

# Global Trends of Cognition-Targeted Interventions in Chronic Lung Disease: A Bibliometric and Visualized Analysis

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**Purpose:** To map the research landscape and synthesize randomized evidence on cognitive interventions for adults with chronic lung disease (CLD).

**Methods:** This two-stage study involved: (i) bibliometric mapping of Web of Science Core Collection (WOSCC) (Jan 2005–May 2025) to evaluate output, collaboration, and thematic trends via VOSviewer, CiteSpace, and Bibliometrix; and (ii) narrative synthesis of Randomized Controlled Trials (RCTs) in adults ( $\geq 18$  y) with chronic lung diseases and validated cognitive outcomes, identified from WOSCC, Scopus, and PubMed (to May 1, 2025). Screening, data extraction, and RoB 2 assessment were conducted in duplicate.

**Results:** Bibliometric mapping (2005–2025) of 3,474 publications showed sustained growth, broad international collaboration, and a shift from epidemiology to mechanisms and patient-centered outcomes. Fifteen RCTs, mostly in stable Chronic Obstructive Pulmonary Disease (COPD), assessed inspiratory-muscle/breathing training, aerobic-resistance or dance exercise, exercise with behavioral/educational components, multimodal cognitive-lifestyle programs, and pharmacological/nutritional or acute physiological therapies Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) were the most common cognitive measures, alongside executive-function tests. Methodological quality was generally moderate.

**Conclusion:** Bibliometrics and randomized-trial synthesis reveal a rapidly growing, globally connected CLD-cognition field moving from epidemiology toward mechanistic and patient-centered research. Multimodal PR, especially exercise and inspiratory-muscle training, shows neurotherapeutic promise, but substantial gaps persist in Low and Middle Income Countries (LMICs) and non-COPD populations.

**Keywords:** chronic lung disease, cognitive impairment, bibliometric analysis, scoping review, lung–brain axis

## Introduction

CLDs are a diverse group of respiratory diseases, including COPD, bronchial asthma, bronchiectasis, and interstitial lung disease (ILD), each of which causes substantial morbidity and mortality worldwide. According to the Global Burden of Disease (GBD) study, the prevalence of CLDs has steadily increased between 1990 and 2019,<sup>1</sup> and these diseases continue to pose a significant public health burden.<sup>2</sup> The GBD 2017 estimated that approximately 544.9 million people worldwide were living with CLDs in 2017, a 39.8% increase compared to 1990.<sup>1</sup> The coronavirus disease 2019 (COVID-19) pandemic has resulted in a large number of survivors with persistent lung dysfunction, further expanding the high-risk population.<sup>3</sup> Meanwhile, the GBD 2019 update further ranked CLDs as the third leading cause of death worldwide.<sup>4</sup> The absolute global burden continues to rise due to an aging population and continued exposure to risk factors such as



smoking and ambient air pollution.<sup>5,6</sup> Long-term respiratory impairment reduces health-related quality of life and places significant strain on healthcare systems.<sup>7,8</sup>

Along with the growing burden of CLD, cognitive impairment, including mild cognitive impairment (MCI) and dementia, has become a major and rapidly expanding global health challenge.<sup>9</sup> Currently, more than 50 million people worldwide suffer from dementia, and the associated economic costs are expected to increase nearly tenfold from \$9.12 trillion in 2015.<sup>10</sup> Epidemiological studies estimate that 3%–42% of adults aged 50 years and older have MCI.<sup>11</sup> Cognitive impairment impairs functional independence and quality of life<sup>12</sup> requires long-term care, and places a significant burden on families and healthcare systems.<sup>13</sup> Given these impacts, dementia was ranked as the fifth leading cause of disability and dependency among older adults in 2016.<sup>14</sup> Of note, CLD and cognitive impairment share several modifiable risk factors, such as smoking, hypoxemia, systemic inflammation, and vascular comorbidities, raising the possibility of a pathophysiological interaction between lung disease and neurocognitive impairment. Given the systemic nature of CLDs and their impact on oxygenation and inflammation, there is increasing recognition that respiratory impairment may contribute to neurocognitive decline.

There is growing evidence of clinically relevant crosstalk between CLDs and cognitive impairment. A recent meta-analysis of over 40,000 participants showed that decreased lung function increased the risk of MCI and dementia by 1.3 to 1.6 times.<sup>15</sup> Population data from the Mayo Clinic Study of Aging confirmed this association, showing that COPD patients were almost twice as likely to develop MCI as age-matched controls.<sup>16</sup> When the two diseases coexist, prognosis worsens. A prospective cohort study of community-dwelling older adults showed that patients with both COPD and cognitive impairment had a 55% increased rate of respiratory hospitalization and an 80% increased overall mortality compared with patients with COPD alone.<sup>17</sup> Mechanistic hypotheses involve chronic and intermittent hypoxemia,<sup>18</sup> systemic inflammation and autonomic dysregulation,<sup>19,20</sup> among others. Despite these insights, systematic reviews have highlighted significant heterogeneity in study designs and diagnostic criteria, and a lack of longitudinal mechanistic studies in this interdisciplinary field.<sup>21</sup>

Therefore, we designed a comprehensive two-step study. In the first phase, bibliometric methods were used to map WOSCC records from 2005 to 2025 to quantify publication growth, focus on topic hotspots, and visualize the global collaborative network connecting CLDs and cognitive impairment research. By integrating macro-level bibliometric mapping with micro-level synthesis of randomized interventions, this study aims to generate a unified, evidence-based framework to guide future mechanistic and clinical research in the pulmonary–neurocognitive axis. Accordingly, we implemented a two-phase approach in which bibliometric mapping provided the structural overview, and trial-level synthesis supplied the clinical granularity needed to construct an evidence-based framework. Based on this, the second phase aggregated all randomized controlled trials (RCTs) found through WOSCC, Scopus, and PubMed, classified their intervention types, summarized key study characteristics, and assessed methodological quality using the RoB 2 tool. By combining macro-scientific mapping with descriptive synthesis of trial design and quality, this study generated a unified knowledge map that illuminated past progress and revealed evidence gaps in the pulmonary–neurocognitive axis. Based on this, the second phase aggregated all RCTs found through WOSCC, Scopus, and PubMed, classified their intervention types, summarized key study characteristics, and assessed methodological quality using the RoB 2 tool. By combining macro-scientific mapping with descriptive synthesis of trial design and quality, this study generated a unified knowledge map that illuminated past progress and revealed evidence gaps in the pulmonary–neurocognitive axis.

## Method

In this study, we employed a two-step strategy. First, we conducted a bibliometric analysis of WOSCC records from 2005 to 2025 to map the scope, thematic evolution, and collaboration patterns in research on CLDs and cognitive impairment. The search was performed on 17 May 2025, covering publications from 1 January 2005 to 1 May 2025. It combined free-text and controlled vocabulary terms related to cognitive decline and CLDs, developed based on prior studies<sup>22,23</sup> and expert consultation to ensure comprehensiveness. Only English-language articles and reviews were included, resulting in 3,474 records. Extracted data included publication year, country, institution, journal, citation counts, keywords, and co-authorship/co-citation networks. Visualisations of growth trends, thematic clusters, and collaboration maps were

generated using VOSviewer 1.6.20, CiteSpace 6.4 R1, and the Bibliometrix package for R (v4.2). Given its descriptive nature, this step did not require risk-of-bias assessment.

Insights from the bibliometric analysis informed a subsequent systematic review of RCTs evaluating interventions targeting cognitive outcomes in adults with CLDs. Using the same lung- and cognition-related terms with an RCT filter, we searched WOSCC, Scopus, and PubMed up to 1 May 2025. Eligible trials enrolled adults ( $\geq 18$  years) with diagnosed CLDs, compared pharmacological, rehabilitative, behavioural, or device-based interventions against control groups (eg, usual care, sham, placebo, or active comparator), and reported at least one validated cognitive outcome. We restricted inclusion to English-language publications to ensure consistent screening, data extraction, and risk-of-bias assessment across databases. We acknowledge that this language restriction may have excluded relevant non-English studies and could introduce language bias and potential publication bias. Two reviewers independently screened titles, abstracts, and full texts, resolving discrepancies by consensus. For each study, we extracted participant characteristics, intervention type and duration, cognitive outcomes, secondary respiratory or functional measures, and follow-up length; total sample sizes ranged from 20 to 647 participants (median 73.5; IQR 30–83). Risk of bias was assessed using the Cochrane RoB 2 tool. Due to heterogeneity in interventions and outcomes, results were synthesised narratively rather than quantitatively.

Both components followed the PRISMA extension for Scoping Reviews (PRISMA-ScR) and the RCT review also adhered to PRISMA 2020 guidelines. A summary workflow is presented in [Figure 1](#).

## Results

### Quantitative Bibliometric Landscape

#### Analysis of Publications

[Figure 2](#) shows the bibliometric landscape of CLDs and cognitive impairment from 2005 to 2025. Annual publications rose from 50 in 2005 to peaks of 311 in 2021 and 323 in 2024 ([Figure 2A](#)), fitting an exponential growth curve. Citation activity paralleled key milestones, with a sharp surge in 2012 (20,468 citations) and sustained levels above 8,000 through 2021, while recent downturns largely reflect citation lag and partial 2025 data (120 papers, 50 citations). In total, 3,474 publications in 1,291 journals were authored by 19,216 researchers, yielding a 10.3% annual growth rate, an average of 6.98 co-authors per paper, and notable international collaboration in 24.18% of publications. The literature cites 175,494 references, contains 7,107 unique author keywords, and achieves a mean article age of 7.4 years with an average of 44.19 citations per paper ([Figure 2B](#)), underscoring the field's rapid expansion, collaborative ethos, and growing scientific influence.

#### Geographical and Institutional Landscape

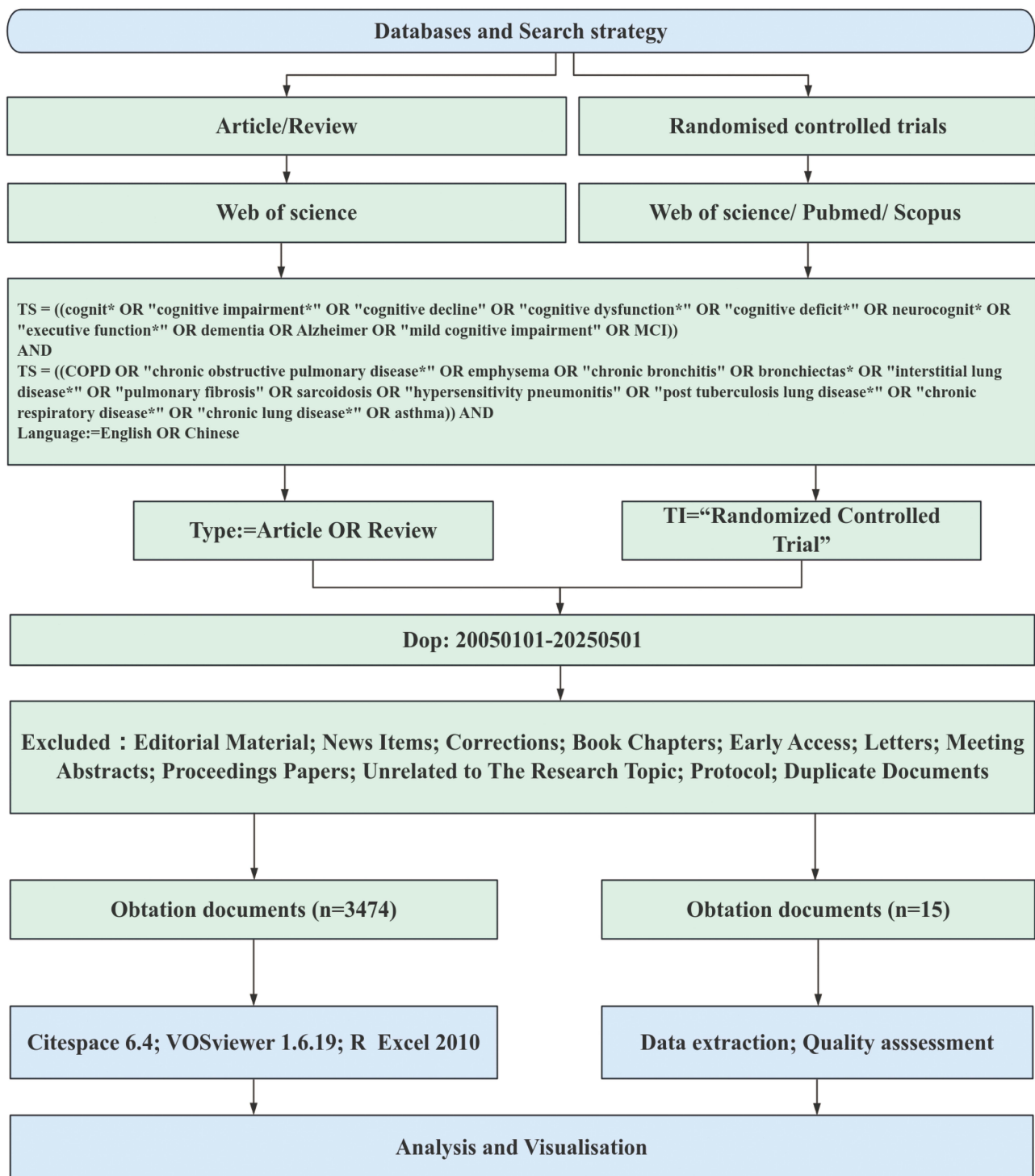
([Figure 3](#)) Research spans 112 countries but is highly concentrated: the United States (1,026; 29.5%), China (418; 12.0%), and the United Kingdom (261; 7.5%) lead. Collaboration is strongest across a U.S.–Western Europe–China triad, with Africa and South America comparatively peripheral. Longitudinally, the US share declined from  $\sim 50\%$  to  $\sim 33\%$ , while China rose; other high-income countries remain stable. Institutionally, Harvard (311), University of London (269), and the University of California system (247) lead, and co-authorship clusters center on Harvard, King's College London, University of Washington, University of Toronto, and Maastricht University.

#### Analysis of Authors and Co-Cited Authors

Top producers are JANSSEN DJA,<sup>24,25</sup> FEDERMAN AD,<sup>26,27</sup> and WOUTERS EFM<sup>28</sup> (15 papers each; [Supplementary Table S1](#)). By co-author citations, PEDONE C,<sup>29</sup> CORSONELLO A,<sup>30</sup> and WOUTERS EFM lead ([Supplementary Table S1](#)). The author network forms six clusters dominated by a large group around JANSSEN DJA ([Figure 4A](#)), with smaller, specialized groups around JONES PW,<sup>31</sup> CORSONELLO A, and PEDONE C. Country layering highlights the US, China, and UK as primary contributors ([Figure 4B](#)). From 2008 to 2025, productivity and citations rose for ZHANG J<sup>32</sup> and Liu Y,<sup>33</sup> whereas CORSONELLO A<sup>34</sup> and PEDONE C<sup>35</sup> peaked earlier ([Figure 4C](#)).

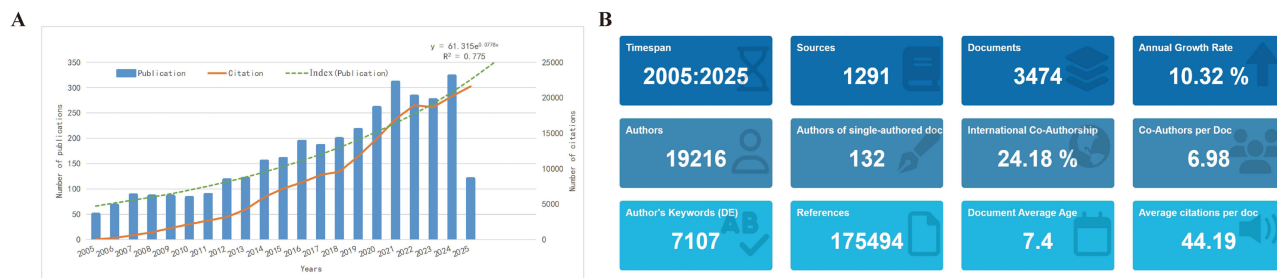
#### Analysis of References

The co-citation analysis of the top 10 seminal references ([Supplementary Table S2](#)) reveals three critical insights into the COPD cognitive dysfunction field. First, JW DODD<sup>36</sup> dominates the foundational literature, contributing four high

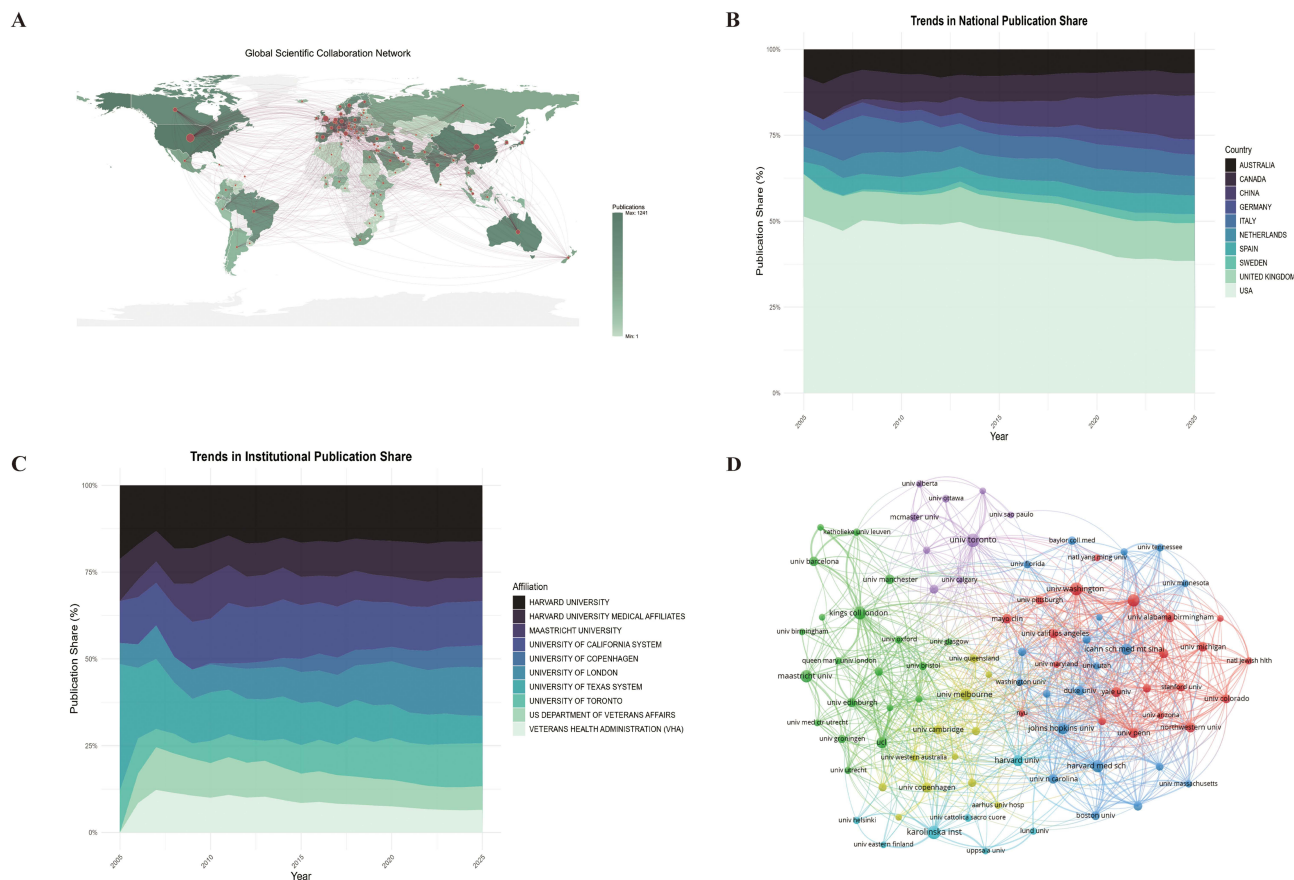


**Figure 1** Flow chart of the progress of literature screening.

impact studies (Rank #1, #4, #7, #9), including the most cited paper (304 citations; Dodd, 2010) establishing cognitive impairment in stable COPD and its association with brain structure/function. Second, neurobiological mechanisms have received extensive attention, such as ORTA PAMUK<sup>37</sup>(2006) who found an association between cerebral perfusion defects and cognitive decline, and DODD<sup>38</sup> (2012) who used multimodal magnetic resonance imaging (MRI) to detect brain structural changes. Third, these findings have been further confirmed by important clinical studies. RAFFAELE<sup>39</sup>



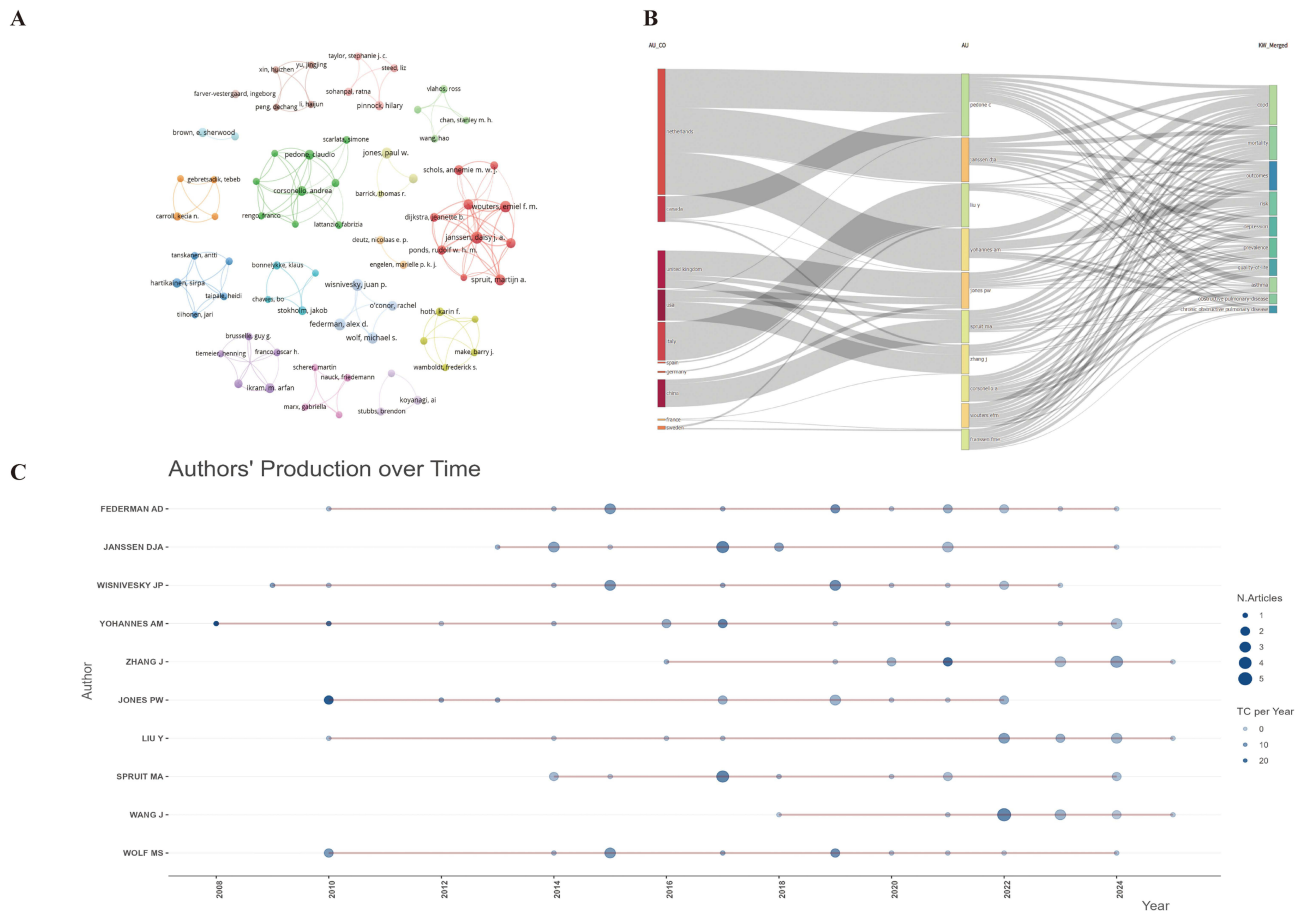
**Figure 2** Analysis of publications (A) Global trends in research publications on CLDs and cognitive impairment over the past 20 years. (B) Summary of key descriptive bibliometric metrics.



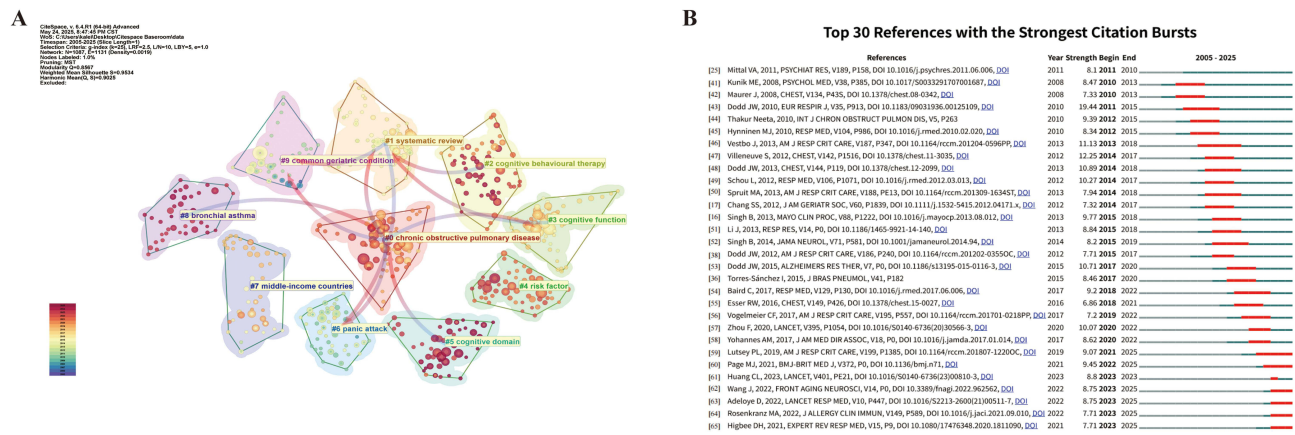
**Figure 3** Analysis of institutions and Country-area cooperation network (A) National cooperation geographic map (B) Stacked area chart of percentage of publications by country over time (C) Stacked area chart of the percentage of papers published by institutions over time (D) Inter-institutional collaboration network map.

(2006) reported that decreased drawing ability was a predictor of mortality in patients with severe COPD, while Chang<sup>17</sup> (2012) demonstrated that the coexistence of COPD and cognitive impairment has a compounding adverse effect on the elderly. In summary, these highly cited studies reflect a trend of interdisciplinary research that combines neurobiological insights with clinical outcomes, and these studies are mainly published in high impact journals.

The co-citation network (Figure 5A) identified ten robust clusters (Modularity Q = 0.867; mean Silhouette = 0.953). The largest cluster (#0, “chronic obstructive pulmonary disease”) occupies the hub position and is densely linked to clusters on “cognitive function” (#3), “cognitive behavioural therapy” (#2) and “risk factors” (#4), indicating that COPD-related cognitive mechanisms and interventions form the intellectual core of the field. A colour gradient for node age shows that most items in the “systematic review” cluster (#1) and in cluster #2 are warm coloured (ie, recently published) signalling that evidence syntheses and behavioural treatments are the current research frontier. By contrast, cooler colours



**Figure 4** Analysis of Authors and co-cited authors. **(A)** A visual authors cooperation map for VOSviewer network. **(B)** Three-layer Sankey diagram of country-author-research topic. **(C)** Authors' production over time.



**Figure 5** Analysis of reference outbursts **(A)** Citation cluster analysis **(B)** Top 28 references with the strongest citation bursts.

dominate the “bronchial asthma” (#8) and “middle income countries” (#7) clusters, reflecting earlier foundational and epidemiological work. Two smaller clusters, “panic attack” (#6) and “common geriatric condition” (#9), highlight emerging extensions into psychiatric and gerontological domains.

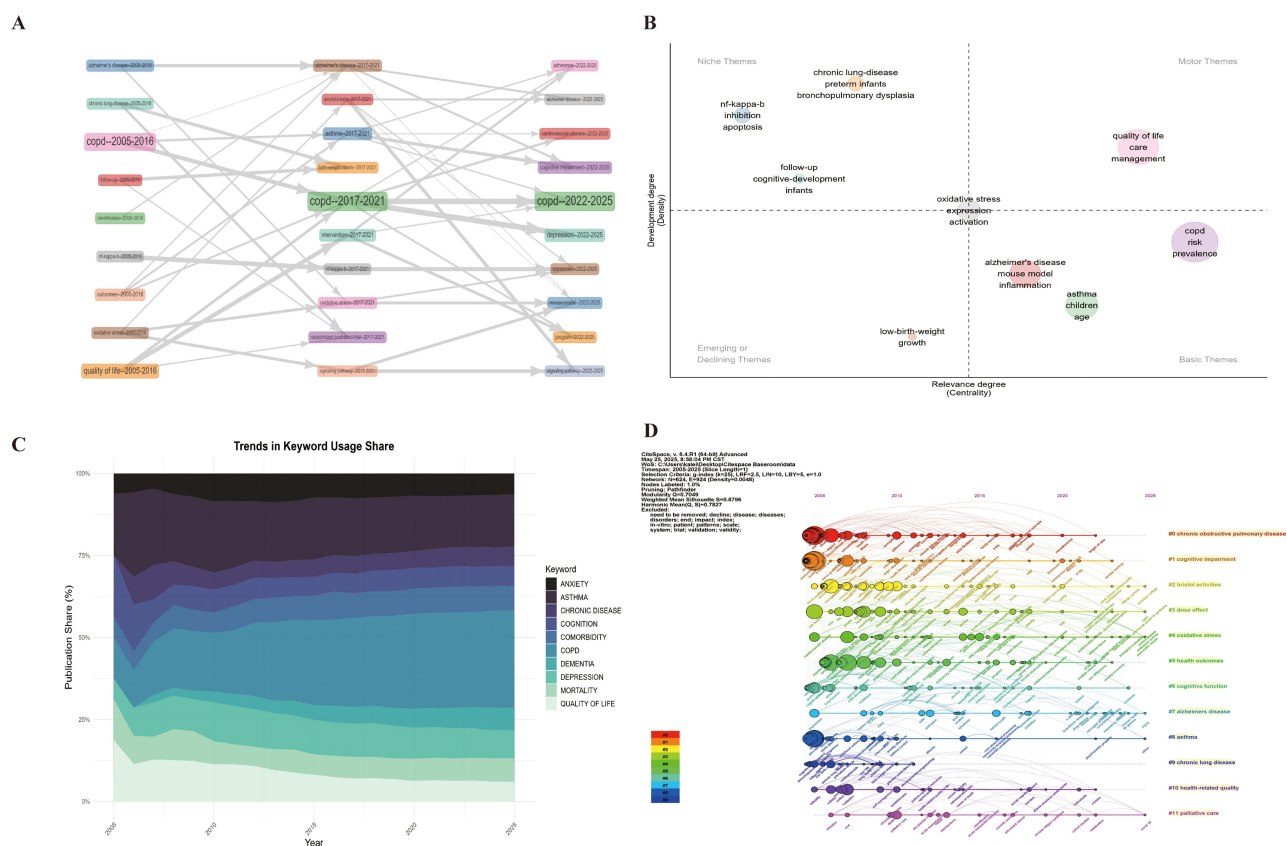
Citation burst analysis (Figure 5B) reveals a distinct temporal progression in the evolution of influential literature, comprising three successive phases involving 30 high impact references. The first phase (2011–2015) was driven by

DODD JW and MAURER J, who explored cognitive decline in COPD.<sup>25,40–43</sup> The second phase (2013–2019) focused on guideline-directed research, risk factors, and PR, with contributions from VESTBO J and SPRUIT MA.<sup>16,17,38,44–50</sup> The most recent phase (2020–present) sees the strongest citation bursts, with research centered on post-Covid sequelae, health equity, and methodological standards.<sup>36,51–63</sup> These references reflect current research frontiers, particularly in viral sequelae, large-scale epidemiological studies, and evidence synthesis frameworks.

## Keywords Analysis

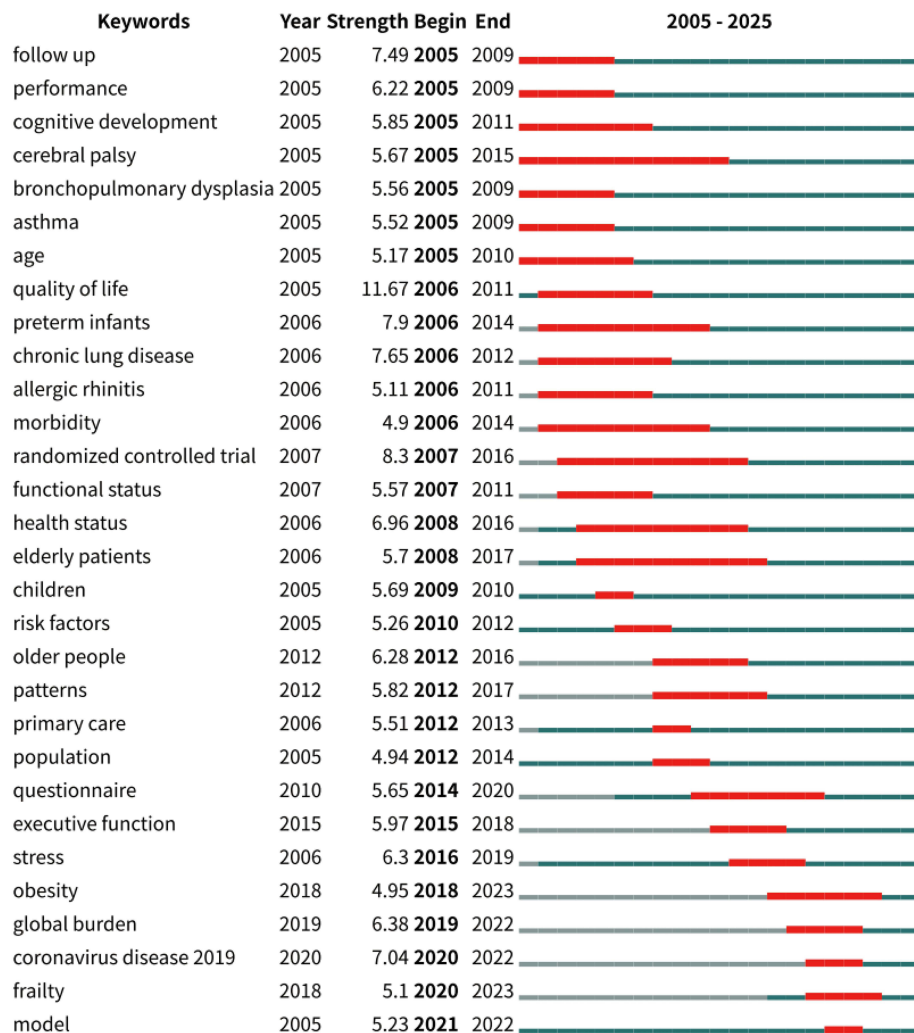
Analysis of keyword evolution from 2005 to 2025 (Figure 6A) shows persistent research themes, such as COPD, Alzheimer's disease, and oxidative stress, which have remained significant over the years. Recently, emerging topics like animal models, depression, and gene expression reflect increased interest in molecular mechanisms and psychological comorbidities in chronic diseases. The thematic map (Figure 6B) highlights key research areas, with quality of life and care management identified as dominant themes. In contrast, COPD risk, prevalence, asthma, Alzheimer's disease, and inflammation remain underdeveloped, concentrated in the basic thematic quadrant. Oxidative stress and its related terms, expression and activation, bridge basic biological processes and disease contexts, indicating their growing research importance. Temporal trends in keyword usage (Figure 6C) reveal that while COPD, comorbidity, and chronic disease have maintained strong focus, recent years have seen a rise in anxiety, depression, and quality of life, highlighting a shift towards psychological and patient-centered outcomes. Figure 6D shows that keywords like oxidative stress, Alzheimer's disease, asthma, and dose effect have experienced notable citation bursts in recent years, marking them as current research hotspots.

The top 30 keywords with the strongest citation bursts from 2005 to 2025 (Figure 7) underscore the shifting research priorities. Early bursts were related to clinical and developmental topics such as follow-up, cognitive development, and



**Figure 6** Analysis of keywords and keywords with strongest citation burst (A) Evolution of topics in the field of CLDs and cognitive impairment. (B) The thematic map of CLDs and cognitive impairment domains. (C) Keyword frequency percentage stacking chart over time - CLDs and cognitive impairment areas. (D) Timeline of keywords in the field of CLDs and cognitive impairment.

## Top 30 Keywords with the Strongest Citation Bursts



**Figure 7** Top 30 keywords with the strongest citation bursts.

bronchopulmonary dysplasia, with quality of life showing the highest burst strength (11.67) during 2006–2011. More recent bursts (from 2020 onward) focus on public health concerns like coronavirus disease 2019, global burden, frailty, stress, and model, reflecting growing attention to aging, systemic vulnerability, and post-pandemic health outcomes.

## Clinical Trial Evidence Synthesis

### Study Selection and Participants

Of the 8,377 records retrieved from the three databases, 34 articles were selected after title and abstract screening; full-text review yielded 15 eligible RCTs (Table 1). The sample size of each trial ranged from 20 to 304. All trials, except one study of acute oxygen therapy,<sup>64</sup> recruited patients with stable or mild-to-moderate COPD. CHENG<sup>65</sup> restricted inclusion to male COPD patients with mild cognitive impairment; another study by SCHOU<sup>66</sup> targeted patients within 24 hours of discharge from hospital after an acute exacerbation. Overall, the study population was predominantly male, aged 55–75 years, and heavy smokers, indicating that women and patients with severe hypoxemia were underrepresented. Notably, several trials were small and short-term, which may increase susceptibility to test–retest learning (practice effects) and expectancy effects in brief cognitive screening outcomes; therefore, short-term cognitive gains should be interpreted cautiously.

Table 1 15 Eligible RCTs

	FIRST AUTHOR, YEAR	Intervention	Sample Size	Main Outcomes	Intervention Duration	Conclusion
1	SONG F, 2025 <sup>67</sup>	Head-Down Strong Abdominal Breathing	63	Cognitive: MoCA Other: Gait performance	12 weeks	The 12-week HDBT program significantly improved cognitive function (MoCA scores) and enhanced obstacle-walking gait parameters (stride length and speed), whereas simple walking metrics showed no significant change.
2	MOMENI SAFARABADI A, 2024 <sup>68</sup>	500 mg capsules of 90% rosemary ( <i>Rosmarinus officinalis</i> ) hydro-alcoholic extract	77	Cognitive: MoCA, MMSE Other: LCADL, Lawton IADL	8 weeks	An 8-week course of oral rosemary hydroalcoholic extract improved global cognitive function and modestly enhanced IADL (post OSA adjustment) in stable GOLD stage 1–3 COPD patients, without significant effects on basic ADLs or other cognitive subdomains, supporting its role as an adjunct herbal therapy pending larger trials with objective functional endpoints.
3	TABKA O, 2023 <sup>69</sup>	Pulmonary rehabilitation and cognitive training	39	Cognitive: MOCA Other: BDS, 6MWT, ERP P300 Latency & Amplitude	12 weeks	Although PR alone improves 6MWT parameters and cognitive function, the addition of CT to PR is more effective in improving cognitive abilities in patients with COPD. This combined approach may provide clinicians with a complementary therapeutic option for improving cognitive abilities in patients with COPD.
4	KAYA M, 2022 <sup>70</sup>	Creative dance-based exercise alongside home-based chest physiotherapy group	24	Cognitive: MOCA Other: 6MWD, Quadriceps muscle strength test, PST, LoST, CTSIB/TSIB, CAT, BODE Index (BMI, airflow Obstruction, Dyspnea, Exercise capacity), mMRC Dyspnea Scale, MBS, VAS for leg pain, Spirometry parameters, Respiratory muscle pressures, BMI	8 weeks	Use of creative dance training in addition to home-based chest PT program was more effective than chest PT program regarding primary and secondary outcomes in COPD patients.
5	CHENG YY, 2022 <sup>65</sup>	Threshold-type breathing trainer 30 breaths, twice daily, 5 days week <sup>-1</sup> , for 8 weeks at home.	49	Cognitive: MMSE Other: 6MWT, CAT, mMRC, Borg Scale, 6MWD	8 weeks	An 8-week RMT program (daily IMT ±EMT) significantly improved cognition, FEV <sub>1</sub> , respiratory muscle strength, diaphragmatic structure/function, and symptoms in male, non-obese COPD patients with MCI; early IMT initiation recommended; EMT added no overall benefit.
6	AQUINO G, 2016 <sup>71</sup>	High-intensity AT and high-intensity aerobic training combined with resistance training (ie, combined training [CT])	28	Cognitive: Rey-IR, Rey-DR, Copy Drawing I, Drawing Copy Test II (Copy Drawing II/Completion), Attentive Matrices Test, Raven's Progressive Matrices (Raven Test), Verbal Fluency Test (Category Fluency: colours, animals, fruits, cities) Other: MRC Dyspnea Scale, Borg Scale (Rate of Perceived Exertion/Dyspnea)	4 weeks	CT may be a possible strategy to prevent cognitive decline and associated comorbidities in male patients with COPD.
7	PRETTO JJ, 2008 <sup>64</sup>	Acute oxygen vs ar cross-over study	30	Cognitive: PVT Other: Driving Simulator (AusEd software)	20 min	Acute supplemental oxygen did not improve simulated driving or PVT performance in hypoxemic COPD; findings do not support the recommendation to use oxygen while driving.
8	GUO-YING, QIAN, 2022 <sup>72</sup>	Montessori-based multimodal intervention	120	Cognitive: MoCA, MMSE Other: Functional ability (Barthel Index), quality of life (WHOQOL-BREF)	24 months	Montessori-based multimodal intervention significantly improved cognition, ADL ability, and multidimensional quality of life in elderly COPD patients with mild cognitive impairment, facilitating functional and social reintegration.

(Continued)

Table 1 (Continued).

	FIRST AUTHOR, YEAR	Intervention	Sample Size	Main Outcomes	Intervention Duration	Conclusion
9	CHARLES F. EMERY, 1998 <sup>73</sup>	Exercise, education, and stress management	79	Cognitive: Digit Vigilance Test, Finger Tapping Test (Halstead-Reitan), Trail Making Test (Parts A & B), Digit Symbol (WAIS-R), Verbal Fluency (letter fluency, Halstead-Reitan) Other: CES-D, Bradburn Affect-Balance Scale, STAI-State), SCL-90-R – Depression & Anxiety subscales, MHLC-Internal /Powerful Others/Chance, SIP, COPD Knowledge Test	10 weeks	A relatively intensive, supervised 10-week exercise program layered onto standard education and stress-management is superior to non-exercise controls for enhancing endurance, mood, daily-function perception, and verbal executive skills in stable COPD patients, even though lung mechanics remain unchanged.
10	KIM L. LAVOIE, 2019 <sup>74</sup>	Self-management behaviour modification (SMBM) program	304	Cognitive: MoCAOther: HADS-A, HADS-D, PHQ-9, SGRQ -Total Score, mMRC	12 weeks	The results indicate that SMBM with/without bronchodilators or ExT was associated with improved psychological and cognitive functioning. Anxiety reduced with increased physical activity, cognitive function improved with increased exercise capacity, and depression reduced with increases in either physical activity or exercise capacity. Interventions that increase daily physical activity or exercise capacity may improve psychological and cognitive outcomes in COPD.
11	ROSENSTEIN B, 2020 <sup>75</sup>	Continuous training at high intensity (CTHI), continuous training at the ventilatory threshold (CTVT) and high-intensity interval training (HIIT)	36	Cognition: MoCA; WAIS Digit Span; Trail Making A/B; Stroop Color-Word Test (parts 2; 3-1; 4-3); Semantic & Letter Verbal Fluency; Rey Auditory-Verbal Learning Test; Rey-Osterrieth Complex Figure; WAIS Block Design; WAIS Digit Symbol Coding Pulmonary & exercise physiology: FEV <sub>1</sub> , FVC, FEV <sub>1</sub> /FVC, TLC, DLCO; peak work (W <sub>peak</sub> ), peak VO <sub>2</sub> , cycle-endurance time Psychological symptoms: BDI, ASI	12 weeks	Across the full cohort, 12 weeks of exercise led to small overall cognitive changes (Cohen dz -0.06 to 0.45). The Rey-O Complex Figure copy showed the largest short-term gain, especially in participants with baseline mild cognitive impairment. Among protocols, CTHI was the only one yielding medium-to-large effects in every cognitive domain assessed. At the 1-year follow-up, cognitive outcomes were mixed, with both gains and losses across all groups. The authors conclude that continuous high-intensity cycling appears most promising for broad cognitive benefits in COPD, but benefits wane without long-term exercise support.
12	ETNIER JL, 2001 <sup>76</sup>	Exercise intervention (long-term group and short-term group)	29	Cognitive: Culture Fair Intelligence TestOther: 6MWT, CES-D, graded exercise test, spirometry	3 months and 18 months	A 3-month exercise program may be a sufficient impetus to foster these cognitive gains in COPD patients.
13	KOZORA, E., 2002 <sup>77</sup>	Exercise, psychosocial, and educational sessions.	80	Cognitive: Digit Symbol, Digit Vigilance Test, Trail Making Test, Logical Memory, Clock Drawing to Command, Boston Naming Test, Controlled Oral Word Association Test, Semantic Naming Test, Story Retention, Clock Score, Digit VigilanceOther: BDI, 6MWT	3 weeks	A 3-week brief rehabilitation lowered depression and increased exercise capacity in COPD; no group-level cognitive interaction, but clinically meaningful gains in attention, verbal memory, visuospatial skills occurred among those initially impaired; supports further larger randomized trials on neurobehavioral benefits of brief multimodal rehab.
14	LONE SCHOU, PHD, 2014 <sup>66</sup>	Within 24 h trained, discharged home; in-home installation of touchscreen PC + pulse oximeter	44	Cognitive: MoCAOther: HADS-A, HADS-D, PHQ-9, SGRQ-Total Score, mMRC	6 weeks	No significant differences in cognitive performance between telemedicine-based and conventional hospitalization groups; severe COPD patients with mild-moderate exacerbations (MMSE≥24) can handle telemedicine self-management; age-related cognitive vulnerability warrants attention.

(Continued)

Table 1 (Continued).

	FIRST AUTHOR, YEAR	Intervention	Sample Size	Main Outcomes	Intervention Duration	Conclusion
15	JOE W RAMSDELL, 1996 <sup>78</sup>	Theophylline SR, ipratropium MDI	20	Cognitive: Visual attention/vigilance, PASAT, Wechsler Memory Scale–Revised Visual Memory Span, Benton Supraspan, Wechsler Adult Intelligence Scale, CVLT, Letter (Phonemic) Fluency Test, Category Fluency Test Other: None	2 weeks	Severe cognitive impairment in the elderly is not usually associated with treatment with theophylline or ipratropium.

**Abbreviations:** MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; LCADL, London Chest Activity of Daily Living Scale; Lawton IADL, Lawton Instrumental Activities of Daily Living Scale; BDS, Borg Dyspnea Scale; 6MWT, Six-Minute Walk Test; 6MWD, 6-Minute Walk Distance; ERP, event-related potential; CAT, COPD Assessment Test; BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity index; BMI, body mass index; mMRC, modified Medical Research Council dyspnea scale; MBS, Modified Borg Scale; VAS, visual analog scale; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; Wpeak, peak work rate; VO<sub>2</sub>, oxygen uptake (peak VO<sub>2</sub>, peak oxygen uptake); PST, Postural Stability Test; LoST, Limits of Stability Test; CTSIB/TSIB, (Clinical) Test of Sensory Integration and Balance/Test of Sensory Integration and Balance; MRC, Medical Research Council dyspnea scale; PVT, Psychomotor Vigilance Task; AusEd, AusEd driving simulator software; WHOQOL-BREF, World Health Organization Quality of Life–BREF; CES-D, Center for Epidemiological Studies Depression Scale; STAI-State, State-Trait Anxiety Inventory–State Anxiety; SCL-90-R, Symptom Checklist-90–Revised; MHLC, Multidimensional Health Locus of Control; SIP, Sickness Impact Profile; HADS-A/HADS-D, Hospital Anxiety and Depression Scale–Anxiety/Depression; PHQ-9, Patient Health Questionnaire-9; BDI, Beck Depression Inventory; ASI, Anxiety Sensitivity Index; PASAT, Paced Auditory Serial Addition Test; CVLT, California Verbal Learning Test; WAIS/WAIS-R, Wechsler Adult Intelligence Scale/Wechsler Adult Intelligence Scale–Revised; WMS-R, Wechsler Memory Scale–Revised.

## Intervention Categories

Interventions clustered into five groups:

1. Inspiratory muscle/breathing-pattern training (2 trials):<sup>65,67</sup> tailored loading or rhythm training to improve ventilatory efficiency.
2. Exercise programmes (5 trials):<sup>69–71,75,76</sup> moderate- to high-intensity aerobic, resistance or dance training.
3. Exercise plus behavioural/psychological/educational components (3 trials):<sup>72–74</sup> PR combined with cognitive training, stress management, education or remote self-management.
4. Multimodal cognitive-lifestyle intervention (2 trial):<sup>66,77</sup> Montessori-based multi-sensory and daily-task training.
5. Pharmacological, nutritional or acute physiological therapy (3 trials):<sup>64,68,78</sup> antioxidant herbs, brief oxygen supplementation, or bronchodilator optimisation.

Four trials were short-term ( $\leq 4$  weeks), eleven lasted 6–15 weeks, and two reported  $\geq 12$ -month follow-up (Etnier 2001; Rosenstein 2020). The paucity of long-term data limits conclusions about durability of benefit.

## Outcomes and Effect Patterns

The MoCA was the primary endpoint in eight trials; the MMSE in three. Executive, attention and memory domains were probed with Trail-Making, Stroop, Digit-Span, Rey and verbal-fluency tests. Functional indices (6-min walk, CAT, mMRC, Borg) were reported in most studies, allowing exploration of cognitive–clinical correlations.

Inspiratory-muscle training and moderate- to high-intensity exercise (interval cycling; combined resistance-aerobic; dance) consistently improved MoCA/MMSE scores and executive–memory domains, accompanied by gains in 6-min walk distance, FEV<sub>1</sub>, CAT, mood and ADL. Combined exercise-behavioural programmes and the Montessori intervention further enhanced daily function and quality of life. In contrast, single-session oxygen and short-term pharmacotherapy showed no immediate cognitive benefit, suggesting isolated physiological correction is insufficient to drive neuroplastic change.

## Risk-of-Bias Assessment

RoB 2 appraisal showed only Pretto 2008 was low risk across all domains ([Supplementary Table S3](#)). Six trials (40%) adequately reported randomisation procedures; five (33%) showed low risk of deviations from intended interventions. Missing-data bias was low in seven trials (47%), but few performed sensitivity analyses. Measurement bias was lowest (12/15 trials, 80% low risk) owing to objective scales and assessor blinding. Reporting bias was most frequent (11/15

trials with some concern or high risk) due to absent preregistration and multiplicity adjustments. Overall quality was moderate, highlighting the need for improved random sequence generation, adherence monitoring and transparent reporting.

## Discussion

### General Information

This study conducted a comprehensive bibliometric analysis using WOSCC to examine the evolving knowledge landscape and research trends in CLDs and cognitive function. A total of 3,474 publications met the inclusion criteria, spanning 546 institutions across 112 countries, reflecting the field's multidisciplinary and global scope. Publication output increased steadily, peaking in 2021, likely due to heightened public health awareness and the impact of the COVID-19 pandemic. Interestingly, citation frequency peaked in 2012, potentially linked to key publications and rising recognition of lung–brain comorbidity. After a brief decline in 2023—possibly due to shifting focus to pandemic recovery—output rebounded in 2024, perhaps reflecting renewed attention to CLDs and cognitive impairment in aging populations.

Geographically, the United States led with nearly one-third of publications, consistent with its established research infrastructure. Among the top authors, FRIED T.R. (Yale) and FEDERMAN A.D. (Mount Sinai) have notably contributed to advancing research on multimorbidity and cognitive decline. Fried emphasizes aligning care with patients' cognitive trajectories and functional goals, while Federman highlights how poor health literacy combined with mild cognitive impairment hampers self-management in chronic illness, advocating integrated cognitive and educational support.

China ranked second (12%), the only developing country in the top three, followed by several European nations. Europe's output reflects its high concentration of developed countries and strong international collaboration. Collaboration patterns showed developed countries tend to partner with each other, while developing countries more often form regional clusters. The marked rise in Chinese publications since 2010 likely reflects growing concern over aging-related health burdens. However, a gap remains in the global influence of institutions from developing regions, underscoring the need for more impactful research and equitable, cross-regional collaboration to address fragmentation in this field. Although we included English-language publications only, cross-validation of the RCT evidence through parallel searches in Scopus and PubMed substantially mitigated the potential bias arising from language restriction and database coverage.

### Hotspots and Frontiers

#### Integrated Mechanism to Evidence Narrative

Evidence from external mechanistic and observational studies suggests that chronic hypoxaemia from asthma, pneumonia, or COPD triggers excess reactive oxygen species (ROS), which stabilise HIF-1 $\alpha$ , activate NF- $\kappa$ B, and weaken tight-junction proteins—disrupting the blood–brain barrier (BBB) and priming microglia for neuroinflammation.<sup>79</sup>

Single-nucleus epigenomic data from Alzheimer's cortex reveal that HIF-1 $\alpha$ –dependent angiogenic stalling and BBB leakage occur early in neurodegeneration,<sup>80</sup> while hypoxia induced BACE1 upregulation and Ca<sup>2+</sup>-mediated tau phosphorylation accelerate amyloid and tau pathology.<sup>81</sup>

Parallel shifts in the low biomass airway microbiome amplify systemic cytokine release and generate neuroactive metabolites that modulate microglial behavior.<sup>82</sup>

Multimodal MRI demonstrates frontoparietal network disintegration and accelerated grey-matter atrophy in COPD and interstitial lung disease, while rodent models show that interventions such as selective HIF-1 $\alpha$  knock-down or ROS scavenging restore synaptic plasticity and memory.<sup>83</sup> Fifteen RCTs support that targeting ventilatory mechanics and cardiopulmonary fitness yields cognitive benefits. Aerobic, resistance, or inspiratory-muscle training improved MoCA/MMSE by 1.8–3.5 points and enhanced executive function, walk distance, and FEV<sub>1</sub> in COPD cohorts aged 55–75.<sup>65,67,69,71</sup> Adding behavioural or cognitive components, such as CBT or creative therapies, amplified effects.<sup>67,73</sup> In contrast, single-session oxygen or short pharmacologic treatments were largely ineffective.<sup>75</sup>

Despite these findings, methodological concerns persist. Only six trials reported robust sequence generation; one-fifth lacked blinding, and most were unregistered, resulting in moderate-to-high risk of bias. Severely hypoxaemic patients and non-smokers were under-represented, and few studies included follow-up beyond one year.

Future trials should adopt stratified randomisation, monitor adherence, apply sensitivity analyses, and use standardised outcome sets capturing both cognition and real-world function. Large, multi-centre trials embedded in standard care, coupled with sub-studies involving spirometry, multi-omics, microbiomics, and advanced neuroimaging, are needed to clarify dose response relationships, identify responders, and validate composite biomarkers for early risk detection along the lung–brain axis.

### Multimodal, Patient-Centred Rehabilitation

Keywords such as “oxidative stress”, “cognitive function”, and “health outcomes” have gained prominence, reflecting a shift toward the lived experience of patients with CLDs. These terms align with the Global Alliance against Chronic Respiratory Diseases (GARD) initiative, which prioritises prevention and equity in the context of the Sustainable Development Goals. Topic clustering also highlights increased attention to vulnerable subgroups and end-of-life care. Recent surges in terms like “self-management” and “post-acute care” suggest a growing emphasis on quality of life (QoL), mental health, and sleep, outcomes that patients often value as much as—if not more than—traditional lung function indices.<sup>84</sup> Notably, several bibliometric hotspots (eg, frailty, obesity/overweight, and related vulnerability constructs) are increasingly mirrored in the RCT literature. In these trials, pulmonary rehabilitation and multi-component programmes commonly target functional reserve, physical activity, weight/metabolic health, and patient-reported outcomes alongside cognitive measures, thereby strengthening the translational link from research priorities to interventional testing. Specifically, hotspots around hypoxemia/oxidative stress and patient-centred outcomes (eg, quality of life and self-management) are reflected in RCTs testing pulmonary rehabilitation packages, particularly exercise and inspiratory-muscle or breathing training, often supplemented with behavioural or educational components. However, mechanistic hotspots are still rarely incorporated as prespecified trial endpoints. Consistent with this convergence, in RCTs with an approximately 12-week intervention period, heterogeneous intervention packages were generally associated with potentially clinically relevant improvements in global cognition, with MoCA or MMSE increasing by approximately 1–3 points. These findings support the plausibility that multidomain, patient-centred strategies can translate into measurable neurocognitive benefit, although interpretation should remain cautious given between-trial heterogeneity. Patient-centered intervention strategies are increasingly supported by evidence. Community-based PR programmes delivered in non-clinical settings show comparable benefits in exercise capacity and disease-specific QoL to hospital-based care, despite low-to-moderate certainty. Trials such as the multicenter TANDEM study demonstrate that integrating brief cognitive behavioural therapy (CBT) into PR significantly improves anxiety, depression, and health status, without increasing provider burden. Digital approaches—such as smartphone-supervised PR—have reported non-inferior outcomes to centre-based PR, with the greatest benefits observed among highly adherent users and in rural settings.<sup>85</sup> Collectively, these findings suggest that accessibility-oriented delivery models can preserve core PR benefits while potentially extending reach to populations facing structural barriers to rehabilitation.

These benefits may extend beyond psychological well-being. For example, a 3-week inpatient PR programme improved functional independence in patients with interstitial lung disease or COPD, indicating that even short, intensive formats may yield meaningful gains in daily function. Innovative formats are also emerging: Singing for Lung Health has been associated with improvements in QoL and well-being comparable to conventional physical training, although effects on core PR outcomes and cognitive endpoints remain uncertain. Taken together, the expanding portfolio of delivery formats and components underscores an ongoing shift from “one-size-fits-all” rehabilitation toward adaptable, preference-sensitive interventions that address physical, psychological, and cognitive domains.

The COVID-19 pandemic intensified interest in neurocognitive sequelae (eg, brain fog, memory loss, accelerated decline) and exposed persistent inequities in respiratory care.<sup>86</sup> In low- and middle-income countries (LMICs), fragile health systems, service disruptions, and lockdown-related barriers exacerbated challenges in diagnosis, follow-up, and rehabilitation. Older adults with CLDs faced greater risks of severe infection,<sup>87,88</sup> prolonged care gaps, worsened mental health, and potentially faster cognitive decline.<sup>87,89,90</sup> Yet despite a rapidly growing burden in LMICs, most research still

originates from high-income settings. Bridging this divide will require longitudinal cohorts with sufficiently long follow-up, culturally adapted screening and cognitive outcome measures (including education- and language-sensitive tools), and implementation strategies that embed equity from the outset—spanning community delivery, digital inclusion, workforce training, and context-appropriate models of PR and cognitive support.

## Limitation

This study has several limitations. First, literature retrieval was limited to WOSCC due to difficulties standardizing raw data from other databases such as Scopus and PubMed, potentially reducing comprehensiveness. Second, restricting inclusion to English language publications may have introduced language bias. In addition, because the RCT evidence was synthesized narratively and trials were heterogeneous, we did not use funnel plots. Publication bias and selective reporting therefore cannot be excluded. Third, bibliometric analysis may not fully reflect evolving trends in a dynamic research landscape. Future studies should consider integrating multiple databases and qualitative analyses to provide a more comprehensive perspective.

## Conclusion

This study provides an integrated view of the lung–brain axis in CLDs by coupling a field-level bibliometric map with a narrative synthesis of randomized trials, thereby extending prior reviews that largely examined epidemiology or clinical associations in isolation. The bibliometric analysis indicates sustained growth led by the United States, Europe, and China, alongside a thematic shift toward mechanisms and patient-centered outcomes, including hypoxemia and oxidative stress, BBB integrity, mood and sleep comorbidities, quality of life, and equity trends; however, LMICs and non-COPD phenotypes remain underrepresented. Across RCTs, multimodal pulmonary rehabilitation was most consistently associated with cognitive and functional improvements. Notably, among trials with a common intervention duration of 12 weeks, heterogeneous intervention packages were generally associated with clinically meaningful gains in global cognition, with MoCA or MMSE improving by approximately 1–3 points. Meanwhile, follow-up was predominantly short (8–12 weeks), and the longest follow-up among included studies was 15 months, limiting inference on durability and long-term decline trajectories. To better address the maintenance and progression of COPD-related cognitive impairment, future intervention studies should extend follow-up to  $\geq 12$  months, incorporate harmonized cognitive and functional endpoints, and embed mechanistic measures to link physiological pathways to cognitive change. Preliminary evidence from small trials suggests that community- or digitally delivered pulmonary rehabilitation may be feasible and potentially beneficial, but adequately powered, multicenter, preregistered RCTs with equity-focused implementation strategies are needed to strengthen effectiveness estimates, improve generalizability, and expand reach in LMICs and other underrepresented groups.

## Abbreviations

CLDs, chronic lung diseases; WOSMCC, Web of Science Core Collection; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; GBD, Global Burden of Disease; MCI, mild cognitive impairment; ROS, reactive oxygen species; GARD, Global Alliance against Chronic Respiratory Diseases; QoL, quality of life; PR, pulmonary rehabilitation; CBT, cognitive behavioral therapy; PExT, physical exercise training; LMICs, middle-income countries.

## Author Contributions

Jirong Zhang, Ning Sun, and Chenming He share first authorship. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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