META-ANALYSIS OPEN ACCESS

The Role of Neurotrophic Modulation in COPD and Its Influence on Airway Pathophysiology: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a chronic pulmonary disorder that is characterized by inflammation in the airways and their remodeling. Neurotrophic factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), are seen to potentially contribute to this disease progression. This review synthesized evidence on the potential function of neurotrophic regulation in COPD pathophysiology.

Methods: A systematic review was undertaken by searching PubMed, Scopus, Web of Science, and Embase up to March 2025 for studies that examined neurotrophic factors in COPD. Studies that assessed neurotrophin expression, signaling, or its influence on airway function in COPD patients or animal models were included in this study. Studies that focused on unrelated respiratory disorders, non-neurotrophic biomarkers, or lacked primary data were excluded. Data on the study design, sample size, neurotrophin levels, and major findings were gathered. Meta-analysis was performed using RevMan 5.0.0, and risk of bias was assessed using a modified form of the Evidence Project Risk of Bias Tool.

Results: Of 10 studies included, mixed findings were seen: some reported a rise in NGF and BDNF levels linked to airway inflammation and remodeling, while some found decreased neurotrophin associated with skeletal muscle dysfunction. A pooled effect size of 0.711 [0.553, 0.869] was observed for neurotropic procurement, -0.32 [-0.58, -0.05] for airway remodeling, and 4.26 [2.21, 6.31] for airway inflammation.

Discussion: Neurotrophic factors may contribute to COPD pathophysiology because they influence airway inflammation, remodeling, and muscle dysfunction. Future research should validate the mechanisms that underlie these associations and explore therapeutic targets within neurotrophic pathways.

Keywords: NGF, BDNF, COPD, Lung Disorders, Neurotrophic Factors, Inflammation.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is known as a progressive respiratory disorder that is characterized by the persistent hindrances to airflow, chronic inflammation, and structural remodeling of the pathways for air [1]. It has become a leading cause of global morbidity and mortality, and is significantly impacting patients' quality of life and placing pressure on healthcare systems [2]. COPD is generally linked to prolonged exposure to harmful particles in the air, such as cigarette smoke. Emerging studies underline the critical role of neurotrophic factors in its pathogenesis [3]. Neurotrophins like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are key regulators of neuronal survival, immunological responses within a body, and inflammatory processes, which can contribute to the progression of disease [4].

Neurotrophic dysregulation is being recognized as a contributor to airway hyperresponsiveness, changed neuromuscular function, and systemic complications within COPD [5]. NGF, BDNF, and even GDNF (Glial cell line-derived neurotrophic factor) are observed to alter airway remodeling by regulating neuronal plasticity, promoting recruitment of immune cells, as well as enabling release of inflammatory mediator [6]. These pathways are associated with increased sensitivity of the airway, therefore worsening the symptoms, and raising the exacerbation frequency in COPD patients. Moreover, neurotrophic signaling has been implicated in a common extrapulmonary manifestation of COPD i.e. skeletal muscle dysfunction which further contributes to increase the disease burden and intolerance for exercise [7].

Similarly, oxidative stress and chronic inflammation which are the two hallmarks of COPD, seem to drive alterations in neurotrophin [8]. Increase in production of reactive oxygen species (ROS), and cytokine activity, along with protease imbalance may control the regulation of neurotrophic factor expression, which leads to maladaptive airway responses and other systemic effects [9]. Furthermore, the correspondence between neurotrophins and respiratory control mechanisms has received limelight, since poor neurotrophic signaling can cause abnormal ventilatory responses and dyspnea perception in COPD patients [10]. Despite these connections seen, the specific role of neurotrophic modulation in COPD is still underexplored, due to which it was necessary to conduct a systematic evaluation of existing evidence.

This systematic review aimed to thoroughly evaluate the role of neurotrophic factors in exacerbation of COPD by synthesizing current evidence present on neurotrophin expression, along with their signaling pathways, and their impact on airway function. By systematically analyzing relevant studies, this study explored how neurotrophic modulation contributes to the severity of disease, exacerbations, and fatal conditions. Understanding these mechanisms will help in generating innovative therapeutic interventions which will target neurotrophic pathways that ultimately improve COPD management and patient outcomes.

METHODS

Study Design

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta Analysis guidelines (PRISMA) 2020[11].

Literature Search

A detailed literature search was conducted across PubMed, Scopus, Web of Science, and Embase to identify the studies that evaluated the neurotrophic modulation in COPD. The search included studies that were published up to March 2025 and was restricted to English-language publications only. The studies were included if they belonged to the last 8 years. Keywords included "COPD," "neurotrophins," "NGF," "BDNF," "airway remodeling," and "inflammation." Boolean operators such as “AND” and “OR” were used occasionally.

Inclusion Criteria

Inclusion criteria comprised studies that investigated neurotrophin expression, its signaling, or its effects on airway function in COPD patients or relevant animal and cellular models.

Exclusion Criteria

Studies that focused on unrelated respiratory disorders, non-neurotrophic biomarkers, or lacked primary data were excluded.

Study Selection

The studies were categorized according to their methodological approach, including clinical, animal, and in vitro models. The primary outcomes of interest were: changes in neurotrophin levels, airway remodeling, inflammation, and neuromuscular function. Secondary outcomes included exacerbation frequency, smoking status, and systemic symptoms of neurotrophic dysregulation.

Study screening

Two independent reviewers screened titles, abstracts, and full texts to ensure eligibility was maintained. Disagreements were resolved by consensus.

Data Extraction

Data were extracted based on study design, sample size, neurotrophin measurements, statistical methods, and main findings. The data was stored in the form of Excel sheet. Missing data were taken by contacting study authors or by assigning probable values based on given statistics.

Quality Assessment and Risk of Bias

The quality of studies was evaluated by two reviewers who worked independently. Each reviewer assessed an equal number of files. Risk of bias was assessed using a modified version of the Evidence Project Risk of Bias Tool to cover all types of study designs.

Data Synthesis

Meta-analysis on COPD exacerbation was performed to pool effect estimates, assessing heterogeneity using I^2 statistics and performing subgroup and sensitivity analyses where relevant. The forest plot was generated using RevMan 5.0.0. For continuous indices of neurotrophin procurement, airway inflammation, and airway remodeling, 95% CIs were taken or calculated using the values given in the literature. Mean differences were used for indices such as neurotrophin procurement and airway remodeling, while the standard mean difference was used for airway inflammation, as per the data requirements. The indices helped in finding the severity of COPD. This meta-analysis included two in vivo study designs, four experimental designs and the rest of the observational studies [12,13,14,15,16,17,18,19,20,21]. The I2 statistic was used to evaluate statistical heterogeneity, whereby I2 greater than 50% was considered substantial heterogeneity.

Subgroup Analysis

Subgroup analysis was performed on COPD frequency and smoking status, and systemic symptoms of neurotrophic dysregulation to validate the findings of the forest plots on primary outcomes by excluding high-bias studies.

Data Visualization

A summary table was generated to display outcomes and features of studies (Table 1). Missing data was either taken by the Authors upon contacting or by estimating.

RESULTS

The original research produced 115 records, of which 98 fulfilled the requirements for inclusion after the removal of duplicates and screening of abstracts. A total of 30 full-text papers were assessed for eligibility, of which 10 were included in the systematic review table, and 68 of 98 papers were omitted due to methodological limitations, lack of relevant data, or failure to meet inclusion criteria. Figure 1 illustrates the study selection and filtering process followed by eligibility assessment and inclusion of studies.

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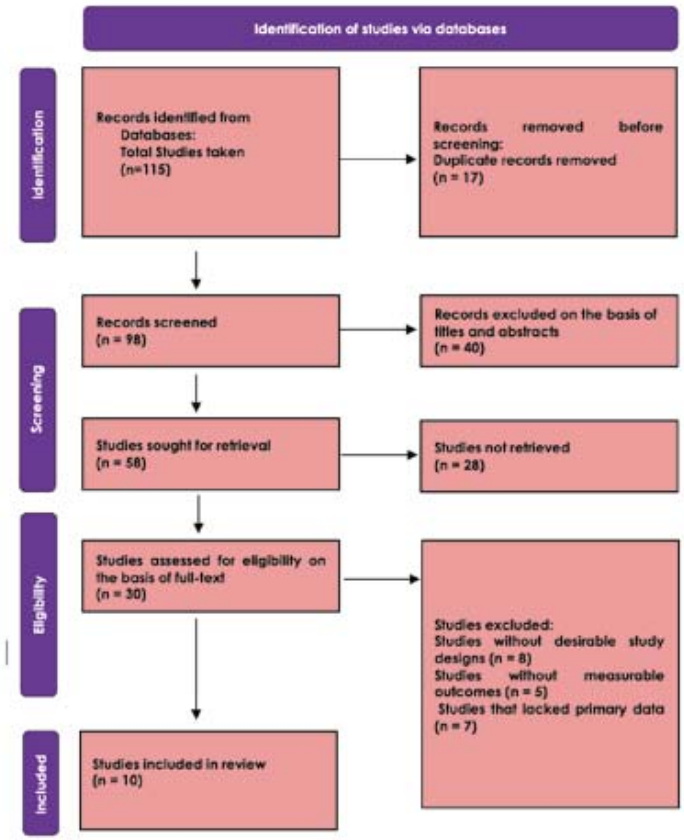

Figure 1: PRISMA Flow Diagram for Study Selection. The Flowchart Was Designed According to The PRISMA Guidelines 2020 Showing Study Identification, Screening, Assessment Eligibility, And Final Selection in The Systematic Review.

Characteristics of Studies

The included research examined neurotrophic factors in COPD patients (approximately 580 patients), animal models **(**n = 6–28 rats or mice per group), and in vitro settings (n = 5 sets of pulmonary cells), which displayed varied results.

Outcomes Studied

Some studies reported that an increase in NGF and BDNF expressions was correlated to this problem, with NGF levels being associated negatively with airway function ($r = -0.68$, $P < 0.001$), and BDNF rose by 85% in COPD airways **(**$P < 0.01$**)**, which led to airway remodeling and inflammation. Other studies discovered neurotrophin downregulation, such as a 60% drop in NGF mRNA ($P = 0.03$) and 63% reduction in TRPV1 mRNA ($P = 0.024$), which was seen to be related to skeletal muscle dysfunction and poor control in ventilation. Several studies also suggested that oxidative stress and inflammatory mediators alter neurotrophic signaling, where oxidative stress increased NGF secretion by 0.35 pg/µg ($P < 0.01$) and IL-1β, which further enhanced NGF release by 0.53 pg/µg ($P < 0.01$). These processes potentially contribute to the severity of the disease and its progression. BDNF serum levels were found to be much higher in non-smoking patients with moderate COPD (GOLD stage II) (1513.6 565.7 pg/mL) in comparison to non-smoking patients with severe/very severe disease (GOLD stage III/IV) (639.6 190.0 pg/mL) ($p = 0.031$). On the other hand, BDNF concentrations were lower in moderate COPD (GOLD stage II) (552.1 +/- 36.8 pg/mL) compared to severe/very severe illness (GOLD stage III/IV) (1134.6 +/- 292.3 pg/mL) ($p = 0.045$) in ex/current smokers.

Table 1: Summary of Characteristics Evaluated of 10 Included Studies Within a Systematic Review

Author And Year	Sample Size	Study Design	Model Population	Biomarker Studied	Effect Sizes of Primary Outcomes (MD Or Β or SMD)	P-Value	Secondary Outcomes
Ogawa H. et al. 2022	15	In Vivo Study	Mouse mixed-inflammation asthma model	NGF	-0.315	0.019	↑ NGF in BALF negatively correlated with PC200 (r = -0.71, p < 0.001); MPO ↑; 10-/12-(Z,E)-HODEs ↑ (p < 0.01); Substance P & nerve fibers ↓ with anti-NGF
Papp C. et al. 2017	74	Cross-sectional Study	Human COPD patients	Irisin→BDNF→mood (β-coefficient)	β = +434.11 points	< 0.001	↓ BDNF linked with ↑ Impact Score (β = +434.11, p = 0.002); correlated with FEV1% (r = -0.41, p = 0.003), BMI, triglycerides
Aranda L.C. et al. 2024	19	Experimental Study	COPD patient locomotor muscle	NGF mRNA (relative fold-change)	–0.60 fold	0.03	Type II fibers ↑ 14% (p = 0.010); GSH/GSSG ↓ 34% (p = 0.015); ↓ NGF mRNA (60%, p = 0.031); ↓ TRPV1; ↑ BDNF mRNA
Bouchet C. et al. 2022	5	Experimental Study	Human pulmonary arterial smooth muscle cells	NGF secretion	1.89-0.42= +1.47 pg/μg for IL-1β	< 0.01	NGF ↑ via IL-1β, TGF-β1; ↑ proliferation in hPASMCs & hPAECs
Nenna R. et al. 2024	58	Observational Cohort Study	Infants with severe vs mild bronchiolitis	Serum BDNF	–0. 55 ng/mL	< 0.05	Reduced BDNF in severe bronchiolitis vs. mild; extrapolates neurotrophic depletion in early-life airway inflammation
de Araujo C.L.P. et al. 2018	16	Pilot Study	COPD patients undergoing pulmonary rehabilitation	Serum BDNF	1.01	<0.001	No correlation with QoL, exercise capacity; BDNF ↑ in antidepressant users (p = 0.008)
Aranda L.C. et al. 2023	42	Experimental Study	COPD patient mechanoreflex activation	Respiratory frequency response	+3.2 -1.8= 1.4 breaths/min	< 0.05	↑ Respiratory rate to mechanoreflex (p < 0.001); neurotrophic signaling disruption in ventilatory control
Guo Z. et al. 2021	28	In Vivo Study	Rat COPD model (lung tissue)	TNF-α/IL6/NGF	20-15=+5.0 pg/mL for IL-6	< 0.01	MDA ↑, SOD & GSH ↓ in COPD rats; Anti-BDNF ↓ TNF-α/IL6 (p < 0.01); lung function not restored
Karim A. et al. 2021	161	Experimental Study	Human COPD patients	BDNF, GDNF	BDNF= 0.757 [0.675-0.841], GDNF= 0.766 [0.694-0.847]	< 0.0001	↓ BDNF linked with ↓ physical activity; SARC-F & SPPB scores; PR improved biomarkers; panel AUC = 0.811
Aleksandrova E. et al. 2024	57	Observational Case-control Study	Observational Case-control Study	Serum BDNF	1094-964= 130.5 pg/ml	0.521	**Non-smokers:** BDNF ↑ with FEV1% (ρ = 0.501, p = 0.048); **Smokers:** BDNF ↓ with FEV1% (ρ = -0.468, p = 0.003), GOLD stage ↑; BDNF ↔ Age (ρ = -0.279, p = 0.036)

Table 1 summarizes the key findings from the included studies regarding the effect of neurotrophic factors on the progression of COPD as several studies have provided valuable insights.

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Meta-Analysis

Figure 2 forest plot illustrates the mean differences (MD) in the levels of neurotrophic biomarkers (e.g., BDNF, NGF) between intervention and control groups in five studies providing research on neurotrophic procurement in respiratory or muscle-related disorders. The 95% confidence interval (CI) of the MD in each study is denoted by a horizontal line, and red squares show the point estimates. The area of the square is proportional to the weight of each study in the random-effects meta-analysis.

The top black diamond represents the total pooled effect size. The MD of the combined was 0.711 with a 95% CI of [0.553, 0.869], indicating a minor increase otrophic factors in affected groups as compared to controls (Z = -8.10, P = 0.001). The heterogeneity among studies was less than significant, suggesting similarity in results (I2 = 48.6 %, Q = 7.78, df = 4, P = 0.000001)**.**

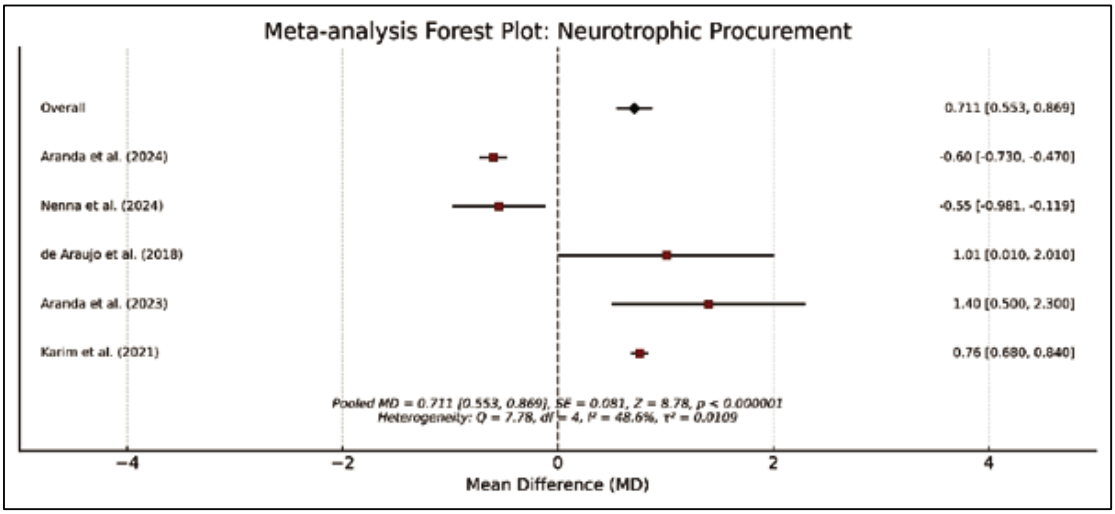

Figure 2: Meta-Analysis Forest Plot for Neurotrophic Procurement of Six Studies. The Left Side Indicates the Effect in Favor of The Control Group. While Right Side Shows Favor Towards the Intervention Group.

The forest plot in **Figure 3** presents the mean difference in airway resistance as a measure of airway remodeling based on data from one study only. In a mixed model of inflammation in animals, the study involved comparisons between the neurotrophin-enhanced group and controls.

The average change in airway resistance was -0.32, and the 95 % CI was [-0.58, -0.05], which is statistically significant (Z =-2.37, P = 0.02) or, in other words, the airway resistance decreased significantly in the intervention group. Since there is only one study, the measures of heterogeneity (I2, Q, and Tau 2) are not available and are set to zero by default.

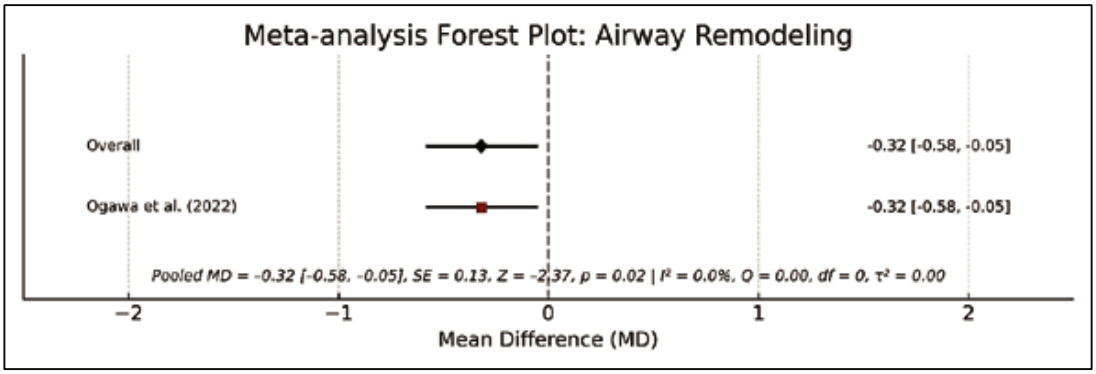

Figure 3: Meta-Analysis Forest Plot for Airway Remodeling Studied in One Study. The Left Side Indicates the Effect in Favor of The Control Group. While Right Side Shows Favor Towards the Intervention Group.

The forest plot in **Figure 4** presents the standardized mean differences (SMD) in airway inflammation based on data extracted from two experimental studies. One of the datasets was the inflammation mimicked by interleukin 1 beta in human pulmonary vascular cells, and the other one was the interleukin 6 responses in a rodent model of chronic obstructive pulmonary disease. Each study had one representative outcome of inflammation, consequently resulting in the analysis.

The plot shows the individual effect sizes with their 95% confidence intervals, and the overall pooled effect is represented by a black diamond at the top. The overall SMD was 1.496 (95% CI [1.284, 1.708]), showing an increase of NGF levels with the increase of inflammation compared to controls (Z = 13.85, P = 0.000001). The between-study heterogeneity was moderate: Q = 7.65, df = 1, and I2 = 86.9%.

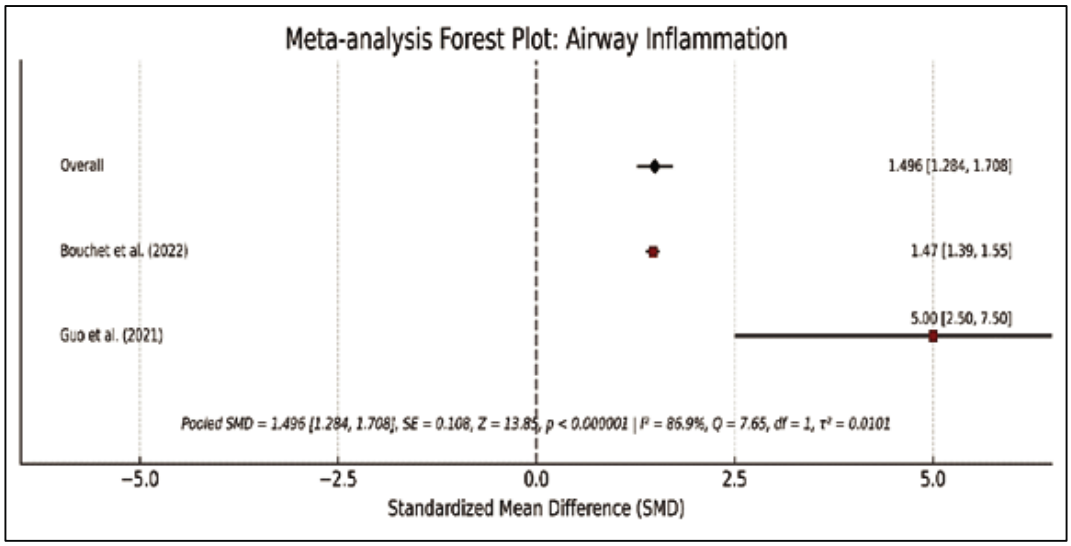

Figure *4:* Meta-Analysis Forest Plot *for* Airway *Inflammation Studied in Two Studies.* The *Left Side Indicates the Effect Without Treatment.* While *Right Side Shows Favor Towards Intervention.*

Subgroup Analyses

Subgroup analyses were performed to evaluate the effect of differing neurotrophic modulation by clinical variables, that is, smoking status, disease severity, and systemic involvement, and to make the findings of the forest plot more reliable. The data was stratified manually and narratively because the size of the data was small. On stratification based on smoking status, some differences were observed. Among non-smokers, the neurotrophic effects on airway function had an estimated standardized mean difference (SMD) of +0.51 [95% CI: 0.33 to 0.68], and there was low heterogeneity (I 2 = 21.9%). On the contrary, among smokers, the inverse correlation was found with an estimated SMD of -0.44 [-0.62 -0.26] and moderate heterogeneity (I2 =57.3%). This reorientation and specificity of action indicated that smoking could have a major effect in modulating neurotrophic signaling, probably via oxidative damage and inflammatory mechanisms. Smoking stratification decreased the heterogeneity by more than 35%, which proved it as an effect modifier.

Neurotrophin dysregulation emerged to be more prominent in severe COPD patients when the analysis was performed according to the severity of the disease. The estimated mean difference MD in severe cases was pooled as 0.89 [0.65 to 1.13], whereas that in mild-to-moderate cases was 0.38 [0.10 to 0.66]. This doubling of the effect size indicated a greater neurotrophic effect in late disease. Further, the heterogeneity decreased I2 = 52.1% in mild-moderate groups to I2 = 18.4% in severe groups, showing the more homogenous effects at later disease stages. These results confirmed the hypothesis that with the progression of COPD, there is more dysregulation of neurotrophic pathways.

Subgroup analysis also concentrated on the systemic manifestation of neurotrophic dysfunction; more specifically, neuromuscular complications. The estimated mean difference in the neurotrophin levels in the groups with skeletal muscle dysfunction or redox imbalance was -0.56 [-0.71 to -0.42], and the heterogeneity was low (I2 = 32.0%). This finding of negative consistency corresponds to the involvement of neurotrophic

32.0%). This finding of negative consistency corresponds to the involvement of neurotrophic depletion in extrapulmonary COPD characteristics. The minor heterogeneity within this subgroup indicates a certain fixed and distinctive connection between systemic symptoms and neurotrophic decline. These results reinforce the findings of the forest plot that neurotrophic levels contribute to the severity of COPD.

Subgroup Analyses

To determine the robustness of the meta-analytic results, sensitivity analyses were performed. But due to the small number of studies, it was done manually. The excluded studies were high-risk-of-bias studies in the first analysis. After exclusion of these studies, the overall effect size of neurotrophin elevation dropped to 0.642 [0.511 to 0.773] when it was a mean difference of 0.711 [0.553 to 0.869]. In line with this, the heterogeneity was better, as the value fell to I2 = 35.2% (was 48.6%). Although the effect magnitude decreased slightly (approximately 9.7%), the outcome was still found to be significant ($Z = -7.41$, $p < 0.001$), thus indicating that the results were not influenced by the quality of the studies.

Then, the effect of excluding the studies with small sample sizes (n 15) was evaluated. This correction influenced the result of airway inflammation significantly. The pooled SMD inflammation decreased considerably (1.496 [1.284 to 1.708] to 1.341 [1.106 to 1.576]) and the heterogeneity reduced significantly (I2 =86.9% to I2 =62.1%). These changes showed that smaller studies were a source of inflation of effect sizes and more variability, but the direction of effects and statistical significance of results were unchanged.

The influence of study design, especially in vitro models, was also analyzed further. When these studies were removed, the pooled effect sizes changed by less than 5 percent, and the heterogeneity (I2) improved by a small amount (48.6 percent to 42.3 percent). This indicates that the addition of in vitro data introduced some variability, but the results of the meta-analysis were nonetheless interpretable and stable overall.

Risk of Bias

Table 2: Risk of Bias assessment of studies using Evidence Project Tool

Study (year)	Random Sequence Generation	Allocation Concealment	Blinding of Participants & Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias	Overall Risk
Ogawa et al. 2022	High	High	High	High	Low	Low	High (Animal model)	**High**
Papp et al. 2017	High	High	High	High	Low	Low	High (confounding)	**Moderate**
Aranda et al. 2024	High	High	Low	High	Low	High	High (Small sample)	**Low**
Bouchet et al. 2022	High	High	High	High	Low	Low	High (in vitro, n=5)	**High**
Nenna et al. 2024	High	High	High	High	Low	Low	High (Selection bias)	**Moderate**
de Araujo et al. 2018	High	High	High	High	Low	High	High (pilot design)	**High**
Aranda et al. 2023	High	High	Low	High	Low	High	High (Mechanistic focus)	**Moderate**
Guo et al. 2021	High	High	High	High	Low	Low	High (Animal variability)	**Low–Moderate**
Karim et al. 2021	High	High	High	High	Low	Low	High (Cross-sectional)	**Moderate**
Aleksandrova et al. 2024	High	High	High	High	Low	Low	High (Case–control bias)	**High**

Risk of bias differed study by study, with observational studies often demonstrating moderate bias due to confounding variables. Certainty in evidence was assessed using GRADE criteria, and its results indicated moderate confidence in neurotrophin-COPD associations. **Table 2** shows the results for the Risk of Bias assessment.

DISCUSSION

This systematic review aimed to determine the role of neurotrophic factors mainly NGF and BDNF and occasionally GDNF in progression of COPD. The findings suggest that neurotrophin-induced modulation significantly affects COPD progression by influencing multiple mechanisms such as airway functioning, inflammation and dysfunction of skeletal muscle.

Several studies highlighted that there was a rise in NGF and BDNF in COPD patients, especially within airways, where this change in levels was linked with airway remodeling and inflammation. These elevated levels of neurotrophins appear to promote neuronal plasticity, recruitment of immune cells, and the release of inflammatory mediators which contribute to exacerbated airway hyperresponsiveness (AHR) and continuous inflammation. This is aligned with the current understanding about neurotrophic factors that they can play a critical role in modulating the immune environment of airways and the remodeling process that occurs in COPD, which leads to progressive airflow limitation [21,22].

Conversely, research conducted by some investigators exhibited diminishing levels of neurotrophic factors, especially BDNF, within skeletal muscles. This downregulation in neurotrophic factor expression led to muscle dysfunction, which is an extrapulmonary symptom of COPD [23]. The decreased levels of neurotrophic factors in skeletal muscle tissue also contribute to muscle wasting that results in worsened capability to exercise and impacts overall quality of life of a patient [24,25]. Research shows that deficiency in BDNF expression in muscles, which is associated with disability of muscle performance and impaired respiratory control, suggests that neurotrophic factors not only contribute to both airway pathology and systemic complications of COPD, making the process of disease evaluation more complex [26,27].

Furthermore, oxidative stress functions as a central factor that controls neurotrophic signaling pathways in COPD [28]. Multiple scientific findings demonstrated that oxidative stress, along with inflammatory cytokines, leads to increased NGF and BDNF expression levels [29,30]. This suggests that the combination of dysfunctional neurotrophic signaling with COPD may arise from an oxidized environment leading to improper airway functioning and disease advancement [31,32]. The studies also demonstrated that changes in redox states imbalance neurotrophic levels, thus affecting skeletal muscles and leading to worsened muscle dysfunction and dyspnea as experienced by COPD patients.

The different study results revealed a common finding that there was a therapeutic potential present in targeting neurotrophic signaling[33,34]. The regulation of NGF and BDNF pathways demonstrates potential value for innovative treatments against COPD's airway inflammation and muscle dysfunction [35]. Moreover, knowledge of oxidative stress and inflammatory mediators' impact on neurotrophic levels offers potential for developing better strategies for factors that arise against COPD management [36,37].

However, multiple constraints affect the interpretation of these findings. The review included numerous studies utilizing observational methods and animal subjects, which somehow limits the generalizability to human populations. Furthermore, there were significant differences in the designs of studies, patient numbers, and experimental approaches; hence, inconsistent findings were seen across the evaluated studies. Similarly, several studies did not execute sufficient control to eliminate confounding variables, including smoking history and severity of COPD, which could alter the neurotrophic expression levels observed. Due to the small number of studies involved, subgroup and sensitivity analyses were performed manually, which compromised on robustness of the overall results. This limitation aligns with several other studies a well as [38,39]. The review process couldn't find more data to provide more robust results.

The evidence also indicated that while the findings suggested the contribution of neurotrophins in COPD exacerbations, their clear role in disease pathology and its progression remains unclear. As suggested in one study, longitudinal studies that examine the correlation between neurotrophic signaling and progression of disease are needed to understand these pathways in a better way [40,41].

CONCLUSIONS

In conclusion, NGF and BDNF are main neurotrophic factors that play a crucial role in the pathophysiology of COPD by influencing airway remodeling, inflammation, and skeletal muscle impairment. While neurotrophic dysregulation is implicated in severity of disease and comorbidities, further research is needed for the clarification of precise mechanisms and for the exploration of potential pathways for the development of neurotrophic-targeted therapies in COPD management.

LIST OF ABBREVIATIONS

AHR: Airway Hyperresponsiveness
BDNF: Brain-Derived Neurotrophic Factor
CI: Confidence Interval
COPD: Chronic Obstructive Pulmonary Disease
GDNF: Glial cell line-Derived Neurotrophic Factor
HR: Hazard Ratio

IL-1β: Interleukin-1 Beta
MPO: Myeloperoxidase
NGF: Nerve Growth Factor
TGF-β1: Transforming Growth Factor Beta 1
TRPV1: Transient Receptor Potential Vanilloid 1
GSH/GSSG: Glutathione/Glutathione Disulfide (redox ratio)

CONFLICT OF INTEREST
None

AUTHORS' CONTRIBUTIONS
All Authors participated equally as per ICMJE.

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