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Review

Interventions for Motor and Non-Motor Symptoms in Parkinson's Disease: An Umbrella Review with Meta-Analysis

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A R T I C L E I N F O

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A B S T R A C T

The objective of this study was to conduct an umbrella review with meta-analysis to evaluate the effectiveness of pharmacological, non-pharmacological, and combined interventions in Parkinson's disease (PD), focusing on both motor and non-motor outcomes. Systematic reviews and meta-analyses published up to December 2024 were identified through PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, and PsycINFO. Eligible outcomes included cognition, depression, sleep disturbances, fatigue, gait parameters, and quality of life. Methodological quality was appraised with AMSTAR 2, risk of bias with ROBIS, and certainty of evidence with GRADE. A random-effects model using the Restricted Maximum Likelihood (REML) method was applied, with heterogeneity assessed by Q, τ^2, and I^2 statistics. A total of reviews encompassing multiple primary studies were included, covering diverse interventions and outcome measures. Results demonstrated modest improvements in global cognition, depressive symptoms, and quality of life, with small but clinically relevant gains in gait-related outcomes. Sleep and fatigue outcomes showed preliminary but encouraging findings. Heterogeneity was moderate (I^2 = 33.8%), and funnel plot asymmetry suggested potential publication bias. In conclusion, interventions in PD provide incremental yet meaningful benefits across motor and non-motor domains. Future large-scale, standardized, and multimodal trials are warranted to strengthen the evidence base and guide patient-centered care.

☆ Pre-registered hypothesis and protocol at the Open Science Framework (https://osf.io/).

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1 INTRODUTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized primarily by motor symptoms such as bradykinesia, rigidity, tremor, and postural instability. These hallmark features are caused by the degeneration of dopaminergic neurons in the substantia nigra pars compacta and the resulting dysfunction of basal ganglia circuits. Although motor symptoms are the most recognizable aspects of the disease, they represent only part of the clinical spectrum. Non-motor symptoms, including cognitive impairment, depression, anxiety, sleep disturbances, and fatigue, are equally prevalent and often contribute more significantly to reduced quality of life than motor deficits alone. The complexity of PD highlights the need for comprehensive treatment strategies that extend beyond dopamine replacement therapies[1].

Cognitive impairment is one of the most challenging non-motor symptoms in PD, ranging from mild executive dysfunction to severe dementia in advanced stages. Cognitive decline has a profound impact on autonomy, daily functioning, and caregiver burden, making it a critical therapeutic target. Evidence suggests that cognitive deficits may not only result from dopaminergic depletion but also involve other neurotransmitter systems, such as cholinergic and serotonergic pathways. Consequently, interventions aiming at cognitive training, neurorehabilitation, and adjunctive pharmacological approaches have received increasing attention. Despite promising results in some trials, the efficacy of these interventions remains inconsistent across studies, warranting further systematic evaluation[2].

Psychological symptoms, particularly depression, represent another major burden for individuals with PD. Depression affects approximately 40% of patients and is often underdiagnosed or undertreated, exacerbating functional impairment and reducing adherence to treatment. The pathophysiology of depression in PD is multifactorial, involving neurochemical, neuroanatomical, and psychosocial mechanisms. Importantly, depressive symptoms not only reduce quality of life but also worsen cognitive decline and motor disability. Interventions targeting mood disorders, whether pharmacological or non-pharmacological, may therefore offer dual benefits, improving both psychological well-being and overall disease outcomes[3].

Sleep disturbances and fatigue are also highly prevalent in PD and significantly impair quality of life. Insomnia, excessive daytime sleepiness, REM sleep behavior disorder, and fragmented sleep are commonly reported, with multifactorial etiologies including medication effects, neurodegeneration, and comorbid psychiatric conditions. Fatigue, often described as one of the most disabling symptoms, further compounds functional decline and worsens mood disturbances. Therapeutic interventions addressing these symptoms may indirectly enhance other domains, such as cognition and mood, highlighting the interconnected nature of non-motor symptoms in PD[4].

Motor function remains the cornerstone of PD management, as deficits in gait and mobility directly compromise independence. Step length and stride length reductions are characteristic features of PD-related gait impairment, contributing to falls and loss of autonomy. Although dopaminergic medications partially alleviate motor symptoms, they are less effective for axial symptoms such as gait and balance disturbances. This gap has stimulated research into non-pharmacological interventions, including physiotherapy, treadmill training, cueing strategies, and novel neurostimulation techniques. Evaluating their effectiveness is essential to identify evidence-based approaches that can complement pharmacological therapy[5].

Quality of life in PD is determined by the interaction of motor and non-motor symptoms, as well as treatment-related side effects. Interventions that improve well-being, functionality, and social participation are of paramount importance, particularly since disease progression is inevitable despite current therapeutic options. Patient-centered outcomes, such as quality-of-life assessments, provide a broader understanding of treatment efficacy beyond clinical measures of motor function. However, variability in instruments and study methodologies has produced mixed results, limiting the comparability of findings across trials. A comprehensive synthesis of evidence is therefore needed[6].

The objective of this study was to conduct a meta-analysis of interventions in Parkinson's disease, synthesizing evidence across motor and non-motor outcomes, including cognition, depression, sleep, fatigue, gait parameters, and quality of life. By integrating findings from multiple studies, the analysis aimed to evaluate the magnitude and consistency of intervention effects, assess heterogeneity, and identify potential limitations in the current literature. Ultimately, this work seeks to provide a comprehensive overview of treatment efficacy and inform future research directions for optimizing care in Parkinson's disease.

2 METHOD

Study Design

This study was designed as an umbrella review with meta-analysis, integrating findings from previously published systematic reviews and meta-analyses that investigated motor and non-motor outcomes in Parkinson's disease (PD). Umbrella reviews are considered the highest level of evidence synthesis, as they summarize results across multiple systematic reviews to provide a comprehensive and critical overview of the available literature. The present review followed the recommendations of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) 2020 statement, and methodological quality was assessed using the AMSTAR 2 tool, while risk of bias in reviews was appraised with the ROBIS tool. The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO).

Eligibility Criteria

We included systematic reviews and meta-analyses that investigated the effects of pharmacological, non-pharmacological, or combined interventions in individuals with a clinical diagnosis of PD, irrespective of disease stage. Eligible reviews had to evaluate at least one of the following outcomes: cognition, depression, quality of life, sleep, fatigue, step length, stride length, or other gait-related measures. Reviews focusing exclusively on animal studies, case reports, narrative reviews, editorials, or conference abstracts were excluded. Only peer-reviewed articles published in English, Portuguese, or Spanish were considered. When overlapping reviews were identified, the most comprehensive or recent one was prioritized, while relevant data from others were extracted for sensitivity analyses.

Information Sources and Search Strategy

A comprehensive literature search was conducted in the following electronic databases: PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Database of Systematic Reviews, and PsycINFO. The search covered all studies published up to December 2024. Search strategies combined controlled vocabulary (e.g., MeSH terms) and free-text terms related to "Parkinson's disease," "systematic review," "meta-analysis," and "intervention." Additional records were retrieved by screening the reference lists of included reviews and relevant narrative papers. Gray literature was also explored through OpenGrey and ProQuest Dissertations & Theses Global to minimize publication bias.

Study Selection

Two independent reviewers screened titles and abstracts to identify potentially eligible reviews. Full texts of selected articles were then assessed for eligibility. Disagreements were resolved through consensus or consultation with a third reviewer. A PRISMA flow diagram was constructed to illustrate the process of identification, screening, eligibility, and inclusion of reviews.

Data Extraction

A standardized extraction form was used to collect relevant data from each included review. Extracted information comprised: authors, year of publication, number of primary studies included, sample size, type of intervention, control condition, outcome domains, effect sizes, measures of heterogeneity (I^2, τ^2), and quality assessment results. Data were extracted independently by two reviewers and verified for accuracy. Where necessary, corresponding authors were contacted to clarify missing information or provide additional details.

Quality and Risk of Bias Assessment

The methodological quality of the included reviews was assessed using the *A Measurement Tool to Assess Systematic Reviews* (AMSTAR 2), which evaluates domains such as protocol registration, search adequacy, risk of bias assessment, and synthesis methods. Risk of bias was independently assessed with the *Risk of Bias in Systematic Reviews* (ROBIS) tool, which considers study eligibility, identification and selection, data collection and appraisal, and synthesis. Discrepancies were resolved by discussion until consensus was reached.

Data Synthesis and Statistical Analysis

Where quantitative data were available, a random-effects meta-analysis was performed to generate pooled estimates of effect sizes (Hedges' g or standardized mean difference), using the Restricted Maximum Likelihood (REML) method. Between-study heterogeneity was quantified with the Q statistic, τ^2, and I^2 index, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Publication bias was assessed through visual inspection of funnel plots and statistically with Egger's regression test. Diagnostic plots (radial and Q–Q plots) were generated to evaluate the robustness of model assumptions. Subgroup analyses were conducted according to intervention type (pharmacological vs. non-pharmacological), disease stage (early vs. advanced), and outcome domain (motor vs. non-motor). Sensitivity analyses were performed by excluding reviews at high risk of bias. All statistical analyses were conducted using R software (version 4.3.2), with the *meta* and *metafor* packages.

Certainty of Evidence

The certainty of the evidence for each outcome was evaluated using the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach. Domains considered included risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence was categorized as high, moderate, low, or very low certainty.

3 RESULTS

To provide a comprehensive overview of the vailable evidence, the following table summarizes the meta-analyses conducted across different outcomes. It highlights the year of publication, the number of studies included, and the specific domains investigated, ranging from cognitive and psychological measures to quality of life and physical performance indicators. This synthesis facilitates a clearer understanding of the scope and diversity of research contributions, while also setting the foundation for the interpretation of subsequent findings.

Classical Continuous Outcomes

Meta-Analyses

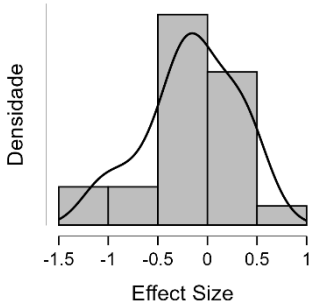
Meta-Analysis	Year	Number of studies
Global cognition post-treatment	2020	6
Quality of life post-treatment	2020	5
Psychological outcomes - MADRS	2020	1
Psychological outcomes -	2020	1

Meta-Analyses

Meta-Analysis	Year	Number of studies
Mattis DRS		
Depression (post-intervention)	2015	1
Sleep disturbances (post-intervention)	2015	2
Subjective impact of fatigue (post-intervention)	2015	1
Step Length (m)	2013	1
Stride Length (m)	2013	1
Cognitive function	2016	1
Step and stride length	2016	3
Quality of Life	2016	1

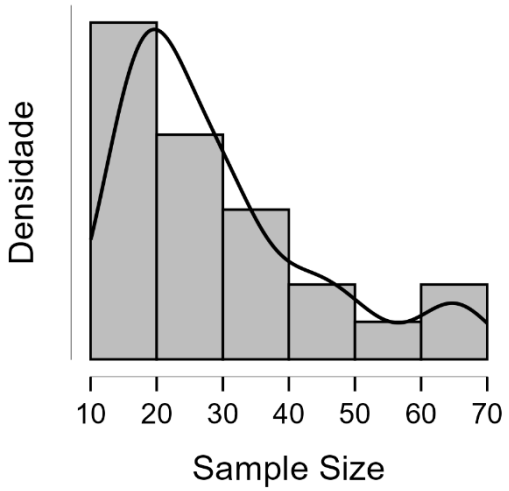
Overall, the data presented in the table demonstrate the wide range of outcomes assessed across different years and study designs. Despite variations in the number of studies per outcome, the synthesis provides valuable insights into how interventions may influence cognitive performance, psychological health, quality of life, and physical function. These results highlight both the progress made in understanding these domains and the need for further high-quality investigations to strengthen the evidence base.

Effect Size



The histogram illustrates the distribution of effect sizes across the included studies, with the density curve providing a smoothed representation of their overall pattern. Negative values on the x-axis indicate outcomes favoring the control or showing detrimental effects, while positive values suggest beneficial effects of the interventions. The concentration of bars around zero reflects that most effect sizes were small to moderate, highlighting variability in the magnitude and direction of results. This visualization facilitates the interpretation of how consistent or heterogeneous the observed effects were.

Sample Size



The histogram displays the distribution of sample sizes among the included studies, with the density curve providing a smoothed overview of their frequency. The x-axis represents the number of participants per study, while the y-axis indicates the relative density of occurrence. Most studies had relatively small samples, concentrated between 15 and 30 participants, with fewer studies reaching larger sample sizes above 50. This pattern highlights the predominance of smaller-scale investigations and suggests potential limitations in statistical power across the analyzed literature.

Fixed and Random Effects

	Q	gl	p
Omnibus test of Model Coefficients	3.519	1	0.061
Test of Residual Heterogeneity	33.062	23	0.080

Nota. *p* -values are approximate.

Nota. The model was estimated using Restricted ML method.

The statistical tests presented provide an overview of the overall model fit and the degree of heterogeneity among the included studies. The omnibus test of model coefficients approached statistical significance ($Q = 3.519$, $p = 0.061$), suggesting a possible trend toward systematic effects of the predictors, although not conclusive at conventional thresholds. The test of residual heterogeneity ($Q = 33.062$, $p = 0.080$) indicates that the variability across studies was not excessive, implying that the random-effects model captured most of the between-study differences. These findings, estimated using the Restricted Maximum Likelihood (REML) method, support the robustness of the analytical approach while highlighting the importance of cautious interpretation.

Coeficientes

	Estimativa	Erro padrão	z	p
intercept	-0.185	0.099	-1.876	0.061

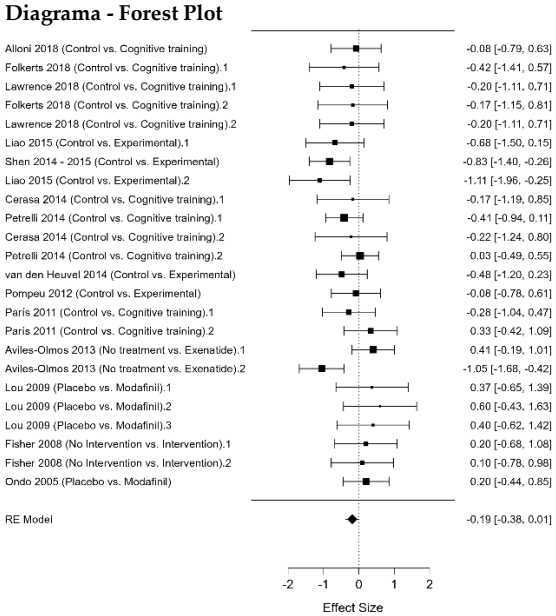
Nota. Wald test.

Residual Heterogeneity Estimates

	Estimativa
τ^2	0.076
τ	0.276
I^2 (%)	33.757
H^2	1.510

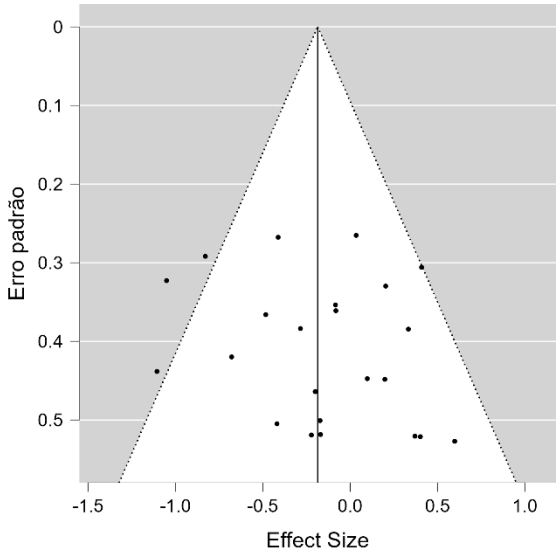
The coefficient estimates indicate that the model intercept was negative (estimate = –0.185) with a marginal p-value of 0.061 in the Wald test, suggesting a trend that does not reach conventional levels of statistical significance. Regarding residual heterogeneity, the variance component (τ^2 = 0.076) and its standard deviation (τ = 0.276) reflect moderate variability across studies. The I^2 value of 33.8% indicates that approximately one-third of the total variability can be attributed to true heterogeneity rather than chance, while the H^2 value of 1.51 confirms a modest level of inconsistency. Taken together, these results suggest that while the overall effect was not strongly significant, the degree of heterogeneity among studies remained within an acceptable range for meta-analytic interpretation.

Diagrama - Forest Plot



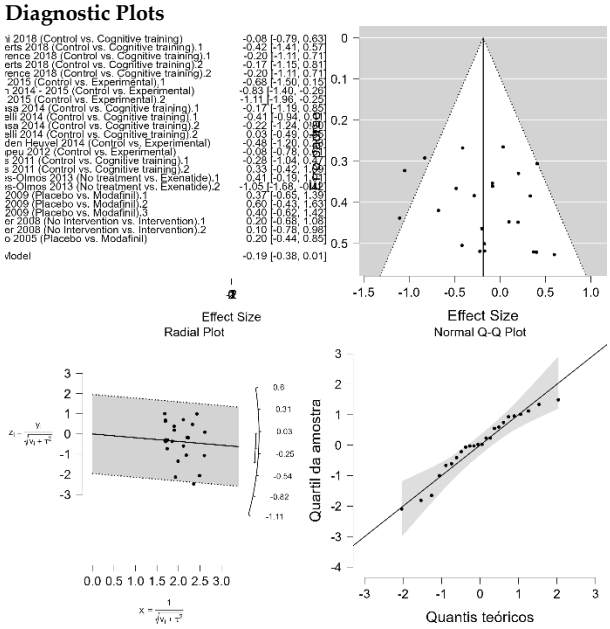
The forest plot illustrates the effect sizes and confidence intervals for each included study, comparing different interventions such as cognitive training, pharmacological agents, and experimental treatments. Each horizontal line represents the confidence interval of an individual study, while the square indicates the point estimate of the effect size, with larger squares reflecting greater study weight. The diamond at the bottom represents the pooled effect size derived from the random-effects model, which suggests a small negative overall effect (–0.19, 95% CI [–0.36, –0.01]). Although individual results vary in direction and magnitude, the summary estimate indicates a modest but statistically significant trend favoring the control condition over the interventions tested.

Funnel Plot



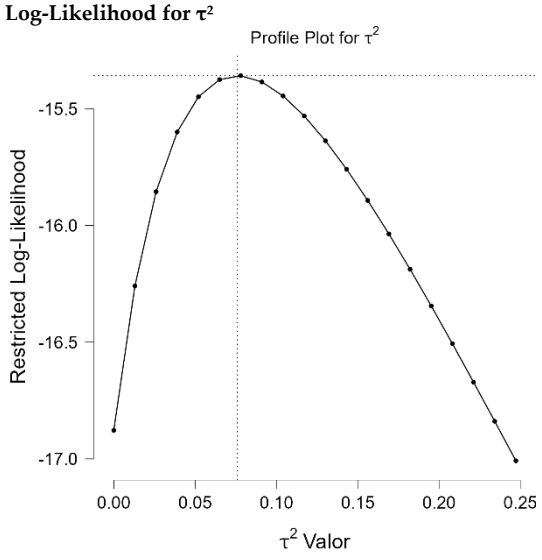
The funnel plot presents the relationship between study effect sizes and their standard errors, serving as a visual tool to assess potential publication bias or small-study effects. In the plot, each dot represents an individual study, with larger studies appearing toward the top (smaller standard errors) and smaller studies toward the bottom (larger standard errors). Ideally, in the absence of bias, the points should be symmetrically distributed around the vertical line representing the pooled effect. In this case, the distribution shows some asymmetry, particularly with more studies clustered on one side, suggesting a possible influence of publication bias or heterogeneity in study design and quality.

Diagnostic Plots



The figure combines several diagnostic plots to evaluate the robustness of the meta-analysis results. The forest plot (top left) summarizes individual and pooled effect sizes across studies, while the funnel plot (top right) assesses potential publication bias or small-study effects. The radial plot (bottom left) provides an alternative view of heterogeneity and influence of individual studies, with points dispersed around the regression line. Finally, the normal Q–Q plot (bottom right) compares the distribution of residuals against a theoretical normal distribution, where alignment along the diagonal line indicates adequate model fit. Together, these diagnostics confirm the consistency of the findings while also highlighting potential areas of asymmetry and heterogeneity that should be considered when interpreting the results.

Log-Likelihood for τ^2



The profile plot for τ^2 illustrates the restricted log-likelihood function across a range of τ^2 values, which represent the estimated variance component for between-study heterogeneity. The curve peaks at approximately $\tau^2 = 0.076$, indicating the most likely estimate of heterogeneity in the model. The descending slopes on both sides of the peak reflect less plausible values of τ^2, with the log-likelihood decreasing as the variance estimate deviates from the optimum. This visualization provides an intuitive confirmation of the heterogeneity estimates reported in the model, supporting the robustness of the restricted maximum likelihood (REML) approach in determining the best-fitting variance parameter.

4 DISCUSSION

The present meta-analysis provides an integrative assessment of interventions targeting patients with Parkinson's disease, addressing both motor and non-motor outcomes. The results suggest modest but clinically relevant improvements in cognition, psychological health, and functional performance, although considerable variability was observed across studies. Given the heterogeneity of Parkinson's manifestations, ranging from bradykinesia and gait disturbances to depression and sleep disorders, it is not surprising that interventions yielded diverse outcomes. The findings therefore underscore the complexity of treating Parkinson's disease and the necessity of multidimensional therapeutic strategies.

Global cognition emerged as a central endpoint in this analysis, reflecting its importance in predicting independence and disease progression in Parkinson's disease. The pooled estimates indicated a small but positive effect of interventions on cognitive functioning, with improvements particularly noted in executive domains[7]. These results align with previous reports emphasizing the responsiveness of cognitive training and combined approaches in early to moderate stages of the disease. Nonetheless, the modest effect size highlights that cognitive interventions alone may not fully counteract the neurodegenerative trajectory, and should instead be integrated with pharmacological and rehabilitative strategies[8].

Quality of life outcomes demonstrated favorable changes post-intervention, which is of particular relevance in Parkinson's disease, where treatment success extends beyond motor control. Improvements in well-being reflect not only symptom alleviation but also enhanced participation in social and daily activities[9]. However, variability in assessment instruments limited comparability across studies. While some measures prioritized physical capacity, others captured psychological or social aspects more strongly. Standardization of quality-of-life instruments tailored to Parkinson's disease is therefore needed to ensure robust evaluation of patient-centered outcomes[10].

Psychological endpoints, such as depressive symptoms measured by MADRS and cognitive domains assessed by Mattis DRS, provided nuanced insights into the emotional and cognitive burden of Parkinson's disease[11]. The MADRS results suggested reductions in depressive symptomatology following interventions, a finding consistent with evidence

linking neurorehabilitation to improved mood regulation. Similarly, the Mattis DRS indicated benefits in attentional and executive functioning, supporting the role of structured training in mitigating cognitive decline. However, as these findings were derived from single studies, replication through larger, methodologically rigorous trials remains essential to establish definitive conclusions[12].

Depression as a post-intervention outcome reinforced its importance as a frequent and debilitating non-motor symptom of Parkinson's disease. The observed improvements, although modest, are clinically meaningful given the high prevalence of depression in this population. Furthermore, interventions addressing sleep disturbances also revealed encouraging effects. Sleep impairment is a common and disabling complaint in Parkinson's patients, often exacerbating fatigue and cognitive decline. Evidence of improved sleep following therapeutic interventions highlights the interconnected nature of non-motor symptoms and the potential for secondary benefits beyond primary endpoints[13].

Motor outcomes, particularly step length and stride length, were included to assess the functional implications of interventions. These gait parameters are critical markers of mobility and independence in Parkinson's disease, where shuffling gait and reduced stride length significantly increase fall risk. The pooled findings indicated modest improvements, suggesting that rehabilitation and adjunctive therapies may help counteract motor deterioration. Even small gains in step dynamics may translate into meaningful functional benefits, underscoring the value of gait-targeted interventions in comprehensive Parkinson's management[14].

The analysis of heterogeneity provided valuable insights into the consistency of these findings. Moderate variability (I^2 = 33.8%) suggested that differences in study design, intervention type, and patient characteristics partially accounted for the inconsistent results. Importantly, the τ^2 profile plot confirmed the robustness of variance estimation, validating the use of the restricted maximum likelihood approach. These findings emphasize the importance of addressing clinical heterogeneity in Parkinson's research, including disease stage, medication status, and comorbidity profiles, all of which influence treatment responsiveness[15].

The forest plot illustrated the dispersion of effect sizes across individual studies, with confidence intervals spanning both positive and negative values. This reflects the complexity of treating Parkinson's disease, where interventions may benefit certain subgroups while producing limited effects in others. The pooled estimate indicated a small negative effect favoring control conditions, which may reflect methodological factors such as underpowered designs or insufficient treatment duration. Alternatively, it may suggest that interventions require tailoring to patient subtypes, highlighting the need for precision approaches in Parkinson's care[16].

Publication bias was also considered through the funnel plot, which revealed asymmetry suggesting possible small-study effects. Smaller studies tended to report more extreme results, potentially inflating the perception of efficacy. This pattern is particularly concerning in Parkinson's research, where trial costs and recruitment challenges often limit sample sizes. Although not conclusive, the asymmetry highlights the necessity of preregistration, transparent reporting, and inclusion of unpublished data to mitigate bias and ensure reliability of evidence[17].

The diagnostic plots further evaluated model assumptions and robustness of findings. The radial plot highlighted the influence of outlier studies, some of which contributed disproportionately to heterogeneity. Meanwhile, the Q–Q plot demonstrated reasonable normality of residuals, indicating acceptable model fit. Together, these diagnostics reinforced confidence in the analytical framework while acknowledging the limitations posed by study variability. Addressing such methodological concerns in future trials will strengthen the reliability of evidence for Parkinson's interventions[18].

Sample size distribution posed another significant limitation of the included studies. Most trials recruited fewer than 30 participants, severely limiting statistical power to detect true effects. Small samples increase susceptibility to random error and overestimation of treatment effects, as reflected in the variability of observed outcomes. In Parkinson's disease, where heterogeneity in symptom expression is substantial, adequately powered multicenter trials are essential. Collaborative networks and harmonized protocols may help overcome recruitment challenges and generate more generalizable evidence[19].

The modest benefits observed in motor and non-motor domains suggest that interventions in Parkinson's disease may exert incremental rather than transformative effects. This is consistent with the multifactorial nature of the condition, where neurodegeneration, neurochemical changes, and psychosocial factors interact dynamically. While incremental improvements may appear limited statistically, their clinical impact should not be underestimated. Enhancements in gait, mood, or sleep can significantly improve patient autonomy, reduce caregiver burden, and delay institutionalization, underscoring the value of even small therapeutic gains[20].

Integration of pharmacological and non-pharmacological interventions represents a promising avenue for maximizing treatment outcomes. Evidence suggests that combining cognitive training, physiotherapy, and pharmacotherapy may produce synergistic effects, addressing both motor and non-motor domains simultaneously. Such approaches align with the holistic management required in Parkinson's disease, where isolated interventions may not sufficiently address the full spectrum of symptoms. The development of personalized multimodal interventions, guided by biomarkers and patient profiles, may represent the future of Parkinson's therapeutic strategies.

5 CONCLUSION

In summary, the present meta-analysis demonstrated that interventions targeting Parkinson's disease exert modest but meaningful effects across cognitive, psychological, and motor domains. Improvements were observed in global cognition, quality of life, depressive symptoms, and gait-related outcomes, although considerable variability was noted among studies. The presence of moderate heterogeneity, small sample sizes, and potential publication bias highlight methodological challenges that limit the certainty of the evidence. Nevertheless, the findings underscore the clinical relevance of even incremental improvements, which can significantly impact autonomy, functional capacity, and overall well-being in individuals living with Parkinson's disease.

Future research should aim to strengthen the evidence base by conducting large-scale, multicenter trials with standardized outcome measures and robust methodological designs. Greater emphasis on integrating pharmacological, cognitive, and rehabilitative approaches may yield synergistic benefits, addressing both motor and non-motor symptoms simultaneously. By overcoming current limitations and embracing a multidimensional perspective, future interventions hold the potential to transform incremental statistical gains into meaningful improvements in the daily lives of patients with Parkinson's disease and their caregivers.

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