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Meta-analysis of the role of proinflammatory biomarkers in Parkinson's disease with non-motor symptoms

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ABSTRACT

Background and objectives. Neuroinflammation, characterized by microglial activation and elevated proinflammatory cytokines, plays a crucial role in Parkinson's disease (PD) pathogenesis and is linked to neurodegeneration and non-motor symptoms. This review aims to identify specific biomarkers associated with these non-motor symptoms, highlighting their roles and implications in PD management and therapy.

Materials and methods. This systematic review followed PRISMA guidelines to assess proinflammatory biomarkers in PD patients with non-motor symptoms. We included 10 studies identified through comprehensive searches in PubMed/Medline, Wiley Online Library, Science Direct, Google Scholar, and Neurona. Bias was assessed using the ROBINS-I tool, and study quality was evaluated with GradePro. Meta-analysis was conducted using the Ordmeta test.

Results. Proinflammatory biomarkers such as IL-6, TNF-α, CRP, and hs-CRP are notably associated with non-motor symptoms in PD. TNF-α shows a moderate correlation with depressive disorders in 194 patients ($p = 0.007 \pm 0.011$), while IL-17A correlates similarly with anxiety, and IL-2 with mood disorders. Furthermore, TNF-α has a low yet meaningful correlation with sleep disorders. Ordmeta results reveal significant elevations of TNF-α in 52 PD patients with cognitive impairment ($p = 0.0003$) and of IL-6 in 361 PD patients ($p = 0.023 \pm 0.008$), underlining their roles in PD pathology.

Conclusions. This study confirms that proinflammatory biomarkers such as CRP, hs-CRP, IL-6, IL-2, IL-17A, and TNF-α are significantly linked to non-motor symptoms in PD. TNF-α is notably elevated in patients with cognitive impairments and depressive disorders, while IL-6 is also significantly increased in those with cognitive issues.

Keywords: Parkinson; inflammatory; biomarker; non-motoric

Abbreviations:

CRP: C-reactive protein

hs-CRP: High-sensitivity C-reactive protein

IL-6: Interleukin-6

IL-17A: Interleukin-17A

PD: Parkinson's disease

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

ROBINS-I: Risk Of Bias In Non-randomized Studies - of Interventions

TNF-α: Tumor necrosis factor-alpha

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's dementia, leading to significant neurological disability. Discovered by the English doctor James Parkinson in 1887, PD is currently diagnosed based on clinical symptoms, with motor symptoms appearing after 50-60% of dopaminergic neurons are already damaged. The use of various biomarkers is expected to aid in the development of diagnostic and treatment strategies [1-3].

PD has a substantial impact on society, commonly affecting individuals aged 40-70, with a peak in the sixth decade of life. In 2016, approximately 6.1 million people worldwide were affected by PD. In Southeast Asia, the prevalence of PD in 2019 was 99.21 per 100,000 population. Studies predict a significant increase in the burden of PD in the coming decades. For instance, it is estimated that

there will be 4.94 million PD patients in China by 2030, accounting for half of the global PD population. The rapid progression of PD imposes a significant burden on society, individuals, and healthcare systems, with disability from PD reducing quality of life and incurring substantial healthcare costs, including medication, rehabilitation, and care [1,4].

Factors influencing the progression of PD include age, with older age associated with more severe motor and non-motor symptoms and greater dopaminergic dysfunction. Female patients are at higher risk for early dyskinesia with slower progression and a lower risk of cognitive impairment compared to males. Environmental factors, such as pesticide exposure and agricultural work, also increase the risk of PD [5,6].

Neuroinflammation plays a crucial role in the pathogenesis of neurodegeneration in PD. This process involves microglial activation, increased proinflammatory factors, and gut microbiota. Research has shown the involvement of neuroinflammation in PD pathogenesis, such as elevated proinflammatory cytokines in the blood. α-Synuclein protein also plays a key role in initiating and sustaining inflammation in PD [7,8].

Currently, there is no effective treatment to halt the progression of PD. Sensitive and practical PD biomarkers are needed, and their efficacy in diagnosing early or pre-symptomatic PD must be validated in clinical trials. Various molecules in cerebrospinal fluid (CSF), such as α-synuclein, DJ-1, amyloid-β, tau, lysosomal enzymes, and proinflammatory biomarkers, can serve as PD biomarkers. Imaging tools like positron emission tomography, single-photon emission computed tomography, and magnetic resonance imaging are important for visualizing dopaminergic nerve projections in the substantia nigra. Research by Ryul Kim et al. found significantly elevated IL-1β levels in early-stage PD patients compared to controls, linking increased IL-1β to neuroinflammatory processes in PD. Other cytokines, such as IL-6 and TNF-α, also play roles in neuroinflammation and are implicated in PD. Understanding the role and mechanisms of neuroinflammation in PD is crucial for developing diagnostics and treatment strategies [7, 9].

MATERIALS AND METHODS

This systematic review and meta-analysis targeted cross-sectional, cohort, and randomized controlled trials (RCTs) evaluating the impact of proinflammatory biomarkers on Parkinson's disease (PD) with non-motor symptoms. The systematic review involved evaluating, classifying, and categorizing previous primary research, while the meta-analysis combined extracted primary data to provide new evidence-based insights. The study was conducted from October 2023 to January 2024.

We formulated research questions, defined background and objectives, established eligibility criteria, conducted literature searches, assessed literature quality, and devised data extraction and synthesis strategies. After defining the research questions and keywords, we set the inclusion and exclusion criteria, adhering to the PRISMA 2020 flow diagram. Inclusion criteria included cross-sectional, cohort, case-control, and RCTs evaluating proinflammatory biomarkers in PD with non-motor symptoms, involving participants with PD and non-motor symptoms, without any intervention, and outcomes focused on levels of proinflammatory biomarkers and PD non-motor symptoms. Exclusion criteria included symposium or proceeding book publications, unpublished dissertations, review articles, and studies not in Indonesian or English.

Operational definitions were as follows: Proinflammatory biomarkers are indicators of inflammation found in cerebrospinal fluid or plasma, measured by p-values and presented on an ordinal scale. Non-motor symptoms of PD include sleep disturbances, neuropsychiatric, and cognitive issues, presented on a nominal scale. Parkinson's disease is a neurodegenerative disease with motor symptoms like tremor, rigidity, akinesia, and postural instability, presented on a nominal scale.

Based on the research questions and eligibility criteria, we defined keywords using Boolean operators (AND, OR) to expand or specify the search. Databases included PubMed/Medline, Science Direct, ResearchGate, Google Scholar, and Wiley Library Online, with no year restrictions. Articles in Indonesian were accessed through Google Scholar. The search strategy aimed to capture the maximum relevant articles.

Following the PRISMA 2020 flow diagram for article selection, three researchers manually screened and assessed articles for inclusion, ensuring alignment with predefined criteria. Data extraction was conducted using the "COVIDENCE" software, including variables such as publication year, study design, country, patient characteristics (age, gender), biomarker assessments, PD diagnosis, disease onset, and non-motor symptoms. We used the ROBINS-I tool to assess bias, resolving discrepancies through discussion. For unclear data, we contacted authors via email.

Quality assessment involved identifying potential biases such as confounding variables, participant selection, exposure measurement, intervention classification, deviations from intervention classification, incomplete outcome data, selective outcome reporting, and reporting bias. We categorized risk of bias as low, moderate, high, or critical using the ROBINS-I tool, illustrated with traffic light and summary plots.

For data synthesis and analysis, we conducted a systematic review followed by a meta-analysis for similar studies. Data were coded, tabulated, and analyzed using Ordmeta, focusing on p-values and sample sizes. Ordmeta is robust for combining p-values in meta-analysis, providing high power even with some unassociated statistics and without effect size and heterogeneity data.

RESULTS

This study reviewed 10 articles focusing on specific proinflammatory biomarkers associated with non-motor symptoms in Parkinson's disease (PD) [10–19]. The identified biomarkers included CRP, hs-CRP, IL-6, IL-2, IL-17A, and TNF-α. **Figure 1** shows the search flow diagram outlining the selection process, while **Table 1** details the characteristics of the included studies.

Bias selection was assessed using the ROBINS-1 tool as the collected sample articles were from non-randomized clinical trials. Overall, the collected studies had a moderate risk of bias due to the small average sample size. As for the study quality, all had a moderate risk of bias due to small sample sizes except for Fu et al. [13], despite meeting inclusion criteria and using standardized evaluation tools. All articles had a low risk for inconsistency, indirectness, and imprecision because

the studies were well-conducted, and interventions were consistently applied. Overall, the 10 selected research articles received a moderate certainty rating.

A systematic review and meta-analysis identified six statistically significant biomarkers linked to non-motor symptoms in PD: CRP, hs-CRP, IL-6, IL-2, IL-17A, and TNF-α. All biomarkers were investigated for cognitive impairments, with four biomarkers (IL-2, IL-6, IL-17A, and TNF-α) also linked to psychiatric disorders, and two biomarkers (IL-6 and TNF-α) related to sleep disorders.

Cognitive impairment

Proinflammatory biomarkers significantly associated with cognitive impairment in PD were identified in 655 patients, as shown in **Table 2,** including IL-6, TNF-α, IL-2, IL-17A, CRP, and hs-CRP. Six studies used the MOCA questionnaire [10–11, 13–14, 16–17], while two studies used the MMSE [18–19]. Moderate correlations were found for IL-6, TNF-α, and hs-CRP, low correlations for IL-17A and CRP, and very weak correlations for IL-2.

This meta-analysis included three cross-sectional studies that aimed to investigate the relationship between proinflammatory biomarkers and cognitive impairment in PD [13, 17, 19]. The Ordmeta method was used to combine p-values efficiently and effectively from these studies. The biomarker TNF-α showed a significant increase in 52 cases in one study [19], while IL-6 increased in 361 patients across three studies [13, 17, 19]. The significance distribution shows three articles related to IL-6 with p-values < 0.05 (0.024; 0.014; 0.0315) respectively and one article related to TNF-α with a p-value of 0.0003. The Ordmeta analysis results in **Figure 2a** show that the average p-value for IL-6 across three studies was 0.023 ± 0.008, and for TNF-α, it was 0.0003.

Psychiatric disorders

Proinflammatory biomarkers significantly associated with psychiatric disorders in Parkinson's disease were found to include IL-2, IL-6, IL-17A, and TNF-α. **Table 3** shows that proinflammatory biomarkers in Parkinson's disease with depressive symptoms have a moderate correlation with

TNF-α, with an increased risk of 1.035 times (95% CI 1.002–1.069). Anxiety disorders have a moderate correlation with IL-17A, while mood disorders show a moderate correlation with IL-2. Three research articles examined the association between depression in Parkinson's disease and the biomarker TNF-α. These studies included a total sample size of 194 cases, with significance levels of 0.001, 0.022, and 0.002, respectively [12, 15, 18]. All three articles had p-values <0.05 and were included in a meta-analysis using the Ordmeta method. The average p-value from these studies was 0.007 ± 0.011 **(Figure 2b).**

Sleep disorders

The proinflammatory biomarker significantly associated with sleep disorders in Parkinson's disease is TNF-α. Results from 52 PD patients with PSQI scores >5 show a statistically significant low correlation (r=0.347; p=0.014). The biomarker IL-6 was also studied in relation to sleep disorders by Fu et al. [13], but the results were not statistically significant.

DISCUSSION

PD is a progressive neurodegenerative disorder characterized by the loss of dopamine (DA) neurons in the substantia nigra pars compacta, leading to specific motor symptoms [20]. However, PD is a complex multisystem disease with unknown etiology, presenting various pathological features and symptoms affecting multiple organs. Patients with PD experience non-motor symptoms, including anosmia, autonomic dysfunction, depression, cognitive impairment, gastrointestinal dysfunction, psychosis, and sleep disorders, which may require additional management [14, 21].

The inflammatory response plays a crucial role in the pathophysiology of non-motor symptoms in PD. Various studies have evolved from observing microglia and inflammatory factors in the brains of PD patients to analyzing the immune response's contribution. Despite many reviews, few studies have focused on proinflammatory biomarkers related to non-motor symptoms in PD [12].

Cognitive impairment

Proinflammatory biomarkers associated with cognitive impairment include CRP, hs-CRP, IL-6, IL-2, IL-17A, and TNF-α, with moderate correlations found for hs-CRP, IL-6, and TNF-α. The Ordmeta analysis revealed significant increases in TNF-α in 52 patients (average p = 0.0003) and IL-6 in 361 patients (average p = 0.023). Cognitive impairment in PD is linked to structural abnormalities in the hippocampus, crucial for cognition. Both IL-6 and TNF-α play essential roles in learning and memory, and their elevated levels are associated with decreased brain-derived neurotrophic factors [18, 22]. Previous studies support these findings, indicating that serum TNF-α correlates with cognitive function scores and higher TNF-α plasma levels are linked to cognitive impairment, depression, and disability in PD patients [12–13, 19, 23].

Psychiatric disorders

IL-2, IL-6, IL-17A, and TNF-α are significantly associated with psychiatric disorders in PD. Depression has a moderate correlation with TNF-α (average p = 0.007 ± 0.011), anxiety with IL-17A, and mood disorders with IL-2. Lindqvist's study suggests that TNF-α and IL-2 influence anxiety and mood disorders by affecting serotonin reuptake and hormonal imbalances in the amygdala. Blocking TNF-α can improve nigral cell loss during progressive degeneration. Increased IL-6 and TNF-α levels are linked to depressive symptoms, potentially reducing serotonin levels through indoleamine 2,3-dioxygenase (IDO) activity. The continuous inflammatory response necessitates comprehensive treatment beyond serotonin replacement [20].

Sleep disorders

Degeneration of the reticular formation and locus coeruleus, involved in sleep regulation, characterizes stage 2 PD pathology. IL-6 regulates normal sleep through diurnal activity, and sleep deprivation alters IL-6 plasma levels. Chronic sleep disorders increase TNF, TNFR1, IL-6, IL-1, IL-17, and B cells. TNF is crucial for nighttime sleep disturbances, as demonstrated by clinical

trials showing TNF inhibitors reduce sleep disturbances in patients with ankylosing spondylitis. Our study found a low but significant correlation between TNF-α and sleep disorders in PD patients with PSQI > 5 (r = 0.347) [19].

Future research should focus on large-scale studies with consistent measurement tools for non-motor symptoms in PD. Identifying and validating additional proinflammatory biomarkers could enhance diagnostic and therapeutic approaches, potentially improving the quality of life for PD patients. Understanding the precise mechanisms of inflammation in PD will be crucial in developing targeted treatments for non-motor symptoms [19].

CONCLUSION

Six proinflammatory biomarkers—CRP, hs-CRP, IL-6, IL-2, IL-17A, and TNF-α—are significantly associated with non-motor symptoms in Parkinson's disease (PD). IL-6 and TNF-α are the most frequently studied. These biomarkers are notably linked to cognitive impairments, with moderate correlations for hs-CRP, IL-6, and TNF-α. IL-2, IL-6, IL-17A, and TNF-α are significantly associated with psychiatric disorders, including mood disorders, depression, and anxiety. Ordmeta analysis confirmed significant increases in TNF-α and IL-6 levels in PD patients with cognitive impairments and depression, underscoring their potential as targets for managing non-motor symptoms in PD.

Conflict of interest: None.

Author's contributions:

Conceptualization: S.S., S.J., A.M.; methodology: S.S., S.J., A.M.; software: S.S., S.J., A.M.; validation: S.S., S.J., A.M.; formal analysis: S.S., S.J., A.M.; investigation: S.S., S.J., A.M.; resources: S.S., S.J., A.M.; data curation: S.S., S.J., A.M.; writing—original draft preparation: S.S., S.J., A.M.; writing—review and editing: S.S., S.J., A.M.; visualization: S.S., S.J., A.M.; supervision: S.J., A.M.; project administration: S.S., S.J., A.M.; funding acquisition: None. All authors have read and agreed to the published version of the manuscript.

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TABLES

Table 1. Study characteristics

No.	Study	Non-motor symptoms	Design	Participants	Biomarker	Key findings
1	Fu et al., 2023	Cognitive impairment	Cross-sectional	PD = 273 Control = 91	IL-6, IL-8, TNF-α	IL-6 is associated with cognitive impairment (p .024)
2	Kim et al., 2022	Cognitive and mood disorders	Cohort	PD = 45 Control = 20	IL-1β, IL-2, IL-6, IL-10, TNF-α, hsCRP	IL-2 and IL-6 are associated with cognitive and mood disorders (p < 0.05)
3	Lian et al., 2020	Depression	Case-control	PD = 58 Control = 28	TNF-α	NF-α is significantly associated with depression OR = 1.035 (95% CI 1.003–1.069) r = -0.247, p = 0.022
4	Green et al., 2019	Cognitive and psychiatric disorders	Cohort	PD = 60 Control = 45	IL-6, TNF-α, TGFβ, IL-17A	IL-17A is significantly associated with cognitive (p < 0.05, r = -0.370) and psychiatric disorders (p < 0.05, r = 0.440)
5	Moghaddam et al., 2018	Cognitive impairment	Cross-sectional	PD = 109	CRP	CRP is significantly associated with cognitive impairment (p = 0.008, r = -.56)
6	Prasetyastuti et al., 2018	Cognitive impairment	Cross-sectional	PD = 35	hsCRP	hs-CRP is significantly associated with cognitive dysfunction by 58.7% (p < 0.05)
7	Yu et al., 2014	Cognitive impairment	Cross-sectional	PD-CI = 36 PD-NCI = 26 Control = 31	TNF-α, IL-1β, IL-6, INF-γ, PGE2	IL-6 is associated with cognitive

No.	Study	Non-motor symptoms	Design	Participants	Biomarker	Key findings
						impairment (p = 0.014)
8	Song et al., 2013	Cognitive impairment (dementia)	Case-control	PDD = 45 PDwoD = 72 72 PDwoD	hsCRP	hsCRP is associated with cognitive impairment (p < 0.001, OR = 2.017, 95% CI 1.180-3.013)
9	Lindqvist et al., 2012	Depression, sleep disorders, anxiety	Cross-sectional	PD = 86 Control = 40	CRP, IL-6, IL-2, TNF-α	IL-2 and TNF-α are significantly associated with depression and anxiety, but not with sleep disorders (p < 0.05)
10	Menza et al., 2010	Sleep disorders, cognitive impairment, and depression	Cross-sectional	PD with depression = 52	IL-1β, IL-6, IL-10, TNF-α	TNF-α is significantly associated with sleep disorders, cognitive impairment, and depression (p 0.05) IL-6 is associated with cognitive impairment (r = 0.43, p = 0.0315)

Table 2. Relationship between proinflammatory biomarkers and cognitive impairment in Parkinson's disease

No	Study	MOCA	N	Correlation value					
				IL-6	IL-2	IL-17A	TNF-α	CRP	hs-CRP
1	Fu et al., 2023	23,4 ± 4,6	273	p = 0,024					
2	Kim et al., 2022	< 24	45	1,52 ± 4,18 pg/ml (p = 0,011; r= -0,152)	0,14±0,12 pg/ml (p= 0,029; r=-0.054				
3	Green et al., 2019	23,1 ± 5,6	60			0,19 ± 0,02 pg/mL (p < 0,05; r =-0,370)			

No	Study	MOCA	N	Correlation value					
				IL-6	IL-2	IL-17A	TNF-α	CRP	hs-CRP
4	Moghaddam et al., 2018	21,9±6,7	109					p = 0,008; r = -0,256	
5	Prasetyastuti et al., 2018	<24	35						p < 0,05; r = 0,587
6	Yu et al., 2014	<24	36	1,72 ± 0,19 (p = 0,014)					
7	Song et al., 2013	MMSE 21.58±4.25	45						1.49±3.21 (p < 0,001)
8	Menza et al., 2010	MMSE< 26	52	r = 0,43 (p = 0,0315)			r =-0,51 p = 0,0003		
Results		6 studies with MOCA < 24 and 2 studies with MMSE < 24	655	Moderate correlation	Very weak correlation	Low correlation	Moderate correlation	Low correlation	Moderate correlation

Table 3. Relationship between proinflammatory biomarkers and psychiatric disorders in parkinson's disease

No	Study	N	Mood	Depression	Anxiety	Correlation value			
						IL-6	IL-2	IL-17A	TNF-α
1	Kim et al., 2022	45	Mood or apathy domain scores 4,1± 2,1			p = 0.025 r = 0.333	p = 0.011 r = 0.464		
2	Lian et al., 2020	58		HAMD-24 ≥8					p = 0,022 r = -0,247
3	Green et al., 2019	46		HADS-Depression 4,9 ± 4,6	HADS-Anxiety 6,4 ± 4,9			Depression (p < 0,05; r = 0,750) Anxiety (p < 0,05; r = 0,440)	
4	Lindqvist et al., 2012	84		HAD-depression 2,5; (1,0–5,0)	HAD-anxiety 3,5; 2,0–6,0		425,0 (332,3–539,5) Depression (p = 0,001; r = 0,380) Anxiety (p = 0,01; r = 0,240)		10,0 (8,0–12,0) Depression (p = 0,001; r = 0,35) Anxiety (p = 0,01; r = 0,21)

No	Study	N	Mood	Depression	Anxiety	Correlation value			
						IL-6	IL-2	IL-17A	TNF-α
5	Menza et al., 2010	52		HAMD-24 ≥8					Depression (p = 0,002; r = 0,440))
Results		655				Mood disorders have a low correlation	Mood disorders have a moderate correlation. Depression and anxiety have a low correlation.	Depression has a low correlation and anxiety has a moderate correlation.	Depression has a moderate correlation

FIGURES

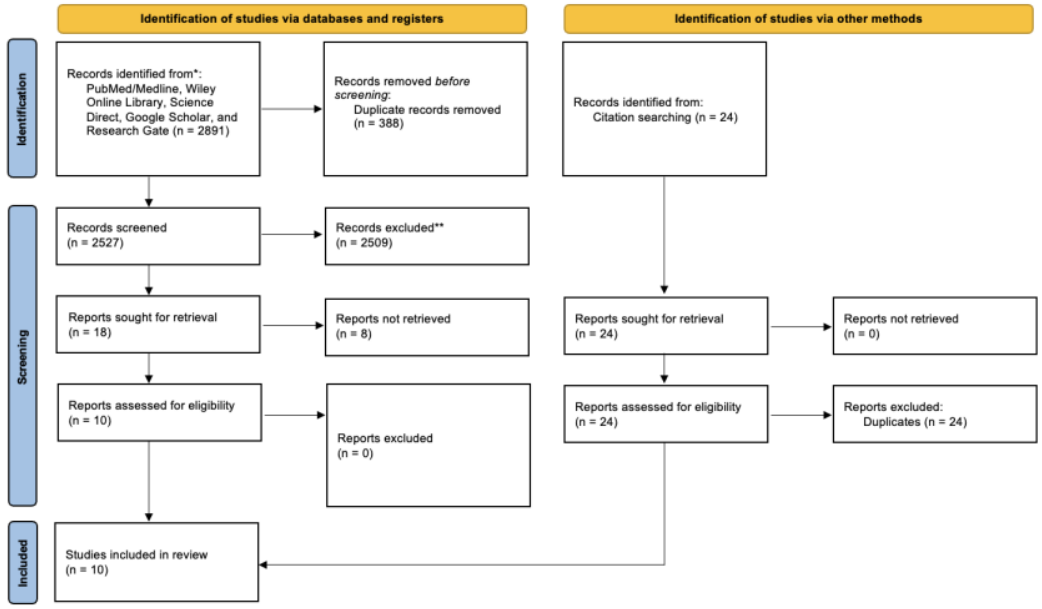

Figure 1. Search flow diagram

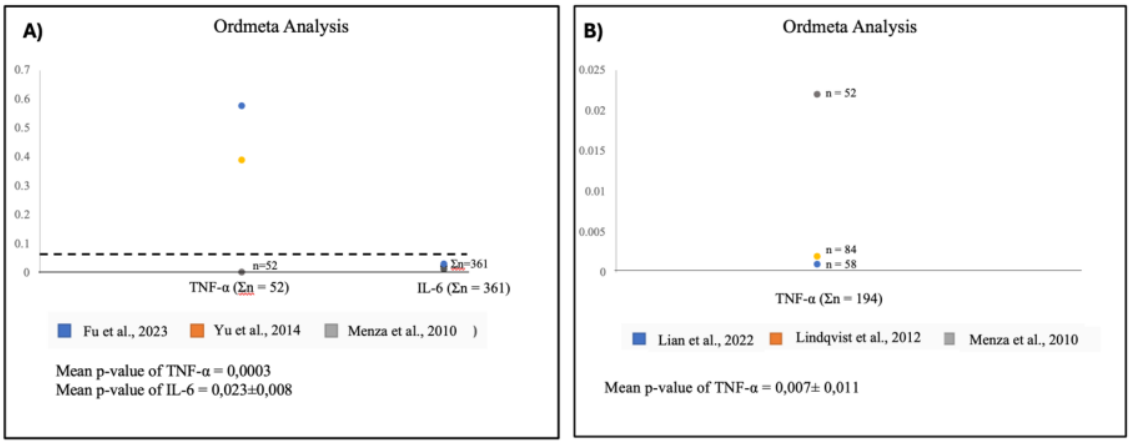

Figure 2. A) Meta-analysis for cognitive impairment; B) Meta-analysis for depression