Blood Levels of Brain-Derived Neurotrophic Factor (BDNF) in People with Multiple Sclerosis (MS): A Systematic Review and Meta-Analysis

Parnian Shobeiri
Tehran University of Medical Sciences (TUMS), Children's Medical Center Hospital
Helia Ashourizadeh
Shahid Beheshti University of Medical Sciences
Boshra Akbarzadeh Pasha
Tehran University of Medical Sciences
Maryam Haghshomar
Tehran University of Medical Sciences (TUMS), Children's Medical Center Hospital
Tahmineh Jouzdani
Tehran University of Medical Sciences
Antônio L. Teixeira
The University of Texas Health Science Center at Houston
Nima Rezaei (rezaei_nima@yahoo.com)
Universal Scientific Education and Research Network (USERN)

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Abstract

Background: Multiple sclerosis is an autoimmune demyelinating disease marked by the involvement of multiple pathophysiological pathways, including BDNF. BDNF (brain-derived neurotrophic factor) is one of the main neurotrophic factors in the adult brain. The amount of BDNF in the blood can be utilized as a surrogate for the central expression of this marker. Given contradicting reports, we set out to answer the question, “How do blood levels of BDNF differ in people with multiple sclerosis (PwMS) compared to controls?”

Methods: We performed a thorough search in MEDLINE, EMBASE, Web of Science, and the Cochrane Library databases, resulting in 13 eligible investigations. Eleven studies compared BDNF in serum of PwMS versus healthy controls (HC), and two studies provided BDNF levels in the plasma of PwMs. R version 4.0.4 was used for meta-analysis and visualizations. Mean difference (MD) was used for the measurement of effect size.

Results: The final analysis included thirteen studies with 689 patients with MS and 583 controls. The preliminary results indicated that MS patients had statistically significant lower levels of BDNF than controls: SMD -5.1992 (95% CI [-8.4488; -1.9496], *p-value* < 0.0001. Additionally, subgroup analysis revealed a statistically significant difference in serum and plasma levels (*p-value*=0.01). Performing univariate meta-regression, disease duration and the proportion of males had, respectively, a significant negative and positive correlation with BDNF levels.

Conclusion: Circulating levels of BDNF are decreased in MS. Future studies should investigate the role of BDNF as a biomarker of disease severity and/or progression for a personalized approach to MS.

1. Background

Multiple sclerosis (MS) is a central nervous system (CNS) inflammatory and demyelinating disease that primarily affects people between the ages of 20 and 40. It is a chronic condition marked by inflammation, demyelination, and axonal loss, and it often results in considerable degrees of disability (1–3). Axonal damage is a crucial factor in determining the severity of long-term neurological (motor, sensory and cognitive) impairments in people with multiple sclerosis (PwMS). Cognitive impairment is well recognized as a key characteristic of MS, affecting up to 70% of patients and having a significant impact on daily activities (4). Information processing speed, attention, working and episodic memory, executive skills, and visuospatial abilities are the most typically disrupted cognitive domains in adult patients. Language and general intelligence are relatively stable unaffected (4, 5). Cognitive impairment in MS has been associated with a variety of risk variables (6), with the function of brain-derived neurotrophic factor (BDNF) polymorphisms garnering increasing attention among genetic factors. Remarkably, BDNF has been associated with not only cognitive, but also motor/sensory performance in MS.

BDNF is a member of the neurotrophin family, including nerve growth factor (NGF) and neurotrophins 3 and 4 (NT3 and NT4). BDNF is secreted by microglial and astroglial cells, in autocrine loops, and across long distances through neural circuits (7–11). In both healthy people and patients with neurological diseases, BDFN is crucial for the development and survival of neurons and oligodendroglia (12). Synaptic plasticity, synaptic growth, dendritic branching, and excitatory/inhibitory neurotransmitter profile modification are all

assisted by BDNF (13). Following a variety of clinical assaults, human immune cells are also capable of generating BDNF, a molecule that protects neurons and axons from damage (14).

According to a substantial body of neuropathological and experimental data, BDNF may have essential roles in MS-related neuroinflammation, neuroprotection and repair (15). However, the results regarding peripheral levels of BDNF are conflicting. The current systematic review and meta-analysis aim to integrate the existing evidence on the blood levels of BDNF in PwMS.

2. Material And Methods

Study protocol, including objectives of the review, PICO Question, inclusion and exclusion criteria – for participants, types of studies, intervention/ exposure and outcome, search strategy, data collection, and methods for data synthesis/analysis, was developed according to The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guideline (16).

2.1. Search Strategy

The preliminary qualifying criteria comprised original publications assessing BDNF concentrations in serum and plasma in PwMS patients, with no language, publication date, or publication status restrictions (e.g., online first or published). Accordingly, a search for relevant articles was conducted using the keywords BDNF, Brain-Derived Neurotrophic Factor, Multiple Sclerosis, and MS. We did not consider CSF, serum, or plasma in our search terms, postulating that studies measuring BDNF in other source(s) could guide unpublished data on BDNF concentrations in CSF or serum. The search was carried out in MEDLINE, EMBASE, Web of Science, and Cochrane Library, and it was updated on September 11th, 2021. We also reviewed reference listings and contacted the corresponding authors of all the articles included in the current systematic review and meta-analysis to find additional investigations.

2.2. Inclusion and Exclusion Criteria

Included studies all met the following criteria: (1) original articles studying human subjects, (2) enrolling individuals with MS, (3) diagnosis of MS established by a neurologist according to international criteria, (4) measuring serum, plasma, or CSF levels of BDNF in MS patients, (5) use of immunoassay or enzyme-linked immunosorbent assay (ELISA) to measure BDNF levels, and (7) reporting sufficient data including the total number of participants and mean and standard deviation (SD) of BDNF measures in both cases and controls.

Exclusion criteria were as follows: (1) review articles, books, book chapters, (2) studying on animal subjects, (3) pediatric MS, (4) studies evaluating tissue expression of BDNF, (5) in-vitro studies or studies on cell cultures, (6) and studies on genetic polymorphisms of BDNF but not levels of BDNF.

2.3. Data Collection and Data Items

Two investigators (H.A and B.A.P) reviewed eligible studies independently. Five studies were selected to produce pilot data extraction sheets and define descriptive factors of study groups to be included in the final data extraction sheets. Finally, the following information was retrieved from each included article: author, publication date, case and control definitions, male to female ratio, age, MS type (RRMS, PPMS, SPMS),

disease severity, and sample size in each group. Any discrepancies in data extraction were handled by discussion or referring the case to a third investigator (P.S).

2.4. Quality Assessment and Risk of Bias of Individual Studies and Across Studies

The quality of included studies was assessed using the standardized critical appraisal instruments from the Joanna Briggs Institute (JBI, http://joannabriggs.org/research/critical-appraisal-tools.html). This is a critical evaluation checklist to see whether a study's design, conduct, and analysis were influenced by bias. Reviewers rated each study's study design based on clarity of inclusion criteria; setting; exposure; standard criteria or adequate matching for individual groups; identification and strategies to overcome confounding factors; validity and reliability of outcome measurement; and adequacy statistical analyses for each. Total positive ratings for each investigation are calculated by scoring each question as Yes (+), Unclear/Not Mentioned (-) or No (-). Studies having a total of fewer than five favorable evaluations were omitted from the synthesis because of their low quality. Two reviewers (H.A and B.A.P) independently examined all papers for methodological validity, and any disagreements were addressed through discussion or with the assistance of a third reviewer (P.S).

2.5. Statistical Analysis

The standardized mean difference (SMD) was used for the measurement of effect. Fixed effects and random effects were interchangeably used as the analysis model. If the values reported in the manuscript were given as a median and interquartile range (IQR) or median and range, and we were not able to retrieve the mean ± standard deviation (SD) from the authors, we used statistical methods suggested by Luo et al. (17) and Wan et al. (18) to convert these values. Heterogeneity was determined using Q statistic tests and the I^2 index. According to the Cochrane guidelines, the $I^2 < 40\%$ would mean that the inconsistency across studies is not important. In this case, we planned to use the fixed effects model. If the I^2 estimates fluctuated more than 40%, we intended to use the random effects procedure as the analysis model. To further assess the causes of heterogeneity, we conducted a sensitivity analysis to identify influential cases for meta-analyses with significant heterogeneity, including ten or more studies. Each time we omitted one study and recalculated the effect size (Leave-One-Out Analyses).

The degree of funnel plot asymmetry and Egger's test (19) detect publication bias. In fact, funnel plots are commonly employed to identify publication bias visually. On the other hand, the Egger's test is an objective metric that allows users to corroborate visual clues offered by funnel plots. When there was evidence of publication bias, we adjusted the effect sizes using the trim-and-fill method (20).

All computations and visualizations were carried out using R version 4.0.4 (R Core Team [2020]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). We used following packages: "meta" (version 4.17-0), "metafor" (version 2.4-0), "dmetar" (version 0.0–9), and "tidyverse" (version 1.3.0). All plots were designed using R. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1. Study Selection

The study selection details are depicted in Fig. 1. The database search returned a total of 2,622 entries. Based on the title/abstract, a preliminary screening eliminated 1,875 papers. The complete text of the remaining 214 publications was retrieved, and each item was carefully reviewed and analyzed against the inclusion criteria using the abstract and, where required, the full text. Twenty-six papers were chosen for comprehensive analysis, and their respective authors were contacted and asked to provide study group characteristics and BDNF levels. Additionally, we contacted the corresponding authors of six studies examining BDNF levels, anticipating they may contain unpublished data on serum/plasma BDNF levels. We omitted 13 articles due to the reasons depicted in Fig. 1. Finally, a comprehensive evaluation of BDNF concentrations in MS included 13 studies comprising 689 patients with multiple sclerosis (MS) and 583 healthy controls (HC).

3.2. Study Characteristics

As summarized in Table 1, thirteen studies published from 2003 to 2021 provided original data on BDNF levels in MS patients and HC (21–33). Ten studies compared BDNF levels in the serum of multiple sclerosis (MS) patients (n = 515) to those in healthy controls (HC) (n = 437) (22, 23, 25–30, 32, 33), while three studies provided additional information on plasma BDNF levels in MS patients (n = 174) and HCs (n = 146) (21, 24, 31). The mean age varied from 31.2 ± 7.99 to 54.07 ± 8.46 years among MS patients and from 29.00 ± 7.80 to 50.71 ± 12.08 years among HC. The EDSS score of the included participants ranged from 1.26 ± 0.73 to 3.22 ± 1.59, reported by all but two studies (23, 31). The type of MS people included in each study is depicted in Table 1. All but three studies (21, 31, 33), contained information on the disease duration ranging from 3 to 31 years. Moreover, all but one (21) of the included studies assessed the BDNF levels using enzyme-linked immunosorbent assay (ELISA) as the analytical procedure.

3.3. Quality Assessment

Table 2 summarizes the results of the quality assessment of the included studies based on the JBI critical appraisal tool.

3.4. Serum and Plasma BDNF Levels in Multiple Sclerosis

Meta-analysis of ten between-group comparisons revealed that serum BDNF levels are significantly (*p-value*< 0.0001) decreased in MS patients (n = 338) in relation to HC (n = 443) with a standardized mean difference (SMD) of -0.9680 pg/mL (95% CI [-1.6092; -0.3268], I^2 = 93.1%, Fig. 2A). Regarding the plasma BDNF levels, meta-analysis of three between-group comparisons showed that the pooled SMD was − 5.1992 (95% CI [-8.4488; -1.9496], *p-value*< 0.0001, I^2 = 98.7%, Fig. 2A) for BDNF levels assessed in plasma. Overall, subgroup comparisons revealed a substantial difference in BDNF concentrations across individuals' serum and plasma samples (*p-value* = 0.0123). Table 3 summarizes the results of the subgroup meta-analysis.

Table 3
Results of meta-analysis and meta-regression of BDNF levels in patients with Multiple Sclerosis.

Comparison	No. of comparisons	No. of subjects		Meta-analysis			Heterogeneity		
		MS	HC	Effect size	95% CI	p-value	I^2%	Q	p-value
Serum vs. Plasma	13	689	583	-1.5738	-2.2637; -0.8839	**0.0123**	95.9%	289.34	**< 0.0001**
Moderator	**No. of comparisons**	**No. of subjects**		**Meta-regression**			**R^2 Analog (proportion of variance explained)**		
		MS	**HC**	**Slope**	**95% CI**	p-value			
Sample Size	13	689	583	0.0049	-0.0080; 0.0177	0.4591	0.00%		
Age (mean, years)	13	689	583	0.1092	-0.0210; 0.2394	0.1001	0.00%		
EDSS score	11	630	530	-0.8327	-1.8139; 0.1484	0.0962	0.00%		
Disease duration	9	508	434	-0.3895	-0.5619; -0.2170	**< 0.0001**	**9.34%**		
Sex (male, %)	13	689	583	0.0740	0.0009; 0.1471	**0.0472**	0.00%		

3.5. Publication Bias

The funnel plot was asymmetric (Fig. 3A). Moreover, Egger's tests revealed significant evidence of publication bias among the included studies (Egger's test, *p-value* = 0.04).

3.6. Trim and Fill analysis (metatrim)

The *p-value* for Egger's regression test was 0.04, confirming the existence of publication bias. We conducted a trim and fill study to examine the effect of publication bias, as we thought that the funnel plot asymmetry was only due to publication bias, which may not be relevant to this type of data. Utilizing the 'trimfill' function, one unpublished investigation was discovered according to the trim and fill analysis. Considering this study in calculating the SMD of BDNF levels yielded an estimated SMD of -0.9247 (95% CI [-1.7514; -0.0980], I^2 = 97.1%, Fig. 3B), when adjusted for the publication bias.

3.7. Sensitivity Analysis and Outliers' Identification

Each study's effect on the overall estimate was assessed through systematic omission of studies and comparison of the pooled estimate from the remaining 12 studies. MS patients had lower peripheral BDNF levels than controls, implying that removing any single study would have little effect on the overall results (Fig. 4).

Using the ‘find.outliers’ command in R software, eight studies (21, 26–31, 33) were identified as outliers; accordingly, we repeated the meta-analysis of five remained studies and obtained the following results: SMD − 0.6619 (95% CI [-0.9391; -0.3848], *p-value* < 0.0001, Fig. 2B), which indicates statistically significant lower BDNF levels in MS participants compared to controls.

3.8. Meta-regression Analysis

We utilized meta-regression analysis to determine the determinants of study heterogeneity and the effect of modifiers. Univariable meta-regression models showed no relationship between the sample size, mean age, and EDSS score and BDNF levels. Interestingly, disease duration and the proportion of males had a significant negative and positive association to BDNF levels, respectively. Additionally, disease duration could explain 9.34% of the existing heterogeneity. (Table 3, Fig. 5)

4. Discussion

BDNF is involved in the pathogenesis of a broad spectrum of diseases, specifically neurologic and psychiatric conditions. BDNF and its high-affinity receptor (TrkB) are widely expressed in the CNS and peripheral tissues, including liver, muscle cells (smooth and skeletal) (34), white blood cells (lymphocytes and monocytes) (35), endothelial cells (36), reproductive tract (37) and adipose tissue (38). BDNF is a key factor in neuronal growth, development, differentiation, synapse formation, and synaptic plasticity, ultimately in ‘optimal’ brain health (39–41). There is also evidence of the role of BDNF in bioenergy homeostasis, thermoregulation, and energy expenditure (42, 43).

Numerous studies have investigated peripheral levels of BDNF in neurologic diseases. In a systematic review and meta-analysis of studies involving patients with epilepsy, BDNF level was not significantly different from healthy controls. However, partial epilepsy patients had lower levels of BDNF than other types of epilepsy in the subgroup analysis (44). A recent systematic review and meta-analysis showed a significant decrease in plasma BDNF levels in PD patients compared to healthy controls (45). Nevertheless, increased plasma levels of BDNF in PD have also been reported and hypothesized to represent a CNS protective response to the neuronal loss resulting from PD pathogenesis (46, 47). In stroke, serum BDNF levels correlated with stroke severity in the acute phase (48), and later with rehabilitation treatment (49, 50). Altogether, these studies suggest the involvement of BDNF in the pathophysiology of CNS pathological conditions and the potential role of this molecule as a biomarker of disease severity and/or staging.

To investigate peripheral/blood levels of BDNF in PwMS, we did a systematic review of literature and meta-analysis of clinical studies investigating BDNF in PwMS compared with healthy controls. Our results demonstrated a statistically significant difference in serum and/or plasma BDNF concentration in PwMS and healthy non-MS individuals.

MS has complex pathophysiology involving inflammation-mediated demyelination and axonal loss. An immune-mediated inflammation against myelin sheath seems to be the main pathologic event leading to MS spectrum diseases (51). A growing body of evidence also implicates a role for BDNF in MS pathogenesis (52).

There is increased BDNF expression in active inflammatory MS lesions (53, 54), and increased peripheral levels of BDNF during the acute inflammatory MS relapses (24, 55, 56). Moreover, BDNF production by peripheral blood mononuclear cells was significantly increased during relapse and in the recovery phase compared with values detected in the stable phase of the disease (57). These findings suggest a neuroprotective role for BDNF that would promote axonal/neuronal regeneration, especially during MS relapses. The results are conflicting in the remission phase, i.e., outside the MS relapses, which we specifically investigated in our study. In some studies, the BDNF blood level was lower in patients than in healthy controls (22, 33, 58–63), whereas in other studies, no significant difference was observed (57, 64, 65). Studies investigating the correlation between BDNF and disease severity, as assessed by EDSS, also have conflicting results. (24, 56, 58)

Our results demonstrated a significant decreased serum and/or plasma BDNF concentration in PwMS compared with healthy non-MS individuals. This finding might reflect neuronal damage with subsequent decrease in BDNF production and/or BDNF consumption through the neuro-regenerative process (60, 63).

BDNF is produced by several neuronal cells in the CNS, including glial cells such as astrocytes and microglia (66) and non-neuronal non-glial cells in the peripheral tissues (36, 37, 67, 68). BDNF can also be transported through the blood-brain barrier in a bidirectional manner between the peripheral circulation and CNS (69). In the blood, around 90% of circulating BDNF is stored in the platelets (70), while in the CNS, BDNF is highly expressed by the hippocampus, amygdala, and cortex neurons (71, 72). As long as BDNF produced in the periphery can be transported through the blood-brain barrier, increased peripheral levels of BDNF could result in an increased entry of this neurotrophin into the CNS, contributing to remyelination and axonal regeneration (69).

Several factors can influence BDNF levels. Physical exercise, for instance, has been investigated as a relevant factor stimulating BDNF synthesis which is implicated in exercise-induced neurogenesis in MS and other neurologic disorders (73–76). Increased BDNF synthesis results in enhanced cognitive function, motor symptoms, and alleviation of psychiatric symptoms (77–79). Physical exercise in MS patients reduces episodes of relapses and disease progression, reduces fatigue, and improves the quality of life(80–83). Based on systematic literature reviews and meta-analyses, regardless of type and duration, physical exercise can increase BDNF circulating levels in MS and PD but not significantly in mild cognitive impairment (84, 85). Exercise-induced increase in BDNF levels was observed in 4 out of 8 studies within PwMS (86). Medication is another factor that can influence BDNF. Glatiramer acetate (GA) is a widely used medication among MS patients. One of the proposed mechanisms of action of GA is the downregulation of proinflammatory cytokines associated with increased production of BDNF (87). GA-treated MS patients showed a progressive increase in BDNF levels from baseline to month three (57). Other drugs which alter BDNF levels include antidepressants (88), Selegiline (89), Metformin (90), Risperidone, and Clozapine (91, 92).

High heterogeneity between studies is a valid concern in interpreting the meta-analyses results. Due to the high heterogeneity of included studies, we performed a meta-regression analysis to further investigate the source of methodologically and/or clinically diversity. Our meta-regression showed that the study heterogeneity could be explained by disease duration. Another explanation for high heterogeneity among included studies is the measurement bias. A diverse range of technical issues (e.g., sampling, ELISA kits) has

complicated BDNF measurement in human samples, resulting in poor reliability of available tests. This detection bias was well studied in a study investigating six commercially available ELISA kits for BDNF level measurement, in which only two of six assays showed reliable results (93). In addition, the limited number of studies with small sample sizes could further increase the heterogeneity of the analysis. Lack of enough data regarding the MS type of included patients and/or diverse MS types included in the studies could result in clinical diversity and bias. Although none of the patients in the included studies was at relapse or acute inflammatory state, there is still the possibility of bias in misclassifying the patients as remission or stable phase. This could falsely increase the BDNF level in the patient group. Disease duration and severity were among the data not comprehensively addressed in some studies, which could further increase the risk of bias. Other comorbid conditions, such as depression, can affect the BDNF level(94, 95). As discussed earlier, numerous drugs alter the BDNF level and expression in both MS patients and the control individuals. In most studies, the use and dosage of these medications were not properly controlled. Information about physical exercise is also missing.

5. Conclusion

Results of this systematic review of literature and meta-analysis showed that circulating BDNF level in MS patients is statistically decreased compared to healthy non-MS individuals. Future studies should investigate the role of BDNF as a biomarker of disease severity and/or progression for a personalized approach in MS.

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Tables

Tables 1 and 2 are available in the Supplementary Files section.

Figures

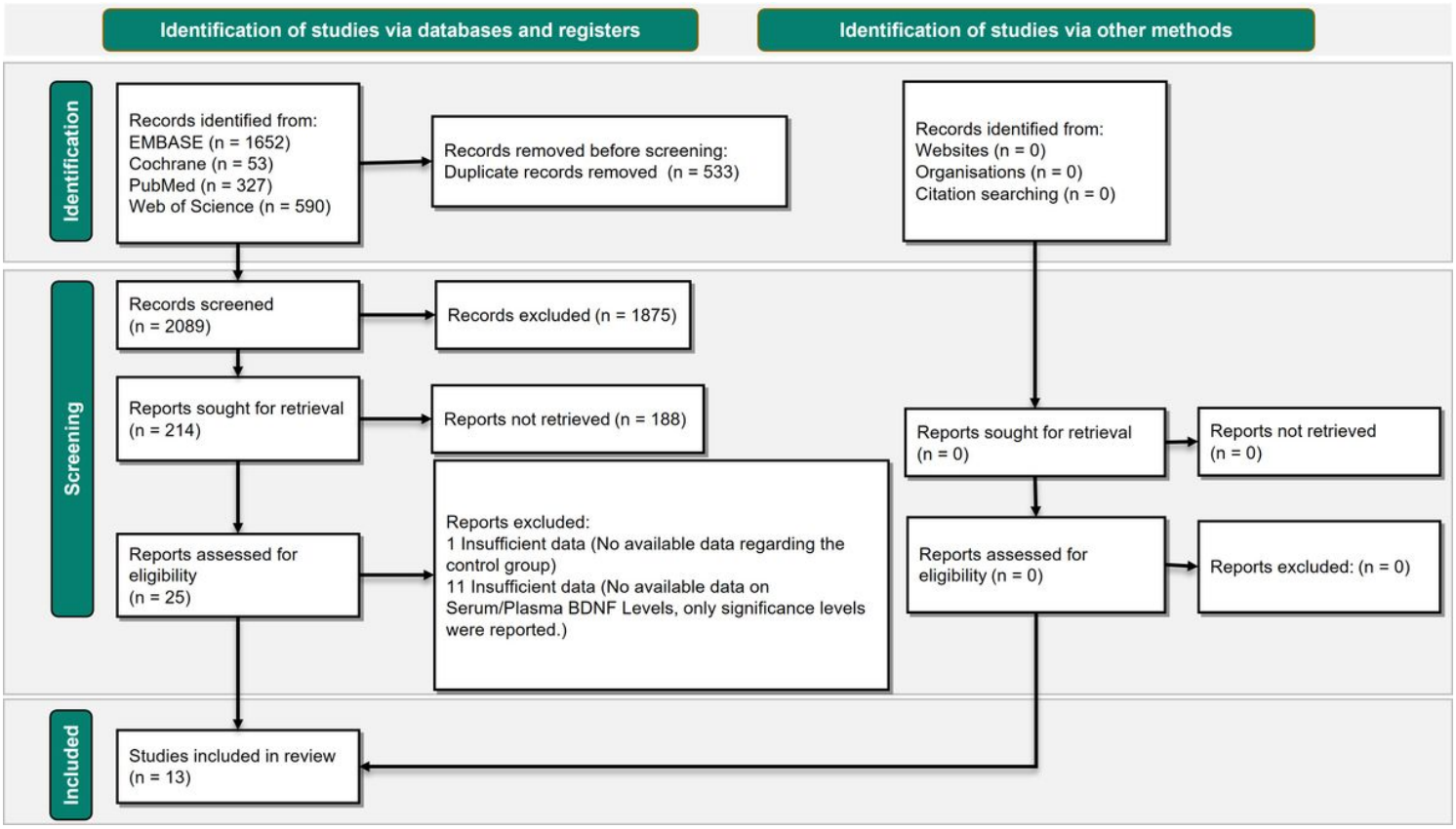

Figure 1

Flow diagram summarizing the selection of eligible studies based on the PRISMA guidelines.

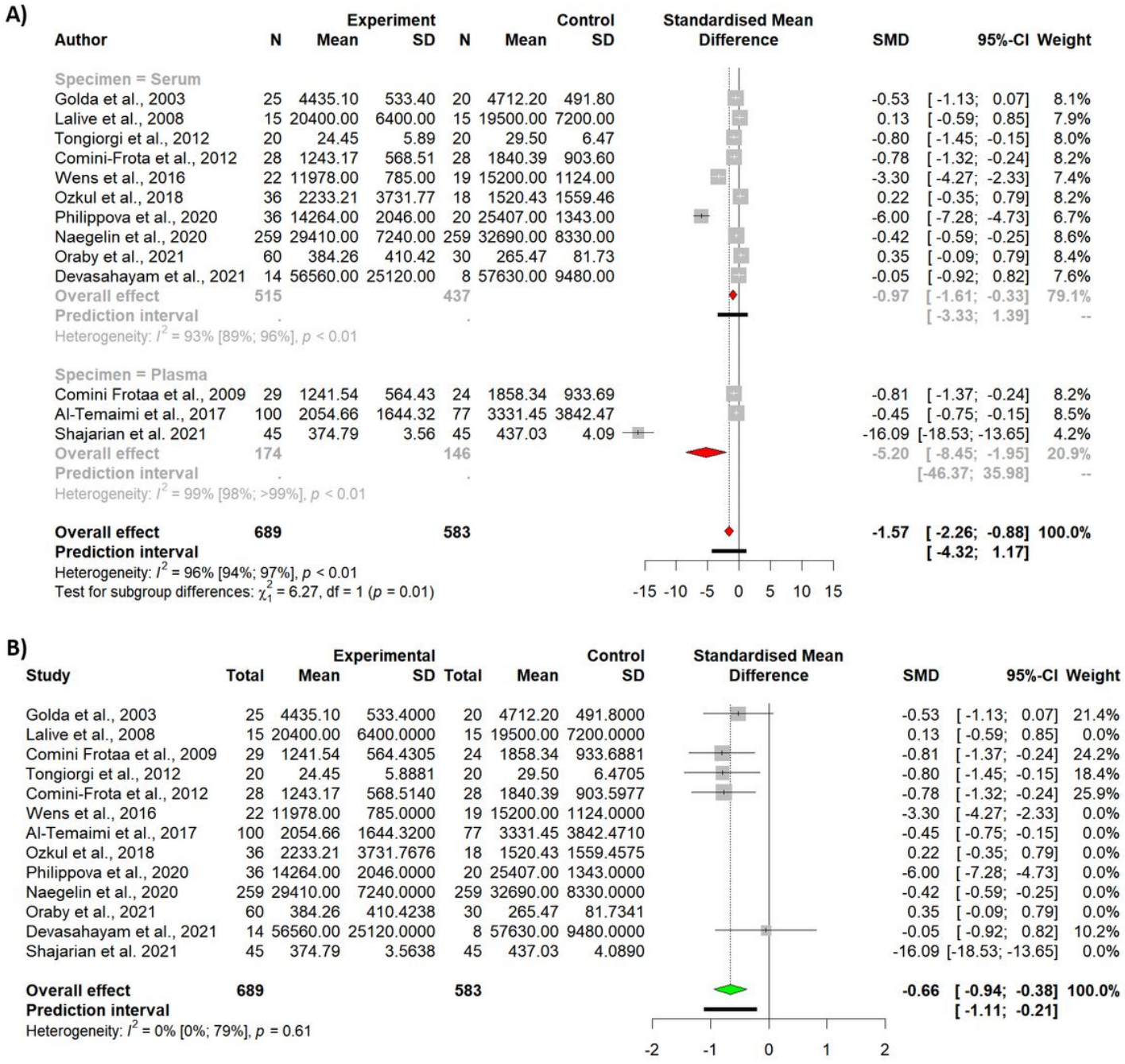

Figure 2

A: Forest plot of subgroup meta-analysis of BDNF levels in MS patients compared to controls. **B:** Forest plot of meta-analysis of BDNF levels in MS patients removing outliers.

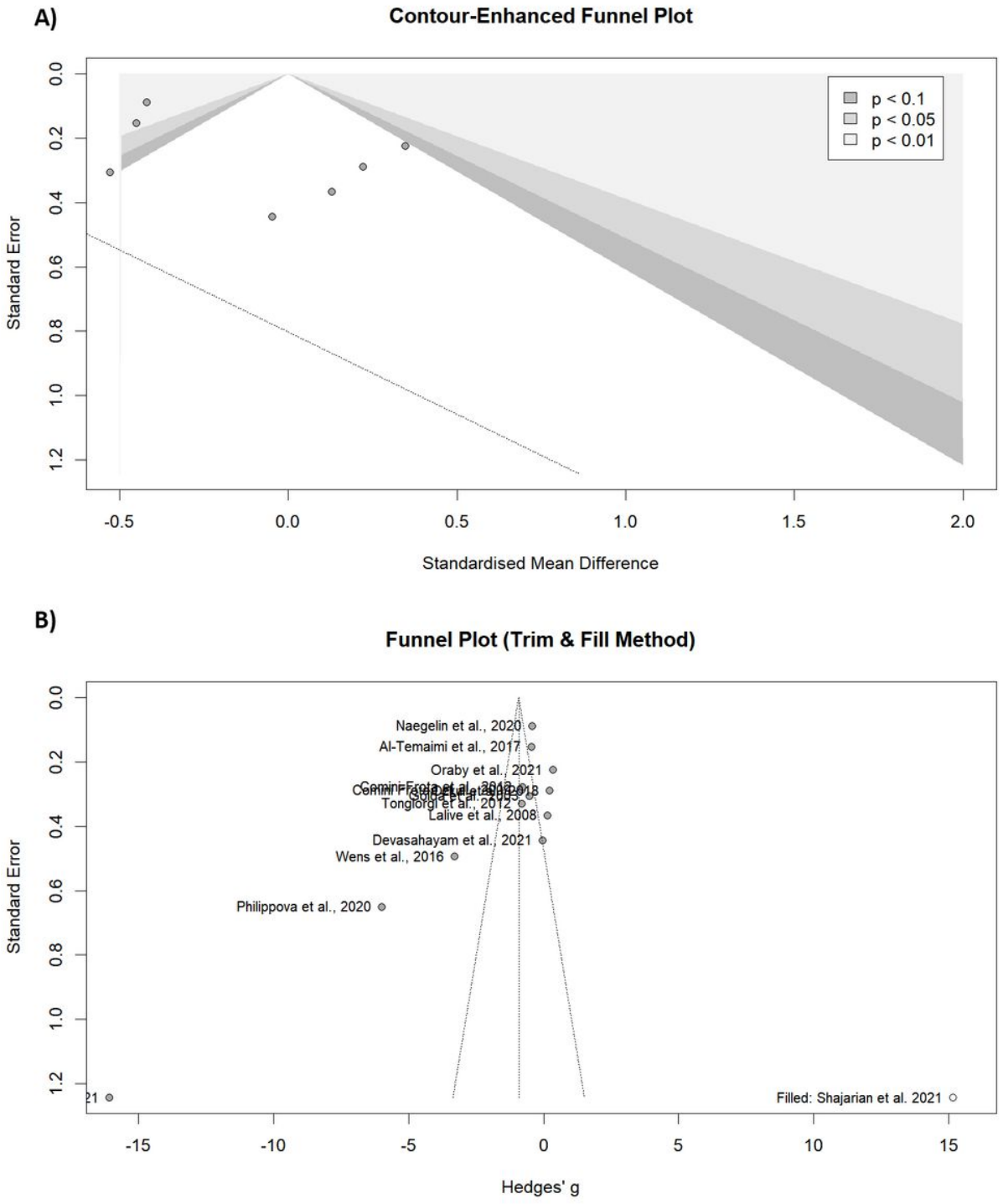

Figure 3

A: The counter-enhanced funnel plot showing evidence of publication bias, statistically supported by Egger's regression test. **B:** The funnel plot resulted from trim and fill analysis

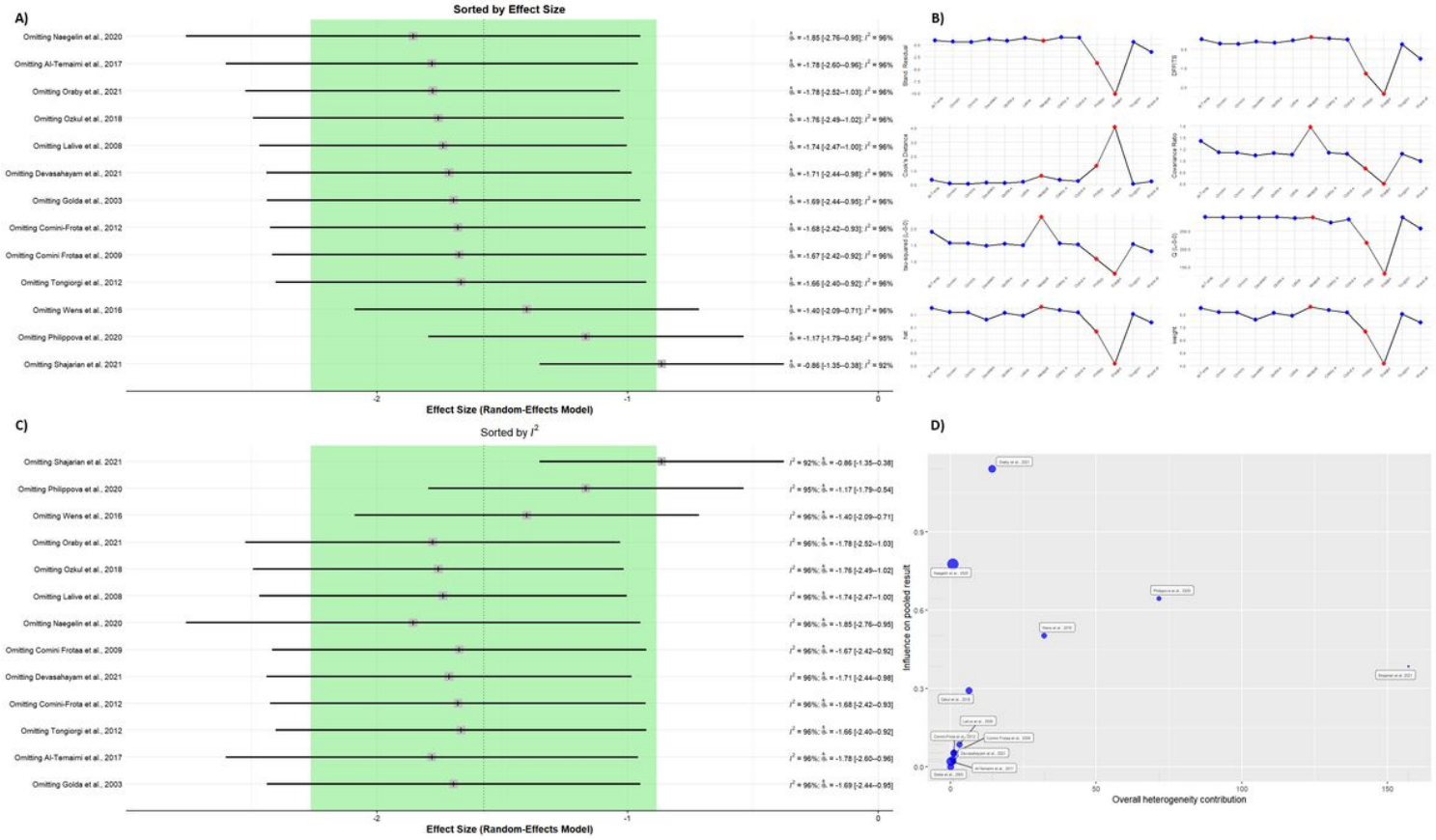

Figure 4

Results of Sensitivity analysis (leave-one-out analysis) of the meta-analysis **A:** Sorted by Effect Sizes; **B:** The influence analysis plot, showing different influence diagnostics including: Externally Standardized Residuals, DFFITS Value, Cook's Distance, Covariance Ratio, Leave-One-Out τ2 and Q Values, and Hat Value and Study Weight.; **C:** Sorted by I^2; **D:** Baujat Plot.

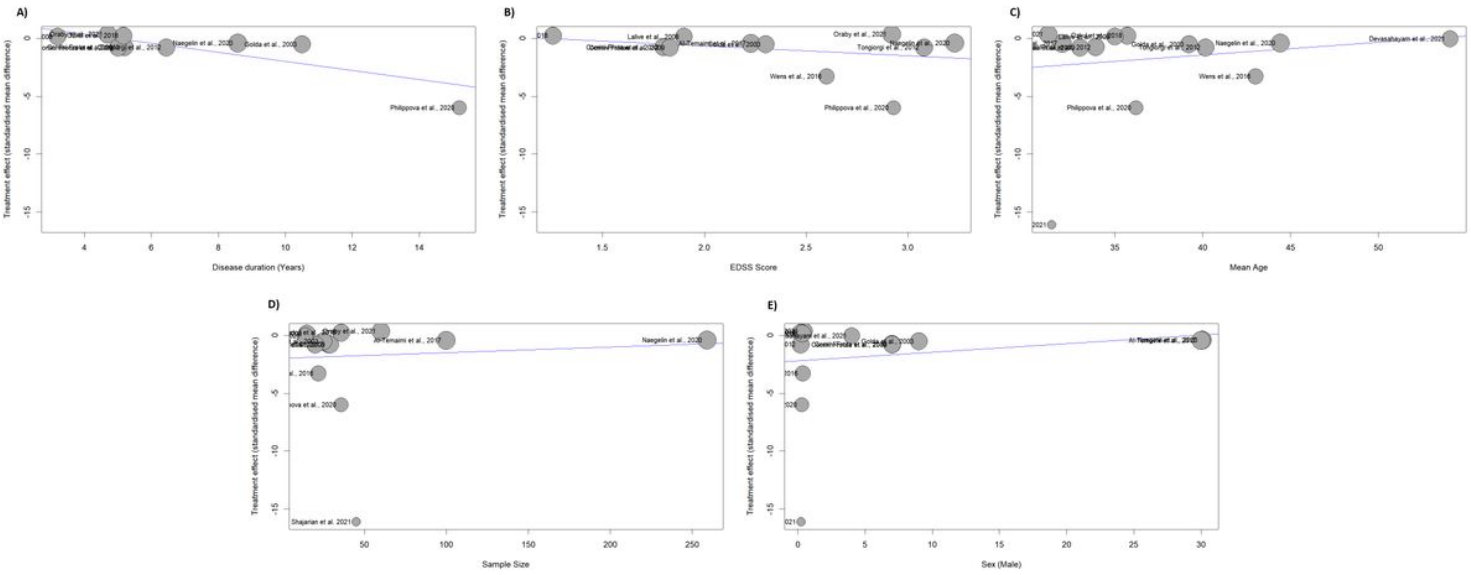

Figure 5

Bubble plot of meta-regression **A:** Disease duration; **B:** EDSS Score; **C:** Mean Age; **D:** Sample Size; **E:** Sex (Male)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- Table2.docx