Advances in Rheumatology

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Blood levels of brain-derived neurotrophic factor (BDNF) in systemic lupus erythematous (SLE): a systematic review and meta-analysis

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Abstract

Objectives BDNF has been implicated in the pathophysiology of systemic lupus erythematosus (SLE), especially its neuropsychiatric symptoms. The purpose of this study was to investigate the profile of blood BDNF levels in patients with SLE.

Methods We searched PubMed, EMBASE, and the Cochrane Library for papers that compared BDNF levels in SLE patients and healthy controls (HCs). The Newcastle–Ottawa scale was used to assess the quality of the included publications, and statistical analyses were carried out using R 4.0.4.

Results The final analysis included eight studies totaling 323 healthy controls and 658 SLE patients. Meta-analysis did not show statistically significant differences in blood BDNF concentrations in SLE patients compared to HCs (SMD 0.08, 95% CI [−1.15; 1.32], *P* value = 0.89). After removing outliers, there was no significant change in the results: SMD -0.3868 (95% CI [−1.17; 0.39], *P* value = 0.33. Univariate meta-regression analysis revealed that sample size, number of males, NOS score, and mean age of the SLE participants accounted for the heterogeneity of the studies (R^2 were 26.89%, 16.53%, 18.8%, and 49.96%, respectively).

Conclusion In conclusion, our meta-analysis found no significant association between blood BDNF levels and SLE. The potential role and relevance of BDNF in SLE need to be further examined in higher quality studies.

Keywords Brain-derived neurotrophic factor, BDNF, Systemic lupus erythematous, SLE, Lupus, Neuropsychiatry lupus

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects several organs in the body and is more common among females [1]. Genetically predisposed individuals seem to develop loss of T-cell tolerance to self-antigens [2], resulting in increased production of autoantibodies and an imbalance between Th17 and regulatory T-cells [3, 4]. The deposition of immune complexes in various organs including kidneys, lungs, and central nervous system (CNS) is partly responsible for the disease symptoms [5, 6].

The diagnosis of SLE is based on international classification criteria which include both clinical and laboratory findings [7]. Clinical manifestations of the disease can range from mild symptoms, like arthralgia and cutaneous lupus, to severe and life-threatening manifestations, including lupus nephritis [8]. Neuropsychiatric features are one of the most common manifestations among SLE patients [9]. It can present a wide spectrum of symptoms, from depression and seizures to stroke [10]. Of note, the CNS is involved in about 75% of SLE patients, and the pathophysiology of neuropsychiatric SLE (NPSLE) remains to be understood [11].

Recent studies have highlighted the role of neurotrophins, especially BDNF, in the pathophysiology of immune-based diseases. Traditionally, BDNF has been implicated in neuronal growth and survival, i.e., neuroprotective effects [12, 13]. BDNF can be produced by lymphocytes, macrophages, endothelial cells, [14], enhancing the proliferation and survival of the lymphocytes by affecting the cell membrane through autocrine or paracrine signaling [15, 16]. To date, several systematic reviews and meta-analysis attempted to shed light on the role BDNF in various disorders, including multiple sclerosis, eating disorders, and sleep apnea [17–20].

Taken together, since there could be a relationship between BDNF and SLE disease neuropsychiatric symptoms and severity; therefore, we conducted a meta-analysis of the studies investigating blood BDNF levels in SLE patients compared to controls.

Materials and methods

The current systematic review and meta-analysis followed the methods of the Cochrane Handbook of Systematic Reviews and the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [21].

Search strategy

PubMed, EMBASE, and Cochrane Library were searched till April 2022 using the retrieval words "Systemic lupus erythematosus", "lupus", "SLE", "Neuropsychiatric lupus", "Brain-Derived Neurotrophic-Factor", "BDNF", and using a combination of subject words and free words. No language, publication date, or publication status restrictions (e.g., online first or published) were applied. To identify additional studies, we further checked reference lists and contacted the corresponding authors of the papers included in the current systematic review and meta-analysis.

Eligibility criteria

Only studies that investigated the circulating blood levels of BDNF in SLE patients were eligible to be included. No language or time restrictions were applied. The main outcome included the BDNF levels in SLE patients and healthy controls (HCs).

Studies that reported only the levels of BDNF for participants with SLE without comparing to an HC group were also excluded. Review articles, books, book chapters, studies on animal subjects, studies assessing tissue expression of BDNF, in vitro studies or studies on cell cultures, and studies on genetic polymorphisms of BDNF but not its levels were also excluded.

Data extraction and quality assessment

The data were pre-extracted from the documents. Two authors performed two-stage screening (title/abstract and full-text), data extraction, and risk of bias assessment independently to select the eligible studies. A third investigator was consulted in case of discrepancies in the data extraction and quality assessment process. The following items were extracted from the included studies: Author, Year, Country, Study Design, BDNF Measurement Protocol Source (Serum, Plasma), Sample size (SLE and HCs), Diagnostic Criteria, Age, Female/Male ratio, BDNF levels, Investigated Markers, and the Main Significant Findings.

Newcastle–Ottawa scale (NOS) was used to evaluate the quality of the included studies [22]. Using this scale, studies can be rated 0–9 stars based on the selection of their samples, the comparability of cases and controls, and the assessment of their outcomes. Studies with a star rating of 7–9 were considered of the best quality, a rating of 4–6 stars, a moderate quality, and a rating of fewer than four had the lowest quality.

Statistical analysis

The standardized mean difference (SMD) was used to measure the effect. Also, random effects were utilized as the analysis model. Statistical methods suggested by Luo et al. [23] and Wan et al. [24] were used when the values reported in the manuscript were expressed as a median and interquartile range (IQR) or median and range, and

we could not get the mean and SD from the authors. Q statistic tests and the I^2 index were used to detect heterogeneity. According to the Cochrane criteria, an $I^2 < 40\%$ indicates that discrepancy across investigations is not significant. We intended to utilize the fixed effects approach in this scenario. We employed the random effects approach as the analytical model if the I^2 estimations changed by more than 40%. We ran a sensitivity analysis to identify influential cases for meta-analyses with considerable heterogeneity, containing ten or more paper to further investigate the sources of heterogeneity. We removed one research each time and recalculated the effect size (Leave-One-Out Analyses).

We assessed publication bias through funnel plot and Egger's test. The degree of asymmetry in the funnel plot and Egger's test [25] identify publication bias. In particular, funnel plots are frequently used to visually identify publication bias. The Egger's test, on the other hand, is an objective statistic that helps individuals to validate visual cues provided by funnel plots.

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 the following packages: "meta" (version 4.17-0), "metafor" (version 2.4-0), "dmetar" (version 0.0-9), and "tidyverse" (version 1.3.0). A P value of < 0.05 was considered statistically significant.

Results

Study selection

The study selection process is shown in Fig. 1. The search database returned a total of 208 entries. After removing duplications, 168 articles were retrieved for preliminary screening. The full text of 17 publications was read by two independent reviewers who assessed the final eligibility under the supervision of a senior team member. Four studies were excluded since these manuscripts did not encompass healthy control groups. We omitted nine articles due to the reasons mentioned in Fig. 1. At the end, we selected eight papers including 660 SLE patients and 323 HCs.

Characteristics of the included studies

According to Table 1, eight studies published from 2009 to 2021 provided original data on BDNF blood levels in SLE patients and HCs [26–33]. SLE patients were selected based on the ACR criteria. Two studies only compared BDNF levels in SLE patients (n = 59) to HCs (n = 64) [27, 29]. Meanwhile, six studies gave

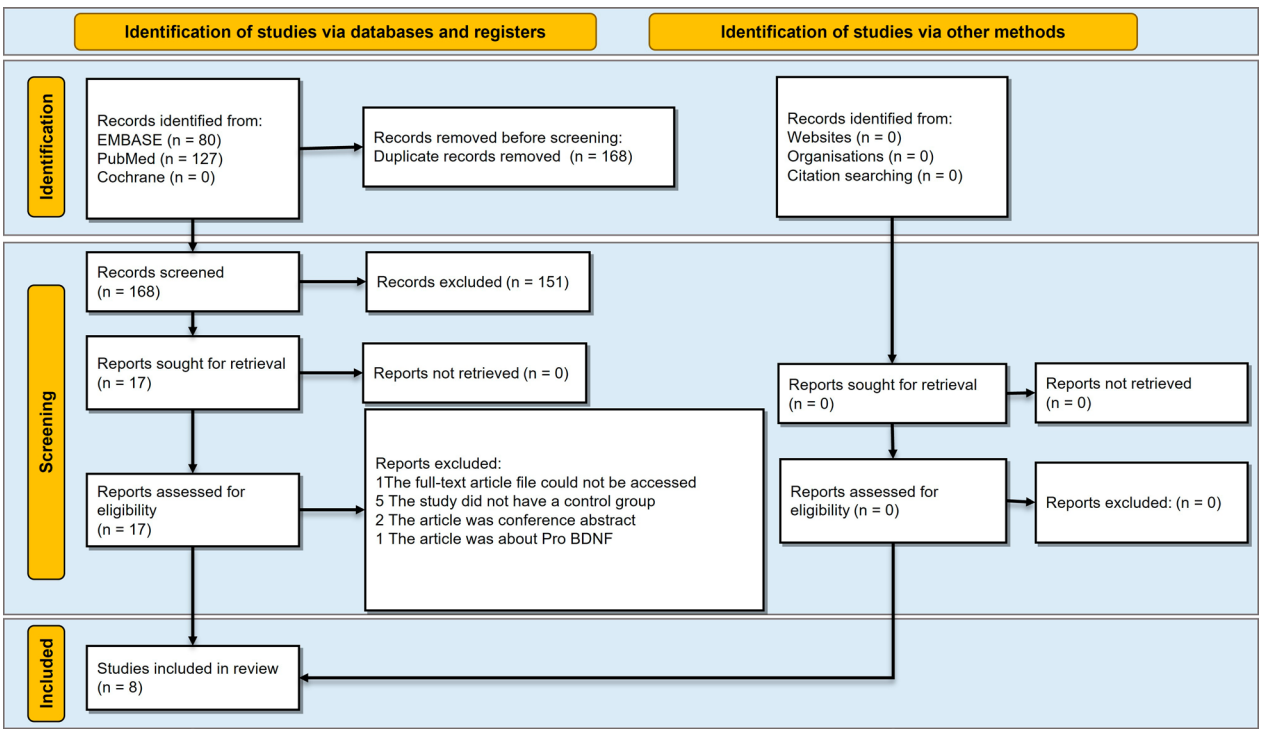

Fig. 1 Flow diagram summarizing the selection of eligible studies based on the PRISMA guidelines

Table 1 Baseline characteristics of included studies

Study ID					Patients					Controls				Results	
References	Country	Study design	BDNF measurement protocol	Source (serum, plasma)	No. (type of SLE)	Diagnostic criteria	Age (mean ± SD), years	Female/male	BDNF levels (mean ± SD), pg/ml	No (Type of control)	Age (mean ± SD), years	Female/male	BDNF levels (mean ± SD), pg/ml	Investigated markers	Main significant findings
Ikenouchi-Sugita et al. [26]	Japan	Cross-sectional	Emax Immunoassey Kit (Promega, Madison, WI, USA)	Serum	54	ACR	40.10 ± 1.98	49/5	15,984.4 ± 11,820.828		40.4 ± 2.08	25/3	11,440 ± 690	BDNF	Serum BDNF levels were significantly increased in the NP group
Fauchais et al. [27]	France	Cross-sectional	ELISA Kits	Serum	26	ACR	44 ± 12	24/2	598.9 ± 129.8	26		24/2	326.10 ± 60.50	BDNF NGF NT3 CH50 Anti-nuclear Ab/nDNA	They have demonstrated that both NGF and BDNF serum levels are higher in SLE patients than healthy controls
Tamashiro et al. [28]	Brazil	Cross-sectional + Longitudinal stage	ELISA (R&D Systems, Minneapolis, MN, USA)	Plasma	131	ACR	32.78 ± 12.36	120/11	3870.8066 ± 4793.357524		33 ± 9	15/9	2205.4269 ± 2938.6665	BDNF ANA aPL Anti-ribosomal P protein Anti-dsDNA C3, C4	BDNF levels were increased in inactive NPSLE when compared with active SLE and controls
Zheng et al. [30]	China	Cross-sectional	ELISA (R&D Systems, Minneapolis, MN, USA)	Serum	208	SDI score, SLEDAI-2 K score, VAS score	55.70 ± 10.45	190/18	33,654.3 ± 9032.9100		55.70 ± 10.53	0/0	14,694.4 ± 4438	BDNF EGFR Anti-dsDNA ANA Anti-sm antibody CRP C3 C4	The serum BDNF levels were significantly higher in SLE patients as compared to normal controls The serum BDNF levels were significantly lower in depression patients at the time of admission as compared with patients without depression

Table 1 (continued)

Study ID					Patients					Controls				Results	
References	Country	Study design	BDNF measurement protocol	Source (serum, plasma)	No. (type of SLE)	Diagnostic criteria	Age (mean ± SD), years	Female/male	BDNF levels (mean ± SD), pg/ml	No (Type of control)	Age (mean ± SD), years	Female/male	BDNF levels (mean ± SD), pg/ml	Investigated markers	Main significant findings
Kalinowska-Łyszczarz et al. [29]	Poland	Cohort	ELISA Kits (Multi-Neurotrophin Rapid Screening ELISA Kit)	Serum	38 (BDNF was detected in 33 patients)	ACR	40 ± 12	36/2	424.8199 ± 676.239	39 BDNF was detected in 38 patients)			1766.9266 ± 1161.4063	BDNF NGF NT3 NT4/5	BDNF levels were reduced in NPSLE compared to the healthy population
Noris-GarCia et al. [32]	Cuba	Cross-sectional	ELISA Kit (BDNF ELISA, Promega, Charbonnieres, France)	Serum	47	ACR-97	47 ± 11	45/2	4210 ± 1783.4	20	47 ± 13	16/4	4494 ± 1739.3	BDNF S100B ANA Anti-dsDNA Anti-cardiolipin antibodies, Anti-neutrophil cytoplasmic antibodies	BDNF levels were significantly decreased in active SLE, when compared with inactive SLE
Tian et al. [33]	China	Cross-sectional	ELISA (DBNT00, R&D Systems, Minneapolis, USA)	Serum	50	ACR	31.9 ± 14.9	45/5	14,742.5 ± 7620.930				33,116.5 ± 7146.5	BDNF TrkB expression	Serum BDNF levels in SLE patient were decreased when compared to the controls BDNF level was increased in inactive SLE group compared to the active SLE group
Alessi et al. [31]	Brazil	Cross-sectional	ELISA (Norcross, GA, USA)	Serum	111	SLICC	38.28 ± 10.64	102/9	788,651.4 ± 458,815.557		41.6 ± 11.1	48/9	1,345,500 ± 438,400	BDNF Anti-sm antibodies, ANA, Anti-LA/SSB Anti-Ro/SSA Anti-P Anti-DNA Anti-RNP	Serum BDNF levels were lower in SLE and NPSLE patients than control group

ELISA Enzyme-Linked Immunosorbent Assay, *BDNF* Brain-derived neurotrophic factor, *NGF* Nerve growth factor, *IGFBP1* Insulin-like growth factor-binding protein 1, *SLE* Systemic Lupus Erythematosus, *NPSLE* Neuropsychiatry SLE, *SLEDAI-2 K* SLE disease activity index 2000, *SDI* Systemic lupus international collaborating/American College of Rheumatology damage index for SLE, *SLICC* Systemic Lupus International Collaborating Clinics criteria

Table 2 Newcastle–Ottawa Scale (NOS) risk of bias assessment of the included studies

References	Selection (0–5)	Comparability (0–2)	Exposure/outcome (0–3)	Total score (0–10)
Ikenouchi-Sugita et al. [26]	3	1	3	7
Fauchais et al. [27]	4	1	3	8
Tamashiro et al. [28]	4	2	3	9
Zheng et al. [30]	3	1	3	7
Kalinowska-Łyszczarz et al. [29]	4	1	3	8
Noris-GarCia et al. [32]	4	1	2	7
Tian et al. [33]	4	2	3	9
Alessi et al. [31]	3	2	3	8

additional information about BDNF levels in different groups of SLE patients. The mean ± SD age range was from 31.9 ± 14.9 to 55.7 ± 10.45 years among SLE patients and from 33 ± 9 to 55.7 ± 10.53 years among HCs. The majority of the participants were females. All but one study [26] used enzyme-linked immunosorbent assay (ELISA) to measure BDNF levels as an analytical procedure. Moreover, all studies assessed serum BDNF levels, except the study by Tamashiro et al. [28] which examined plasma levels of BDNF.

The methodological quality of studies

The results of quality assessments of the included studies using the Newcastle Ottawa scale (NOS) for cross-sectional studies are depicted in Table 2.

Comparison of BDNF levels in SLE patients versus healthy controls (HCs)

Meta-analysis results of the eight studies did not reveal statistically significant difference in blood BDNF

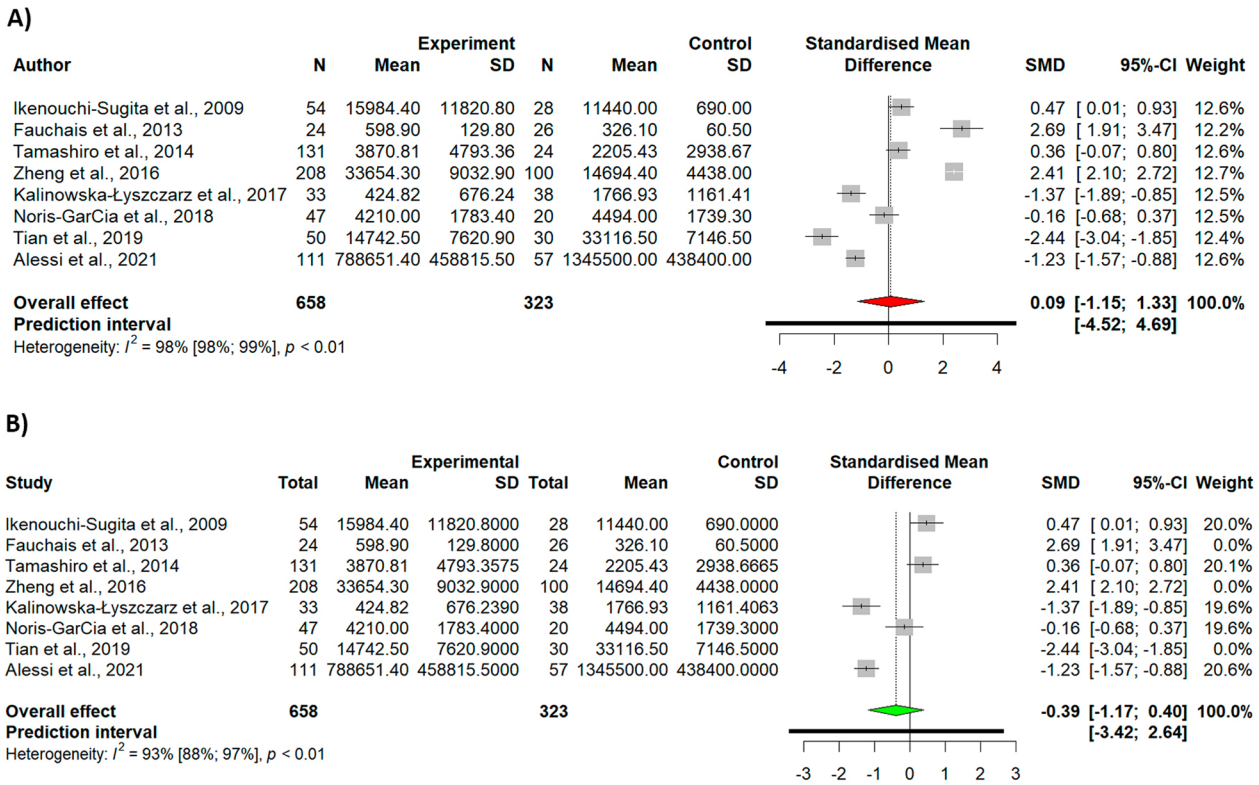

Fig. 2 **A** Forest plot of meta-analysis of BDNF levels in SLE patients compared to controls., **B** Forest plot of meta-analysis of BDNF levels in SLE patients removing outliers

concentrations in SLE patients compared to HCs (SMD 0.0872, 95% CI [−1.1538; 1.3282], *P*value = 0.8904, $I^2 = 98.3\%$, test of heterogeneity: Q = 418.20, *P*value < 0.0001, Fig. 2A).

The heterogeneity between studies was statistically significant (*P*value < 0.0001), with a variance of $\tau^2 = 3.1387$ [1.2670; 13.1168] and an I^2 value of 98.3% [97.7%; 98.8%]. The prediction CI ranged from −4.5164 to 4.6908, suggesting that negative intervention effects in future trials cannot be ruled out.

Publication bias

The Eggers' test did not indicate the presence of substantial funnel plot asymmetry (*P*value = 0.47). Also, the funnel plot was symmetric (Fig. 3).

Outliers' identification and sensitivity analysis

By means of the 'find.outliers' command in R software, three studies [27, 30, 33] were regarded as outliers; therefore, the remaining five studies were re-analyzed, and the following results were acquired: SMD −0.3868 (95% CI

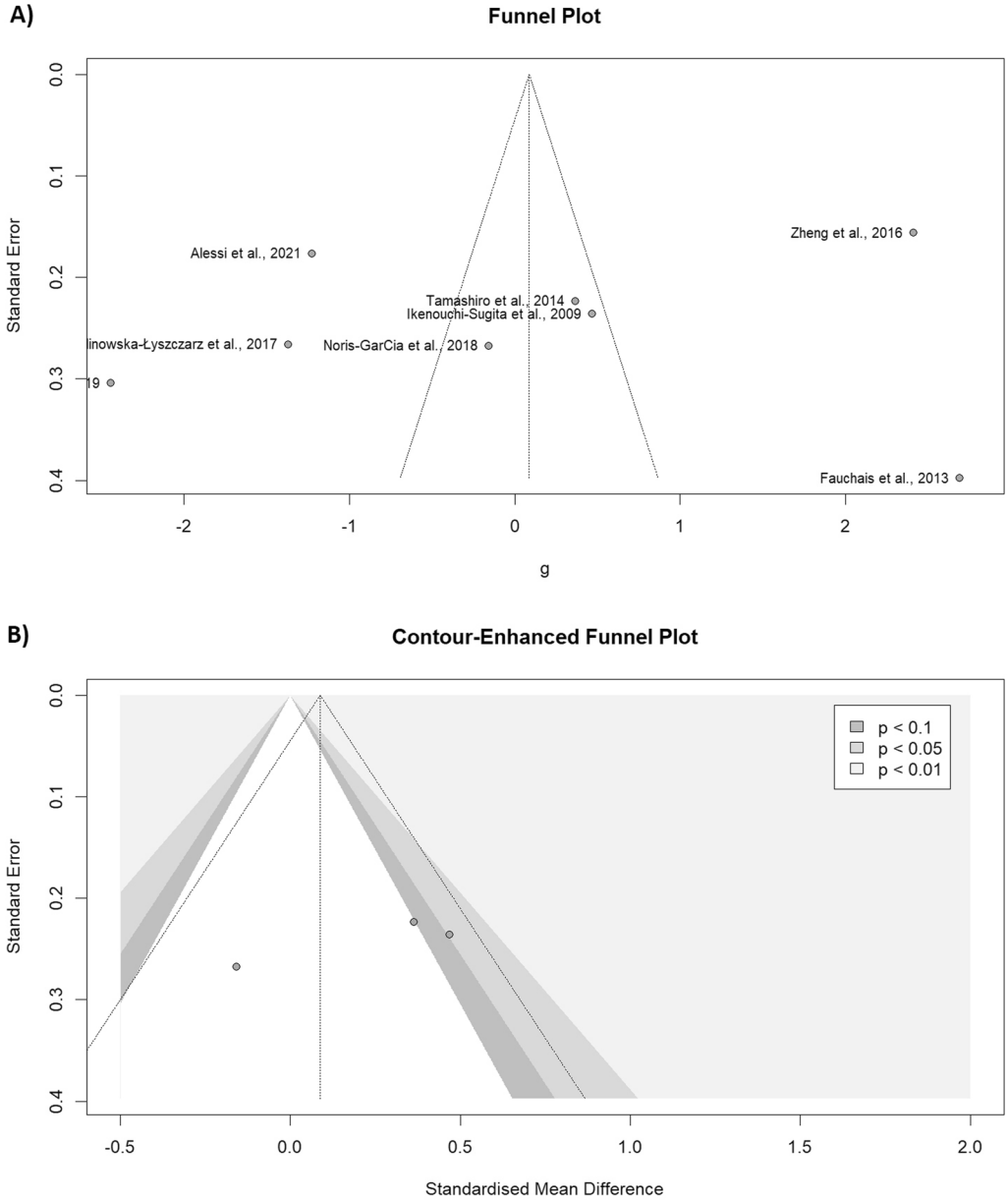

Fig. 3 **A** The funnel plot showing no evidence of publication bias, statistically supported by Egger's regression test. **B** Counter-enhanced funnel plot

[−1.1714; 0.3978], *P*value = 0.3339, $I^2 = 93.4\%$, test of heterogeneity: Q = 61.01, *P*value < 0.0001, Fig. 2B). These results corroborate that BDNF levels were not statistically different between SLE patients and HCs.

The impact of each study on the total estimate was evaluated by systematically eliminating studies and comparing the pooled estimate from the remaining seven investigations. SLE patients exhibited higher peripheral BDNF levels than controls, meaning that eliminating any research work would have minimal influence on the overall findings (Fig. 4).

Meta-regression

We employed meta-regression analysis to identify the origins of study heterogeneity and the impact of modifiers. Univariate meta-regression analysis revealed that sample size, number of males, NOS score, and mean age of the SLE participants account for the existing heterogeneity (R^2 were 26.89%, 16.53%, 18.8%, and 49.96%, respectively). Also, according to meta-regression results, the mean age of the SLE participants had a statistically positive correlation to BDNF levels. Table 3

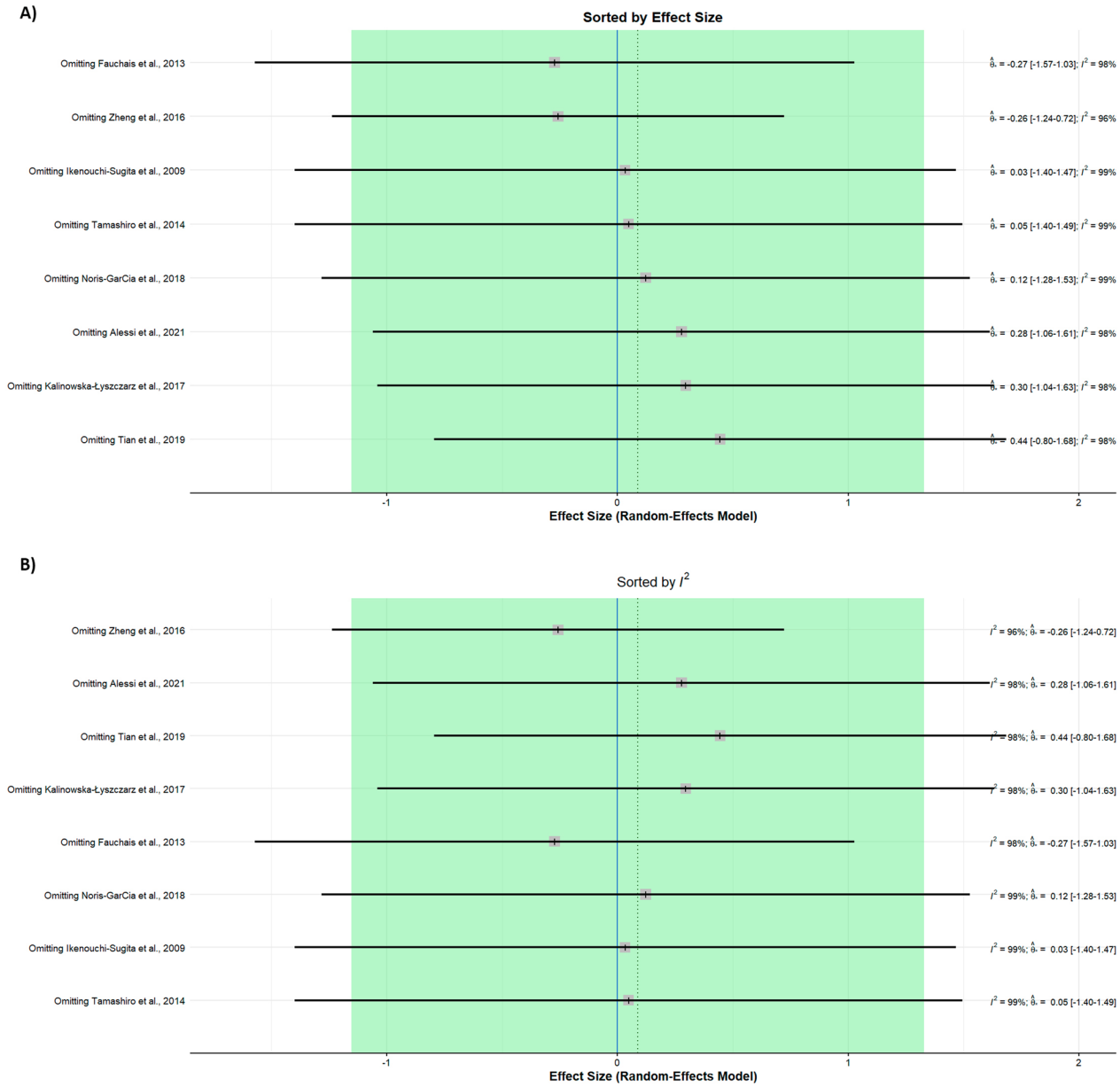

Fig. 4 Results of Sensitivity analysis (leave-one-out analysis) of the meta-analysis **A** Sorted by I^2; **B** Sorted by Effect Sizes

Table 3 Meta-regression of BDNF levels in SLE patients and healthy controls

Moderator	No. of comparisons	No. of subjects		Meta-regression			R^2 Analog (proportion of variance explained) (%)
		IHD	HC	Slope	95% CI	*P* value	
Sample size	8	658	323	0.0099	−0.0081; 0.0278	0.2818	26.89
Age (mean, years)	8	658	323	0.1556	0.0339; 0.2772	**0.0122**	49.96
NOS score	8	658	323	−0.9676	−2.4017; 0.4665	0.1860	18.80
Sex (male, %)	7	625	285	0.0836	−0.1464; 0.3135	0.4762	16.53

P value < 0.05 is shown in Bold

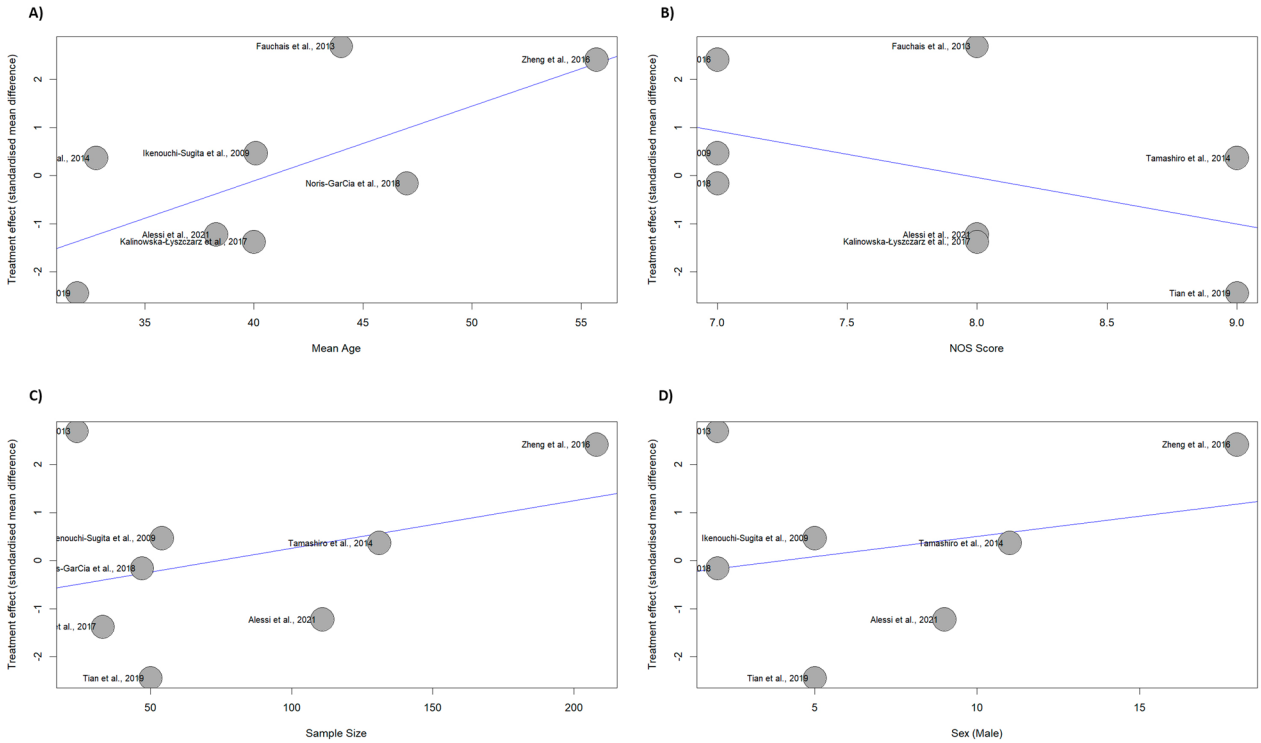

Fig. 5 Bubble plot of meta-regression **A** Mean Age; **B** NOS Score; **C** Sample Size; **D** Sex (Male)

summarizes the results of meta-regression analysis, and the bubble plots are shown in Fig. 5.

Discussion

To the best of our knowledge, this is the first meta-analysis of BDNF blood levels in SLE patients. Pooling the results of the eight studies did not show statistically significant differences between SLE patients and HCs.

SLE is a systemic autoimmune disease manifesting with various symptoms ranging from mild mucocutaneous symptoms to systemic and multiorgan involvement [34]. SLE can be associated with a series of neurological and neuropsychiatric manifestations, including headaches, seizures, cerebrovascular events, psychosis, movement disorders, and cognitive dysfunction [35]. There is still no single sensitive and specific test for diagnosing SLE-associated neurologic/neuropsychiatric manifestations; therefore, the assessment of SLE patients for CNS-related manifestations is based on the consideration of clinical findings, brain imaging, and immunoserologic markers [35]. Several studies have suggested alterations in the serum BDNF levels in SLE patients [31, 36, 37]. BDNF is one of the most studied neurotrophic factors in the CNS, which serves as an autocrine and paracrine factor on pre-synaptic and post-synaptic sites [38]. BDNF is known to be a key molecule in regulating neurogenesis, synaptic plasticity, and, thus, learning and memory functions [39]. Memory impairment is one of the neurological

symptoms associated with SLE [40]; however, the mediating role of BDNF level alterations in the pathophysiology of SLE-related memory and cognitive impairment is unclear. Alessi et al. observed that serum BDNF levels were lower among SLE and NPSLE cases compared with controls; but were not associated with NPSLE-related cognitive dysfunction [31]. On the other hand, serum BDNF levels seem to be lower in SLE subjects exhibiting depressive symptoms, indicating the role of BDNF in maintaining mental health in SLE patients [30]. In line with the previously mentioned findings, Ikenouchi-Sugita et al. [26] observed that patients with NPSLE were found to have lower levels of BDNF than controls, and this reduction was related to the progression and severity of psychiatric symptoms. Of note, serum BDNF levels have been reported to be decreased in major depression and to improve with antidepressants treatment [41, 42]. Interestingly, consistent with the findings of human studies, preclinical studies have shown that different types of stress suppress the expression of BDNF in limbic regions [43].

Tamashiro et al. [28] conducted a study with 131 SLE patients and 24 HCs. Plasma BDNF levels were elevated in asymptomatic NPSLE compared with both active SLE and HCs. Moreover, plasma BDNF levels increased as the neuropsychiatric symptoms improved, which corroborates the hypothesis that BDNF may lead to symptoms' alleviations [28]. Conversely, a case report study described that plasma levels of BDNF increased in parallel with the severity of psychotic symptoms in a patient with CNS lupus [37]. While this latter finding challenges the view that lower levels of serum BDNF are associated with psychiatric symptoms, it provides a more nuanced scenario in SLE. The higher levels of BDNF in the context of SLE-related psychosis probably indicates immune system hyperactivation and, therefore, greater production of BDNF [37]. Indeed, it has been suggested that activated B and T lymphocytes induce the production of BDNF, highlighting the regulating role of inflammation in BDNF levels [44, 45]. Moreover, it should be noted that blood BDNF levels do not always reflect its brain concentrations [46, 47]. For example, in depression, BNDF levels are increased in specific brain regions, however, they decrease in the blood [46], which points to the possible discordance between the blood and brain concentrations of BDNF.

The correlation between serum BDNF levels and the severity of SLE course seems complicated. Tamashiro et al. noticed that the level of plasma BDNF levels were higher in patients with inactive disease; indeed, SLE disease activity index (SLEDAI) scores, which show the systemic activity in SLE, were negatively correlated with plasma BDNF levels [28]. The same findings were suggested in Tian et al.'s study [33]. In addition, they observed lower levels of serum BDNF in SLE patients without lupus nephritis [33]. Consistently, Noris-García et al. [32] found that BDNF levels were significantly lower among patients with active SLE, compared with individuals inactive SLE, however, not when compared with HCs. On the other hand, Ikenouchi et al. found no correlations between SLEDAI scores and serum BDNF levels in SLE patients [26]. This is in line with the findings of Fauchais et al. [27]; accordingly, BDNF serum levels was not associated with initial SLEDAI scores. Taken together, there is inconsistency between the results of the studies regarding the relationship of BDNF with SLE clinical course which may arise from different sample sizes, taking medications interfering with BDNF serum levels, or other possible reasons. Hence, further concise evaluations should be conducted to shed light on the variations of BDNF levels in different clinical stages of SLE, which may enable clinicians to use BDNF or other neurotrophins as a biomarker of SLE treatment response in the future.

Our study has limitations. First, most of the included studies had relatively small sample sizes; hence the findings cannot be generalized to the SLE total population. Second, the SLE and control groups were not matched for age and sex in some of the studies.

Conclusion

In sum, according to our meta-analysis, SLE was not associated with the blood levels of BDNF. Future studies with larger sample sizes are required to determine the role of BDNF in SLE taking into account different subgroups of patients (e.g., NPSLE vs. non-NPSLE; active vs. controlled SLE) and its potential relation with established disease biomarkers.

Abbreviations

ACLE	Acute cutaneous lupus erythematosus
BDNF	Brain-derived neurotrophic factor
CI	Confidence interval
CNS	Central nervous system
DLE	Discoid lupus erythematosus
HCs	Healthy controls
IQR	Interquartile range
NOS	Newcastle–Ottawa scale
NPSLE	Neuropsychiatric systemic lupus erythematosus
SCLE	Subacute cutaneous lupus erythematosus
SD	Standard deviation
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus disease activity index
SMD	Standardized mean difference

Acknowledgements

This study was supported by a Grant from Tehran University of Medical Sciences (Grant number: 64944).

Author contributions

PS: drafting of the manuscript/study conception and design/data acquisition, analysis and data interpretation, SM: drafting of the manuscript/data

acquisition, MA, AH: drafting of the manuscript, ALT: critical revision, NR: study conception and design/critical revision. All authors read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
All recorded data from data extraction process of this study is available upon request to the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 31 October 2022 Accepted: 26 February 2023
Published online: 06 March 2023

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