

**Are chronic pain syndromes associated with a unique cytokine profile?**

**A systematic review and meta-analysis**

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## **ABSTRACT**

### **Background**

The aetiology of primary chronic pain syndromes (CPS) is highly disputed. One theory suggests that pain sensation is due to a pro-inflammatory cytokine milieu leading to excessive nociceptive activation. We performed a systematic review and meta-analysis aiming to assess differences in circulating cytokines levels in CPS patients versus healthy controls (HC).

### **Methods**

Human studies published in English from the PubMed and MEDLINE/Scopus and Cochrane databases were systematically searched from inception up to January 2020. We included full text cross-sectional or longitudinal studies with baseline cytokine measurements, reporting differences in circulating cytokine levels between CPS patients and HC. We excluded animal studies and human studies of patients with CPS and underlying organic pathology. Quality assessment was completed using a modified version of the Newcastle-Ottawa Scale. Random-effects meta-analysis models were used to report pooled effects and 95% CIs. This study is registered with PROSPERO, registration number: CRD42020193774

### **Findings**

Our initial search yielded 324 papers, and identified 36 studies (3229 participants) eligible for systematic review and 26 studies (2048 participants) suitable for meta-analysis. The systematic analysis revealed reproducible findings supporting different trends of cytokine levels when CPS patients were compared to HC, with the exception of the chemokine eotaxin, which was consistently raised in CPS. Meta-analysis showed significantly increased tumour necrosis factor alpha (TNF- $\alpha$ ) ( $SMD=0.39$ ,  $p=0.0009$ ,  $95\%CI=0.16-0.63$ ,  $p<0.001$ ;  $I^2=70\%$ ,  $Q^2 p<0.001$ ), interleukin (IL)-6 ( $SMD=0.15$ ,  $p=0.037$ ,  $%95CI=0.01-0.28$ ;  $I^2=34\%$ ,  $Q^2 p=0.08$ ), IL-

8 (SMD=0.26, p=0.01, 95%CI =0.05-0.47;  $I^2=61\%$ ,  $Q^2$  p=0.005) and IL-10 (SMD=0.61; %95 = 0.34-0.89, p<0.001;  $I^2 = 10\%$ ,  $Q^2$  p=0.34) in CPS compared to HC.

### **Interpretation**

We found evidence of significant differences in the peripheral blood cytokine profiles of CPS patients compared to HC. However, the distinctive profile associated with CPS includes both pro-inflammatory (TNF- $\alpha$ , IL-6, IL-8), and anti-inflammatory cytokines (IL-10) in pooled analysis, as well as chemokine (eotaxin) signatures. Further research is required to elucidate the role of cytokines in CPS.

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