. Firstly, our pooled meta-analysis results were derived from pooling unadjusted findings of eligible studies since the authors did not have the raw data from them [20]. Secondly, environmental factors might also influence the relationship between TNF-α/IL-1/IL-6/IL-10 polymorphisms and PCOS. However, most investigators only focused on genetic associations in their works, and so the genetic-environmental interactions were not explored in this meta-analysis [21]. Thirdly, we did not consider grey literature. Therefore, despite the fact that funnel plots were overall symmetrical, publication biases still might affect the robustness of our pooled results [22].

In conclusion, this meta-analysis demonstrated that TNF-α −238 G/A, TNF-α −857 C/T, and IL-1B −51 C/T polymorphisms might influence susceptibility to PCOS in overall pooled population. Moreover, we found that TNF-α −308 G/A and IL-1B −51 C/T polymorphisms might influence susceptibility to PCOS in Asians, whereas IL-6 −174 G/C and IL-1A −889 C/T polymorphisms might influence susceptibility to PCOS in Caucasians. These results also suggested that TNF-α, IL-1, and IL-6 might be involved in the development of PCOS and that they might serve as potential therapeutic targets for PCOS.

**Authors’ Contributions**

Yunli Zhang and Jiaoyan He designed this meta-analysis. Yunli Zhang and Lina Che searched the literature databases. Mingyan Zhang analyzed the data. Yunli
Zhang and Jiaoyan He wrote the manuscript. All authors approved the final manuscript as submitted.

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None.

Conflicts of Interest

None.

Ethical Statement

Ethical approval and informed consent are not applicable to meta-analyses.

Data Availability Statement

Data sharing is not applicable to meta-analyses.

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