INPLASY PROTOCOL

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Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Association of IL-4 and IL-10 Polymorphisms with Preterm Birth Susceptibility: A Systematic Review and Meta-Analysis

Cao, XL[1]; Zhou, XY[2]; Xu, NX[3]; Chen, SC[4]; Xu, CM[5].

Review question / Objective: **The aim of our systematic review and meta-analysis was to summarize the effects of IL-4 and IL-10 gene polymorphism and clarify their possible association with PTB.**
Condition being studied: **World Health Organization (WHO) defines preterm birth (PTB) as babies born alive before 37 weeks of pregnancy are completed. The new estimates show that the prevalence of PTB during 2014 ranged from 8.7% to13.4% of all live births, about 15 million preterm babies born each year. Besides, PTB is the leading cause of death worldwide for children below 5 years of age. Babies born preterm are at an increased risk of short-term and long-term complications attributed to immaturity of multiple organ systems, such as cerebral palsy, intellectual disabilities, vision and hearing impairments, and impaired cognitive development. PTB has become a worldwide public health problem, but its etiology remains unclear. Accumulating evidence shows that PTB is a syndrome that can be attributed to a variety of pathological processes(5). Inflammatory diseases and genetic background are known risk factors for PTB, many studies had shown that genetic variations in proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1 α (IL-1 α) are associated with increased risk of PTB, but the relationship between genetic polymorphism in anti-inflammatory cytokines and risk of PTB remains controversial.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 April 2022 and was last updated on 07 April 2022 (registration number INPLASY202240044).

INTRODUCTION

Review question / Objective: **The aim of our systematic review and meta-analysis was to summarize the effects of IL-4 and IL-10 gene polymorphism and clarify their possible association with PTB.**

Rationale: **nflammatory imbalance can promote the excessive secretion of inflammatory factors, leading to PTB. As an**

anti-inflammatory cytokine, interleukin-4 (IL-4) and interleukin-10 (IL-10) can antagonize the pro-inflammatory effects of other cytokines, thus playing a major inhibitory role in a variety of inflammatory diseases. Due to the role of inflammation in PTB, anti-inflammatory factors IL4 and IL10 and their nearby polymorphisms have become the targets of relevant research. Studies investigating the association between IL-4 gene promoter -590C/T (rs2243250) polymorphism and IL-10 gene promoter -592A/C(rs1800872), -819T/C(rs1800871) or -1082A/G(rs1800896) polymorphism and PTB report conflicting results.

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METHODS

Search strategy: A systematic literature search will be performed using PubMed, Web of Science and Cochrane Library. In addition, the reference lists of the included studies and related reviews were also manually searched and screened to ensure a comprehensive literature search. No language restriction was applied. Two authors(XL and XY) independently searched all the databases using the following search terms: ("Polymorphism, Genetic" OR "Polymorphisms, Genetic" OR "Genetic Polymorphism" OR "Genetic Polymorphisms" OR "Gene Polymorphism" OR "Gene Polymorphisms" OR "Polymorphism, Gene" OR "Polymorphisms, Gene" OR "Polymorphism (Genetics)" OR "Polymorphisms (Genetics)" OR "Genetic Variation" OR "Genetic Variations" OR "Variations, Genetic" OR "Variation, Genetic" OR "Diversity, Genetic" OR "Diversities, Genetic" OR "Genetic Diversities" OR "Genetic Diversity") AND ("Birth, Premature" OR "Births, Premature" OR "Premature Births" OR "Preterm Birth" OR "Birth, Preterm" OR "Births, Preterm" OR "Preterm Births" OR "Premature Birth" OR "Preterm Premature Rupture of the Membranes" OR "PPROM" OR "spontaneous preterm birth" OR "premature labor" OR "Obstetric Labor, Premature" OR "Labor, Premature Obstetric" OR "Preterm Labor" OR "Labor, Preterm" OR "Premature Obstetric Labor" OR "Labor, Premature" OR "Premature Labor" OR "Premature delivery" OR "Preterm delivery") AND (("CSIF" OR "TGIF" OR "GVHDS" OR "IL-10" OR "IL10A" OR "Interleukin 10" OR "IL10" OR "CSIF-10" OR "Cytokine Synthesis Inhibitory Factor") OR ("BSF1" OR "BCGF1" OR "BSF-1" OR "Interleukin 4" OR "Interleukin-4" OR "B-Cell Growth Factor-1" OR "B Cell Growth Factor 1" OR "B-Cell Growth Factor-I" OR "B Cell Growth Factor I" OR "B-Cell Proliferating Factor" OR "B Cell Proliferating Factor" OR "B-Cell Stimulating Factor-1" OR "B Cell Stimulating Factor 1" OR "B-Cell Stimulatory Factor 1" OR "B-Cell Stimulatory Factor-1" OR "BCGF-1" OR "Binetrakin" OR "IL-4" OR "IL4" OR "Mast Cell Growth Factor-2" OR "Mast Cell Growth Factor 2" OR "MCGF-2" OR "B Cell Stimulatory Factor-1" OR "B Cell Stimulatory Factor 1")).

Participant or population: Preterm birth women and term birth controls.

Intervention: Non-interventional study.

Comparator: To evaluate the association between IL-4-590C/T (rs2243250), IL-10-592A/C(rs1800872), IL-10-819T/C (rs1800871) and IL-10-1082A/G (rs1800896) polymorphism and PTB in the allele model T-allele vs. C-allele, C-allele vs. A-allele, C-allele vs. T-allele and G-allele vs. A-allele, recessive model TT vs. CT+CC, CC vs. AA+AC, CC vs. TT+TC and GG vs. AA+AG, dominant model CT+TT vs. CC, AC+CC vs. AA, TC+CC vs. TT and AG+GG vs. AA, co-dominant model TT vs. CC and CT vs. CC, CC vs. AA and AC vs. AA, CC vs. TT and TC vs. TT, AG vs. AA and GG vs. AA and over-dominant model CC+TT vs. CT, AA+CC vs. AC, TT+CC vs. TC and AA+GG vs. AG respectively.

Study designs to be included: Case-control or cohort study.

Eligibility criteria: The inclusion criteria of our systematic review and meta-analysis were as follows: 1) case-control or cohort studies; 2) the case groups consisted of patients diagnosed with PTB or preterm premature rupture of membranes (PPROM), and the control groups consisted of term birth healthy individuals; 3) studying the association between IL-4 and IL-10 polymorphisms and PTB or PPROM; 4) sufficient data supporting the genotype distribution were provided for the calculation of odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Information sources: A systematic literature search will be performed using PubMed, Web of Science and Cochrane Library. In addition, the reference lists of the included studies and related reviews were also manually searched and screened to ensure a comprehensive literature search, We will also contact with authors for eligible data.

Main outcome(s): Association of different gene models of IL-4-590C/T (rs2243250), IL-10-592A/C(rs1800872), IL-10-819T/C (rs1800871) and IL-10-1082A/G (rs1800896) polymorphism and risk of preterm birth.

Additional outcome(s): Not applicable.

Data management: All data can be obtained from the online database.

Quality assessment / Risk of bias analysis: The quality of the methods for the included literature will be independently assessed by the two reviewers (XL and XY) using the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. The NOS uses a star rating system to assess quality. Studies with scores ranging from 0 to 9 stars and ≥7 stars were considered of high quality. Discrepancies between the two reviewers will be resovled by disscusing.

Strategy of data synthesis: The meta-analysis was performed using the Stata (version 16.0) software. ORs and 95% CIs wii be analyzed to evaluate the association between IL-4-590C/T (rs2243250), IL-10-592A/C(rs1800872), IL-10-819T/C (rs1800871) and IL-10-1082A/G (rs1800896) polymorphism and PTB in the allele model T-allele vs. C-allele, C-allele vs. A-allele, C-allele vs. T-allele and G-allele vs. A-allele, recessive model TT vs. CT+CC, CC vs. AA+AC, CC vs. TT+TC and GG vs. AA+AG, dominant model CT+TT vs. CC, AC+CC vs. AA, TC+CC vs. TT and AG+GG vs. AA, co-dominant model TT vs. CC and CT vs. CC, CC vs. AA and AC vs. AA, CC vs. TT and TC vs. TT, AG vs. AA and GG vs. AA and over-dominant model CC+TT vs. CT, AA+CC vs. AC, TT+CC vs. TC and AA+GG vs. AG respectively.

Subgroup analysis: Subgroup analysis will be conducted according to the different racial and Hardy-Weinberg Equilibrium (HWE) P value of controls.

Sensitivity analysis: The sensitivity analysis should be performed to assess the reliability of the meta-analysis, Analysis

software uses STATA 16.0 software for sensitivity analysis.

Language: **No language limits.**

Country(ies) involved: **China.**

Keywords: **preterm birth, genetic polymorphism, IL-4, IL-10, meta-analysis.**

Dissemination plans: **The findings will be disseminated through conference presentations and publication in a peer-reviewed, scientific journal.**

Contributions of each author:

Author 1 - Xianling Cao - XL conceived the idea for this meta-analysis.
Email: caoxianlingling@163.com
Author 2 - Xuanyou Zhou - XZ developed the methodology for the meta-analysis.
Author 3 - Naixin Xu - NX developed the methodology for the meta-analysis.
Author 4 - Songchang Chang - SC developed the methodology for the meta-analysis.
Author 5 - Chenming Xu - CM will revise this meta-analysis.