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Neurofilament light chain as a promising biomarker for depression diagnosis: a systematic review and meta-analysis

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Abstract

Background Depression is a prevalent and serious mental health disorder that significantly impacts daily life and functioning. Neurofilament Light chain (NfL), associated with axonal neuronal damage, has been identified as a promising biomarker, potentially aiding in early diagnosis of depression, personalized treatment, and tracking disease progression. This study used meta-analysis to evaluate the potential of plasma NfL as a biomarker for depression patients.

Methods A systematic search following the PRISMA guidelines was conducted across PubMed, Web of Science, Scopus, and Google Scholar databases to find relevant studies on plasma NfL levels in patients with depression. A random effects model meta-analysis was applied to determine its potential as a biomarker for differentiating patients from controls.

Results Our meta-analysis, based on four articles with six datasets, revealed that plasma NfL levels were notably higher in individuals with depression (228 cases) compared to healthy controls (118 individuals). The weighted mean difference (WMD) was 8.78 (95% CI: 5.28, 12.28; $P < 0.01$), indicating a significant effect size. Given the diverse confounding factors inherent in the included observational studies, the observed variability can be attributed to these influences. Due to the observed heterogeneity (heterogeneity Chi-Square: 54.91, $p < 0.05$), we performed a subgroup analysis. Subgroup analyses based on depression type and analysis method consistently supported the association between NfL and depression, strengthening the evidence.

Conclusion Our meta-analysis demonstrates that elevated NfL levels may serve as a promising biomarker for diagnosing depressive disorders. Further research on diverse subtypes and longitudinal changes is needed to validate its clinical utility.

Keywords Depression, Neurofilament light chain, Review, Axonal damage, Diagnosis, Biomarkers

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Introduction

Depression has emerged as a significant global health concern due to its widespread epidemiology and its substantial impact on both individuals and society, which is regarded as one of the most crucial contributors to disability by the World Health Organization (WHO). The etiology and contributing factors to the development of this disease remain incompletely elucidated [1, 2]. Reliable biomarkers for depressive disorders can increase the accuracy of differential diagnosis, prognosis, and treatment response [3]. Identifying biomarkers representing pathological processes related to mood and cognitive changes can facilitate early and more individualized therapeutic interventions. Neurofilament Light chain (NfL) is a promising biomarker associated with axonal neuronal damage, which can be detected using immunoassay technology [4]. NfL is one of five subunits of the Neurofilament protein, which plays a crucial role in the integrity and stability of neurons. This protein belongs to the intermediate filament protein family and is typically present in normal physiological conditions in healthy individuals. However, its levels may increase in certain pathological conditions such as neuroaxonal injuries and neurodegenerative and psychiatric disorders [4]. Increased concentrations of cerebrospinal fluid (CSF) and serum NfL have been found in depressive disorders. Recent research shows evidence of a correlation between NfL concentration in the CSF or serum and psychiatric diseases, which can be helpful in monitoring and prognosis evaluation. It is now possible to detect NfL levels in both CSF and serum with a high level of accuracy. In healthy individuals, neurofilament proteins in CSF are approximately 40 times more concentrated than in the bloodstream [4, 5]. Although NfL is derived from the CNS, the exact mechanism by which it travels to the CSF and blood remains unclear [4]. Over the past two decades, studies have shown that altered blood and CSF levels of NfL in depressive diseases might be related to the symptoms of depression and correlate with the condition's severity [6]. NfL is a potential biomarker for diagnosing and assessing neurodegeneration in white matter. Previous studies demonstrated that elevated CSF NfL levels correlate with axonal damage in white matter and other subcortical brain structures rich in myelinated tissue that can release NfL during neurodegeneration [7].

Besides, the association of NfL levels with changes in white matter fibers, overall brain volume, and local atrophy (such as that occurring in the hippocampus), gray and white matter loss has been demonstrated by imaging studies [8–10]. Aggio et al. observed a significant positive correlation between serum NfL levels and impaired white matter microstructure in depressed bipolar disorder patients [11].

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According to the relationship between NfL levels and cognitive performance in healthy individuals, NfL levels are highly responsive to microstructural changes at the subclinical level. It remains controversial whether structural brain changes play a role in psychiatric disorders, such as schizophrenia (SZ) and major depressive disorder (MDD) [12]. There is limited evidence regarding changes in NfL level and its association with psychiatric disorders, especially mood disorders. Studies on the diagnostic validity of NfL biomarkers have been inconsistent, and diagnostic performance hasn't yet been evaluated comprehensively in meta-analyses. Even though studies have identified changes in potential biomarkers in serum samples, neurochemical blood biomarkers for diagnosing MDD patients, predicting treatment response, and monitoring treatment response are still lacking [13]. Our study represents the first meta-analysis that aims to explore the utility of NfL in clinical practice, specifically focusing on its role in the diagnosis of depressive disorder.

Method

A systematic literature review and meta-analysis were meticulously conducted following The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [14]. The current study was conducted with PROSPERO registration number CRD42023460332.

Search strategy and study selection

Two investigators (A.H. and S.K.) independently executed comprehensive searches across several reputable databases, including PubMed, Web of Science, Scopus, and Google Scholar, for articles published before August 2023. The following keywords were used during our search process: "Neurofilament light chain", "novel biomarker for depression", "serum and blood biomarker", "major depressive disorder (MDD)", "Bipolar disorder", "unipolar depression", "neurofilament light chain proteins", "NfL", and "NF-L". In addition, we checked the reference lists of the included studies to find additional relevant articles. As a result of the literature search, two independent reviewers (A.H. and S.K.) reviewed the titles, abstracts, and full texts of the articles considered potentially eligible after removing duplicates. Discussions were conducted to resolve any disagreements.

Inclusion and exclusion criteria

The following criteria were used to select studies for inclusion in this meta-analysis: (1) Design of the study: observational studies either with case-control, or cohort

design that have been published in peer-reviewed journals. (2) Studies that reported the mean level of NfL (pg/ml) in the cerebrospinal fluid (CSF), serum, or plasma for subjects with any type of depression, as well as in control groups. (3) Depressive disorder was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DMS-5) or ICD-10 criteria (4) in patients aged 15 years old and above.

The exclusion of studies was based on the following criteria: (1) No control group (2) duplicate articles (3) studies that lacked sufficient data for the extraction of NfL expression levels among depression patients and comparison groups (4) animal model or cell line research (5) patients with medical or neurological conditions.

Data extraction and quality assessment

In each included study, two researchers (A.H. and R.T.) conducted an independent and thorough data extraction process, capturing critical information, including study details such as the first author's name, year of publication, the mean age of participants, essential characteristics of the study population (including individual demographics and sample size in the depressive patients and control groups), study design, specimen collection methods, timing of specimen collection, NfL detection methods, mean NfL levels, analysis methods, the specific analysis kit brands employed, and information about control subjects. In cases where inconsistencies arose, consensus was diligently achieved through consultation with other researchers, ensuring data accuracy and reliability. To evaluate the potential bias within all included studies, a comprehensive Newcastle-Ottawa Scale (NOS) assessment was employed in this study. The NOS is a well-recognized tool designed to evaluate research quality by assessing three crucial aspects: selection bias, group comparability, and cohort exposure. A higher NOS score indicates a superior study quality [1, 15–20]. The total NOS score ranges from 0 to 9 points, signifying the overall study quality. Two researchers conducted this evaluation process independently to ensure robustness and consistency in the assessment.

Statistical analysis

To calculate the combined effect size, we computed the Weighted Mean Difference (WMD) and its corresponding 95% Confidence Interval (CI) for mean NfL levels between the depression and the control groups across the included studies. To assess the presence of heterogeneity among the studies, we conducted Cochrane's Q test. Additionally, we used I^2, which quantifies the proportion of total variation in the outcome estimates. We employed subgroup analysis and meta-regression analysis, considering the potential moderator variables such as study population characteristics, sample collection timing, NfL analysis methods, sample size, and NOS score across included studies. The individual impact of each study on the pooled estimates was calculated using a sensitivity analysis with the leave-one-out method. We reviewed a funnel plot to assess publication bias and conducted statistical tests, including Egger's regression and Begg's adjusted rank correlation tests, utilizing the meta-bias commands integrated into STATA version 14.0 (Stata Corp., College Station, TX). Statistical significance was defined as a p-value below 0.05.

Results

Search strategy and characteristics of included studies

After screening studies, Four articles (and six datasets) [1, 18, 20, 21] were proved to be eligible for meta-analysis. Figure 1 shows the details of step-by-step study identification and selection. Studies were published between 2021 and 2023. Our study included a total of 228 (31 BD and 197 MDD) individuals diagnosed with depression and 118 healthy control subjects. The key characteristics of the studies are summarized in Table 1. If there were any missing data, the article was excluded from meta-analysis. The quality of the included trials was assessed by the Newcastle-Ottawa Scale (NOS), which displayed levels of research quality among the five studies reviewed. Most studies (3 out of 5) were rated 4 out of 9, indicating a moderate to high risk of bias. Chen et al. [1] had a quality score of 6 out of 9, indicating better methodological quality. On the contrary, Steinacker et al.'s study had a score of 2 out of 9, indicating a high risk of bias (Table 2).

Main outcome

Figure 2 indicates the forest plot of the pooled WMD NfL levels in patients with depression. Our meta-analysis revealed that the WMD of plasma NfL levels (pg/ml) was 8.78 (95% CI: 5.28, 12.28; $P<0.01$), significantly elevated in individuals with depression when compared to controls. Notably, there was considerable heterogeneity among the included studies (I^2: 90.9%, P-value<0.001). Therefore, additional analyses, including subgroups, meta-regression, and sensitivity analyses, were conducted.

Subgroup analysis

As shown in Table 3, the subgroup analysis based on depression types (bipolar vs. MDD) remained relatively consistent with pooled results. In stratified analyses based on the methods of molecular analysis (single molecule array (SIMOA) vs. enzyme-linked immunosorbent assay (ELISA) vs. a combination of both), the ELISA (WMD = 9.20; 95%CI: 4.74, 13.66; I^2 = 96.3%) and the combination of SIMOA and ELISA (WMD = 9.75; 95%CI: 0.62, 20.13; I^2 = 0.0%) indicated significant WMD.

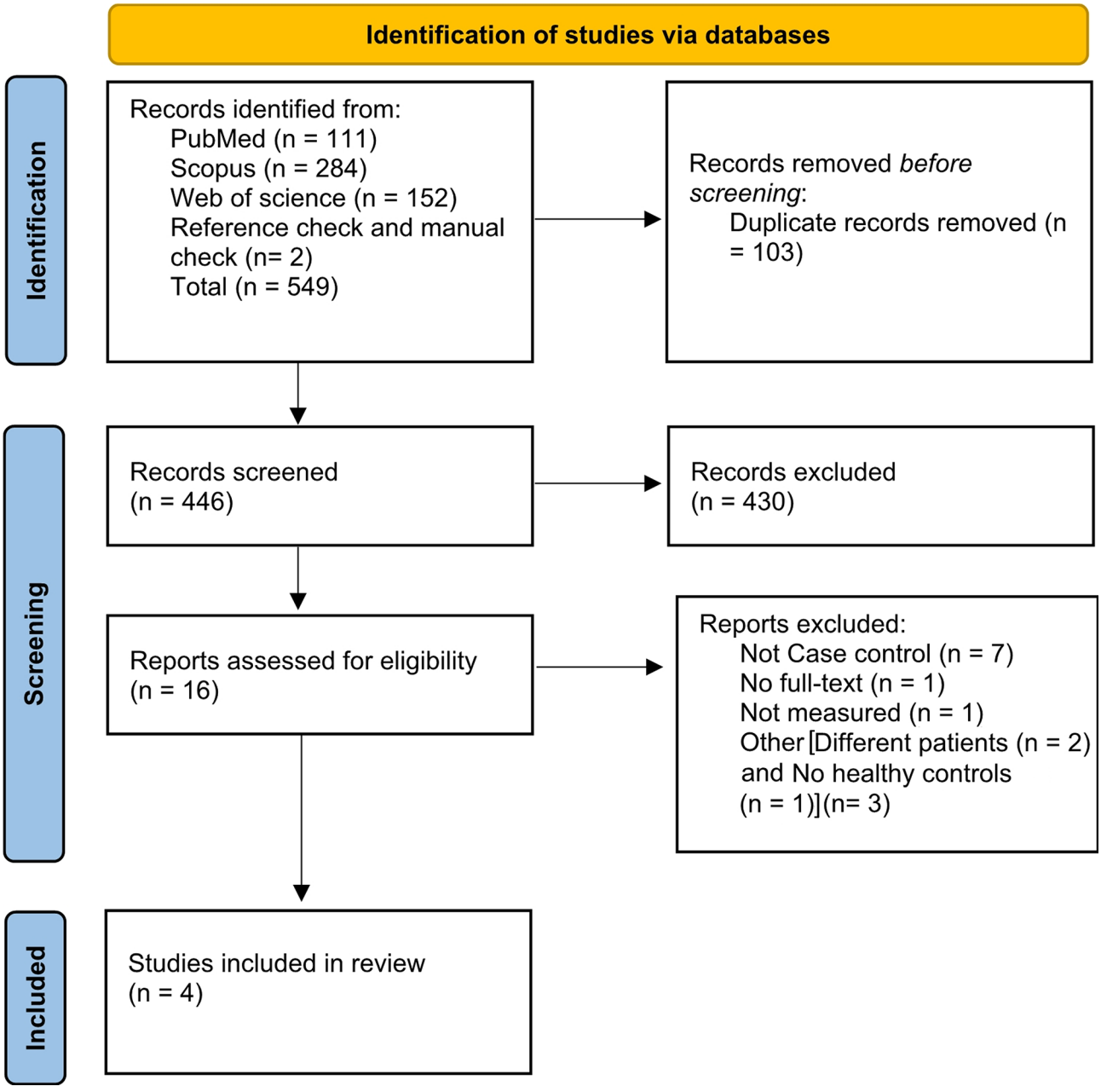

Fig. 1 Search and study selection

Sensitivity analysis and meta-regression analysis

In sensitivity analysis, to explore the effect of each study on the reliability of the association between plasma NfL levels and individuals with depression, the pooled WMDs were estimated after excluding one by one study from the meta-analysis. The sensitivity analysis indicates that the estimated WMD for plasma NfL levels in individuals with depression remains relatively consistent when omitting each study from the meta-analysis. However, the maximum WMD was observed when excluding Bia et al.(b) study [18], with an estimated WMD of 10.46 (95% CI: 8.77 to 12.14), resulting in a decrease to I^2=10.6% and P=0.35. Conversely, the minimum WMD was observed after omitting the study by Bai et al.(a) [18], yielding an estimated WMD of 6.13 (95% CI: 5.20 to 7.07), along with a decrease in I^2=0.0% and P=0.42. Meta-regression analysis was conducted to synthesize research findings from multiple studies while adjusting for the effects of available covariates, including sample size and NOS score across included on an overall WMD. The results indicated that neither the NOS score (Beta=1.01, P=0.56) nor the sample size (Beta = -0.01, P=0.81) had a significant impact on the overall WMD.

Table 1 Study characteristics

Author	Year	Country	Study type	Source	Method analysis	pt condition	pt N	pt Age	pt Gender f%	NfL concentration	HC condition	HC N	HC Age	HC Gender	Nfl concentration	Cognitive test	Main findings
Hviid et al.,	2023	Denmark	Case Control	Serum	Single Molecule Array	Treatment-naïve patients with MDD	110	42 (11)	65%	16.1 (3)	Healthy	33	39 (14)	70%	9 (2.5)	Comprehensive cognitive evaluation	did not suggest elevated NfL in unipolar depressed patients and also did not report positive associations with depression severity or cognitive function.
Bai et al.,	2023	Taiwan	Case Control	Serum	ELISA	BD	25	33.20 (13.24)	60%	25.19 (1.53)	Healthy	14	30.90 (10.70)	62.10%	14.12 (1.49)	N – back test for evaluating working memory	Patients with BD and MDD had elevated levels of NfL compared to healthy controls. NfL level was conversely associated with the memory task.
Bai et al.,	2023	Taiwan	Case Control	Serum	ELISA	MDD	24	30.83 (13.04)	66.70%	20.06 (1.53)	Healthy	15	30.90 (10.70)	62.10%	14.12 (1.49)		

Table 1 (continued)

Author	Year	Country	Study type	Source	Method analysis	pt condition	pt N	pt Age	pt Gender f%	NfL concentration	HC condition	HC N	HC Age	HC Gender	Nfl concentration	Cognitive test	Main findings
Chen et al.,	2021	Taiwan	Case Control	Serum	ELISA	MDD	40	28.25 (14.35)	67.50%	28.76 (22.53)	Healthy	40	28.25 (14.08)	67.50%	16.65 (8.07)	Wisconsin Card Sorting Test	MDD patients showed higher NfL levels compared to healthy controls. NfL levels were positively related to TNF- α and altogether associated with executive dysfunction.
Steinacker et al.,	2021	Germany	Case Control	Serum	single molecule array and ELISA	MDD	23	48 (19–69)	64.40%	29.3 (35.3)	Healthy	8	45 (27–64)	75%	15.2 (7.1)		MDD patients showed higher NfL levels compared to healthy controls.
Steinacker et al.,	2021	Germany	Case Control	Serum	single molecule array and ELISA	BD	6	48 (18–56)	27.27%	21.2 (16.6)	Healthy	8	45 (27–64)	75%	15.2 (7.1)		

Abbreviations: pt: Patients; N: number; f: Female; Nfl: Neurofilament light chain; HC: Healthy controls; ELISA: enzyme-linked immunosorbent assay; BD: Bipolar disorder; MDD: Major deppresive disorder

Table 2 The quality assessment findings based on NOS tools

First Author	Year of Study	1q	2q	3q	4q	5Aq	5 Bq	6q	7q	8q	NOS score
Hviid et al. (20)	2023	Yes ★	Yes ★	No	No	Yes ★	No	No description	Yes	No	5
Bai et al. (18)	2023a	Yes ★	Yes ★	No description	No	Yes ★	Yes	No description	No	No	4
Chen et al. (1)	2021	Yes ★	Yes ★	Yes	No	Yes ★	Yes ★	No	Yes ★	No	6
Steinacker et al. (13)	2021	Yes ★	Yes	No description	No	Yes ★	Yes ★	No description	No	No	4

Abbreviations: NOS: Newcastle-Ottawa Scale; q: question

Description for each question: 1q: indicates cases independently validated; 2q: cases are representative of population; 3q: community controls; 4q: controls have history of inflammatory or neuropsychiatric disease; 5Aq: study controls for age; 5 Bq: study controls for additional factor(s) (Number and Sex); 6q: structured interview where blind to case/control status; 7q: same method of ascertainment used for cases and controls; and 8q: nonresponse rate the same for cases and controls

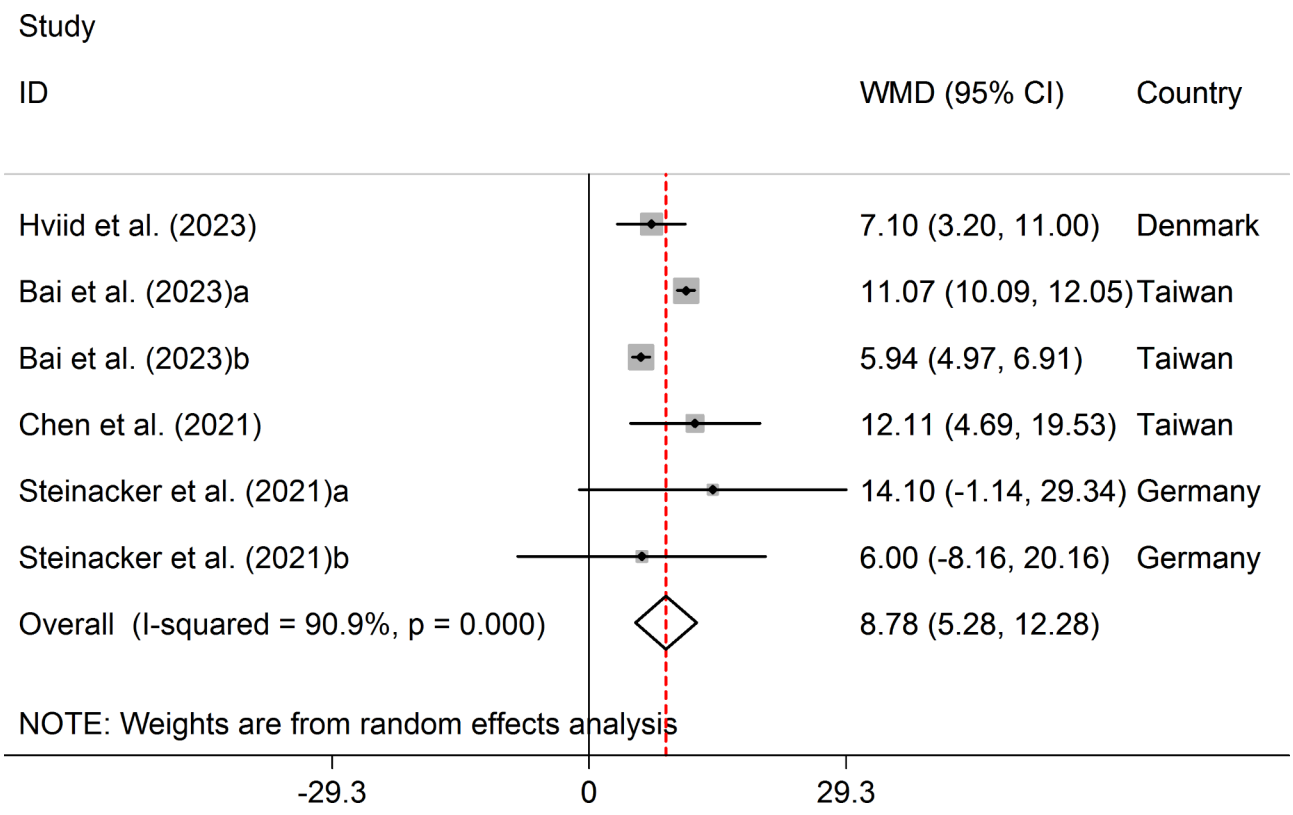

Fig. 2 The forest plot of the pooled weighted mean difference (WMD) NfL levels in patients with depression

Table 3 Subgroup analysis

Variable	Subgroup	*N* of SMD included	Pooled effect estimate	95% CI	I^2 (%), *P*-value
Patient group	BP-D	2	11.05	10.06, 12.03	0.0%, 0.48
	MDD	4	6.81	4.68, 8.94	23.7%, 0.27
Analysis method	SIMOA	1	7.10	3.20, 11.01	-
	ELISA	3	9.20	4.74, 13.66	96.3%, < 0.05
	SIMOA and ELISA	4	9.75	0.62, 20.13	0.0%, 0.45

Abbreviations: N: Number; SMD: standardized mean difference; CI: confidence interval; BP-D: Bipolar disorder; MDD: Major depressive disorder; SIMOA: single molecule array; ELISA: enzyme-linked immunosorbent assay

Publication bias assessment

The funnel plot did not indicate visually significant asymmetry, suggesting a lack of evidence of publication bias (Fig. 3). Egger (P=0.91) and Begg (P=0.57) tests further supported the absence of publication bias statistically.

Discussion

In this meta-analysis, we evaluated the potential of NfL as a biomarker by examining the differences in NfL concentrations between individuals with depressive disorders and controls. We found that NfL levels were significantly higher in people with depression compared

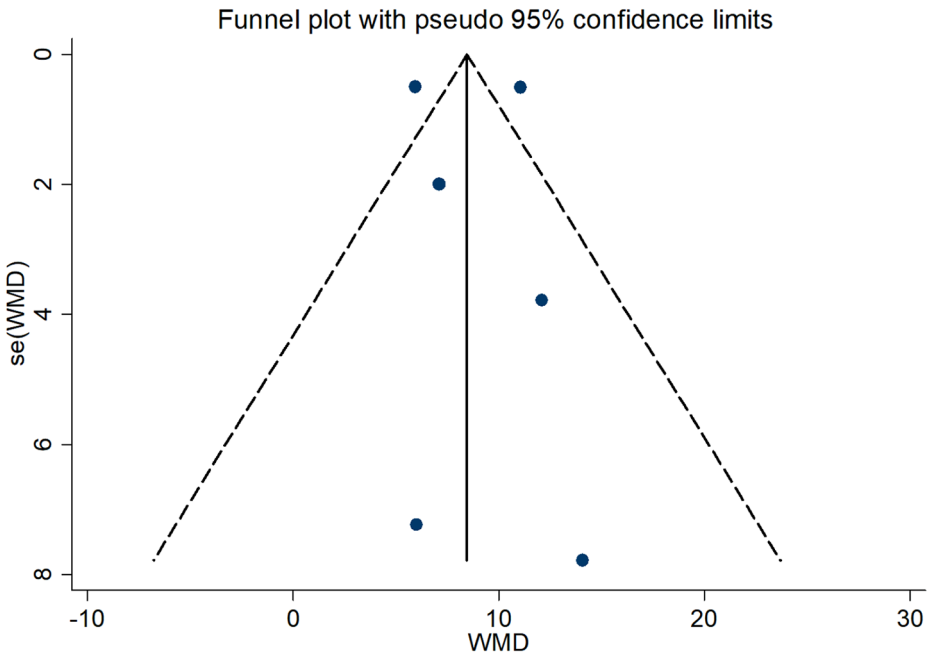

Fig. 3 The funnel plot for assessing the evidence of publication bias across included studies

to controls. The high levels of NfL in depressive-related disorders (bipolar disorder (BD), and MDD) suggest that NfL may be useful as a biomarker for diagnosing depressive disorders.

It is assumed that various mechanisms are involved in the increase in NfL, one of the most important of which may be increasing inflammation. Bai et al. suggested that the hyperinflammatory states associated with BD and MDD may contribute to the release of proinflammatory cytokines [18]. Prior research has demonstrated a notable and positive association between NfL concentration in the serum and proinflammatory cytokines, particularly tumor necrosis factor-α [1]. Nevertheless, Bavato et al. discovered no correlation between peripheral inflammatory indicators, such as C-reactive protein (CRP) and interleukins (IL-6 and IL-10), and NfL levels [19]. Increased levels of NfL and TNF-α are associated with executive dysfunction in major depressive disorder [1]. This evidence suggests that neuroaxonal injury and inflammatory processes may occur concurrently, contributing to the development of neurodegenerative and psychiatric diseases. Although the relationship between NfL, inflammatory markers, and cognitive function is still unclear in detail, Chen et al. proposed a positive correlation between cognitive function impairment and both NfLs and proinflammatory cytokines [1]. Similarly, Bavato et al. suggested that elevated levels of NfL are associated with decreased processing speed and attention, executive dysfunction, and delayed recognition memories in patients with mild cognitive impairment as well as cognitively intact individuals [19].

NfL may follow the general pathways of CSF drainage, either directly into the blood or via lymphatic vessels. Alternatively, NfL may share a similar drainage pathway to glial fibrillary acidic protein (GFAP), which flows into the blood via the arachnoid villi, along the lymphatic system, and through the cervical lymph nodes [22, 23]. Blood NfL test could serve as a less invasive method for detecting or monitoring depression and other neurodegenerative diseases. Given that studies have shown strong correlations between serum and CSF levels of neurobiomarkers, it might be possible to avoid invasive detection procedures such as a lumbar puncture [24].

Future studies should consider different sample collection methods for measuring NfL concentrations to support blood and CSF level correlations. Researchers have used multiple commercial assays, such as ELISA and SIMOA, to measure NfL levels in CSF and blood. In 1996, using ELISA Rosengren et al. [25] showed the first evidence of increased NfL levels in animal models of neurodegenerative diseases. More sensitive methods have been developed, like the SIMOA, which was first introduced by Rissin et al. [26]. It was recently demonstrated that SIMOA technology could significantly increase the sensitivity of digital immunoassays. It is currently not possible to establish a single cut-off point, as absolute concentrations of plasma NfL may vary between different assays, resulting in different cut-off values [6]. However, our meta-analysis showed that different immunoassay

techniques generated relatively similar results. Even though studies have identified changes in proteins and potential biomarkers in serum samples, neurochemical blood biomarkers for diagnosing MDD patients, predicting treatment response, and monitoring treatment response are still lacking [13].

There is an association between higher levels of NfL and rapid and extensive neuronal degeneration [27, 28]. However, different types of depressive disorders can overlap, and NfL elevations may vary depending on the certain types of disease. Previous studies demonstrated that elevated CSF NfL levels correlate with axonal damage in white matter and other subcortical brain structures rich in myelinated tissue that can release NfL during neurodegeneration [7]. However, NfL's diagnostic and prognostic potential in depressive disorders requires further research.

According to Ashton et al., plasma NfL showed a remarkable level of accuracy in distinguishing moderate and severe depression from other neurodegenerative disorders, with an AUC value of 0.95. Also, plasma NfL demonstrated superior capabilities in detecting neurodegeneration among younger individuals compared to older individuals [6]. This might be due to the possible neurodegenerative processes in older adults, which can result in higher NfL levels than in younger patients. Further studies are required to explore this age-dependent pattern [6, 29, 30].Yilmaz et al. demonstrated that NfL levels increase more than 100% between ages 20 and 50 and then double again by age 70 [31]. It is noteworthy that there is no consensus about the influence of sex on the NFL level. However, Bridel et al. showed that the CNS level of NfL in neurodegenerative disorders is higher in men [32]. It is worth mentioning that pharmacological and non-pharmacological interventions can influence NfL concentration. However, most evidence comes from animal studies [21, 33], and the mechanisms remain unclear.

It has been recommended that antidepressants may exhibit an anti-inflammatory effect in individuals with major depressive disorder [34]. A study by Lin et al. demonstrated that NfL may provide a predictor of the antidepressant effects of low-dose ketamine [35]. Similarly, Disanto et al. demonstrated that treatment could affect serum NfL levels, which could decrease with a longer duration of disease-modifying therapy in patients with neurodegenerative diseases. They also proposed that higher serum NfL levels are associated with an increased risk of future relapses [36]. However, Bavato et al. showed that NfL levels were not significantly different between patients under antidepressant treatment and those without it [19]. Antidepressants' effects on NfL require further study, for example, the possibility that the anti-inflammatory potentials of antidepressants might exert an effect on NfL levels or not.

Based on all studies that were conducted, we concluded that serum NfL could distinguish patients with BD, and MDD from healthy individuals and might serve as a useful biomarker for diagnosing depressive disorders.

Limitations and future directions

Our study, while informative, has several limitations. The limited number of available studies and the relatively small patient cohort included in our meta-analyses could impact the robustness of our results. Variations in the severity and duration of the underlying diseases in these studies added to the heterogeneity observed across our analyses, potentially influencing the outcomes. Another limitation is that the duration and type of treatment used could affect serum NfL levels, leading to interindividual variability in patients receiving treatment; consequently, it is important to consider the role of medical treatment and disease relapses, and also the effects of other systems, such as the cardiovascular and renal systems, on NfL levels. Further studies should be conducted to examine the role of NfL as a potential diagnostic biomarker for depressive disorders and its subtypes. Furthermore, efforts should be directed toward studying the early detection of NfL elevations at the onset of depression, even before cognitive impairment symptoms manifest. Lastly, psychiatrists, neurologists, and researchers should collaborate to establish specific cut-off values, including age-specific, sex-specific, and even disease-specific reference values, facilitating the clinical utility of NfL in diagnosing and managing different forms of depression.

Conclusion

Our meta-analysis indicates that increased NfL levels might be helpful as a biomarker for diagnosing depressive disorders. However, further research encompassing a broader range of disease subtypes is necessary to elucidate the role of NfL in the pathogenesis of neuropsychiatric conditions. Additionally, longitudinal studies are essential to characterize NfL fluctuations throughout the disease course and to establish the use of NfL in clinical settings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-024-06051-0.

Supplementary Material 1

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Author contributions
All authors contributed to the study's conception and design. All authors read and approved the final manuscript. A.H.: Literature search, conception and design of the study, data collection, drafting the manuscript. VR.O.: Analysis and interpretation of data, critical revision of the manuscript. MA.G.: Data collection, and drafting the manuscript. K.K.: Literature search, data collection, and drafting of the manuscript. S.K.: Study design, data interpretation, and drafting of the manuscript. R.T.: Supervision, critical revision of the manuscript, and analysis and interpretation of data.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed after obtaining the ethics approval of Fasa University of Medical Sciences with ID: 402190.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Conflict of interest
The authors declare that there is no conflict of interest.

Competing interests
The authors declare no competing interests.

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