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Review

The Lung-Brain Axis in Cognitive Impairment and Dementia: Mechanisms and Therapeutic Prospects

Liying Zhang[1], Abigail Dove[2,3,4], Juan Du[1], Dan Yang[1], Qiaoli Su[5], Xiaoli Huang[1], Jiao Wang[1*], Jirong Yue[1*]

[1]National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, China. [2]Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden. [3]Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden. [4]Department of Neurology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. [5]General Practice Ward, West China Hospital/Wangjiang Hospital, Sichuan University, Chengdu 610041, China.

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ABSTRACT: The lung-brain axis has been recognized as a critical interface linking lung health to cognitive disorders, including cognitive impairment, Alzheimer's disease, and dementia. Epidemiological and clinical evidence shows a close association between compromised lung health—including chronic obstructive pulmonary disease (COPD), asthma, obstructive sleep apnea (OSA), and pulmonary infections—and cognitive impairment and dementia. Potential mechanisms include established factors (systemic inflammation and immune crosstalk, hypoxic injury, and air-pollutant-induced neurotoxicity) and exploratory mechanisms (lung microbiome dysregulation). Notably, lung-centric strategies targeting the lung-brain axis involve repurposing pulmonary medications, intervening in shared mechanisms, and employing non-pharmacological strategies. Furthermore, realizing this promise will require future randomized controlled trials (RCTs) to develop comprehensive management strategies and alleviate the global burden of cognitive impairment and dementia.

Keywords: Lung-brain axis, Cognitive impairment, Dementia, Alzheimer's disease, Mechanisms, Therapeutic strategies

1. Introduction

Cognitive impairment encompasses deficits in cognitive domains, including learning and memory, language, executive function, attention, perceptual-motor skills, and social cognition, ranging in severity from mild cognitive impairment (MCI) to dementia [1]. Specifically, Alzheimer's disease (AD) is a form of dementia characterized by the accumulation of amyloid-β (Aβ) plaques and hyperphosphorylated tau protein [2, 3], accounting for approximately 60% to 70% of dementia cases worldwide [4]. Cognitive impairment affects up to 25% of individuals aged 65 and older, and the lifetime burden of cognitive impairment is estimated at $124,000 per person, totaling $627 billion in the United States [5].

Epidemiological studies have shown that chronic lung diseases, such as chronic obstructive pulmonary disease (COPD) and asthma, frequently co-occur with cognitive impairment in older adults [6-8]. Growing evidence suggests that this relationship goes beyond mere comorbidity, pointing to a potential direct link between compromised lung health and brain dysfunction [9-11]. This literature has sparked interest in the concept of the "lung-brain axis"—a bidirectional communication network between the respiratory system and central nervous system (CNS) [12]. Greater recognition of this bidirectional axis could highlight new potential

***Correspondence should be addressed to:** Dr. Jiao Wang, PhD Email: wangjiaoisme@foxmail.com and Jirong Yue, Email: yuejirong11@hotmail.com. West China Hospital, Sichuan University, No.37 Guoxue Lane, Wuhou District, Chengdu 610041, China.

therapeutic strategies for the diagnosis and management of cognitive impairment. However, existing research on the connection between lung health and brain health remains scattered, and few reviews have synthesized the evidence [13, 14].

We aim to systematically and critically evaluate the lung-brain axis and highlight its potential as a modifiable target for the early prevention of and intervention against cognitive impairment. In this review, we first summarize epidemiological and clinical evidence linking compromised lung health to cognitive impairment. We then examine the underlying mechanisms, with a focus on those associated with AD pathology. Finally, we discuss how this cross-system association could open novel therapeutic avenues for cognitive impairment.

2. Epidemiological and clinical evidence concerning the lung-brain axis: linking compromised lung health to cognitive impairment

Growing epidemiological and clinical evidence indicates a higher prevalence and risk of cognitive impairment in individuals with compromised lung health [7]. In this review, compromised lung health refers to conditions such as COPD, asthma, obstructive sleep apnea (OSA), and pulmonary infections. Those conditions induce chronic hypoxia, systemic inflammation, and oxidative stress, thereby possibly being associated with a higher risk of cognitive impairment [15, 16].

2.1 COPD

Strong evidence indicates that COPD is associated with an elevated risk of cognitive impairment [13, 17-19]. Furthermore, a Mendelian randomization study demonstrated that a low Forced Expiratory Volume in one second (FEV1) — a key indicator for diagnosing and assessing COPD severity — is causally associated with a higher risk of AD [20]. A meta-analysis of 10 cohort studies (total n=625,644 participants from 4 countries) with follow-up ranging from 3 to over 25 years found that patients with COPD faced a 39% higher risk of cognitive impairment (Hazard Ratio [HR]=1.39, 95% CI: 1.25–1.54) [21]. This association is further corroborated by a meta-analysis of 6 cohort studies involving 428,030 participants, which reported a 24% higher risk of dementia among COPD patients (Risk Ratio [RR] = 1.24, 95% CI: 1.03–1.50), with little variation by sex [17].

The age-dependent association, however, remains unclear. The former meta-analysis found no significant age-dependent trend in the association between COPD and cognitive impairment (P=0.08) [21], whereas the latter analysis reported a pronounced association between COPD and dementia among individuals younger than 65 years [17]. This suggests that younger individuals may face a higher risk of dementia associated with COPD. Notably, this age-related finding was based on two studies from the same region with a combined sample size of 87,177; thus, it may be influenced by regional factors or chance variation, and confirmation through broader, more diverse studies is essential.

Additionally, a subgroup analysis of 2 cohort studies from 2 countries showed that COPD patients had a more than twofold higher risk of developing non-amnestic dementia than those without COPD (HR = 2.36, 95% CI: 1.68–3.31) [21]. Notably, a systematic review of 5 cohort studies (80,026 participants across 11 countries) found that the length of follow-ups influences the results. Mixed findings emerged in studies with follow-ups shorter than five years, whereas a significantly higher risk of cognitive impairment in COPD patients was consistently observed in studies with follow-ups exceeding five years [22].

2.2 Asthma

Cognitive impairment affects approximately 44% of adults with asthma, particularly older individuals [23, 24]. Growing evidence now suggests that asthma is an independent risk factor for general cognitive decline and AD [25-27]. Bushi et al. conducted a meta-analysis of 10 observational studies with 500,502 participants. They reported a 47% higher risk of cognitive impairment in individuals with asthma versus those without (HR = 1.47, 95% CI: 1.09–1.84) [6]. This pattern extends to dementia: all-cause dementia was more prevalent among patients with asthma than in those without (20.3% vs. 12.9%) [28]. Furthermore, a large, community-based prospective cohort study in Korea, comprising 6,785,948 adults (> 40 years) with a median follow-up of 8.1 years, found that asthma was associated with a 20% higher risk of dementia (HR = 1.20, 95% CI: 1.19–1.22) [29]. However, a nested case–control study of 57,210 adults aged 60 years and older in the Republic of Korea found no significant association between a history of asthma and incident dementia (Odds Ratio [OR] = 0.97, 95% CI: 0.92–1.02) [30]. The discrepancy may stem from methodological differences. The prospective cohort study included participants across a wide age range and adjusted for extensive confounders [29], whereas the nested case-control study was restricted to older adults and matched on a limited set of variables [30]. Thus, differences in population age structure and residual confounding are probable key explanations. Such heterogeneity highlights the necessity for future prospective studies with standardized designs, detailed asthma phenotypes, and comprehensive confounder adjustment to clarify this association.

Asthma is associated with AD. A meta-analysis of 2 observational studies with 6,841,098 participants suggested a higher risk of AD in asthma patients (HR = 1.80, 95% CI: 0.45–3.15). However, the result should be interpreted with caution, as a confidence interval that crosses the null indicates low precision [6]. More convincingly, the large prospective cohort study with a median follow-up of 8.1 years further reported a 22% higher risk of AD among asthma patients (HR = 1.22, 95% CI: 1.20–1.24) [29].

Collectively, the evidence from observational studies indicates that asthma is associated with cognitive impairment. However, we should note that meta-analyses in this field often exhibit high heterogeneity ($I^2 \geq 60\%$), possibly because of variations in study populations, cognitive assessment tools, and asthma management regimens. Additionally, publication bias may contribute to this inconsistency, as a meta-analysis found that positive outcomes are frequently published in this research area [6].

2.3 OSA

OSA has been found to be associated with cognitive impairment. Specifically, OSA is linked to poorer attention, memory, and executive function [31-35]. Systematic reviews further support that OSA is correlated with a higher risk of general cognitive decline and AD [36-40]. A recent meta-analysis encompassing 23 cross-sectional studies revealed that cognitive impairment affects 37% of OSA patients [38]. Prevalence tended to increase with OSA severity, with rates of 32% in mild OSA, 37% in moderate OSA, and 44% in severe OSA; however, this trend was not statistically significant ($P > 0.05$) [38].

Recent studies have focused on blood and cerebrospinal fluid (CSF) biomarkers that reflect the core pathologies of AD to clarify OSA's pathogenic role. These biomarkers include Aβ (the main component of amyloid plaques), total tau (T-tau, a marker of general neuronal damage), and phosphorylated tau (P-tau, a specific marker of AD-related neurofibrillary tangles [NFTs]) [41, 42]. For instance, a meta-analysis of 8 studies involving 2,154 participants found no significant differences in CSF levels of Aβ, T-tau, or P-tau between individuals with OSA and controls [40]. In contrast, an earlier meta-analysis by Cui et al., based on data from 7 studies (n=544), found lower CSF Aβ42 levels in patients with OSA versus controls (Standardized Mean Difference [SMD] = –0.93, 95% CI: –1.57 to –0.29), suggesting a greater burden of amyloid pathology. This association was particularly pronounced among those older than 67 years or with a BMI greater than 27.6 kg/m² [36]. This conflicting result may stem from differences in study sample characteristics. Notably, Cui et al. identified age and BMI as important confounding factors [36]. Inadequate control for these variables in other meta-analyses may therefore explain the observed inconsistencies. Although CSF P-tau showed no significant change, PET scan revealed a higher cerebral Aβ burden in OSA patients (SMD = 0.37, 95% CI: 0.13–0.61), suggesting a small but consistent increase in amyloid plaque deposition [36].

In contrast, previous studies on blood-based AD biomarkers have yielded more consistent results. One subgroup analysis based on 5 studies found higher blood Aβ42 levels (SMD = 0.66, 95% CI: 0.19–1.12). Another subgroup analysis of 7 studies (n=614) found higher T-tau levels (SMD = 0.66, 95% CI: 0.26–1.07) [40]. Both effect sizes were moderate-to-large and statistically significant, suggesting that OSA may be associated with measurable alterations in peripheral AD-related proteins. This correlation is further supported by a meta-analysis, which reported that, despite high heterogeneity, blood T-tau levels were elevated in OSA patients (SMD = 1.32, 95% CI: 0.60–2.04), and the result remained unchanged in sensitivity and subgroup analyses [37]. Regarding blood P-tau, a recent and comprehensive meta-analysis of 4 studies across 3 countries, building upon earlier reviews, found significantly elevated levels in patients with OSA (SMD = 0.34, 95% CI: 0.12–0.56) [37].

Several quantitative meta-analyses have identified a connection between OSA and cognitive impairment. However, it is important to bear in mind that these effect sizes are limited by high heterogeneity, which might be attributed to variations in age, OSA severity, assessment methods, BMI, and regional differences [36, 38, 40].

2.4 Pulmonary infections

Emerging research underscores a significant association between pulmonary infections—such as pneumonia or COVID-19—and cognitive impairment. In a meta-analysis of 8 cohort studies with follow-up durations ranging from 6.1 to 17 years, pneumonia was associated with a 74% higher risk of dementia (HR = 1.74; 95% CI: 1.36–2.23) [43]. Notably, no significant difference in the risk of dementia was found between bacterial and non-bacterial pneumonia (P=0.71) [43]. Similarly, a systematic review found a comparable risk of new-onset dementia following COVID-19 and other respiratory infections [44]. These findings may have public health implications: preventing various types of respiratory infections may be equally important for cognitive health.
The impact of COVID-19 on cognition has gained considerable attention in the aftermath of the pandemic. Several studies have observed that COVID-19 is associated with cognitive decline and a higher risk of AD.

A cohort study of 919,731 patients revealed that COVID-19 survivors had a 3.5-fold higher risk of AD (RR = 3.50; 95% CI: 2.20–5.50) within 1-year post-infection compared with uninfected individuals, suggesting a strong association between COVID-19 and subsequent AD risk [45]. A meta-analysis of 608 patients across 5 observational studies demonstrated that COVID-19 patients had lower Montreal Cognitive Assessment (MoCA) scores at six months post-infection. The pooled mean difference (MD) was –0.94 (95% CI: –1.59 to –0.29), representing a small but statistically significant cognitive decline. These patients also showed more pronounced deficits in cognitive domains such as executive function, attention, and memory [46]. Furthermore, another meta-analysis of 6,335,327 participants from 4 countries reported that COVID-19 survivors had a 56% higher risk of incident dementia one year after infection (HR = 1.56, 95% CI: 1.21–2.01) [44]. In summary, substantial evidence indicates a close association between compromised lung health and cognitive impairment. However, several key limitations should be noted. The current evidence largely derives from observational studies, which are susceptible to residual confounding, measurement bias, and an inherent inability to establish causality. Although prospective designs improve temporality, they cannot eliminate all non-causal explanations. Therefore, the observed associations should be interpreted as robust epidemiological links that support—but do not prove—causality. To determine whether improving lung health directly reduces the risk of cognitive impairment, causal inference approaches (e.g., Mendelian randomization) and interventional trials are required.

Moreover, existing studies have largely neglected the heterogeneity inherent in compromised lung health. Most fail to account for critical disease characteristics, including severity, duration, and treatment status, while age- or sex-related variations remain underexplored. These methodological shortcomings hinder a precise understanding of the association. Future research should rigorously define and stratify study populations based on these clinical and demographic factors to elucidate the specific relationship between compromised lung health and cognitive impairment.

3. Mechanisms underlying the lung-brain axis

Compromised lung health has been found to be connected with general cognitive decline and the pathological process of AD. The underlying mechanisms involve the established factors such as systemic inflammation and immune crosstalk, hypoxic injury, and air pollutant-induced neurotoxic effects, as well as exploratory mechanisms such as lung microbiome dysregulation [47, 48] (Fig. 1). Table 1 summarizes the mechanisms linking compromised lung health to cognitive impairment and AD pathology.

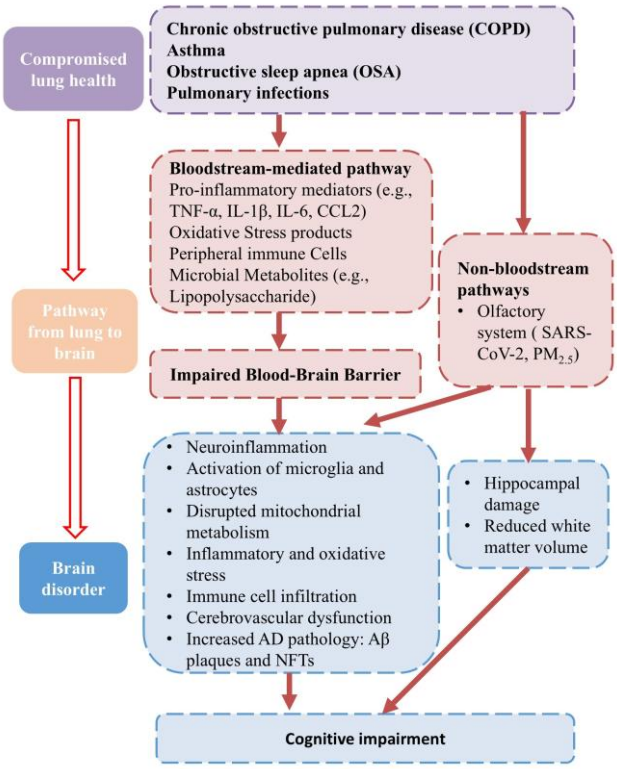

Figure 1. The lung-brain axis: linking compromised lung health to cognitive impairment. Abbreviation: $PM_{2.5}$: Particulate Matter $_{2.5}$; Aβ plaques: Amyloid-β plaques; NFTs: Neurofibrillary tangles.

3.1 Systemic inflammation and immune crosstalk

Systemic inflammation and immune crosstalk have been recognized as the established mechanisms that connect compromised lung health with cognitive impairment. Pulmonary inflammation can induce a systemic immune response that impacts the brain. Under pathological conditions, the lungs release pro-inflammatory molecules, such as Tumor Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β), Interleukin-6 (IL-6), and C-C motif chemokine ligand 2 (CCL2) into the circulation. The mediators impair the blood-brain barrier (BBB) and activate microglia [49-52], promoting the infiltration of immune cells into the brain and stimulating the production of reactive oxygen species (ROS), nitric oxide, and other inflammatory mediators. This cascade directly injures neurons and accelerates the formation of Aβ plaques and NFTs [48, 53].

Table 1. Compromised lung health-related mechanisms and their proposed contributions to cognitive impairment and AD pathology

Mechanism	Key pathways/mediators	Proposed contribution to cognitive impairment	Proposed contribution to AD pathology	Refs.
Systemic inflammation and immune crosstalk	· Pulmonary release of pro-inflammatory mediators (e.g., TNF-α, IL-1β, IL-6, CCL2) into circulation.	· Impairs the BBB · Activates microglia · Induces neuroinflammation · Causes direct neuronal injury · Leading to general cognitive decline.	· Promotes and accelerates the formation of Aβ plaques and neurofibrillary tangles (NFTs).	[49-53]
Hypoxic injury	· Induction of systemic and neuroinflammation · Disruption of microglial mitochondrial metabolism · HIF-1α signaling	· Impairs hippocampal structure/function and neurophysiology · Disrupts microglial homeostasis · Contributing to learning and memory deficits	· Upregulates BACE1/γ-secretase activity, increasing Aβ production. · Promotes tau hyperphosphorylation via kinase activation (e.g., ERK, GSK3β, CDK5), dysregulation of RNA splicing, and PP2A inhibition	[54-60]
Air pollutants-induced neurotoxicity	Particulate matter (e.g., $PM_{2.5}$) entering the central nervous system via the olfactory tract or bloodstream; glial cell activation.	· Induces neuroinflammation and oxidative stress · Alters synaptic function and induces neuronal apoptosis · Impairs BBB and cerebrovascular function · Disrupts glymphatic clearance	· Promotes Aβ deposition and tau hyperphosphorylation · May also reduce white matter volume and disrupt ER stress-mitochondria function.	[67, 74-80]
Lung microbiome dysregulation	· Dysbiosis · Translocation of microbes (e.g., *C. pneumoniae*, SARS-CoV-2) and their metabolites (e.g., LPS) · Immunoregulation	· May impair cognition via induced neuroinflammation, metabolite permeation, and disruption of systemic immune homeostasis.	· Specific pathogens can directly invade the CNS, provoking neuroinflammation that promotes Aβ plaque deposition and tau hyperphosphorylation. · Can also disrupt the BBB via mechanisms such as RAAS inhibition and NF-κB activation.	[90-95]

Abbreviation: TNF-α, Tumor necrosis factor-alpha; IL, interleukin; CCL2, C-C motif chemokine ligand 2; Aβ, amyloid-beta; NFTs: Neurofibrillary tangles; HIF-1α, hypoxia-inducible factor 1-alpha; BACE1, β-site APP cleaving enzyme 1; ERK, extracellular signal-regulated kinase; GSK3β, glycogen synthase kinase 3β; CDK5, cyclin-dependent kinase 5; PP2A, protein phosphatase 2A; ER, endoplasmic reticulum; LPS, lipopolysaccharide; CNS, central nervous system; RAAS, renin-angiotensin-aldosterone system; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; AD, Alzheimer's disease; BBB, blood-brain barrier; PM, particulate matter.

3.2 Hypoxic injury

Substantial evidence also suggests that hypoxic injury is another established mechanism. Specifically, hypoxia contributes to the pathogenesis and progression of AD via multiple pathways. Primarily, it triggers systemic inflammation and upregulates the expression of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α), which can directly induce neurodegenerative changes [54]. Hypoxia also impairs microglial homeostatic function by disrupting mitochondrial metabolism through activation of the hypoxia-inducible factor 1α (HIF-1α) signaling pathway. This disruption of microglial homeostasis subsequently triggers neuroinflammation, which further exacerbates AD-related pathological progression [55]. Furthermore, hypoxia impairs hippocampal neurophysiology, structural integrity, and cellular morphology—key determinants of learning and memory—thereby contributing to progressive cognitive decline in AD [56].

Concurrently, hypoxia upregulates the enzymatic activity of β-site amyloid precursor protein cleaving enzyme 1 (BACE1) and γ-secretase, thereby accelerating Aβ production and amyloid plaque deposition [57]. Additionally, hypoxia facilitates tau hyperphosphorylation via several mechanisms: (1) activation of tau kinases (e.g., extracellular signal-regulated kinase [ERK], glycogen synthase kinase 3β [GSK3β], and cyclin-dependent kinase 5 [CDK5]) in neurons [54]; (2) dysregulation of RNA splicing [58]; and (3) transcriptional upregulation of HIF-1α. Elevated HIF-1α promotes the degradation of leucine carboxyl methyltransferase 1 (LCMT1)—a key regulator of protein phosphatase 2A (PP2A) methylation. Reduced LCMT1 expression compromises PP2A catalytic activity, disrupting the tau phosphorylation-dephosphorylation balance and could ultimately drive tau hyperphosphorylation [59].

In summary, hypoxia accelerates AD progression through synergistic pathways, including systemic inflammation, neuroinflammation, mitochondrial dysfunction, Aβ deposition, and tau hyperphosphorylation [60].

3.3 Air pollutant-induced neurotoxic effects

Exposure to air pollutants (e.g., particulate matter [$PM_{2.5}$, PM_{10}], nitrogen oxides [NO, NO_2], and ozone [O_3]) not only exacerbates symptoms of chronic respiratory diseases such as COPD and asthma but may also contribute to their development [61, 62]. Furthermore, growing evidence suggests that air pollution is associated with a higher risk of cognitive impairment [63-67]. Moreover, long-term exposure is also linked to a higher risk of incident dementia [68-73].

Air pollutant-induced neurotoxic effects have also been proposed as an established mechanism. Air pollutants, particularly $PM_{2.5}$, can directly infiltrate the CNS via the olfactory system or enter the bloodstream through the lungs and gastrointestinal tract before accessing the brain [74]. Current research widely recognizes that air pollutants are associated with cognitive impairment through several key mechanisms: (1) they activate glial cells, which in turn elicit neuroinflammation and elevate oxidative stress, thereby altering synaptic function, inducing neuronal morphological changes, and triggering neuronal apoptosis; (2) they impair the BBB and induce cerebrovascular dysfunction; (3) they promote Aβ deposition and tau hyperphosphorylation [67, 75, 76]. Additionally, emerging evidence suggests that air pollution exposure could reduce white matter volume [77], disrupt glymphatic system function [74], impair endoplasmic reticulum (ER) stress-mitochondria-associated endoplasmic reticulum membrane (ERS-MAM) function [78], alter the lung and gut microbiota as well as their metabolites and signaling pathways [79], and induce neuro-excitotoxicity [80]. These factors act synergistically to impair cognitive function and drive the initiation and progression of AD.

3.4 Lung microbiome dysregulation

The microbiome is important to maintain systemic homeostasis [81-83]. Current evidence has suggested that the gut microbiome may be a modifiable target in AD progression [84]. The lung microbiome, which is primarily composed of bacterial phyla such as Firmicutes and Actinobacteria, plays a crucial role in maintaining pulmonary homeostasis within the gut-brain network [85]. However, various factors—including disease (e.g., COPD, infections, and asthma), smoking, and therapeutic interventions (e.g., antibiotic treatment and immuno-therapy)—are associated with reduced alpha diversity of the lung microbiome, increased bacterial load, and altered composition [86-89].

An emerging theoretical framework proposes that the lung microbiome may impair cognitive function through several potential pathways, including dysbiosis, permeation of metabolites, translocation of microbes and their metabolites (e.g., lipopolysaccharide [LPS]), and immunoregulation [90-92]. Specifically, Chlamydia pneumoniae and SARS-CoV-2 may directly invade the CNS, provoking neuroinflammation that promotes Aβ plaque deposition and tau hyperphosphorylation [93]. Furthermore, SARS-CoV-2 can disrupt the renin-angiotensin-aldosterone system (RAAS), inhibit the Wnt/β-catenin pathway, and activate the NF-κB pathway, collectively leading to impaired BBB function and exacerbated neuroinflammation [94]. Consistent with this concept, a rat study suggests that the lung microbiota can shape the susceptibility to and pathological progression of autoimmune CNS diseases [95]. The study indicates that neomycin alters the lung microbiota (i.e., increased Bacteroidetes) and elevates LPS levels. LPS then crosses the BBB and triggers a type I interferon signature in pulmonary immune cells, reducing the accumulation of myelin basic protein-specific T cells in the CNS. This subsequently downregulates the expression of inflammatory cytokines, alters microglial morphologies, and ultimately slows the progression of experimental autoimmune encephalomyelitis [95].

Lung microbiome dysregulation is an emerging research area in cognitive impairment. However, this mechanism is currently supported by limited preclinical evidence, and direct translational evidence linking it to human cognition is lacking. Thus, the lung-brain-microbiome axis remains a promising yet predominantly speculative concept. Future research is needed to validate its underlying mechanisms and therapeutic potential in humans.

4. Potential lung-centric strategies for cognitive impairment

This section discusses potential lung-centric strategies for cognitive impairment (Fig. 2). Evidence levels are presented in Table 2. Strategies such as “targeting shared mechanisms (anti-inflammation and anti-oxidative stress)” and “repurposing pulmonary medications” are promising. However, evidence is mainly derived from the preclinical and observational clinical studies and thus requires further validation in multi-center, well-designed, large-scale RCTs. By contrast, evidence for “non-pharmacological strategies” is supported by RCTs and meta-analyses, representing a more compelling intervention.

4.1 Targeting shared mechanisms

In the context of the lung-brain axis, therapeutic approaches focus on shared mechanisms, including inflammation and oxidative stress.

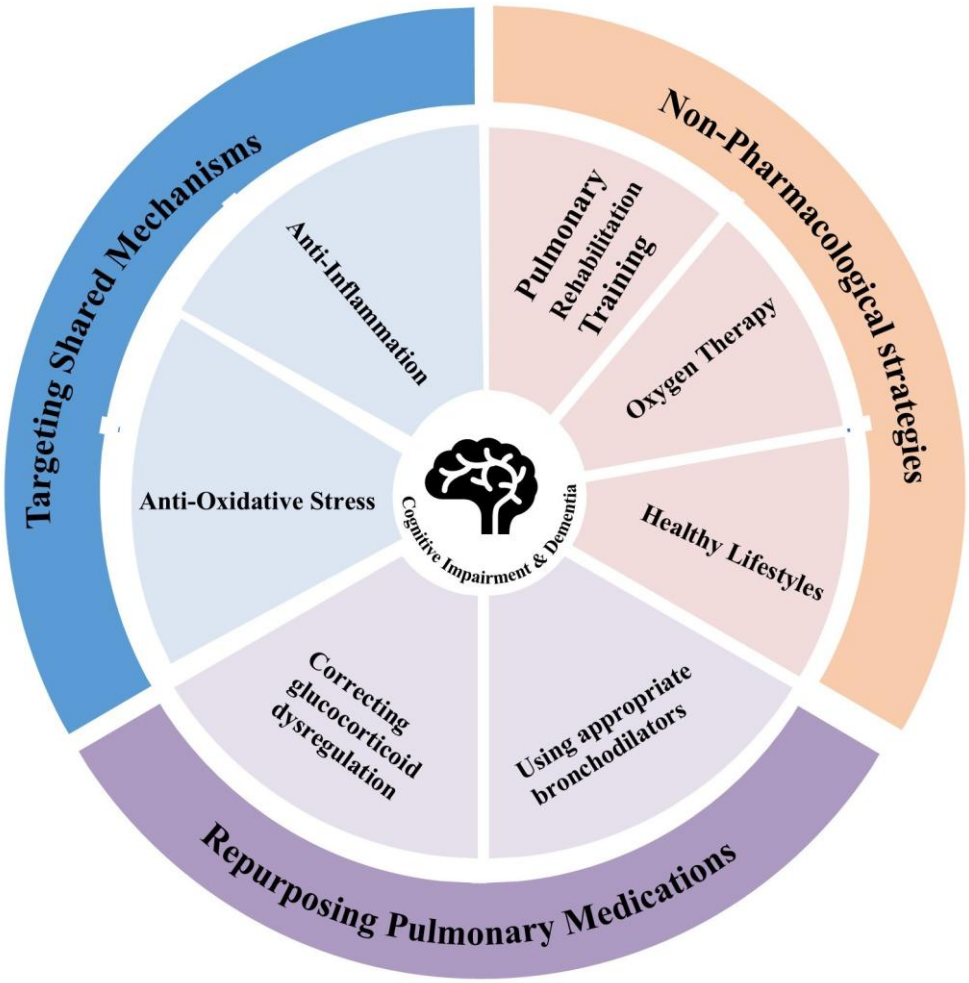

Figure 2. Leveraging the lung-brain axis: potential therapeutic strategies for cognitive impairment and dementia.

4.1.1 Anti-inflammation

In murine models, several studies have shown that anti-inflammation is a potential therapeutic approach for cognitive impairment. For example, inhibiting IL-6 can alleviate neuroinflammation by targeting two key mediators: the signal transducer and activator of transcription 3 (STAT3) signaling pathway and the cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS–STING) pathway [96]. Additionally, TNF-α inhibitors can increase triggering receptors expressed on myeloid cells 2 (TREM2)-positive microglia and preserve cognitive function in mice [97]. Similarly, blocking the IL-1β and C-X-C chemokine receptor type 4 (CXCR4) axis may improve memory and mitigate AD-related symptoms by reducing neuroinflammation in mouse models [98]. Bindarit, a CCL2 inhibitor, can improve cognition in mice [99]. The NLR family pyrin domain-containing 3 (NLRP3) inflammasome drives IL-1β release in AD; A study has demonstrated that inhibiting the NLRP3 inflammasome can reduce AD pathology and improve cognitive performance in rat models of early AD [100]. Notably, NLRP3 inhibitors have been proposed as potential AD therapeutics in a drug discovery compound disclosure [101]. Moreover, several preclinical studies indicated that anti-inflammatory drugs, such as leflunomide, meloxicam, infliximab, tocilizumab, and α-pinene, could protect cognitive function [102-106]. Although anti-inflammation strategies are promising, this preliminary evidence lacks clinical support and requires validation in further human RCTs.

4.1.2 Anti-oxidative stress

Anti-oxidative stress is another promising therapy, which is primarily supported by preclinical evidence. Preliminary data from human studies also suggest this potential benefit. First, antioxidants, including Cistanche flavonoids, rosmarinic acid, and carnosic acid, can activate the Kelch-like ECH-associated protein 1/Nuclear

factor erythroid 2-related factor 2/Antioxidant Response Element (Keap1/Nrf2/ARE) signaling pathway, mitigating oxidative damage and neuronal apoptosis and thereby improving cognition [107, 108]. Additionally, several antioxidants, such as vitamin C, vitamin E, caffeine, curcumin, fish oil, and resveratrol, can suppress oxidative stress and inflammation and modulate neurotransmitter levels. These effects may reduce Aβ aggregation and improve memory and attention [109, 110]. Collectively, these findings highlight the potential of dietary and pharmacological antioxidants to slow AD progression.

Table 2. Summary of potential therapeutic strategies targeting the lung-brain axis for cognitive impairment: mechanisms and levels of evidence.

Potential therapeutic strategies	Proposed Mechanism / key evidence	Levels of evidence	Refs.
Targeting Shared Mechanisms			
Anti-inflammation		Preclinical	
IL-6 inhibition	Alleviates neuroinflammation by targeting the STAT3 and cGAS-STING pathways.	Preclinical (mice)	[96]
TNF-α inhibitors	Increase TREM2-positive microglia to preserve cognitive function.	Preclinical (mice)	[97]
Blocking IL-1β/CXCR4 axis	Reduces neuroinflammation to improve memory and mitigate AD symptoms.	Preclinical (mice)	[98]
CCL2 inhibitor (Bindarit)	Inhibits chemokine signaling involved in neuroinflammation.	Preclinical (mice)	[99]
NLRP3 inflammasome inhibitors	· Reduces IL-1β release, a driver of AD-related inflammation. · Reduces AD pathology and improves cognitive performance	Preclinical (rat) drug discovery compound disclosure	[100, 101]
Other anti-inflammatory drugs (e.g., Leflunomide, Meloxicam)	Suppress inflammation through various pharmacological actions to protect cognitive function.	Preclinical (Rat and mice)	[102-106]
Anti-oxidative stress		Preclinical and limited clinical	
Antioxidants (e.g., Cistanche flavonoids, Vitamin E, Curcumin)	Activate Keap1/Nrf2/ARE pathway or directly scavenge ROS to mitigate oxidative damage.	Preclinical (Mice) Clinical	[107-110]
Repurposing Pulmonary Medications		Preclinical and limited clinical	
Glucocorticoid receptor antagonists (e.g., Dazucorilant)	Inhibit glucocorticoid receptor overactivation to reduce neuroinflammation and Aβ/tau deposition.	Preclinical (Mice)	[112, 115]
Selective β_2-agonists (e.g., Formoterol)	May promote neurogenesis and reduce neuroinflammation and Aβ/tau pathology.	Preclinical and clinical	[116-118]
Non-pharmacological Strategies		Clinical	
Pulmonary rehabilitation (e.g., respiratory training)	Improves pulmonary function, potentially mitigating systemic consequences like hypoxia.	Clinical (Prospective interventional cohort)	[125, 126]
Oxygen therapy / CPAP	Corrects hypoxia, a key mechanism linking lung disease to cognitive impairment.	Clinical (RCT, systematic review and meta-analysis of RCTs)	[19, 31]
Healthy lifestyle (smoking cessation, vaccination, exercise)	Reduces systemic risk factors (inflammation, vascular health) and may counteract air pollution effects.	Clinical (retrospective cohort study, RCT, and systematic review and meta-analysis of RCTs)	[128-130]

Abbreviation: TNF-α, Tumor necrosis factor-alpha; IL, interleukin; CCL2, C-C motif chemokine ligand 2; Aβ, amyloid-beta; AD, Alzheimer's disease; CXCR4, C-X-C chemokine receptor type 4; NLRP3, NLR family pyrin domain containing 3; STAT3, signal transducer and activator of transcription 3; cGAS–STING, cyclic GMP-AMP synthase–stimulator of interferon genes; TREM2, triggering receptor expressed on myeloid cells 2; Keap1/Nrf2/ARE, Kelch-like ECH-associated protein 1/Nuclear factor erythroid 2-related factor 2/Antioxidant Response Element; CPAP, continuous positive airway pressure; RCT, Randomized Controlled Trial.

Although anti-inflammation and anti-oxidative stress hold promise for treating cognitive impairment and AD, robust human trial data are scarce. Key translational challenges include optimizing BBB permeability, determining effective dosing and treatment duration, ensuring long-term safety, and identifying the optimal therapeutic window [109, 110].

4.2 Repurposing pulmonary medications

Preclinical evidence from mice and observational data in humans suggest that glucocorticoids and bronchodilators, key therapeutic agents for COPD and asthma, are associated with better cognitive performance. The mechanisms may involve improving the primary pulmonary condition and mitigating systemic

pathophysiology processes (e.g., hypoxia and inflammation).

Preclinical studies found that appropriate glucocorticoid use is associated with improved cognitive function, whereas sustained high-dose use correlates with poorer cognitive performance [100, 111-114]. The proposed mechanism involves short-term glucocorticoid receptor activation upregulating serum-glucocorticoid-regulated kinase 1 (SGK1) and inhibiting neuronal apoptosis via the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway. However, chronic, sustained SGK1 overactivation may activate glycogen synthase kinase-3β (GSK-3β), disrupt channel function, and enhance neuroinflammation. Preclinical studies indicate that this cascade promotes tau hyperphosphorylation and ultimately exacerbates AD pathology [113]. Additionally, long-term glucocorticoid use can hyperactivate the hypothalamic-pituitary-adrenal (HPA) axis, impair receptor signaling, exacerbate neuroinflammation, and ultimately impair hippocampal function [114]. Therefore, correcting glucocorticoid dysregulation may be a promising therapeutic strategy. For instance, dazucorilant, an inhibitor of glucocorticoid receptor activation, may reduce neuroinflammation and the deposition of Aβ and tau protein, thereby improving memory in mice [112]. Similarly, the glucocorticoid receptor antagonist mifepristone reduces microglial density and improves cognitive behavior in AD mouse models [115]. Although appropriate glucocorticoid use to improve cognitive performance is an attractive strategy, it has only been explored in preclinical studies, leaving significant translational gaps that require validation in clinical trials.

Regarding bronchodilators, observational studies have suggested that using selective β_2-agonists (e.g., albuterol and formoterol) is associated with a lower risk of AD [116, 117]. The underlying mechanisms may involve promoting neurogenesis, reducing neuroinflammation, and decreasing Aβ deposition and tau hyperphosphorylation [118]. However, due to the limited ability to cross the BBB and the risk of side effects (e.g., higher risk of major adverse cardiovascular events), β_2-agonists have not been used to improve cognitive function [118, 119]. Anticholinergic drugs (e.g., ipratropium and tiotropium) and cholinesterase inhibitors exert opposing pharmacological effects. They are indicated for different conditions: the former for bronchodilation, and the latter for cognitive impairment [120]. A meta-analysis indicates that weak anticholinergics (e.g., ipratropium bromide and tiotropium bromide) show no clear link to general cognitive decline or AD [121, 122], whereas strong anticholinergic agents—including urinary antispasmodics, antihistamines, and psychotropics—are associated with a higher risk of vascular and Lewy body dementia [123]. Additionally, 8% of patients with AD experience clinically relevant drug-drug interactions between cholinesterase inhibitors and anticholinergic agents [124], highlighting the potentially risk of such interactions and the underlying disease-disease interplay [121]. This finding underscores the need for caution when prescribing these medications to individuals with preexisting cognitive impairment.

Repurposing pulmonary medications for neuroprotection remains an exploratory research area. Current evidence comes primarily from preclinical models and observational studies; the benefits need to be confirmed in large-scale RCTs. Furthermore, the side effects and therapeutic window require thorough evaluation before clinical application.

4.3 Non-pharmacological strategies

Non-pharmacological strategies, including pulmonary rehabilitation, oxygen therapy, and a healthy lifestyle, have been shown to benefit cognitive function in clinical studies. A prospective interventional cohort study demonstrated that pulmonary rehabilitation benefits cognition [125]. Following a 12-week respiratory training program, cognitive function was significantly enhanced in patients with stable COPD [126]. Additionally, continuous oxygen therapy is associated with a lower risk of cognitive impairment in COPD patients [19], while continuous positive airway pressure (CPAP) can slow cerebral atrophy in individuals with OSA [31]. Despite the effectiveness of these interventions, adherence remains a major challenge among patients with cognitive impairment [13, 32, 127]. Evidence from clinical studies and a systematic review indicates that broader healthy lifestyles (e.g., quitting smoking, getting a pneumococcal vaccination, and engaging in regular aerobic activity) are associated with a lower risk of AD [128-130]. Furthermore, healthy lifestyles can counteract the negative effects of air pollution on cognitive function in middle-aged and older adults [64]. These findings suggest that adhering to a healthy lifestyle is a long-term cognitive safeguard and may be most effective when initiated early.

5. Evidence gaps and future directions

Although epidemiological evidence indicates a close association between compromised lung health and cognitive impairment, it should be noted that most of this evidence is observational in nature, and causal inference cannot be firmly established. Mechanistic studies have identified several established and exploratory mechanisms. These lines of evidence collectively suggest that lung-centric strategies may represent promising therapeutic approaches for preventing cognitive

impairment. However, the supporting evidence is primarily derived from preclinical studies, which face significant challenges in clinical translation.

Within the lung-brain axis framework, both researchers and clinicians should greatly recognize that this axis is a promising, modifiable target for cognitive impairment. Moving forward, further in-depth exploration of lung-centric strategies is urgently warranted to develop a comprehensive, cost-effective, and home-applicable management strategy. This strategy should include: (1) risk identification via screening of high-risk populations (e.g., individuals with compromised lung health); (2) foundational interventions through detailed healthy lifestyle recommendations (e.g., optimal exercise type, frequency, and intensity); and (3) the lung-centric strategies (e.g., abdominal breathing training, slow breathing exercises, or structured pulmonary rehabilitation programs).

6. Conclusion

The lung-brain axis is a promising regulatory node in the development of cognitive impairment. Observational evidence indicates that compromised lung health is closely associated with cognitive impairment, with potential mechanisms involving inflammation, hypoxia, air pollutants, and lung microbiome dysregulation. Potential lung-centric strategies include targeting shared mechanisms, repurposing pulmonary medications, as well as non-pharmacological strategies. However, this promise requires further validation in interventional studies.

The lung-brain axis not only challenges the view that cognitive impairment is solely a CNS disorder but also expands the possible scope of strategies for preventing and managing cognitive impairment. Exploring and leveraging the lung-brain axis as a modifiable bridge connecting systemic health and cognition may provide a novel, accessible approach to alleviating the global burden of cognitive impairment in aging populations and advancing healthy aging goals.

Authorship contribution

L.Z.: conceived, drafted, and revised the review and edited the final manuscript. J.W. and J.Y.: conceptualization, supervision, revising the review, and editing the final manuscript. All authors read and approved the final manuscript.

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Declaration of Competing Interest

The author reports no conflicts of interest in this work.

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