Research Article

A moderator-mediator analysis of inflammatory cytokine levels in Parkinson's disease: A systematic review and meta-analysis

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ABSTRACT

Introduction & Aim: Systemic inflammation is implicated in Parkinson's disease (PD) pathogenesis, but evidence regarding peripheral cytokine levels remains inconsistent. This meta-analysis aimed to summarize the available data on peripheral blood cytokine concentrations in PD patients compared to healthy controls (HCs), and investigate key moderator variables that may affect cytokine concentrations.

Materials & Methods: A systematic literature search was conducted across multiple electronic databases from August 06 to August 26, 2025. Eligible studies reporting peripheral blood cytokine levels in PD patients and a matched HC group, were included. Data from 100 studies, comprising 7,369 PD patients and 10,978 HCs, were extracted, and the meta-analysis was performed using a random-effects model, with effect sizes expressed as standardized mean differences (Hedges' g).

Results: Concentrations of interleukin-6, tumour necrosis factor, interleukin-1 beta, and C-reactive protein were elevated in PD patient's relative to HCs. In contrast, no significant differences were observed for interleukin-2, interleukin-4, interleukin-8, and interleukin-10. Subgroup analyses revealed that the analytical methodology, sample source (serum, plasma, or cerebrospinal fluid), and geographic origin of the study population significantly influenced effect sizes, whereas patient age, motor severity (UPDRS-III), and disease stage (Hoehn & Yahr) did not demonstrate a significant moderating effect.

Conclusion: This meta-analysis confirms a distinct peripheral inflammatory profile in PD, characterized by elevated levels of specific pro-inflammatory cytokines. The findings underscore the potential role of systemic inflammation in PD pathophysiology and highlight methodological and demographic variables as key sources of heterogeneity in the literature, which must be considered in future biomarker studies.

Keywords: Parkinson's disease; meta analysis; interleukins; cytokines; biomarkers

1. INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative disorders globally, surpassed in prevalence only by Alzheimer's disease. Its clinical presentation encompasses a spectrum of motor features - including bradykinesia, postural instability, rigidity, and resting tremor - as well as non-motor symptoms such as cognitive impairment, gastrointestinal dysfunction, affective disorders, and autonomic and sensory changes. The primary pathological origin of these diverse clinical signs is the progressive and selective degeneration of dopaminergic neurons located within the substantia nigra pars compacta (SN) [1, 2].

Recent studies implicate neuro-inflammation as a significant contributor to PD pathogenesis [3]. However, it is unclear whether it is a cause of disease or it arises only as a secondary effect. The involvement of inflammatory cytokines was first highlighted by Mogi et al., who reported an increase in the amount of tumour necrosis factor alpha (TNFα) in the cerebrospinal fluid (CSF) and striatum and of PD patients [4]. Subsequent investigations revealed increased CSF levels of interleukin-2 (IL-2) and interleukin-6 (IL-6) in PD, with unchanged interleukin-1 beta (IL-1β) and interleukin-4 (IL-4) levels. At the same time, they observed an increased CSF levels of IL-1β, IL-2, IL-4 in patients with juvenile parkinsonism

[5]. Further work corroborated the upregulation of various cytokines, including IL-1β, IL-2, IL-4, IL-6, and TNFα, in the striatum and CSF of patients with PD [6]. Mogi et al. showed an increased level of interferon gamma (IFNγ) in the brain parenchyma of patients with PD, and increased expression of TNFα and IL-6 in activated microglia in the putamen of PD patients was observed by Nagatsu *et al.*, [7, 8]. In a number of studies, it was shown with the method of intra-vital neuroimaging that microglia can activate in SN of PD patients, which may lead to an increase in levels of pro-inflammatory cytokines [9, 10].

The most attention is given to the peripheral markers of inflammation due to the availability of blood samples [11]. However, association between blood concentration of various cytokines and PD is uncertain because of the sparse and somewhat contradictory data. For instance, Stypuła *et al.*, reported increased blood levels of IL-2, but not IL-1β or IL-6, in PD patients [12], whereas other studies described decreased IL-2 alongside elevated IL-1β, IL-6, and TNFα [13, 14]. More recent research has attempted to correlate cytokine levels with clinical features, such as the association between elevated IL-6 and TNFα and the severity of cognitive impairment [15], or the negative correlation between IL-6 blood levels and scores on activities of daily living scale [16]. Thus, the data are sparse and somewhat contradictory, and therefore conducting a meta-analysis is required. A previous meta-analysis by Qin et al. sought to consolidate this evidence, reporting elevated blood concentrations of interleukins -1β, -2, -6, -10, TNFα, and C-reactive protein (CRP) in PD [17]. However, that analysis was limited by the small number of studies available for several cytokines (e.g., IL-2, IL-4, IL-8) and reported significant heterogeneity for the majority of the analysts investigated. A large number of articles dedicated to the study of peripheral cytokines concentrations in PD have been published over the past years, hence the research interest in the topic continues to grow. Therefore, conducting an updated and more robust meta-analysis is warranted to clarify the peripheral inflammatory profile of PD, investigate key moderator variables that may affect cytokine concentrations, and integrate the findings of recent studies.

2. MATERIALS & METHODS

2.1 Literature search strategy

The present meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. A systematic search of published English-language articles was performed independently by K.E. and D.T. using Google Scholar, Web of Science, Scopus, Cochrane, and PubMed databases with no year limitation. Our final search terms were as follows: (((chemokine) OR (cytokine) OR (C-reactive protein) OR (CRP) OR (tumour necrosis factor) OR (TNF) OR (interleukin) OR (IL) OR (interferon) OR (inflammation)) AND (Parkinson disease)) NOT (Review[Publication Type]). The search was conducted from August 06 to August 26, 2025.

2.2 Study selection criteria

The inclusion criterion for this analysis was original clinical research reporting quantitative measurements of peripheral blood cytokine levels in human subjects with a diagnosis of Parkinson's disease and in a healthy control group.

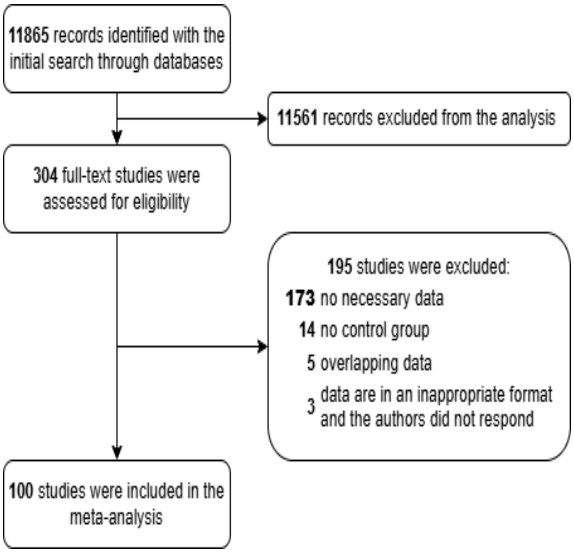

Fig. 1 PRISMA flowchart of the search process and study selection

2.3 Data extraction

The study selection process, detailed in the PRISMA flowchart (Figure 1), applied the following exclusion criteria: (1) non-original

research (e.g., reviews, case reports, commentaries); (2) studies using animal or cellular models; (3) *in-vitro* studies; (4) duplicate studies reporting of identical or overlapping datasets; (5) patients without PD diagnosis at the time of blood sampling; (6) studies in a language other than English.

Data on mean cytokine concentrations with either standard error of the mean (SEM) or standard deviation (SD), and sample size were extracted by D.T. and E.K. If the study contained the data with the use of another measure of central tendency or another measure of the amount of variation, authors of the study were asked to provide either the raw data or the data in the form of mean±SD.

Data on sex, age, disease severity (Unified Parkinson's Disease Rating Scale (UPDRS) [19] and Hoehn & Yahr Scale [20] scores), disease duration, medication status, sampling source, and assay type were also extracted.

2.4 Statistical analysis

Meta-analysis was conducted for each cytokine whenever data were available from at least three independent studies. All analyses employed a random effects model, which is considered more conservative in situations where there is clear heterogeneity among studies regarding setting, sampling methods, and assessments. Statistical analyses were conducted using ProMeta3 software (version 3.0; Internovi). Effect sizes (ES) for the difference in cytokine levels between PD patients and controls were primarily calculated using sample size along with mean and SD values, or, in cases where mean and SD data were unavailable, from the sample size and p-value. The primary outcome was the standardized mean difference, expressed as Hedges' g statistic to correct for potential small-sample bias. A separate ES was computed for each cytokine.

To assess the robustness of the findings, a sensitivity analysis was performed by iteratively excluding individual studies 1 at a time. Publication bias was evaluated using a linear regression test of funnel plot asymmetry performed according to Egger *et al.*, [21], also the classic fail-safe N method was used [22]. Heterogeneity across studies was quantified using I2 statistics and Cochrane Q test, with the following ranges for I2 statistics being used: < 25% (no heterogeneity), 25–50% (low), 51–75% (moderate), and > 75% (high heterogeneity) [23]. The threshold for statistical significance for all tests was set at $p < 0.05$.

3. RESULTS

The systematic literature search initially identified 11,865 records. Following a screening of titles and abstracts, 304 articles underwent full-text review for eligibility. After applying the predefined exclusion criteria, a total of 100 studies were deemed suitable for inclusion in the final meta-analysis. These studies collectively provided data on 18,347 unique participants, comprising 7,369 patients diagnosed with Parkinson's disease and 10,978 healthy controls (Figure 1).

Table 1. Summary of Comparative Outcomes for Measurements of Peripheral Blood Cytokine Levels. CI – confidence interval.

Cytokine	No. of Studies	PD / Controls	Main Effect				Heterogeneity				Publication Bias	
			Hedges g	(95% CI)		P Value	Q Statistic	df	P Value	I2 Statistic, %	Egger Intercept	P Value
IL-1β	34	1987 / 1298	0.89	0.568	1.212	<0.0001	537.06	33	<0.0001	93.67	4.12	0.016
IL-2	11	537 / 361	0.037	-0.311	0.384	0.836	54.79	10	<0.0001	81.75	0.13	0.948
IL-4	8	340 / 268	0.192	-0.385	0.768	0.515	73.91	7	<0.0001	90.53	3.39	0.312
IL-6	58	3852 / 8245	0.32	0.173	0.468	<0.0001	447.63	57	<0.0001	86.82	0.96	0.345
IL-8	17	1324 / 786	-0.139	-0.52	0.242	0.476	252.97	16	<0.0001	93.28	-2.47	0.267
IL-10	24	1340 / 898	0.163	-0.03	0.356	0.097	101.65	23	<0.0001	75.41	0.73	0.523
CRP	35	3376 / 8074	0.428	0.24	0.617	<0.0001	391.9	34	<0.0001	91.07	1.6	0.258
TNFα	52	3581 / 2569	0.431	0.232	0.629	<0.0001	487.92	51	<0.0001	89.14	0.94	0.385

3.1 Main association of PD with cytokine levels

The pooled results from the random-effects model revealed a distinct inflammatory profile in PD patients relative to healthy controls. Significantly elevated concentrations were observed in peripheral blood for IL-1β, IL-6, and TNFα (Figures 2, 3, 4; Table 1). Conversely, the analysis found no statistically significant differences between groups for the levels of IL-8, IL-10, and CRP (Table 1).

The results align with the findings reported in previously conducted meta-analyses. Specifically, increased levels of TNFα, IL-1β, and IL-6 have previously been reported in patients with PD [17, 24].

The characteristics of the studies included in the meta-analysis, along with the corresponding forest plots illustrating the associations between each cytokine level and Parkinson's disease, are provided in the Supplementary Materials.

3.2 Publication bias

No significant risk of publication bias was identified, as indicated by the results of the Egger test (in all analyses P > .10). All funnel plots are included in the Supplementary Materials (S10, S20, S30, S40, S50, S60, S70, S80). Additionally, the fail-safe N values were found to be 532 missing studies for IL-6, 687 missing studies for IL-1β, and 301 missing studies for TNFα, all of which exceed Rosenthal's rule of thumb. Based on these analyses, it is unlikely that the significant associations observed in the present study are caused by publication bias (see Table 1).

3.3 Sensitivity analysis

No individual study significantly affected the observed differences in peripheral IL-1β, IL-6, and TNFα levels between patients with PD and healthy controls.

3.4 Investigation of heterogeneity

The meta-analysis identified a substantial degree of statistical heterogeneity across all of the cytokines that were investigated, as detailed in Table 1. Conducting subgroup analyses, which were designed to account for the influence of various moderating variables, resulted in a slight reduction of heterogeneity, and did not significantly alter the heterogeneity of the studies.

3.5 Investigation of moderators

We investigated the impact of various parameters that may affect cytokine concentrations, including the age of patients (both Parkinson's disease and healthy individuals), disease severity (as measured by the mean UPDRS-III score and mean Hoehn & Yahr score), medication usage, year of publication, assay type, country of patients, and sample source (serum, plasma, or CSF).

Different analytical procedures are used to analyse cytokine levels in patients, with ELISA being the most frequently used (n = 50 for studies in current meta-analysis). The other methodological approaches include Meso Scale Discovery (n = 10), Luminex xMap (n = 7), Nephelometric (n = 7), Radioimmunoassay (n = 2), and some others (n = 15). Given the relatively small number of studies employing methods other than ELISA, it was determined to pool them together under the "Non-ELISA" category. Our findings suggest that the method of analysis significantly influenced the effect size of differences in IL-6 and TNFα levels measured in PD individuals and controls applying different analytical procedures (ANOVA Q-test of difference: $Q = 9.50$, $p = 0.002$ for IL-6; $Q = 6.71$, $p = 0.010$ for TNFα) (Supplementary figures S18, S78).

The systematic review identified four distinct sample sources utilized for the measurement of cytokine levels: serum, plasma, whole blood, and cerebrospinal fluid (CSF). Moderator analysis showed that the source of the samples could impact the effect size of difference for IL-1β ($Q = 107.98$, $p < 0.001$), IL-2 ($Q = 21.27$, $p < 0.001$), CRP ($Q = 8.04$, $p = 0.045$), and TNFα ($Q = 35.59$, $p < 0.001$) (Supplementary figures S9, S19, S69, S79). The highest concentrations of cytokines were observed in the whole blood samples, whereas the CSF exhibited the lowest levels of cytokines.

Additionally, the country of residence of the patients exerted a significant influence on all examined cytokines (ANOVA Q-test of difference: $p < 0.01$ for all cytokines)

(Supplementary figures S3, S13, S23, S33, S43, S53, S63, S73). It is plausible that the levels of interleukins in patients with PD may be influenced by their ethnic backgrounds.

Furthermore, we examined potential correlations with patient age, disease duration and severity, and treatment status. However, no significant relationships were identified, except for the positive correlation between age of PD patients and effective size (Hedges's g) for TNFα ($p = 0.022$) (Supplementary figure S72).

4. DISCUSSION

There is a critical need for the development of targeted therapeutics for the Parkinson's Disease (PD) treatment. A comprehensive understanding of the pathogenesis of PD, coupled with the identification of objective biomarkers related to disease progression, will greatly enhance the potential for successfully identifying disease-modifying therapies and effective treatment strategies. Consequently, investigating the biochemical characteristics associated with PD development is essential for creating targeted symptomatic therapies.

Nowadays, it is suggested that an immune/inflammatory component may be a primary or secondary event in PD, and more and more attention is focused on the role of anti- and proinflammatory cytokines in the process of neurodegeneration [25]. Considerable experimental effort was devoted to determining the content of individual cytokines in the blood of patients with PD. In the PUBMED database, the query "Parkinson disease, cytokines" reveals more than 3000 studies, among which 8 meta-analyses and systematic reviews. The earliest meta-analysis on this topic, published in 2010, had the objective of obtaining a precise estimate for the connection between specific single nucleotide polymorphisms - namely, interleukin-1 alpha (IL-1alpha-889) and interleukin-1 beta (IL-1beta-511) — and the risk of PD development [26]. This research analyzed data from 11 individual studies, which collectively included a cohort of 2803 patients with PD and 2539 healthy control subjects, and its results demonstrated no significant association. The list of SNPs that may be potentially associated with PD was expanded in studies published between 2012 to 2014. It was discovered that IL-1RA VNTR, IL-6-174, and TNFα-1031 gene polymorphisms could potentially be linked to an elevated risk for PD [27], while a separate analysis determined no such relationship between IL-10 (-592C/A and -1082A/G) polymorphisms and the risk of PD [28]. An investigation by Holmans and colleagues identified genes responsible for "cytokine-mediated signaling" and also those involved in the "regulation of leukocyte/lymphocyte activity" as factors that confer a heightened susceptibility to PD [29]. These findings provide additional evidence that neuro-inflammation is associated with the pathogenesis of PD.

The first analysis focusing specifically on levels of peripheral inflammatory cytokines in PD was published in 2016 [17]. This meta-analysis examined data pooled from 25 individual studies, which involved a combined total of 1547 patients diagnosed with PD and 1107 healthy control subjects, and it demonstrated that peripheral levels of IL-1β, IL-2, IL-6, IL-10, CRP, and TNFα were significantly elevated in PD patients. This served as another confirmation that an inflammatory response is a consistent feature accompanying Parkinson's disease. One more study that analysed the relationship between CSF cytokine levels (IL-1β, IL-6, TGF-β1, TNFα) and the risk of developing PD found that the CSF levels of TGF-β1, IL-1β, and IL-6 were higher in PD patients [30]. Finally, a meta-analysis was published in 2023, which included 152 articles [31]. The study reported a specific pattern of inflammatory alterations in the PD group, characterized by elevated concentrations of IL-1β, IL-6, TNFα, CRP, CXCL12, CX3CL1, CCL2, and STNFR1 concurrently with a decrease in the levels of IL-4 and IFN-γ. Additionally, the analysis revealed elevated IL-1β, IL-6, CRP, TNFα, and CCL2 levels in PD patients relative to the control subjects. These data are completely consistent with our results (Table 1). We note that the results may depend on the method used for detecting and analysing cytokines (e.x. ELISA, Luminex, etc.). The results also depended on the factor "country of the study", which could be due to the possible

influence of the dietary habits of different ethnic groups on the cytokine content in the blood.

The possible relationships between blood cytokine levels and the patients age, disease duration and disease severity (based on the UPDRS score) were analysed. No statistically significant dependencies were found, except for the positive correlation between age of PD patients and effective size (Hedges's g) for TNFα (Supplementary figure S72). The reason for this may be the fact that increased levels of blood cytokines is a basic (universal) pathogenetic link in the chain of events leading to neurodegeneration. It is also possible that there is some other PD-related factor that leads to increased blood cytokine levels which has not yet been identified. Such a factor may be the rate of progression in PD, the presence of non-motor manifestations in PD, or the form of PD. These factors are indicated only in a small number of studies, which does not allow any of the factors to be included in the present meta-analysis.

In recent years, a number of studies have been published that compare changes in cytokine levels with a set of clinical signs of the disease [32, 33, 34]. For example, there are studies that illustrate a relationship between TNFα levels and non-motor symptoms in individuals with PD. The study conducted by Menza and colleagues demonstrated that TNFα levels were significantly correlated with the severity of cognitive impairment and depression in PD patients [34]. Similar results were obtained in another study focusing on the cytokine profile in the patients with newly diagnosed PD (n=230). The authors found that TNFα and IL-6 blood levels correlated with the severity of cognitive impairment, whereas IL-1β level correlated with more rapid progression of cognitive impairment. Additionally, the authors identified that TNFα concentrations correlated with the progression rate of motor impairments in patients with PD [35]. Other studies have also shown a link between TNFα levels and clinical manifestations of the disease, indicating a positive correlation between TNFα levels and the severity of anxiety and pathological fatigue [15]. A recent study conducted by Kim *et al.,* (2022) examined the relationship between inflammatory markers (specifically IL-10, IL-6, IL-2, IL-1β, TNFα, and CRP) and the progression of non-motor symptoms in the early stages of PD. The findings indicated that levels of IL-2 and IL-6 were elevated significantly in PD compared to the control group. Moreover, higher concentrations of pro-inflammatory cytokines in patients with PD were linked to a more rapid progression of total non-motor symptom scores and mood/apathy scale scores over a three-year follow-up period [36].

When evaluating the cytokine profile of patients with PD, it is essential to consider the influence of antiparkinsonian medications. This thesis is substantiated by the findings outlined in our study. While PD is generally not associated with an increase in blood IL-8 concentrations (see Table 1), our analysis discovered elevated levels of IL-8 among patients undergoing antiparkinsonian therapy (Supplementary figure S47). Additionally, in patients with PD, we noted an elevation in blood IL-6 levels. Notably, when examining subgroups of patients who are either on or off antiparkinsonian therapy, this trend persists solely in the therapy group (Supplementary figure S37). The absence of any correlation between the concentrations of IL-6 and IL-8 and either the severity or the stage of the disease suggests a plausible hypothesis that L-DOPA has a direct influence on the cytokine profile, as supported by experimental research. Specifically, in animal models, chronic administration of L-DOPA has been shown to activate microglia and astroglia, leading to the development of L-DOPA-induced dyskinesia [37].

In this review, we aim to emphasize the importance of thoroughly characterizing each subject in clinical trials. This detailed characterization is essential for identifying the most significant pharmacodynamics-related factors that influence the cytokine profile, enabling us to mitigate or slow down these changes effectively.

5. CONCLUSION

This meta-analysis establishes that patients with Parkinson's disease exhibit significantly elevated peripheral concentrations of IL-1β, IL-6, TNFα,

and CRP compared to healthy controls. It also demonstrated that factors such as the analytical method employed, the source of the biological samples, and the country of residence of the subjects may modulate cytokine concentrations, whereas variables including age, Hoehn & Yahr stage, and Unified Parkinson's Disease Rating Scale Part III (UPDRS III) score do not appear to have a significant impact. The dissociation between cytokine levels and motor scores, coupled with their putative link to non-motor symptoms, suggests that systemic inflammation may be more closely associated with specific pathogenic processes or subtypes than with overall motor progression. Moving forward, more detailed study designs are needed, including detailed clinical phenotyping, standardized biomarker protocols, and careful consideration of confounders like medication. This approach will be vital for validating the prognostic and pathogenic utility of inflammatory biomarkers and for developing targeted anti-inflammatory strategies for PD.

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Conflict of Interest

The authors declare no conflicts of interest.

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Ethical Information

The work does not involve any use of animal or human subjects.

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