JAMA Neurology | Original Investigation

Aberrations in Peripheral Inflammatory Cytokine Levels in Parkinson Disease

A Systematic Review and Meta-analysis

Xiao-Yan Qin, MD; Shu-Ping Zhang, PhD; Chang Cao, BS; Y. Peng Loh, PhD; Yong Cheng, PhD

Editorial page 1282

Supplemental content

IMPORTANCE The association of nonmotor features and Parkinson disease (PD) is increasingly recognized. Evidence suggests that inflammation may play a role in PD pathologic features and symptoms.

OBJECTIVE To quantitatively summarize the peripheral inflammatory cytokine data available for patients with PD.

DATA SOURCE A systematic search of peer-reviewed English-language articles from PubMed, PsycINFO, and the Cochrane Library without year limitation was performed from December 7, 2015, to March 23, 2016. The search terms included *inflammation* or *cytokine* or *chemokine* or *tumor necrosis factor* or *interleukin* or *interferon* or *C-reactive protein* AND *Parkinson disease*.

STUDY SELECTION Studies were included if they provided data on peripheral blood cytokine concentrations in patients with PD and a healthy control group. Studies were excluded if they contained in vitro analysis of stimulated or unstimulated levels of cytokines, samples that overlapped with other studies, patients not diagnosed with PD at blood sampling, or if the cytokine analyzed was assessed in fewer than 3 studies.

DATA EXTRACTION AND SYNTHESIS Data were extracted from the 25 included studies encompassing 1547 unique patients with PD and 1107 unique controls by 2 independent investigators. Data were pooled using a random-effects model with the Comprehensive Meta-analysis software. Effect sizes were generated as standardized mean differences of cytokine concentrations between patients with PD and healthy controls and converted to the Hedges *g* statistic.

MAIN OUTCOMES AND MEASURES Blood cytokine concentrations in patients with PD compared with controls. Aberrations in peripheral cytokine levels were hypothesized to be related to PD.

RESULTS Among the 2654 study participants, concentrations of interleukin 6 (IL-6) (Hedges *g*, 0.325; 95% CI, 0.007-0.643; *P* = .045) in 13 studies, tumor necrosis factor (Hedges *g*, 0.354; 95% CI, 0.144-0.563; *P* = .001) in 9 studies, IL-1β (Hedges *g*, 0.382; 95% CI, 0.142-0.621; *P* = .002) in 6 studies, C-reactive protein (Hedges *g*, 0.323; 95% CI, 0.052-0.593; *P* = .02) in 6 studies, IL-10 (Hedges *g*, 0.329; 95% CI, 0.051-0.607; *P* = .02) in 5 studies, RANTES (regulated on activation, normal T-expressed, and presumably secreted) (Hedges *g*, 0.605; 95% CI, 0.111-1.099; *P* = .02) in 5 studies, and IL-2 (Hedges *g*, 0.789; 95% CI, 0.105-1.472; *P* = .02) in 3 studies were significantly higher in patients with PD compared with healthy controls. No differences were found between patients with PD and healthy controls for concentrations of interferon-γ (Hedges *g*, 0.745; 95% CI, −0.192 to 1.682; *P* = .12) in 5 studies, IL-4 (Hedges *g*, 0.031; 95% CI, −0.191 to 0.253; *P* = .79) in 3 studies, and IL-8 (Hedges *g*, 0.072; 95% CI, −0.136 to 0.279; *P* = .50) in 3 studies.

CONCLUSIONS AND RELEVANCE The findings of the meta-analysis demonstrated higher peripheral concentrations of IL-6, tumor necrosis factor, IL-1β, IL-2, IL-10, C-reactive protein, and RANTES in patients with PD, strengthening the clinical evidence that PD is accompanied by an inflammatory response.

JAMA Neurol. 2016;73(11):1316-1324. doi:10.1001/jamaneurol.2016.2742
Published online September 26, 2016.

Author Affiliations: Center on Translational Neuroscience, College of Life and Environmental Sciences, MinZu University of China, Beijing, China (Qin, Zhang, Cao); Section on Cellular Neurobiology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland (Loh, Cheng).

Corresponding Author: Yong Cheng, PhD, Section on Cellular Neurobiology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 49 Convent Dr, Bldg 49, Room 6C80, Bethesda, MD 20892 (chengy4@mail.nih.gov).

Parkinson disease (PD) is the second most common neurodegenerative disease after Alzheimer disease, and 7 to 10 million people are estimated to be affected globally.[1] The most obvious symptoms of the disease are movement related, including tremor, rigidity, slowness of movement, and postural instability.[2] Although PD is characterized by the significant loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of intraneuronal proteinacious cytoplasmic inclusions termed *Lewy bodies*,[3] the etiology of the disease is still poorly understood. The typical treatments for PD are the antiparkinson medications levodopa and dopamine agonists, which have symptomatic benefits during the early stage of the disease. However, these medications become ineffective as the disease progresses, and they have adverse effects.[4,5] Therefore, the need to better understand the etiology of PD and subsequently develop new therapies to prevent or slow the disease progression is urgent.

Growing evidence suggests that inflammation plays an important role in the pathologic features and symptoms of PD.[6,7] Inflammatory markers, such as tumor necrosis factors (TNFs) and interleukins, are critical signaling molecules of immune activation that exert effects in the brain and in the periphery.[8] Meta-analyses have demonstrated elevated levels of these inflammatory cytokines in patients with depression,[9] schizophrenia,[10] Alzheimer disease,[11] and autism spectrum disorder.[12] In patients with PD, postmortem and in vivo positron emission tomographic studies showed increased inflammatory responses, including microglial activation[13,14] and increased levels of the immune markers in the brain.[15-18]

In addition, peripheral inflammation could contribute to the etiology and progress of PD.[19] The easy access to blood samples has led to a substantial number of studies analyzing peripheral inflammatory cytokine levels in patients with PD compared with healthy control individuals in the hope of better understanding the etiology of PD and providing candidate biomarkers for the disease. Although a number of studies showed associations between inflammatory cytokine concentrations and PD, those associations were inconsistent for individual cytokines and between studies.[20-25] To address the inconsistency in clinical data, a meta-analysis on this subject is warranted.

Key Points

Question Are peripheral blood levels of inflammatory cytokines altered in patients with Parkinson disease (PD)?

Findings In this meta-analysis of 25 studies with 2654 unique participants, patients with PD demonstrated significantly higher blood levels of interleukin 6 (IL-6), tumor necrosis factor, IL-1β, IL-2, IL-10, C-reactive protein, and RANTES (regulated on activation, normal T-expressed, and presumably secreted) compared with healthy control individuals.

Meaning This study provides a novel perspective into the etiology of PD, and future investigations into the cytokines as biomarkers and therapeutic targets for PD may be warranted.

Methods

Search Strategy and Study Selection

Two of us (X.-Y.Q. and S.-P.Z.) performed a systematic review of peer-reviewed English-language articles from the databases of PubMed, PsycINFO, and the Cochrane Library with no year limitation from December 7, 2015, to March 23, 2016. The database search terms included *inflammation* or *cytokine* or *chemokine* or *tumor necrosis factor* or *interleukin* or *interferon* or *C-reactive protein* AND *Parkinson disease*. Original clinical studies that reported data on peripheral cytokine concentrations in patients with PD and healthy controls were included. The following exclusion criteria were applied: (1) in vitro studies that reported stimulated or unstimulated levels of cytokines; (2) samples overlapped with other studies; (3) patients were not diagnosed with PD at the time of blood sampling; and (4) the cytokine analyzed was assessed in fewer than 3 studies. The meta-analyses performed in this study adhered to the guidelines that are recommended by the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analysis).[26]

Data Extraction

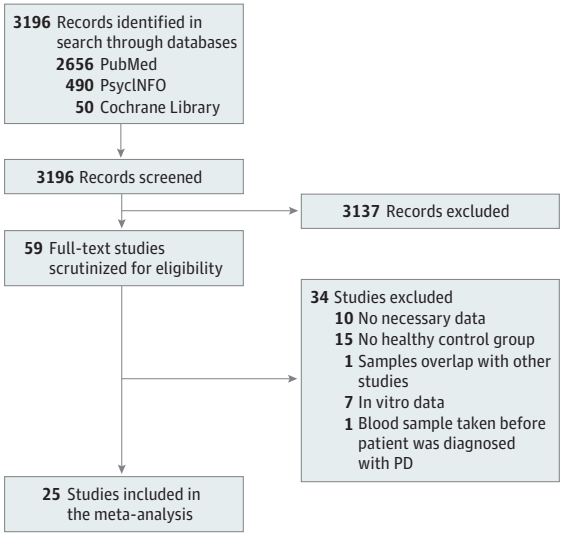
Two of us (X.-Y.Q. and S.-P.Z.) extracted the data. Data on sample size, mean (SD) cytokine concentration, and *P* values were extracted as primary outcomes. Data for potential moderator analysis of age, sex, disease duration, disease severity (Hoehn and Yahr Scale[27] and Unified Parkinson's Disease Rating Scale[28] scores), sampling source, medication status, and assay type were also extracted (eTable in the Supplement). We observed some inconsistent reports of data (RANTES [regulated on activation, normal T-expressed, and presumably secreted]) in one study,[22] and the correct data were obtained from the authors.

Statistical Analysis

We used Comprehensive Meta-analysis software (version 2; Biostat Inc) to perform all the statistical analyses. Effect sizes (ESs) were primarily generated from sample size and mean (SD) values or from sample size and *P* values if mean (SD) data were not available. Effect sizes were calculated as standardized mean differences of cytokine concentrations between patients with PD and healthy controls and converted to the Hedges *g* statistic,[29] which provides an unbiased ES adjusted for sample size. An ES estimate was calculated for each cytokine assessed in all included studies. We chose a random-effects model for the meta-analysis because within-study and between-study variances were hypothesized to affect the true ES. The random-effects model is a more conservative approach: if a significant heterogeneity is found among analyzed studies, the random-effects model yields a wider 95% CI than the fixed-effects model (which estimates study weight based on sample size).[12] Sensitivity analysis was undertaken by removing 1 study at a time to assess the stability of the outcome of the meta-analysis.

Between-study heterogeneity was assessed using the Cochrane Q test and I^2 statistic as described previously.[30] Statistical difference for the Cochrane Q test was set at $P < .10$; I^2 sta-

Figure 1. PRISMA Flowchart of the Literature Search



PD indicates Parkinson disease.

tistics of 0.25, 0.50, and 0.75 denoted small, moderate, and high levels of heterogeneity, respectively. Unrestricted maximum-likelihood random-effects meta-regressions of ES[31] were performed to analyze whether the continuous variables, including patient mean age and sex distribution (proportion of male individuals), had moderating effects on the outcomes of the meta-analysis. Publication bias was determined by the Egger test,[32] which assesses the funnel plot asymmetry. Publication bias was further evaluated using the classic fail-safe N method,[33] which computes the number of missing studies (with a mean effect of zero) that would need to be added to the analysis to yield a statistically nonsignificant overall effect. All values for significances in this study were set at $P < .05$ except where noted. $P < .10$ was not considered statistically significant.

Results

The initial search identified 2656 records from PubMed, 490 records from PsycINFO, and 50 records from the Cochrane Library. Scanning of titles and abstracts resulted in identification of 59 articles for full-text scrutiny. Several studies were excluded because they reported cytokine levels in vitro (7 studies), lacked necessary data (10 studies), lacked a healthy control group (15 studies), had samples that overlapped with other studies (1 study), and obtained blood samples before the patients were diagnosed with PD (1 study). Thus, a total of 25 studies encompassing 2654 unique study participants, including 1547 patients with PD and 1107 healthy controls, were included in the meta-analysis[20-25,34-52] (**Figure 1**).

Main Association of PD With Cytokine Levels

Random-effects meta-analysis demonstrated that patients with PD had significantly higher peripheral blood cytokine levels compared with healthy controls for interleukin 6 (IL-6) (Hedges *g*, 0.325; 95% CI, 0.007-0.643; $P = .045$), TNF (Hedges *g*, 0.354; 95% CI, 0.144-0.563; $P = .001$), IL-1β (Hedges *g*, 0.382; 95% CI, 0.142-0.621; $P = .002$), C-reactive protein (CRP) (Hedges *g*, 0.323; 95% CI, 0.052-0.593; $P = .02$), IL-10 (Hedges *g*, 0.329; 95% CI, 0.051-0.607; $P = .02$), RANTES (Hedges *g*, 0.605; 95% CI, 0.111-1.099; $P = .02$), and IL-2 (Hedges *g*, 0.789; 95% CI, 0.105-1.472; $P = .02$) (**Figures 2**, **3**, and **4** and **Table**). In contrast, concentrations of interferon-γ (IFN-γ) (Hedges *g*, 0.745; 95% CI, −0.192 to 1.682; $P = .12$), IL-4 (Hedges *g*, 0.031; 95% CI, −0.191 to 0.253; $P = .79$), and IL-8 (Hedges *g*, 0.072; 95% CI, −0.136 to 0.279; $P = .50$) yielded nonsignificant ES estimates (Table).

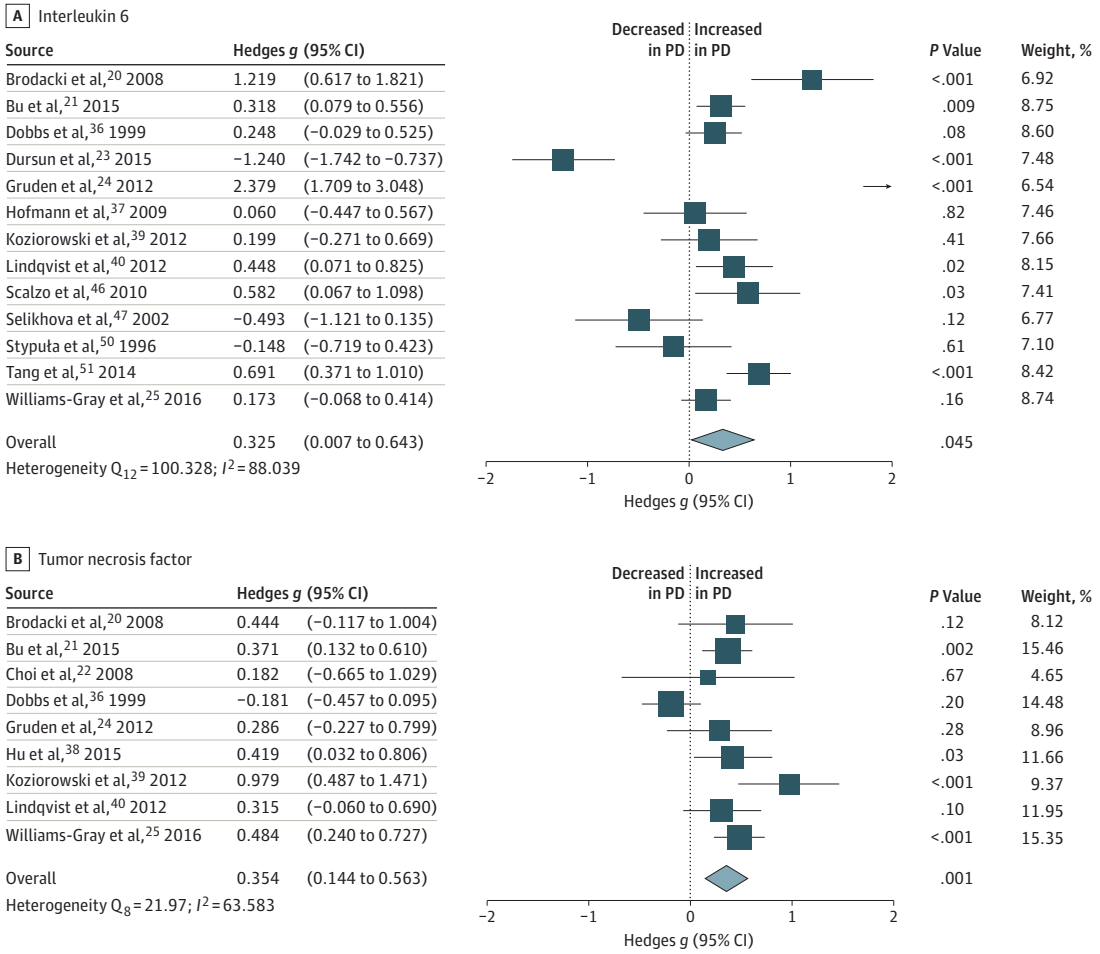
Investigation of Heterogeneity

Significant heterogeneity was found for 7 of 10 cytokines. Interleukin 6, CRP, IFN-γ, and IL-2 showed high levels of heterogeneity, whereas TNF, IL-1β, and RANTES showed moderate levels of heterogeneity (Table). We next attempted to adjust for potential moderators that accounted for the heterogeneity in the meta-analysis, which included theoretically relevant categorical variables (sampling source, assay type, and medication status) and continuous variables (age, sex, disease duration, and disease severity). As shown in the eTable in the Supplement, the information on mean disease duration, disease severity, and medication status were limited. In terms of the sampling source (serum and plasma), only 3 studies analyzed plasma cytokine concentrations. Therefore, we next performed subgroup analysis based on assay type (enzyme-linked immunoassay [ELISA] and non-ELISA) and meta-regression analysis on age and sex. Because the numbers of studies were limited for most of the cytokines, the subgroup and meta-regression analyses were mainly performed for IL-6 and TNF.

For IL-6, the impact of heterogeneity was reduced 26% ($Q_5 = 13.202$; $P = .02$; $I^2 = 62.126$), and the significance of the association between elevated IL-6 levels and PD was retained for the non-ELISA method (eFigure 1 in the Supplement). For the ELISA method, the impact of heterogeneity was slightly increased ($Q_6 = 86.974$; $P < .001$; $I^2 = 93.101$), and the significant association was lost (eFigure 1 in the Supplement). For TNF, no significant heterogeneity was found for the non-ELISA method ($Q_4 = 5.167$; $P = .27$; $I^2 = 22.587$), and the impact of heterogeneity was slightly increased for the ELISA method ($Q_3 = 10.599$; $P = .01$; $I^2 = 71.695$). In addition, the significance of the association between elevated TNF levels and PD was retained for the non-ELISA method but not the ELISA method (eFigure 2 in the Supplement).

Meta-regression analyses revealed that sex had no moderating effects on the outcomes of the meta-analysis (eFigure 3 in the Supplement). A significant association was found between age and ES (eFigure 3A in the Supplement) (regression coefficient [SE], −0.061 [0.024]; 95% CI, −0.108 to −0.015; $P = .01$) for studies measuring TNF levels. In addition, age was nonsignificantly associated with ES for studies measuring IL-6 levels (eFigure 3B in the Supplement) (regression coefficient [SE], −0.075 [0.043]; 95% CI, −0.159 to 0.009; $P = .08$). These

Figure 2. Studies of Peripheral Blood Levels of Interleukin 6 (IL-6) and Tumor Necrosis Factor (TNF)



Forest plot displays random-effects meta-analysis results of the association between IL-6 and TNF levels and Parkinson disease (PD). The sizes of the squares are proportional to study weights.

results indicated that age had moderating effects on the outcomes of the meta-analysis.

Sensitivity analysis suggested that a single study could influence the statistically significant difference in blood IL-6 levels between patients with PD and healthy controls. This finding is not surprising because the *P* value of the meta-analysis outcome was slightly less than .05 for IL-6. In contrast, no individual study significantly influenced the significant difference for blood TNF levels between patients with PD and healthy controls. Furthermore, no single study explained the significant heterogeneity for IL-6 and TNF.

No significant risk for publication bias was detected in the included studies as demonstrated by the Egger test (Egger intercept range, −0.44 to 4.11; $P > .10$ in all analyses) (Table). Furthermore, analyses from the classic fail-safe N method showed that 88 missing studies were required for IL-6 levels to reach $P > .05$ in the meta-analysis; 61 studies, for TNF; 31 studies, for IL-1β; 21 studies, for IL-2; 9 studies, for IL-10; 29 studies, for CRP; and 23 studies, for RANTES. These results suggested that the significant associations in our meta-analyses were unlikely to be caused by publication bias.

Discussion

To the best of our knowledge, this meta-analysis is the first undertaken to investigate alterations of peripheral inflammatory cytokine levels in patients with PD. We found significant elevations of peripheral blood proinflammatory cytokine levels for IL-6, TNF, IL-1β, CRP, and IL-2 in patients with PD compared with healthy controls. Levels of the chemokine RANTES associated with recruitment of inflammatory cells were also elevated in patients with PD. For those cytokines significantly associated with PD, the ESs associated with the results of IL-2 and RANTES were the largest, and the ESs for other individual cytokines ranged from small to medium. Although inconsistent results have been reported for individual cytokines and between studies in the literature, our meta-analysis provides evidence of a heightened proinflammatory cytokine profile in PD, strengthening the clinical evidence that patients with PD have an increased inflammatory response. In addition to the association between TNF levels and PD found in this meta-analysis, 2 studies[53,54] have consistently demon-

Figure 3. Studies of Peripheral Blood Levels of Interleukin 1β (IL-1β), C-reactive Protein (CRP), and IL-2

A Interleukin 1β

Source	Hedges *g* (95% CI)		*P* Value	Weight, %
Bu et al,[21] 2015	0.322	(0.083 to 0.561)	.008	23.79
Dursun et al,[23] 2015	0.955	(0.470 to 1.441)	<.001	13.65
Hu et al,[38] 2015	0.656	(0.266 to 1.047)	.001	17.04
Koziorowski et al,[39] 2012	0.198	(−0.272 to 0.668)	.41	14.16
Pirttila et al,[42] 1994	−0.120	(−0.872 to 0.631)	.75	7.66
Williams-Gray et al,[25] 2016	0.185	(−0.056 to 0.426)	.13	23.70
Overall	0.382	(0.142 to 0.621)	.002	

Heterogeneity $Q_5 = 12.098$; $I^2 = 58.67$

B C-reactive protein

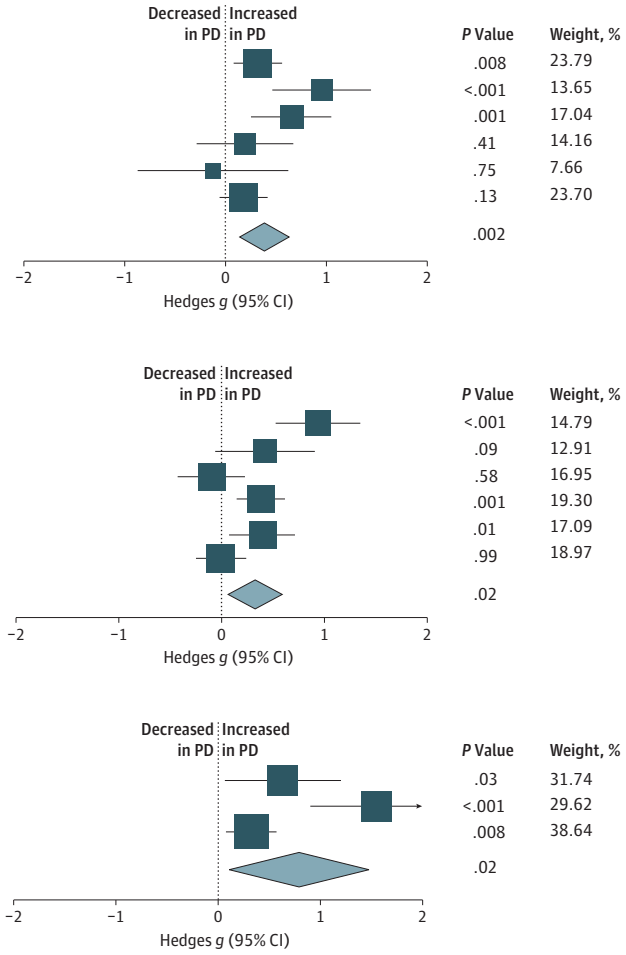
Source	Hedges *g* (95% CI)		*P* Value	Weight, %
Akıl et al,[34] 2015	0.944	(0.536 to 1.353)	<.001	14.79
Andican et al,[35] 2012	0.426	(−0.062 to 0.915)	.09	12.91
Lindqvist et al,[40] 2012	−0.091	(−0.413 to 0.231)	.58	16.95
Song et al,[48] 2009	0.388	(0.163 to 0.614)	.001	19.30
Song et al,[49] 2013	0.402	(0.086 to 0.718)	.01	17.09
Williams-Gray et al,[25] 2016	−0.001	(−0.242 to 0.239)	.99	18.97
Overall	0.323	(0.052 to 0.593)	.02	

Heterogeneity $Q_5 = 22.317$; $I^2 = 77.595$

C Interleukin 2

Source	Hedges *g* (95% CI)		*P* Value	Weight, %
Brodacki et al,[20] 2008	0.632	(0.065 to 1.199)	.03	31.74
Stypuła et al,[50] 1996	1.559	(0.906 to 2.212)	<.001	29.62
Williams-Gray et al,[25] 2016	0.327	(0.085 to 0.569)	.008	38.64
Overall	0.789	(0.105 to 1.472)	.02	

Heterogeneity $Q_2 = 12.247$; $I^2 = 83.706$



Forest plot displays random-effects meta-analysis results of the association between IL-1β, CRP, and IL-2 levels and Parkinson disease (PD). The sizes of the squares are proportional to study weights.

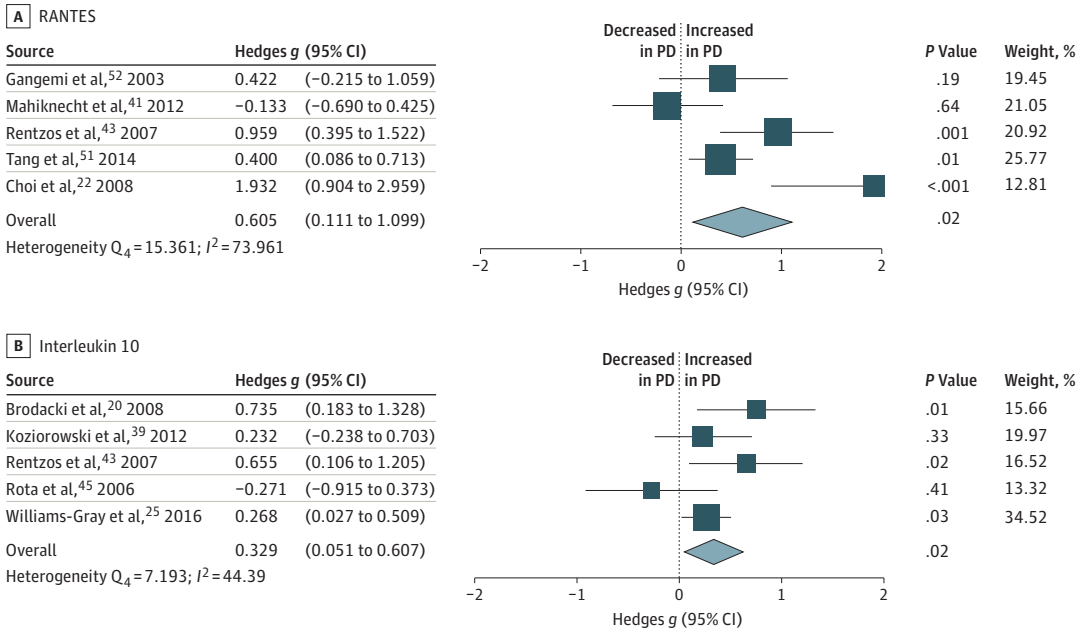
strated that peripheral blood TNF-receptor levels are increased in patients with PD, providing more clinical evidence of proinflammatory responses in patients with PD.

This meta-analysis did not find altered levels of proinflammatory cytokines IFN-γ and IL-8 in patients with PD compared with healthy controls, although the limited number of studies with a smaller sample size may have made observation of significant associations difficult. In addition, the anti-inflammatory cytokines IL-4 and IL-10 showed distinct profiles in peripheral blood samples of patients with PD, with concentrations in PD significantly increased for IL-10 and no association between IL-4 and PD. Although IL-10 is generally considered to oppose the actions of the proinflammatory cytokines, its bioactivity is highly complex, with roles involved in costimulation of B-cell activation and natural killer cell proliferation, prolonged B-cell survival, contribution to class switching in B cells, and production of IFN-γ.[55,56]

The heterogeneity for the individual cytokines in this meta-analysis varied from zero to high. The strength of this study is that we used a meta-analytic technique with subgroup and meta-regression analyses to adjust for potential confounders. The subgroup analyses suggested that different assay types (ELISA vs non-ELISA) partially explained the heterogeneity. However, another possible explanation for the lower heterogeneity in studies using non-ELISA analysis is the low power that the test for heterogeneity has in meta-analyses with a smaller number of studies.[57]

Meta-regression analyses revealed that age is a confounding factor for the outcome of the meta-analysis. However, we cannot exclude the possibility that the moderating effect of age was secondary to other clinical variables, including disease duration, disease severity, and duration of medication use. The limitation of this meta-analysis is that most of the included studies did not provide detailed information on these clinical variables (eTable in the Supplement), which precluded us from further analysis. Nevertheless, these limits highlight the need for continued investigation of cytokine levels in patients with PD, with control for the relevant methodologic and clinical variables. Another limitation of this study is that the meta-analysis on peripheral blood cytokine levels in patients with

Figure 4. Studies of Peripheral Blood Levels of RANTES (Regulated on Activation, Normal T-expressed, and Presumably Secreted) and Interleukin 10 (IL-10)



Forest plot displays random-effects meta-analysis results of the association between RANTES and IL-10 levels and Parkinson disease (PD). The sizes of the squares are proportional to study weights.

Table. Summary of Comparative Outcomes for Measurements of Peripheral Blood Cytokine Levels

Cytokine	No. of Studies	No. With PD/ Controls	Main Effect			Heterogeneity				Publication Bias	
			Hedges g (95% CI)	z Score	P Value	Q Statistic	df	P Value	I^2 Statistic	Egger Intercept	P Value
IL-6	13	898/678	0.325 (0.007 to 0.643)	2.002	.045	100.328	12	<.001	88.039	0.57	.81
TNF	9	809/528	0.354 (0.144 to 0.563)	3.31	.001	21.968	8	.005	63.583	0.83	.63
IL-1β	6	623/339	0.382 (0.142 to 0.621)	3.124	.002	12.098	5	.03	58.670	0.90	.66
CRP	6	696/411	0.323 (0.052 to 0.593)	2.338	.02	22.317	5	<.001	77.595	3.11	.42
IL-10	5	376/181	0.329 (0.051 to 0.607)	2.323	.02	7.193	4	.13	44.390	0.41	.83
RANTES	5	171/154	0.605 (0.111 to 1.099)	2.402	.02	15.361	4	.004	73.961	2.47	.38
IFN-γ	5	432/293	0.745 (−0.192 to 1.682)	1.558	.12	101.479	4	<.001	96.058	4.08	.43
IL-2	3	282/138	0.789 (0.105 to 1.472)	2.261	.02	12.274	2	.002	83.706	4.11	.32
IL-4	3	269/126	0.031 (−0.191 to 0.253)	0.273	.79	2.046	2	.36	2.244	0.03	.99
IL-8	3	298/130	0.072 (−0.136 to 0.279)	0.677	.50	1.078	2	.58	0	−0.44	.79

Abbreviations: CRP, C-reactive protein; *df*, degrees of freedom; IFN-γ, interferon γ; IL, interleukin; PD, Parkinson disease; RANTES, regulated on activation, normal T-expressed, and presumably secreted; TNF, tumor necrosis factor.

PD compared with healthy controls provides us with pooled results originating from cross-sectional studies. Therefore, whether the inflammatory marker changes would predict a more aggressive disease course remains unclear, and longitudinal studies are necessary to address this question. In fact, when Sawada et al[58] used a longitudinal approach in 375 patients with PD, they found that the baseline CRP levels were associated with the risk for death and estimated the life expectancy of patients with PD.

The central nervous system is generally considered to be immunologically privileged owing to the existence of the blood-brain barrier under physiologic conditions. The compromise of the blood-brain barrier has been identified as a critical factor for neurodegenerative diseases, including PD,[59,60]

which can lead to the increased infiltration of peripheral immune cells, such as T and B lymphocytes, into the central nervous system. In addition, the peripheral inflammatory cytokines, such as IL-1β, TNF, and IL-6, could also cross the blood-brain barrier to stimulate neuroinflammatory reactions under pathologic conditions.[6] Our present meta-analysis demonstrates an increased peripheral proinflammatory cytokine profile in patients with PD, with the peripheral measurements limited in that we do not know how much they reflect the inflammatory activity within the brain. However, several studies[15-18] showed that inflammatory cytokine levels, including IL-1β, TNF, and IL-6, were elevated in the brains of patients with PD. Therefore, changes in peripheral inflammatory markers in PD are likely correlated with changes in inflammatory markers that occurred in the central nervous system, although further studies are necessary to substantiate this proposal.

The clinical significance of elevated cytokine levels remains a subject of debate, and whether it is a cause or consequence in the progress of PD is unclear. The hypothesis that inflammatory cytokines contribute to the progress of PD is plausible in view of the considerable evidence showing the toxic effects of inflammatory cytokines, such as IL-6, IL-1, and TNF, to neurons.[61-63] In addition, mice deficient in the genes involved in the generation of inflammatory markers (such as cyclooxygenase 2[64] and TNF receptors[65]) were found to be protected against dopaminergic neurotoxicity. The early blockade of neuroinflammation by nonsteroidal anti-inflammatory drugs or cytokine inhibitors consistently attenuated dopaminergic neuron degeneration in the animal models of PD.[66,67] Epidemiologic studies[68,69] suggested that the risk for developing PD was decreased in long-term users of nonsteroidal anti-inflammatory drugs, although a meta-analysis revealed that only ibuprofen provides significant protection against PD.[70] These results support the idea that inflammation is important in PD pathogenesis. However, an alternative explanation for the observed effects in the meta-analysis is that cytokine elevations are just signs of PD or rather a result of PD, which is possible if patients with PD are more prone to infections. In fact, one study[21] showed that patients with PD had a higher infectious burden compared with healthy controls.

Identifying biomarkers in PD holds the promise of removing roadblocks to therapeutic discovery. One of the leading efforts to identify biomarkers in the field is the Parkinson Progression Marker Initiative (PPMI) sponsored by the Michael J. Fox Foundation.[71] The PPMI planned to recruit 400 patients with PD and 200 healthy controls to be followed up longitudinally for clinical, imaging, and biospecimen (blood, urine, and cerebrospinal fluid) biomarker assessment.[71] Since the PPMI's launch in 2010, researchers have already published findings using the PPMI cohort. For example, apolipoprotein A1 was found to be associated with age at onset and motor severity in patients with early PD.[72] Our present meta-analysis suggests that some blood inflammatory cytokines are potential diagnostic biomarkers in PD, and validating the results with the PPMI cohort would be of interest, thus providing a strong rationale for researchers to request blood samples from the PPMI. Moreover, evaluation of the PPMI cohort will also reveal the potential of the cytokines to serve as biomarkers for disease progression. One study included in our meta-analysis[51] reported that RANTES levels significantly correlated with disease severity (Hoehn and Yahr scale) and disease duration in patients with PD. Another study[40] showed a significant correlation between blood TNF levels and nonmotor symptoms in patients with PD. In addition to the PPMI, the COPPADIS-2015 (Cohort of Patients With Parkinson's Disease in Spain, 2015) project recently published a proposal.[73] As part of this proposal, the investigators are recruiting patients with PD and control participants from November 2015 to February 2017, with follow-up for 5 years. The proposed objectives include analyses of potential serum biomarkers, such as TNF, IL-1, IL-2, IL-6, and CRP, at baseline and at the end of follow-up. We hope that this project will provide valuable information for the association between inflammation and PD. After validation of these cytokines as diagnosis or disease progression biomarkers in PD, the next step is to target the biomarkers for potential new and better treatments for the growing number of individuals with PD worldwide.

Conclusions

Our meta-analysis findings demonstrated elevated peripheral concentrations of IL-6, TNF, IL-1β, IL-2, IL-10, CRP, and RANTES in patients with PD. This finding strengthens the clinical evidence that PD is accompanied by an inflammatory response.

ARTICLE INFORMATION

Accepted for Publication: June 2, 2016.

Published Online: September 26, 2016. doi:10.1001/jamaneurol.2016.2742

Author Contributions: Drs Qin and Zhang contributed equally to this work. Dr Cheng had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Cheng.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Cheng.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Qin, Zhang.
Obtained funding: Qin, Loh.
Administrative, technical, or material support: Qin, Cheng.
Study supervision: Cheng.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health; grants YLDX01013 and 2015MDTD13C from the 985 Academic Team-building Fund of MinZu University; and the grant B08044 from the 111 Project of China.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Bhimani R. Understanding the burden on caregivers of people with Parkinson's: a scoping review of the literature. *Rehabil Res Pract*. 2014;2014:718527.

2. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry*. 2008;79(4):368-376.

3. Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. *Neuron*. 2003;39(6):889-909.

4. Bonuccelli U, Del Dotto P, Rascol O. Role of dopamine receptor agonists in the treatment of early Parkinson's disease. *Parkinsonism Relat Disord*. 2009;15(suppl 4):S44-S53.

5. Marsden CD. Problems with long-term levodopa therapy for Parkinson's disease. *Clin Neuropharmacol*. 1994;17(suppl 2):S32-S44.

6. Wang Q, Liu Y, Zhou J. Neuroinflammation in Parkinson's disease and its potential as therapeutic target. *Transl Neurodegener*. 2015;4:19.

7. Whitton PS. Inflammation as a causative factor in the aetiology of Parkinson's disease. *Br J Pharmacol*. 2007;150(8):963-976.

8. Tabas I, Glass CK. Anti-inflammatory therapy in chronic disease: challenges and opportunities. *Science*. 2013;339(6116):166-172.

9. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446-457.

10. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry*. 2011;70(7):663-671.

11. Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. *Biol Psychiatry*. 2010;68(10):930-941.

12. Masi A, Quintana DS, Glozier N, Lloyd AR, Hickie IB, Guastella AJ. Cytokine aberrations in autism spectrum disorder: a systematic review and meta-analysis. *Mol Psychiatry*. 2015;20(4):440-446.

13. McGeer PL, Itagaki S, Boyes BE, McGeer EG. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. *Neurology*. 1988;38(8):1285-1291.

14. Ouchi Y, Yoshikawa E, Sekine Y, et al. Microglial activation and dopamine terminal loss in early Parkinson's disease. *Ann Neurol*. 2005;57(2):168-175.

15. Boka G, Anglade P, Wallach D, Javoy-Agid F, Agid Y, Hirsch EC. Immunocytochemical analysis of tumor necrosis factor and its receptors in Parkinson's disease. *Neurosci Lett*. 1994;172(1-2):151-154.

16. Mogi M, Harada M, Kondo T, et al. Interleukin-1 β, interleukin-6, epidermal growth factor and transforming growth factor-α are elevated in the brain from parkinsonian patients. *Neurosci Lett*. 1994;180(2):147-150.

17. Mogi M, Harada M, Narabayashi H, Inagaki H, Minami M, Nagatsu T. Interleukin (IL)-1 β, IL-2, IL-4, IL-6 and transforming growth factor-α levels are elevated in ventricular cerebrospinal fluid in juvenile parkinsonism and Parkinson's disease. *Neurosci Lett*. 1996;211(1):13-16.

18. Mogi M, Harada M, Riederer P, Narabayashi H, Fujita K, Nagatsu T. Tumor necrosis factor-alpha (TNF-α) increases both in the brain and in the cerebrospinal fluid from parkinsonian patients. *Neurosci Lett*. 1994;165(1-2):208-210.

19. Mosley RL, Hutter-Saunders JA, Stone DK, Gendelman HE. Inflammation and adaptive immunity in Parkinson's disease. *Cold Spring Harb Perspect Med*. 2012;2(1):a009381.

20. Brodacki B, Staszewski J, Toczyłowska B, et al. Serum interleukin (IL-2, IL-10, IL-6, IL-4), TNFα, and INFγ concentrations are elevated in patients with atypical and idiopathic parkinsonism. *Neurosci Lett*. 2008;441(2):158-162.

21. Bu XL, Wang X, Xiang Y, et al. The association between infectious burden and Parkinson's disease: a case-control study. *Parkinsonism Relat Disord*. 2015;21(8):877-881.

22. Choi C, Jeong JH, Jang JS, et al. Multiplex analysis of cytokines in the serum and cerebrospinal fluid of patients with Alzheimer's disease by color-coded bead technology. *J Clin Neurol*. 2008;4(2):84-88.

23. Dursun E, Gezen-Ak D, Hanağası H, et al. The interleukin 1α, interleukin 1β, interleukin 6 and α-2-macroglobulin serum levels in patients with early or late onset Alzheimer's disease, mild cognitive impairment or Parkinson's disease. *J Neuroimmunol*. 2015;283:50-57.

24. Gruden MA, Yanamandra K, Kucheryanu VG, et al. Correlation between protective immunity to α-synuclein aggregates, oxidative stress and inflammation. *Neuroimmunomodulation*. 2012;19(6):334-342.

25. Williams-Gray CH, Wijeyekoon R, Yarnall AJ, et al; ICICLE-PD study group. Serum immune markers and disease progression in an incident Parkinson's disease cohort (ICICLE-PD). *Mov Disord*. 2016;31(7):995-1003.

26. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.

27. Goetz CG, Poewe W, Rascol O, et al; Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. *Mov Disord*. 2004;19(9):1020-1028.

28. Ramaker C, Marinus J, Stiggelbout AM, Van Hilten BJ. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. *Mov Disord*. 2002;17(5):867-876.

29. Hedges LV, Olkin I. *Statistical Methods for Meta-analysis*. New York, NY: Academic Press; 1985.

30. Qin XY, Cao C, Cawley NX, et al. Decreased peripheral brain-derived neurotrophic factor levels in Alzheimer's disease: a meta-analysis study (N=7277) [published online April 26, 2016]. *Mol Psychiatry*. doi:10.1038/mp.2016.62

31. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med*. 1997;127(9):820-826.

32. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.

33. Soeken KL, Sripusanapan A. Assessing publication bias in meta-analysis. *Nurs Res*. 2003;52(1):57-60.

34. Akıl E, Bulut A, Kaplan İ, Özdemir HH, Arslan D, Aluçlu MU. The increase of carcinoembryonic antigen (CEA), high-sensitivity C-reactive protein, and neutrophil/lymphocyte ratio in Parkinson's disease. *Neurol Sci*. 2015;36(3):423-428.

35. Andican G, Konukoglu D, Bozluolcay M, Bayülkem K, Firtiına S, Burcak G. Plasma oxidative and inflammatory markers in patients with idiopathic Parkinson's disease. *Acta Neurol Belg*. 2012;112(2):155-159.

36. Dobbs RJ, Charlett A, Purkiss AG, Dobbs SM, Weller C, Peterson DW. Association of circulating TNF-α and IL-6 with ageing and parkinsonism. *Acta Neurol Scand*. 1999;100(1):34-41.

37. Hofmann KW, Schuh AF, Saute J, et al. Interleukin-6 serum levels in patients with Parkinson's disease. *Neurochem Res*. 2009;34(8):1401-1404.

38. Hu Y, Yu SY, Zuo LJ, et al. Parkinson disease with REM sleep behavior disorder: features, α-synuclein, and inflammation. *Neurology*. 2015;84(9):888-894.

39. Koziorowski D, Tomasiuk R, Szlufik S, Friedman A. Inflammatory cytokines and NT-proCNP in Parkinson's disease patients. *Cytokine*. 2012;60(3):762-766.

40. Lindqvist D, Kaufman E, Brundin L, Hall S, Surova Y, Hansson O. Non-motor symptoms in patients with Parkinson's disease: correlations with inflammatory cytokines in serum. *PLoS One*. 2012;7(10):e47387.

41. Mahlknecht P, Stemberger S, Sprenger F, et al. An antibody microarray analysis of serum cytokines in neurodegenerative Parkinsonian syndromes. *Proteome Sci*. 2012;10(1):71.

42. Pirttila T, Mehta PD, Frey H, Wisniewski HM. α_1-Antichymotrypsin and IL-1β are not increased in CSF or serum in Alzheimer's disease. *Neurobiol Aging*. 1994;15(3):313-317.

43. Rentzos M, Nikolaou C, Andreadou E, et al. Circulating interleukin-15 and RANTES chemokine in Parkinson's disease. *Acta Neurol Scand*. 2007;116(6):374-379.

44. Rentzos M, Nikolaou C, Andreadou E, et al. Circulating interleukin-10 and interleukin-12 in Parkinson's disease. *Acta Neurol Scand*. 2009;119(5):332-337.

45. Rota E, Bellone G, Rocca P, Bergamasco B, Emanuelli G, Ferrero P. Increased intrathecal TGF-β1, but not IL-12, IFN-γ and IL-10 levels in Alzheimer's disease patients. *Neurol Sci*. 2006;27(1):33-39.

46. Scalzo P, Kümmer A, Cardoso F, Teixeira AL. Serum levels of interleukin-6 are elevated in patients with Parkinson's disease and correlate with physical performance. *Neurosci Lett*. 2010;468(1):56-58.

47. Selikhova MV, Kushlinskii NE, Lyubimova NV, Gusev EI. Impaired production of plasma interleukin-6 in patients with Parkinson's disease. *Bull Exp Biol Med*. 2002;133(1):81-83.

48. Song IU, Kim JS, Chung SW, Lee KS. Is there an association between the level of high-sensitivity C-reactive protein and idiopathic Parkinson's disease? a comparison of Parkinson's disease patients, disease controls and healthy individuals. *Eur Neurol*. 2009;62(2):99-104.

49. Song IU, Kim YD, Cho HJ, Chung SW. Is neuroinflammation involved in the development of dementia in patients with Parkinson's disease? *Intern Med*. 2013;52(16):1787-1792.

50. Stypuła G, Kunert-Radek J, Stepień H, Zylińska K, Pawlikowski M. Evaluation of interleukins, ACTH, cortisol and prolactin concentrations in the blood of patients with Parkinson's disease. *Neuroimmunomodulation*. 1996;3(2-3):131-134.

51. Tang P, Chong L, Li X, et al. Correlation between serum RANTES levels and the severity of Parkinson's disease. *Oxid Med Cell Longev*. 2014;2014:208408.

52. Gangemi S, Basile G, Merendino RA, et al. Effect of levodopa on interleukin-15 and RANTES circulating levels in patients affected by Parkinson's disease. *Mediators Inflamm*. 2003;12(4):251-253.

53. Rocha NP, Teixeira AL, Scalzo PL, et al. Plasma levels of soluble tumor necrosis factor receptors are associated with cognitive performance in Parkinson's disease. *Mov Disord*. 2014;29(4):527-531.

54. Scalzo P, Kümmer A, Cardoso F, Teixeira AL. Increased serum levels of soluble tumor necrosis factor-α receptor-1 in patients with Parkinson's disease. *J Neuroimmunol*. 2009;216(1-2):122-125.

55. Cai G, Kastelein RA, Hunter CA. IL-10 enhances NK cell proliferation, cytotoxicity and production of IFN-γ when combined with IL-18. *Eur J Immunol*. 1999;29(9):2658-2665.

56. Mosser DM, Zhang X. Interleukin-10: new perspectives on an old cytokine. *Immunol Rev*. 2008;226:205-218.

57. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.

58. Sawada H, Oeda T, Umemura A, et al. Baseline C-reactive protein levels and life prognosis in Parkinson disease. *PLoS One*. 2015;10(7):e0134118.

59. Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? *Lancet Neurol*. 2009;8(4):382-397.

60. Kortekaas R, Leenders KL, van Oostrom JC, et al. Blood-brain barrier dysfunction in parkinsonian midbrain in vivo. *Ann Neurol*. 2005;57(2):176-179.

61. Allan SM, Tyrrell PJ, Rothwell NJ. Interleukin-1 and neuronal injury. *Nat Rev Immunol*. 2005;5(8):629-640.

62. Conroy SM, Nguyen V, Quina LA, et al. Interleukin-6 produces neuronal loss in developing cerebellar granule neuron cultures. *J Neuroimmunol*. 2004;155(1-2):43-54.

63. Venters HD, Dantzer R, Kelley KW. Tumor necrosis factor-α induces neuronal death by silencing survival signals generated by the type I insulin-like growth factor receptor. *Ann N Y Acad Sci*. 2000;917:210-220.

64. Feng ZH, Wang TG, Li DD, et al. Cyclooxygenase-2–deficient mice are resistant to 1-methyl-4-phenyl1, 2, 3, 6-tetrahydropyridine–induced damage of dopaminergic neurons in the substantia nigra. *Neurosci Lett*. 2002;329(3):354-358.

65. Sriram K, Matheson JM, Benkovic SA, Miller DB, Luster MI, O'Callaghan JP. Mice deficient in TNF receptors are protected against dopaminergic neurotoxicity: implications for Parkinson's disease. *FASEB J*. 2002;16(11):1474-1476.

66. Deleidi M, Gasser T. The role of inflammation in sporadic and familial Parkinson's disease. *Cell Mol Life Sci*. 2013;70(22):4259-4273.

67. McCoy MK, Martinez TN, Ruhn KA, et al. Blocking soluble tumor necrosis factor signaling with dominant-negative tumor necrosis factor inhibitor attenuates loss of dopaminergic neurons in models of Parkinson's disease. *J Neurosci*. 2006;26(37):9365-9375.

68. Chen H, Zhang SM, Hernán MA, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. *Arch Neurol*. 2003;60(8):1059-1064.

69. Wahner AD, Bronstein JM, Bordelon YM, Ritz B. Nonsteroidal anti-inflammatory drugs may protect against Parkinson disease. *Neurology*. 2007;69(19):1836-1842.

70. Gao X, Chen H, Schwarzschild MA, Ascherio A. Use of ibuprofen and risk of Parkinson disease. *Neurology*. 2011;76(10):863-869.

71. Parkinson Progression Marker Initiative. The Parkinson Progression Marker Initiative (PPMI). *Prog Neurobiol*. 2011;95(4):629-635.

72. Swanson CR, Berlyand Y, Xie SX, Alcalay RN, Chahine LM, Chen-Plotkin AS. Plasma apolipoprotein A1 associates with age at onset and motor severity in early Parkinson's disease patients. *Mov Disord*. 2015;30(12):1648-1656.

73. Santos-García D, Mir P, Cubo E, et al; COPPADIS Study Group. COPPADIS-2015 (Cohort of Patients with Parkinson's Disease in Spain, 2015), a global—clinical evaluations, serum biomarkers, genetic studies and neuroimaging—prospective, multicenter, non-interventional, long-term study on Parkinson's disease progression. *BMC Neurol*. 2016;16:26.