

A meta-analysis on the role of brain-derived neurotrophic factor in Parkinson's disease patients

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
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Abstract

Background. Brain-derived neurotrophic factor (BDNF) is essential for the development of dopaminergic neurons in the substantia nigra.

Objectives. To investigate the level of BDNF among Parkinson's disease (PD) subjects and the influence of depression on BDNF levels.

Materials and methods. A total of 1920 subjects were included in the analysis; of these, 1034 had PD and 886 were healthy controls. A thorough literature search up to May 2022 was conducted. The mean difference (MD) of BDNF levels and 95% confidence intervals (95% CIs) were calculated with random or fixed effects models.

Results. Compared to healthy controls, levels of BDNF were significantly lower in patients with PD (MD = –1.60, 95% CI (–2.49, –0.70), $p < 0.001$). Patients with PD and depression had significantly lower levels of BDNF (MD = –3.39, 95% CI (–5.55, –1.23), $p = 0.002$), as well as those with PD without depression (MD = –0.80, 95% CI (–1.56, –0.03), $p = 0.04$). However, there was no discernible change in BDNF levels (MD = –0.82, 95% CI (1.75, 0.10), $p = 0.08$) between the participants with PD and depression compared to the PD patients alone.

Conclusions. Compared with healthy controls, BDNF levels were significantly lower in the subjects with PD combined with depression, and PD without depression. However, there was no discernible difference in BDNF levels between subjects with PD with depression compared to those with PD without depression.

Key words: Parkinson's disease, BDNF, depression, dopaminergic neurons, substantia nigra

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Introduction

Parkinson's disease (PD) is a degenerative neurological illness. Recent research has suggested that inflammatory processes are involved in PD, which contradicts the monoamine depletion hypothesis (the traditional approach to depression).^{1,2} Given this, we might speak of an inflammatory hypothesis to explain the serotonergic, noradrenergic and dopaminergic dysfunctions that are characteristic of depression.³ In addition, low-quality diets are linked to the aforementioned negative physical, mental and cognitive health effects. Many different processes, including oxidative stress, plasticity, the microbiota–gut–brain axis, and most notably, inflammatory responses, are modulated by diet, which makes it a major risk factor for chronic diseases.⁴ The ventrolateral cell groups (i.e., A9 or nigrostriatal pathway) in the substantia nigra are the most susceptible to damage, whereas the dorsal and medial cell groups (i.e., A10 or mesolimbic pathway) are the most resilient ones.⁵ It has been hypothesized that the pacemaker-like features of dopaminergic neurons, which cause frequent intracellular calcium transients are the molecular basis for the selective vulnerability of these cells. There is some evidence that A9 neurons have impaired calcium buffering, which can contribute to cellular stress and, ultimately, the disruption of cellular homeostasis. The first affected neurons are those in the olfactory bulb (anterior olfactory nucleus) and dorsal motor nucleus of the vagus (medulla), then those in the pons (locus ceruleus), and finally those in the substantia nigra (dopaminergic neurons).⁵ In addition, recent evidence from studies on action control conducted on healthy individuals supported a causal role of dopamine in action control, and others addressed how PD is accompanied by impairments in covert cognitive processes.^{6,7} Still, other studies investigated underlying goal-directed motor functioning (e.g., action planning, conflict adaptation, motor inhibition)^{8,9} and how dopaminergic medication may modulate these action control components.

The symptoms of PD can be divided into motor symptoms and non-motor symptoms (NMSs). Motor-related symptoms include muscle rigidity, tremors and changes in speech. Sensory complaints, mental abnormalities, sleep disturbances, and autonomic dysfunction are common NMSs experienced by people with PD. Non-motor symptoms can occur in the earliest stages of the disease, even before motor impairment is clinically apparent. Depression is a notable NMS that is particularly prevalent in the early stages of the disease. It has a substantial influence on the quality of life and disability.¹⁰ The loss of dopamine-producing cells and the development of Lewy bodies in the brain commonly lead to NMSs in PD, which decreases the quality of life and presents significant hurdles in disease management. The modulation of autonomic nervous system responses is crucial for behavioral regulation.^{11,12} Synuclein aggregations and the denervation of the dopaminergic nigrostriatal system are thought to play major roles in the pathophysiology of PD.^{13,14} Anxiety disorders

respond well to antidepressants, such as selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors, because of their proposed shared neurobiological basis: alterations in prefrontal-limbic pathways^{15,16} and serotonergic projections arising from the raphe nuclei.¹⁷ However, current transcranial magnetic stimulation (TMS) has pinpointed 2 separate circuit targets for symptom clusters of depression (i.e., sorrow) and anxiety (i.e., irritability). Transcranial magnetic stimulation of the dorsomedial prefrontal cortex lowers depression symptoms and alleviates anxiety symptoms.¹⁸ Depression and other non-motor symptoms, such as reduced nonverbal communication and expressivity, may present themselves early in people with PD. Depression and other NMSs may be triggered by quinolinic acid. Research has shown that the neurotoxicity of the quinolinic acid contributes to the etiology of PD.¹⁹ The uncertainty associated with PD and coronavirus disease 2019 (COVID-19) magnified each other, and the cancellation of clinical appointments and restrictions on physical activity had substantial adverse effects on the well-being of this group of individuals.²⁰

Neuropeptides and neurohormones play an important role in cognitive, emotional, social, and arousal functions, and are biomarkers to help evaluate risk, diagnosis, disease course, and therapeutic outcomes of a disease.²¹ Prior research has demonstrated that the levels of A42 and tau protein in the serum of PD patients are highly variable and do not correlate with the mean scores on tests used to evaluate the severity of cognitive disorders. Therefore, A42 and tau protein in serum cannot be used as biomarkers of neurodegenerative changes in PD with cognitive impairment.²² On the other hand, patients with neurodegenerative diseases such as PD or psychiatric disorders such as depression have decreased levels of kynurenic acid.²³

In adult brains, the neurotrophin known as the brain-derived neurotrophic factor (BDNF) promotes dendrite morphogenesis, synaptic plasticity, arborization, and even neurogenesis.^{24,25} Brain-derived neurotrophic factor is essential for the development of dopaminergic neurons in the substantia nigra,²⁴ which are widely dispersed in cortical and subcortical regions. Brain-derived neurotrophic factor stimulates neurite growth and supports the survival of nigral dopaminergic neurons within the substantia nigra. Therefore, blocking the expression of BDNF results in the death of adult dopaminergic neurons.²⁶ Parkinson's disease patients have a lower expression of BDNF in the pars compacta of the substantia nigra,^{27–29} reducing trophic support for dopaminergic neurons. At the same time, the remaining dopaminergic neurons in the substantia nigra produce dwindling levels of BDNF.³⁰

Objectives

The aim of the current meta-analysis is to investigate the level of BDNF among PD subjects and the influence of comorbid depressive symptoms on BDNF levels.

Materials and methods

Study design

This meta-analysis consisted of clinical research studies that were a part of the epidemiological declaration³¹ and had a set study protocol. For data collection and analysis, a wide variety of databases were consulted, including PubMed, Ovid, Cochrane Library, Embase, and Google Scholar.

Data collection

Data were collected from clinical trials as well as human observational research papers that were written in any language. Studies were used regardless of sample size. Articles that did not give an association measurement, such as reviews, editorials or research letters, were not included.

Identification

According to the PICOS principle, a protocol of search strategies was developed³² and defined as follows: 1) patients (P): subjects diagnosed with PD; 2) intervention/exposure (I): BDNF; 3) comparison (C): BDNF in various subject groups; 4) outcome (O): PD compared to controls, PD with depression compared to controls, PD without depression compared to controls, and PD with depression compared to PD without depression; 5) study design (S): no restriction.³³

Using the keywords and associated phrases listed in Table 1 (search strategies for different databases),

Table 1. Search strategy for each database

Database	Search strategy
PubMed	#1 "Parkinson's disease" (MeSH terms) OR "brain-derived neurotrophic factor" (all fields) #2 "brain" (MeSH terms) OR "depression" (all fields) #3 #1 AND #2
Ovid	#1 "Parkinson's disease" (all fields) OR "brain-derived neurotrophic factor" (all fields) #2 "brain" (all fields) OR "depression" (all fields) #3 #1 AND #2
Google Scholar	#1 "Parkinson's disease" OR "brain-derived neurotrophic factor" #2 "brain" OR "depression" #3 #1 AND #2
Embase	#1 "Parkinson's disease"/exp OR "brain-derived neurotrophic factor" #2 "brain"/exp OR "depression" #3 #1 AND #2
Cochrane Library	#1 "Parkinson's disease": ti, ab, kw; "brain-derived neurotrophic factor": ti, ab, kw (word variations have been searched) #2 "brain": ti, ab, kw OR "depression": ti, ab, kw (word variations have been searched) #3 #1 AND #2

ti, ab, kw – terms in either title or abstract or keyword fields; exp – exploded indexing term.

we conducted a complete search of the PubMed, Ovid, Cochrane Library, Embase, and Google Scholar databases up to May 2022. The titles and abstracts of the collected publications that did not link the levels of BDNF to PD were excluded from the analysis. Two authors, ZC and HZ, acted as reviewers to identify suitable studies.

Eligibility and inclusion

The following criteria had to be met for an article to be considered for the inclusion in the meta-analysis:

1. The study was either prospective, observational, randomized, or retrospective;
2. The target intervention population consisted of individuals with PD;
3. The intervention regimen of the included studies was based on plasma samples of BDNF;
4. The study examined BDNF levels in several subject categories.

Exclusion criteria were:

1. Studies that failed to identify the plasma levels of BDNF in PD patients;
2. Studies that did not focus on the impact of comparison outcomes.

Figure 1 illustrates our selection process.

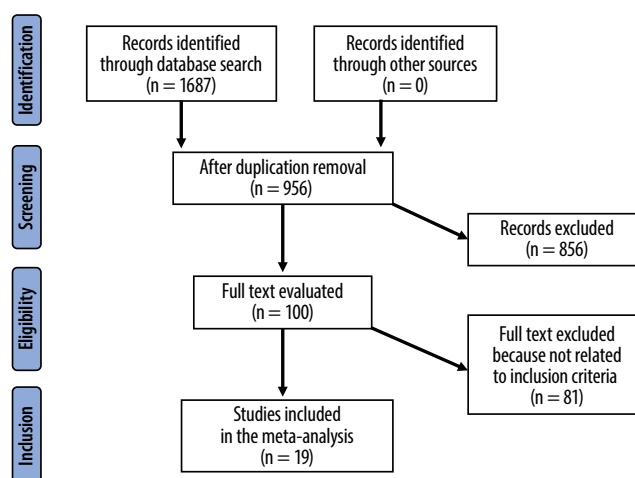


Fig. 1. Schematic diagram of the study procedure

Identification

Data extracted from the studies included: study- and subject-related features in a standard format; the surname of the first author; the period of the study, the year of publication; the country of the study; the design of the study; the population type recruited in the study; the total number of subjects; categories; qualitative and quantitative evaluation method; demographic data; clinical and treatment characteristics; information source; outcome evaluation; and statistical analysis.³⁴ A single study evaluating BDNF in PD patients yielded inconsistent results, so it was

isolated. Each study was assessed for bias, and the methodological quality of the chosen studies was evaluated by the 2 authors in a blinded fashion using the risk of bias tool from the Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0.³⁵

The Newcastle-Ottawa Scale (NOS), a quality and bias assessment tool developed specifically for observational research, was also used to evaluate the bias. The NOS examines the sample, the comparability of cases and controls, and the exposure in observational studies, with studies being assigned values between 0 and 9. Studies with a rating of 7–9 are of the highest quality and have the lowest risk of bias compared to those of lower ratings. Studies with a quality and bias risk rating from 4 to 6 are considered to have moderate quality. Each study was reviewed by the 2 authors.

Statistical analyses

The mean difference (MD) with a 95% confidence interval (95% CI) was calculated using a random or fixed effects model. All groups were analyzed using the random effects model due to high heterogeneity, whereas the use of fixed effects model required the confirmation of high similarity between the included study and a low heterogeneity (I^2) level. The I^2 index (determined using Reviewer Manager and expressed in forest plots), expressed as a numeric value ranging from 0 to 100, was calculated (as a percentage). Percentages ranging from 0% to 25%, 25% to 50%, 50% to 75%, and 75% to 100% indicated no, low, moderate, and high heterogeneity, respectively.³⁶ Fixed effects models were used when the heterogeneity was low. As previously stated, the subcategory analysis was performed by stratifying the initial evaluation into result categories. The publication bias was investigated quantitatively with the Begg's test (the publication bias was

considered present if $p < 0.05$).³⁷ A two-tailed test was used to calculate the p-value. The statistical analysis and graphs were created with the Reviewer Manager v. 5.3 software (The Cochrane Collaboration, Copenhagen, Denmark) and Jamovi software v. 2.3 (<https://www.jamovi.org/>) using a continuous model.

Results

Nineteen articles (out of 1765 reviewed) published between 2009 and 2022 satisfied the inclusion criteria and were included in the meta-analysis.^{38–61} Table 2 summarizes the findings of these investigations. Ultimately, more than 1000 people had PD and 886 were healthy controls. Number of subjects in the included studies ranged from 29 to 369.

PD patients compared to controls

Fifteen studies, which included 634 subjects, reported data stratified according to PD compared to the control group (Fig. 2). Parkinson's disease was associated with significantly lower levels of BDNF compared to controls (MD = -1.60, 95% CI [-2.49, -0.70], $p < 0.001$), with a heterogeneity of 99%.

PD patients with depression compared to controls

Five studies, which included 232 subjects, reported data stratified according to PD with depression (Fig. 3). Parkinson's disease with depression was associated with significantly lower levels of BDNF (MD = -3.39, 95% CI [-5.55, -1.23], $p = 0.002$), with a heterogeneity of 99%.

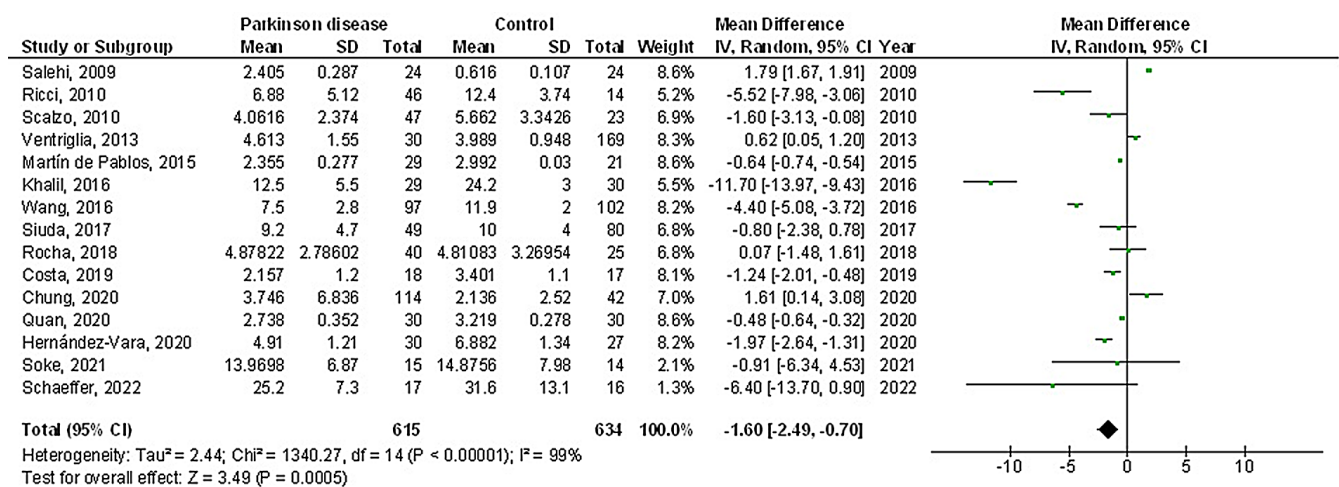


Fig. 2. Forest plot of brain-derived neurotrophic factor (BDNF) levels in Parkinson's disease (PD) patients compared with healthy controls

SD – standard deviation; 95% CI – 95% confidence interval; df – degrees of freedom.

Table 2. Characteristics of the selected studies included in the meta-analysis

Study and year	Country	Total	Parkinson's disease	Control	Age	Gender (M/F)	Disease duration	H&Y in PD	UPDRS part III in PD	Depression scale	NOS	Sampling time
Salehi and Mashayekhi, 2009 ³⁸	Iran	48	24	24	65.3 ± 7.2	–	–	–	–	–	3	–
Scalzo et al., 2010 ³⁹	Brazil	70	47	23	65.7 ± 8.8	32/38	7.6 ± 4.5	2	34.5 ± 23.3	–	7	morning
Ricci et al., 2010 ⁴⁰	Italy	60	46	14	63.7 ± 8.87	29/31	8.05 ± 2.41	2.7 ± 0.7	–	16 ≤ HAM-D	7	–
Pålhagen et al., 2010 ⁴¹	Sweden	25	11	14	65.3 ± 7.2	14/11	6.9 ± 2.4	1.8 ± 0.4	22.6 ± 10.1	–	7	–
Ventriglia et al., 2013 ⁴²	Italy	199	30	169	67.6 ± 8.4	114/91	–	16 ≤ HAM-D score	–	–	6	morning
Martín de Pablos et al., 2015 ⁴³	Spain	50	29	21	63.4 ± 0.9	27/23	–	2.16 ± 1.04	–	–	4	–
Khalil et al., 2016 ⁴⁴	Jordan	59	29	30	59.4 ± 13.1	35/24	4.4 ± 2.7	2.4 ± 0.7	49.2 ± 16.5	–	7	–
Wang et al., 2016 ⁴⁵	China	199	97	102	63.6 ± 9.32	112/87	4.23 ± 3.1	1.59 ± 0.43	–	–	8	morning
Siuda et al., 2017 ⁴⁶	Poland	129	49	80	63.3 ± 10.5	63/66	8.41 ± 5.8	2.7 ± 0.7	–	19 ≤ BDI score	8	morning
Wang et al., 2017 ⁴⁷	China	198	96	102	61.64 ± 8.87	113/85	3.76 ± 2.56	1.6 ± 0.7	–	53 ≤ SDS score	7	morning
Rocha et al., 2018 ⁴⁸	Brazil	65	40	25	68.71 ± 10.7	46/19	5.45 ± 4.13	2.44 ± 0.69	34.57 ± 18.43	–	8	evening
Costa et al., 2019 ⁴⁹	Brazil	35	18	17	68 (62.5–71.5)	22/13	4.5 (3–14.25)	2.16 ± 0.44	–	HAM-D r = –0.44	8	morning
Hernández-Vara et al., 2020 ⁵⁰	Spain	57	30	27	63.97 ± 9.59 (38–77)	36/21	1 (0.92–1.5)	1 (1–2)	16.5 (12.75–22.00)	mean HAM-D: 5.63, SD = 3.79	6	morning
Quan et al., 2020 ⁵¹	China	60	30	30	67.19 ± 8.12	32/28	4.13 ± 1.50	2.12 ± 0.75	–	–	5	morning
Chung et al., 2020 ⁵²	Taiwan	156	114	42	69.67 ± 8.44	91/65	2.70 ± 2.45	–	22.89 ± 10.00	–	8	–
Shi et al., 2021 ⁵³	China	79	53	26	65.04 ± 10.55	37/42	2 ± 2.6	1.33 ± 2.89	–	–	7	morning
Soke et al., 2021 ⁵⁴	Turkey	29	15	14	57.07 ± 8.18	19/10	8.13 ± 4.81	–	8.13 ± 4.81	–	6	morning
Huang et al., 2021 ⁵⁵	China	369	259	110	62.84 ± 8.73	199/170	4.96 ± 2.09	2.07 ± 1.02	33.78 ± 8.31	HAM-D: 17 (33.78 ± 8.31)	8	morning
Schaeffer, 2022 ⁵⁶	Germany	33	17	16	58 ± 10	17/16	5.6 ± 5.0	1.85 ± 0.42	25 ± 10	–	6	–
Total		1920	1034	886	–	–	–	–	–	–	–	–

PD – patients with Parkinson's disease; H&Y – Hoehn and Yahr's motor stage; UPDRS – Unified Parkinson's Disease Rating Scale; NOS – Newcastle-Ottawa Scale; HAM-D – Hamilton Depression Rating Scale; SD – standard deviation; BDI – Beck Depression Inventory; SDS – Self-Rating Depression Scale.

PD patients without depression compared to controls

Five studies, which included 259 subjects, reported data stratified according to PD without depression (Fig. 4). Parkinson's disease without depression was associated with significantly lower levels of BDNF (MD = –0.80, 95% CI (–1.56, –0.03), $p = 0.04$), with a heterogeneity of 94%.

PD patients with depression compared to PD patients without depression

Seven studies, which included 305 subjects, reported data stratified according to PD with depression compared to PD without depression (Fig. 5). Parkinson's disease patients with depression and PD patients without depression had no statistically significant difference in BDNF levels (MD = –0.82, 95% CI (–1.75, 0.10), $p = 0.08$) and a heterogeneity of 95%.

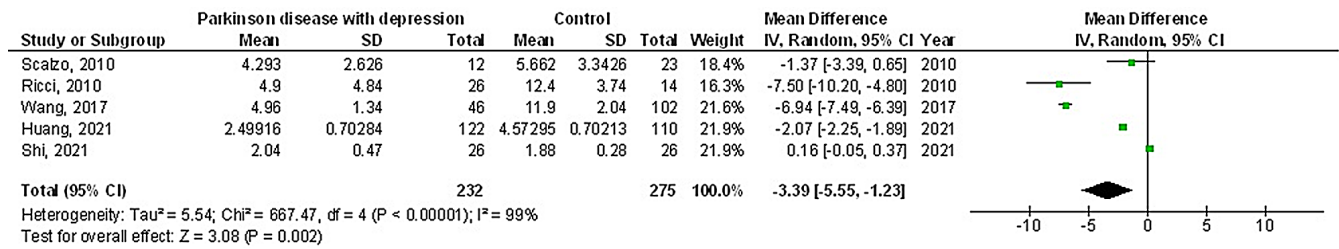


Fig. 3. Forest plot of brain-derived neurotrophic factor (BDNF) levels in Parkinson's disease (PD) patients with depression compared with healthy controls

SD – standard deviation; 95% CI – 95% confidence interval; df – degrees of freedom.

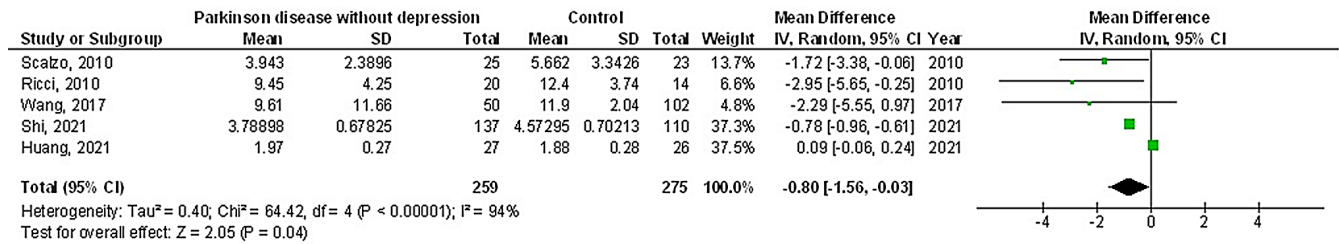


Fig. 4. Forest plot of brain-derived neurotrophic factor (BDNF) levels in Parkinson's disease (PD) patients without depression compared with healthy controls

SD – standard deviation; 95% CI – 95% confidence interval; df – degrees of freedom.

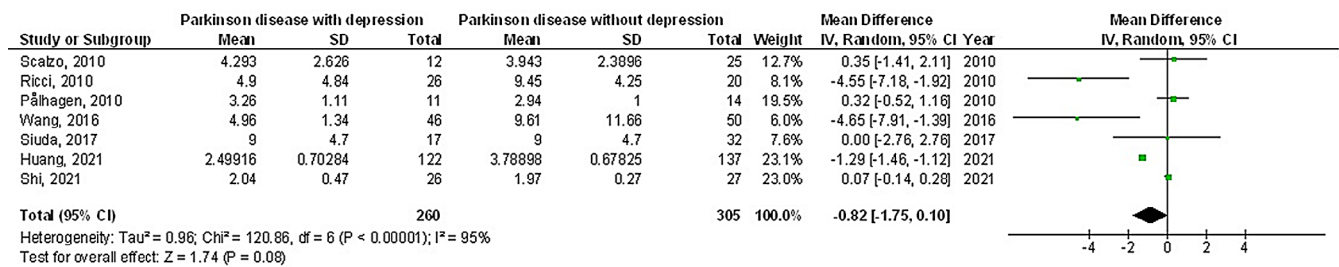


Fig. 5. Forest plot of brain-derived neurotrophic factor (BDNF) levels in Parkinson's disease (PD) patients with depression compared with PD patients without depression

SD – standard deviation; 95% CI – 95% confidence interval; df – degrees of freedom.

Analysis of other potential covariates/factors

The analysis of studies with defined sampling time (morning) similarly found significantly lower BDNF levels in PD patients compared with controls (Fig. 6) ($MD = -1.24$, 95% CI $(-2.30, -0.17)$, $p = 0.002$), with a heterogeneity of 95%.

It was not possible to assess the impact of individual characteristics such as gender and ethnicity on the comparison results as data on these variables were not collected. In addition, the publication bias was found to not be statistically different for PD subjects compared with controls ($p = 0.62$). Similarly, the analysis of studies with defined sampling time (i.e., morning) failed to identify statistically significant bias ($p = 0.61$). In addition, the results of the Begg's test for PD patients with depression, PD patients without depression, and PD patients with depression compared to PD patients without depression were $p = 0.82$, $p = 0.99$ and $p = 0.77$, respectively, indicating a lack of publication bias.

The risk of bias assessment was evaluated with NOS (Table 2). Twelve studies were found to have a score between 7 and 9 points, which reflects a low risk of bias. Six studies showed a moderate risk of bias, with scores ranging from 4 to 6 points. Only one study scored 3 points, reflecting a high risk of bias resulting from low quality methodology.

Discussion

A total of 1920 individuals, 1034 of whom were diagnosed with PD and 886 of whom were healthy controls, were included in the current meta-analysis.^{38–56} Parkinson's disease patients, both with and without depression, had lower levels of BDNF than healthy controls. Parkinson's disease patients with depression did not have lower levels of BDNF than PD patients without depression. It is important to be cautious when interpreting the results comparing PD patients with and without depression, as these data come from relatively small sample sizes (13 out of 19) and a limited number of studies (<100).

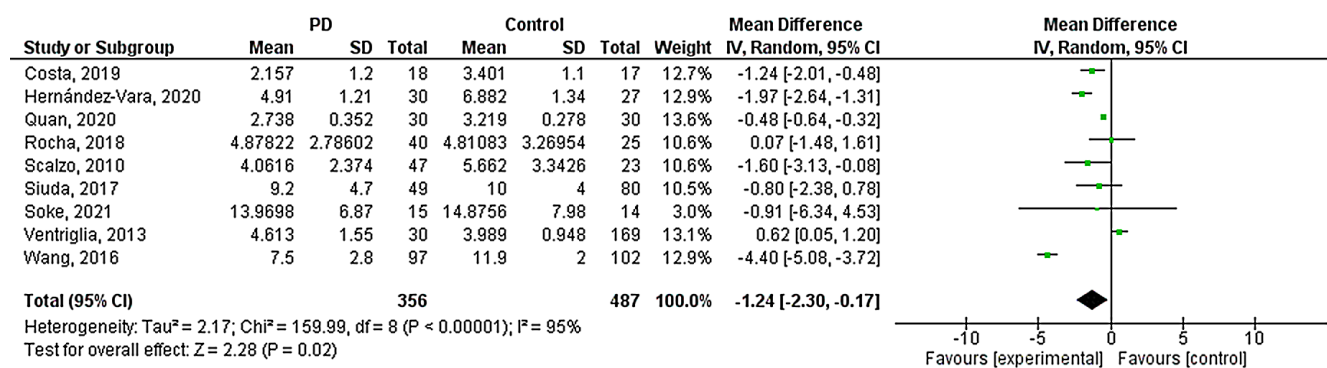


Fig. 6. Forest plot of the morning samples BDNF levels in Parkinson's disease (PD) patients compared with healthy controls

SD – standard deviation; 95% CI – 95% confidence interval; df – degrees of freedom.

It is critical to determine if circulating BDNF levels may be used as a surrogate for BDNF expression in the central nervous system and neurons, given the role of this factor in PD. The association between blood levels of BDNF and hippocampal BDNF is highest in mice ($R^2 = 0.81$).³⁷ However, whether this association applies to people remains debated. We know that BDNF is produced by glial cells, like astrocytes and microglia, as well as extra-central nervous system cell types, such as endothelium cells and peripheral blood mononuclear cells.⁵⁷ Circulating BDNF appears to originate mainly in the central nervous system, given that it may cross the blood–brain barrier and that endothelial and mononuclear cells express extremely low quantities of it.⁵⁸ Therefore, studying the levels of BDNF in the serum of PD patients as a surrogate for its expression in the central nervous system is now possible. Due to their inherent ability to retain proteins, platelets are the principal source of BDNF in the blood.

Patients with PD had a lower BDNF expression and more dopamine in their striatum, according to the dopamine transporter scans.⁵⁹ The expression of BDNF can be affected by a wide range of factors, including the 196 A/G single nucleotide polymorphism. This 196 A/G polymorphism, which results in a Val66Met substitution, was initially discovered by Momose et al. as a possible homozygote mutation linked to an increased risk of PD.⁶⁰ This mutation was confirmed to consistently downregulate the expression of BDNF⁶¹ and it was the subject of future research to determine its link to PD risk.^{62,63}

Reduced expression of BDNF, irrespective of nigral dopaminergic expression, alters dopaminergic outflow to the striatum and mimics the motor symptoms of PD in mice.⁶⁴ In addition, synuclein, the primary component of Lewy body fibrils in people with Parkinson's disease, inhibits BDNF's neurotrophic action in the substantia nigra by first downregulating BDNF expression⁶⁵ and then, by competitively inhibiting BDNF signaling at the receptor level.⁶⁶ Exogenous BDNF lowers the loss of dopaminergic neurons in PD models employing 6-hydroxydopamine hydrobromide and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine as well as neuronal cultures, according to the majority

of research.^{67–70} Extensive data are suggesting the protective effect of BDNF on the dopaminergic substantia nigra population in PD and its downregulation in individuals with PD.⁷¹ On the flip side, the development of PD has been associated with increasing levels of BDNF in blood and cerebrospinal fluid.^{38,39} Also, an important role of physical training and exercise had been recognized, since acute exercise can boost blood levels of BDNF and then improve cognitive function shortly after exercise.⁷² Memory enhancement is more noticeable and strongest shortly following training matched to other cognitive areas. In addition, it was shown that both dopamine replacement therapy and anti-parkinsonism medicines upregulate BDNF to a small degree.⁷³ As noted, these findings have sparked tremendous interest in the potential for exercise-induced alterations in BDNF to arrest neurodegeneration in Parkinson's disease.⁷⁴ Several studies reveal reduced serum levels of BDNF in PD subjects.^{38–56,75–79} The Val66Met polymorphisms were not identified as predictors of PD risk except for a slight increase in risk linked with the AA+AG genotype.⁸⁰ Even though some research suggests that the Val66Met variant can alter the expression of BDNF in PD, a growing body of evidence suggests that acute exercise can increase the serum levels of BDNF and alleviate the symptoms of Parkinson's disease.⁸¹ For many, the cognitive benefits of exercise can be attributed to an increase in serum BDNF.^{82,83} Parikh et al. found that the BDNF regulates the striatal dopamine levels in mice, specifically affecting the balance of glutamate and the ability to adapt cognitively and executively.⁸⁴

The benefits of exercise on neuroplasticity and protection from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity were lost in animals with a complete deletion or insufficient expression of BDNF.^{85,86} It is possible that the alleviation of depression and motor symptoms due to continuous exercise may also be due to an increase in BDNF protein in the striatum of mice.⁸⁷

One study found a paradoxical increase in serum BDNF with increased depression duration and decreased motor capacity, whereas another study found no difference in serum BDNF when considering patients' physical capacity.⁸⁸ Brain-derived neurotrophic factor levels are higher in patients with

PD who have had long-term dopamine replacement therapy, according to a study by Scalzo et al.³⁹ This suggests that the increased expression of BDNF in advanced PD is not only due to medication-induced release of the pool of BDNF.

It is hoped that nonpharmaceutical interventions, such as exercise, can reduce the symptoms of PD. Hirsch et al. found that regulated exercise could improve blood BDNF levels and decrease Rating Scale III (RS-III) scores in individuals with PD.⁸⁸ These data support the efficacy of non-pharmacological methods to induce BDNF in PD. Serum BDNF rises incrementally in the early stages of PD, most likely due to a compensatory increase in the production of BDNF by the surviving dopaminergic neurons. According to Hirsch et al., exercising a few times a week can help PD patients improve their motor scores and increase their blood levels of BDNF.⁸⁸ Despite the findings stating that physical training and BDNF levels increase as PD symptoms decrease, it is unclear if this is mediated by BDNF. The findings of Scalzo et al. contradict the results of this study; however, the authors do not acknowledge or explain this discrepancy.³⁹ Furthermore, it is important to point out that the aforementioned research supports the idea that exercise can improve depressive symptoms in PD patients by promoting BDNF expression and signaling. The effects of medications must be considered when analyzing data from PD patients. Even though numerous studies have qualitatively documented the use of common medications in study groups, many of these studies have not controlled for the effect of dosage or frequency of use. For example, it is thought that increased levels of BDNF are a contributing component in treating depression with serotonin reuptake inhibitors.⁸⁹ Selegiline, an inhibitor of monoamine oxidase, an agonist of the N-methyl-D-aspartate receptor, and metformin, a tricyclic antidepressant, have been shown to have neuroprotective characteristics.^{90–93} Many studies offered only a dichotomous assessment of depression in PD patients and did not use psychological tests to establish a quantitative score.

The results of this meta-analysis indicate that BDNF levels are decreased in patients with PD and perhaps in PD patients with depression.^{89–98} For these potential connections to be demonstrated and compared with other subjects in terms of the examined consequences, further research is needed. Larger and more uniform samples are required for this type of study.^{99–103} A previous meta-analysis similarly showed that BDNF had favorable advantages in treating PD and reducing PD with depression.^{104–110} To determine whether age and ethnicity are connected to the outcomes of our study, well-conducted randomized controlled trials are needed.

Limitations

While this study may have been skewed by excluding so many trials from our meta-analysis, these studies failed to meet our rigorous inclusion criteria. Of the 19 papers

analyzed, 13 had sample sizes of less than 100 people. In addition, some of the included studies did not mention the sampling time of BDNF. There is no way to tell if the results are due to gender or ethnicity, as data on these variables were not included in our study. Patients with PD were evaluated for BDNF using data from previous research, which may have been skewed due to a lack of relevant information. Uncollected variables such as the respondents' age, gender and nutritional status may have also skewed the results.

Conclusions

Parkinson's disease combined with depression, and PD patients without depression had significantly lower levels of BDNF than healthy controls. Parkinson's disease patients with depression did not have lower levels of BDNF than PD patients without depression. In individuals with PD, acute exercise and physical training are consistently associated with increased serum BDNF and, by extension, better motor function and lower Unified Parkinson Disease Rating Scale (UPDRS) stage III scores. Our research suggests that depression, a major comorbidity in PD, and PD both have the capacity to downregulate the expression of BDNF. In addition, possible drug effects, such as antidepressants and dopamine replacement treatment, are reflected here as well.

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