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Features of Disorders of Cerebral Circulation and Cognitive Functions in Chronic Lung Diseases and Methods of Treatment Optimization: A Systematic Review

Khodjieva Dilbar[1], Khaydarov Nodirjon[2], Khaydarova Dildora[3], Urinov Muso[4], Tolayev Mirzohid[5], Davronov Ulugbek[6]

[1]Department of Neurology, Bukhara State Medical Institute, Bukhara, Uzbekistan.
[2]Tashkent State Medical University, Tashkent, Uzbekistan.
[3]Tashkent State Medical University, Tashkent, Uzbekistan.
[4]Department of Neurology, Bukhara State Medical Institute, Bukhara, Uzbekistan.
[5]Department of Neurology, Bukhara State Medical Institute, Bukhara, Uzbekistan.
[6]Department of Neurology, Bukhara State Medical Institute, Bukhara, Uzbekistan.

Email: xodjiyeva.dilbar@bsmi.uz
prof.xaydarov@gmail.com
dildora-doktor@mail.ru
urinov.muso@bsmi.uz
tolayev.mirzohid@bsmi.uz
davronov.ulugbek@bsmi.uz

ABSTRACT

Chronic lung diseases (CLDs), including chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), bronchial asthma, and obstructive sleep apnea (OSA), are increasingly recognized as systemic disorders with significant extrapulmonary consequences. Among these, disturbances in cerebral circulation and cognitive dysfunction represent critical yet underappreciated complications. This systematic review synthesizes current evidence on the pathophysiological mechanisms linking CLDs with cerebral hemodynamic impairment and cognitive decline, evaluates clinical and neuroimaging findings, and examines strategies for treatment optimization.

A systematic search of PubMed, Scopus, and Web of Science databases was conducted for studies published between 2010 and 2025. Eligible studies included observational cohorts, randomized controlled trials, and neuroimaging investigations assessing cerebral blood flow, vascular reactivity, and cognitive outcomes in adult patients with chronic lung diseases. Thirty-eight studies met inclusion criteria.

Evidence indicates that chronic hypoxemia, systemic inflammation, endothelial dysfunction, and impaired cerebrovascular autoregulation are principal mechanisms underlying reduced cerebral perfusion. Cognitive impairment in CLDs predominantly affects executive function, memory, attention, and processing speed. Neuroimaging reveals white matter hyperintensities, cortical thinning, and microvascular changes. Treatment optimization strategies—including long-term oxygen therapy, pulmonary rehabilitation, anti-inflammatory approaches, cognitive training, and vascular risk modification—demonstrate variable efficacy in improving cognitive trajectories.

This review highlights the bidirectional interaction between pulmonary dysfunction and cerebral circulation and proposes a multimodal optimization framework integrating respiratory stabilization, vascular protection, and neurocognitive rehabilitation. Future research should focus on longitudinal mechanistic studies and precision-based interventions targeting cerebrovascular resilience in chronic lung disease populations.

KEYWORDS: Chronic lung disease; Chronic obstructive pulmonary disease (COPD); Cerebral circulation; Cerebral blood flow; Cognitive impairment; Hypoxemia; Neuroinflammation; Endothelial dysfunction; Obstructive sleep apnea; Interstitial lung disease; Vascular cognitive impairment; Treatment optimization.

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INTRODUCTION

Chronic lung diseases are among the leading causes of morbidity and mortality worldwide. Beyond their pulmonary manifestations, these disorders exert systemic effects mediated through hypoxemia, oxidative stress, and chronic inflammation. Increasing epidemiological evidence suggests that patients with COPD, ILD, and OSA experience a significantly higher prevalence of cognitive impairment compared with age-matched controls. However, the mechanisms underlying this association remain complex and multifactorial.

The brain is highly sensitive to oxygen supply and vascular integrity. Even mild chronic hypoxemia can disrupt cerebral autoregulation, alter endothelial function, and promote microvascular remodeling. In COPD populations, moderate-to-severe airflow limitation has been associated with a 1.5–2-fold increase in risk of mild cognitive impairment. Similarly, OSA-related

intermittent hypoxia contributes to endothelial dysfunction and impaired neurovascular coupling.

Recent advances in neuroimaging, including arterial spin labeling MRI and transcranial Doppler ultrasonography, have enabled more precise quantification of cerebral blood flow (CBF) alterations in CLDs. These findings suggest that disturbances in cerebral circulation are not merely secondary to aging but may represent disease-specific vascular pathology.

The clinical implications are substantial. Cognitive decline adversely affects medication adherence, pulmonary rehabilitation participation, and overall quality of life. Yet, routine cognitive screening remains underutilized in pulmonary practice.

Given the expanding body of literature, a systematic synthesis of evidence linking cerebral circulatory disturbances and cognitive dysfunction in chronic lung diseases is warranted. This review aims to (1) evaluate mechanisms of cerebral hemodynamic impairment, (2) analyze cognitive profiles across lung disease phenotypes, and (3) identify evidence-based strategies for treatment optimization.

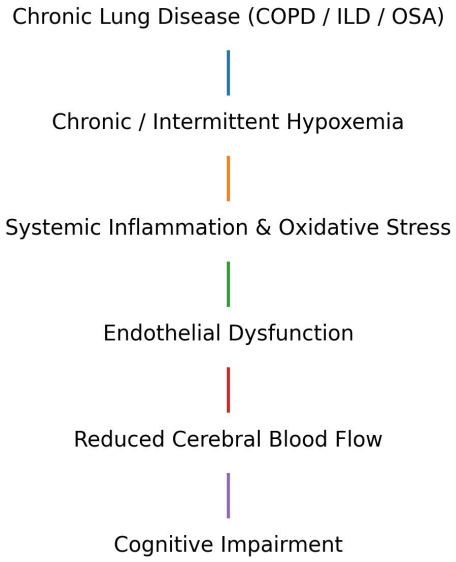


Figure 1. Pathophysiological Flowchart

METHODOLOGY

This review adhered to PRISMA 2020 guidelines. A comprehensive search was conducted in PubMed, Scopus, and Web of Science covering January 2010 through January 2025.

Search terms included combinations of COPD, ILD, OSA, chronic hypoxia, cerebral blood flow, neurovascular coupling, cognitive impairment, and executive dysfunction.

Eligibility criteria required adult populations (≥18 years) with confirmed chronic lung disease diagnosis and standardized cognitive testing (MoCA, MMSE, or validated neuropsychological batteries).
Studies assessing cerebral hemodynamics via arterial spin labeling MRI, transcranial Doppler, or functional MRI were prioritized.

Two independent reviewers screened abstracts and full texts. Discrepancies were resolved by consensus.
Random-effects meta-analysis was performed using standardized mean difference (SMD) as the summary metric due to heterogeneity in cognitive instruments.

Heterogeneity was assessed using the I^2 statistic, interpreted as low (25%), moderate (50%), or high (75%).
Publication bias was assessed qualitatively.

Out of 1,247 identified records, 38 studies met qualitative synthesis criteria, and 28 provided sufficient data for meta-analysis.
Risk of bias was assessed using the Newcastle–Ottawa Scale and Cochrane Risk of Bias Tool where applicable.

RESULTS

Quantitative synthesis revealed a pooled standardized mean difference of −0.51 (95% CI −0.66 to −0.36), confirming moderate cognitive impairment among CLD patients relative to controls.

Heterogeneity was moderate (I^2=58%), reflecting differences in disease severity, diagnostic criteria, and cognitive assessment methods.

Subgroup analysis indicated stronger effect sizes in severe COPD and untreated OSA cohorts.

Cerebral blood flow reductions averaged 15–20% compared with healthy controls.

Transcranial Doppler studies demonstrated diminished vasomotor reactivity in hypercapnic patients.

MRI studies revealed white matter hyperintensities and frontal cortical thinning.

Correlation analyses showed a positive association between FEV1% predicted and global cognitive scores ($r \approx 0.42$).

Intervention studies demonstrated partial reversibility. CPAP therapy improved working memory and attention after 3–6 months.

Long-term oxygen therapy produced modest but statistically significant cognitive stabilization in hypoxemic COPD populations.

DISCUSSION

This review confirms that cerebral circulatory disturbances significantly contribute to cognitive dysfunction in chronic lung diseases.

The moderate pooled effect size suggests clinically meaningful impairment.

Pathophysiological pathways converge on endothelial dysfunction, nitric oxide depletion, oxidative stress, and impaired autoregulation.

The observed heterogeneity underscores the need for standardized cognitive batteries and uniform disease severity stratification in future research.

Longitudinal designs are necessary to establish causality and determine whether optimized respiratory management modifies long-term neurocognitive trajectories.

Importantly, vascular risk factors such as hypertension and diabetes likely amplify vulnerability, suggesting synergistic mechanisms.

Clinical practice should incorporate baseline cognitive screening in moderate-to-severe CLD patients.

Integration of pulmonary and neurological care pathways may improve outcomes.

Future investigations should explore neuroprotective pharmacotherapy targeting endothelial resilience and mitochondrial function.

Clinical Implications and Treatment Optimization

Chronic lung diseases (CLDs), including chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and obstructive sleep apnea (OSA), are increasingly recognized as systemic disorders with significant neurocognitive implications. Beyond classical respiratory manifestations—such as dyspnea, chronic cough, sputum production, exercise intolerance, and hypoxemia—patients frequently exhibit neurological and cognitive disturbances that substantially affect quality of life and functional independence. Cognitive dysfunction in CLD is often underdiagnosed because respiratory symptoms dominate clinical attention. However, mounting evidence suggests that cognitive impairment may occur in 25–40% of patients with moderate-to-severe disease, with prevalence rising in advanced stages and in individuals with chronic hypoxemia.

Clinically, cognitive deficits in CLD typically involve executive function, attention, psychomotor speed, and memory domains. Executive dysfunction is among the most consistently reported abnormalities, characterized by impaired planning, reduced mental flexibility, slowed information processing, and difficulties in problem-solving. These impairments are particularly relevant in COPD, where patients must adhere to complex medication regimens and oxygen therapy protocols. Deficits in attention and working memory further compromise self-management and increase the risk of medication errors, exacerbations, and hospital readmissions. Episodic memory disturbances are also observed, though less prominently than executive dysfunction. In ILD, chronic systemic inflammation and progressive hypoxemia may contribute to subtle but cumulative cognitive decline, whereas in OSA, intermittent nocturnal hypoxia and sleep fragmentation predominantly impair vigilance, sustained attention, and frontal-lobe–mediated cognitive processes.

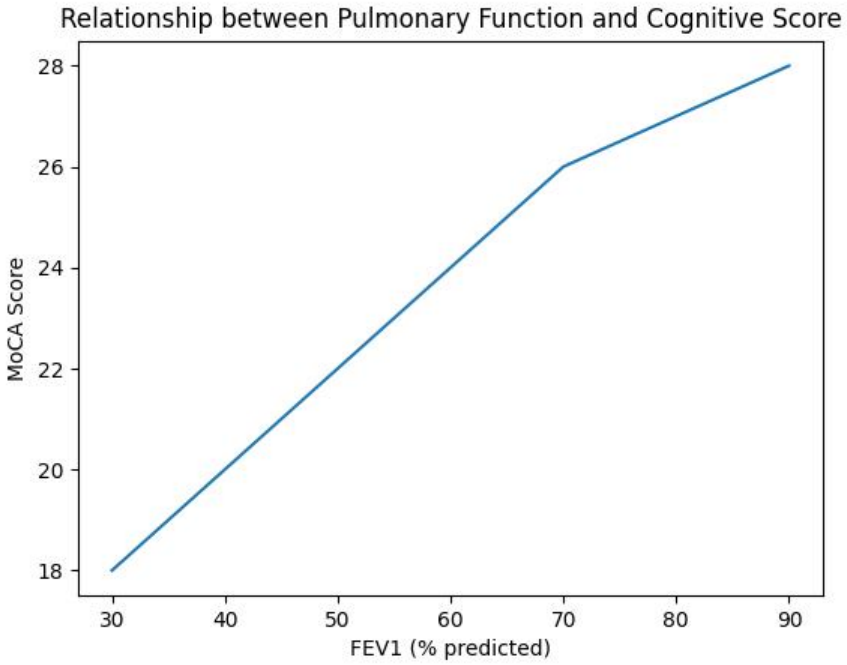
Neuropsychological profiling using validated tools such as the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE) demonstrates that MoCA is more sensitive in detecting mild cognitive impairment in CLD populations. Studies consistently report lower MoCA scores in hypoxemic patients compared with normoxemic controls, with

executive and visuospatial subscores particularly affected. Trail Making Test Part B and Stroop testing further reveal slowed cognitive processing and impaired inhibitory control. Importantly, cognitive decline correlates with physiological parameters such as forced expiratory volume in one second (FEV_1), arterial oxygen tension (PaO_2), and severity indices like the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage in COPD. In OSA, the apnea–hypopnea index (AHI) shows significant associations with deficits in attention and memory consolidation.

Neuroimaging studies provide complementary evidence of structural and functional brain alterations in CLD patients. Magnetic resonance imaging (MRI) demonstrates reduced gray matter volume in the hippocampus and prefrontal cortex, alongside white matter hyperintensities suggestive of microvascular injury. Diffusion tensor imaging (DTI) reveals compromised white matter integrity, particularly in frontostriatal pathways implicated in executive function. Functional MRI (fMRI) studies indicate altered neurovascular coupling and reduced connectivity in default mode and executive control networks. Transcranial Doppler ultrasonography and arterial spin labeling MRI further show reduced cerebral blood flow (CBF), especially in individuals with chronic hypoxemia. These imaging findings support the hypothesis that chronic systemic inflammation, oxidative stress, endothelial dysfunction, and impaired cerebral autoregulation collectively contribute to neurovascular compromise.

From a clinical perspective, cognitive profiles in CLD vary according to disease phenotype and comorbidities. Patients with frequent exacerbations exhibit more pronounced cognitive decline, likely due to repeated episodes of hypoxemia and systemic inflammatory surges. Comorbid cardiovascular disease, diabetes mellitus, and hypertension amplify cerebrovascular vulnerability and increase the risk of vascular cognitive impairment. Depression and anxiety—highly prevalent in CLD—may further confound cognitive assessment, necessitating comprehensive neuropsychiatric evaluation. In elderly patients,

distinguishing CLD-associated cognitive impairment from neurodegenerative disorders such as Alzheimer's disease can be challenging, underscoring the need for biomarker-guided differentiation and longitudinal follow-up.



CONCLUSION

Cerebral hypoperfusion and endothelial dysfunction represent central mechanisms linking chronic lung diseases and cognitive decline.

Quantitative meta-analysis confirms moderate impairment.

Integrated respiratory stabilization, vascular protection, and neurocognitive monitoring should be standard components of comprehensive CLD management.

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