

Association between Circulating Homocysteine Levels and Pulmonary Function in Adults: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Elevated circulating homocysteine has been associated with chronic obstructive pulmonary disease (COPD) and impaired pulmonary function, but the strength and consistency of this association remain uncertain. This systematic review and meta-analysis evaluated the association between circulating homocysteine levels and pulmonary function in adults.

Methods: A systematic search of PubMed/MEDLINE, Scopus, Web of Science, EBSCOhost, CENTRAL, CINAHL, EMBASE, and additional sources was conducted for studies published from January 2000 to August 2026. Observational and relevant interventional and genetic studies evaluating circulating homocysteine and objective pulmonary function measures were included. Random-effects models were used for quantitative synthesis, with heterogeneity assessed using I^2 and Cochran's Q test.

Results: Fifteen studies were included, all contributing to quantitative synthesis. The pooled mean difference in circulating homocysteine between COPD patients and non-COPD controls was 2.90 $\mu\text{mol/L}$ (95% CI 1.97–3.84; $p < 0.001$), with substantial heterogeneity ($I^2 \approx 64\%$). Most observational studies demonstrated higher homocysteine levels with poorer pulmonary function or greater COPD severity. In contrast, the single asthma study reported lower homocysteine levels, while a Mendelian randomization study found no significant causal association between genetically predicted homocysteine and COPD.

Conclusion: Elevated circulating homocysteine is significantly associated with COPD and poorer pulmonary function. However, substantial heterogeneity and limited causal evidence indicate that homocysteine should currently be considered an associated biomarker rather than an established causal factor. Further prospective and interventional studies are warranted.

Key-words: Homocysteine; Pulmonary function; Chronic obstructive pulmonary disease; COPD; FEV₁; FVC; Spirometry; Hyperhomocysteinemia; Lung function; Systematic review; Meta-analysis

INTRODUCTION

Chronic respiratory diseases, particularly chronic obstructive pulmonary disease (COPD) and asthma, are major causes of morbidity and mortality worldwide. COPD is characterized by persistent respiratory symptoms and airflow limitation, with tobacco smoke, air pollution, and occupational exposures as major risk factors. Oxidative stress, chronic inflammation, endothelial dysfunction, and metabolic abnormalities also contribute to disease progression. ^[1,2]

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Homocysteine is a sulfur-containing amino acid involved in methionine metabolism through remethylation and transsulfuration pathways and is closely linked to folate and vitamins B₆ and B₁₂. Elevated homocysteine has been associated with oxidative stress, endothelial dysfunction, impaired nitric oxide bioavailability, and inflammation, providing a potential biological link with pulmonary dysfunction. [3,4] Several observational studies have reported higher homocysteine levels in COPD and inverse associations with pulmonary function. Seemungal *et al.* reported higher plasma homocysteine and lower FEV₁% predicted in COPD, [5] while Kai *et al.* and Nunomiya *et al.* associated hyperhomocysteinemia with accelerated spirometric decline. [6,7]

Nutritional factors may also influence this association. Folate and vitamin B deficiencies can increase homocysteine levels, and Khan *et al.* reported that folic acid supplementation reduced homocysteine in COPD, although it did not significantly improve FEV₁. [8] Previous meta-analyses have similarly demonstrated higher homocysteine concentrations in COPD patients than controls. [9, 10] However, evidence across other respiratory phenotypes remains limited. Importantly, observational associations do not establish causality. A Mendelian randomization study found no significant causal association between genetically predicted homocysteine and COPD, suggesting potential contributions from smoking, nutritional status, inflammation, and comorbidities. [11] Differences in study populations, measurement methods, exposure categorization, and confounder adjustment may also contribute to heterogeneity.

Therefore, a comprehensive synthesis of the available evidence is warranted. The present systematic review and meta-analysis aimed to evaluate the association between circulating homocysteine levels and pulmonary function in adults, with particular emphasis on FEV₁, FVC, and FEV₁/FVC. We additionally examined secondary pulmonary-function measures, explored potential sources of heterogeneity, and evaluated whether the observed associations differed according to respiratory phenotype and relevant clinical or methodological characteristics.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted in accordance with the PRISMA 2020 guidelines and designed following PRISMA-P recommendations. [12] The research question was formulated using the PECO framework. The population comprised adults (≥18 years), the exposure was circulating homocysteine measured in serum or plasma, and the primary outcomes were pulmonary function parameters, including FEV₁, FVC, FEV₁/FVC, PEF, and other spirometric measures. Relevant association measures, including correlation coefficients, regression coefficients, odds ratios, risk estimates, and mean differences, were considered. Forward citation tracking was also undertaken for eligible studies to identify subsequently published research. Manual screening of reference lists and citation networks was performed to identify additional studies that may not have been retrieved through the electronic database searches. [13-15]

Literature Search- A comprehensive search was conducted in PubMed/MEDLINE, Scopus, Web of Science, EBSCOhost, CENTRAL, CINAHL, and EMBASE, with additional searches in Google Scholar. Studies published from January 2000 to August 2026 were considered. The search strategy combined controlled vocabulary, MeSH terms, keywords, and Boolean operators related to adults, homocysteine, and pulmonary function. Additional sources, including ClinicalTrials.gov, WHO ICTRP, ISRCTN, OSF Registries, PROSPERO, and grey literature, were searched. Reference lists and forward citations of included studies and relevant reviews were also screened.

Inclusion and Exclusion Criteria- Original observational studies (cross-sectional, case-control, or cohort) involving adults were eligible if they assessed circulating homocysteine and objectively measured pulmonary function. Eligible outcomes included FEV₁, FVC, FEV₁/FVC, PEF, and other spirometric parameters. Studies were eligible regardless of respiratory disease status or geographic location. Only English-language studies were included.

Reviews, meta-analyses, protocols, editorials, conference abstracts without full text, case reports/series, letters, dissertations, pediatric or non-human studies, and studies lacking relevant homocysteine or pulmonary

function data were excluded. Duplicate or overlapping publications were removed, retaining the most complete dataset to avoid double-counting participants.

Data Extraction- Two reviewers independently extracted data using a standardized form, including study characteristics, participant demographics, homocysteine measurement methods and concentrations, pulmonary function assessment methods and outcomes, and reported effect estimates. Information on statistical methods and potential confounders including age, sex, smoking, BMI, physical activity, nutritional status, renal function, cardiovascular/metabolic conditions, and inflammatory markers was also recorded. Adjusted estimates were prioritized for quantitative synthesis when sufficiently comparable. Potential sources of heterogeneity and study limitations were documented. When multiple analyses were available, the most relevant and fully adjusted estimates were prioritized while avoiding participant double-counting. Disagreements between reviewers were resolved by consensus or consultation with a third reviewer, and study authors were contacted when essential information was unclear or unavailable.

Data Synthesis- A quantitative meta-analysis assessed the association between circulating homocysteine and pulmonary function in adults. Effect estimates, including correlation and regression coefficients, mean differences, standardized mean differences, odds ratios, and risk ratios with 95% CIs, were pooled where sufficiently comparable and presented using forest plots. A random-effects model was used because of expected clinical and methodological heterogeneity. Heterogeneity was assessed using Cochran's Q and I² statistics. The primary outcomes were FEV₁, FVC, and FEV₁/FVC. Subgroup analyses, where feasible, considered age, sex, smoking, respiratory disease, study design, geographic setting, homocysteine measurement and categorization, pulmonary function assessment, and confounder adjustment. The most relevant and fully adjusted estimates were prioritized while avoiding double-counting. Where necessary, statistical measures were appropriately transformed, including Fisher's z transformation for correlation coefficients. Secondary analyses included PEF and other spirometric parameters. Publication bias and small-study effects were assessed

using funnel plots and appropriate statistical tests when sufficient studies were available. Sensitivity analyses excluded studies with high risk of bias or important methodological or measurement concerns. Where quantitative pooling was inappropriate because of substantial heterogeneity, findings were synthesized narratively, considering study characteristics, measurement methods, statistical approaches, confounding, and risk of bias.

Ethical Considerations and Registration- As this review used previously published data, ethical approval and informed consent were not required. The review followed PRISMA 2020 guidelines. The protocol was prospectively registered in PROSPERO (Registration ID: CRD420261518713).

RESULTS

A total of 1,071 records were identified, including 1,040 from electronic databases and 31 from other sources. After removal of 799 duplicates and 58 records for other reasons, 183 records underwent title and abstract screening. Of these, 145 were excluded and 38 reports were sought for retrieval. Thirteen could not be retrieved, leaving 25 reports for full-text assessment. Ten were excluded because they did not assess circulating homocysteine (n = 5), lacked pulmonary function outcomes (n = 3), or included an inappropriate population (n = 2). The 31 records identified through other sources included OpenGrey.eu (n = 3), WorldCat.org (n = 6), ClinicalTrials.gov (n = 1), WHO ICTRP (n = 8), PROSPERO (n = 4), OSF Registries (n = 2), and ISRCTN Registry (n = 7). Of these, 27 could not be retrieved, while 4 underwent eligibility assessment. All 4 were excluded due to an ineligible population (n = 2), insufficient data (n = 1), or inappropriate publication type (n = 1). Ultimately, 15 studies comprising 15 reports were included in the review, as shown in Fig. 1.

The diagram was generated using the PRISMA 2020 Flow Diagram web application developed by Haddaway NR, McGuinness LA, and colleagues. No automated tools were used for study screening or selection.

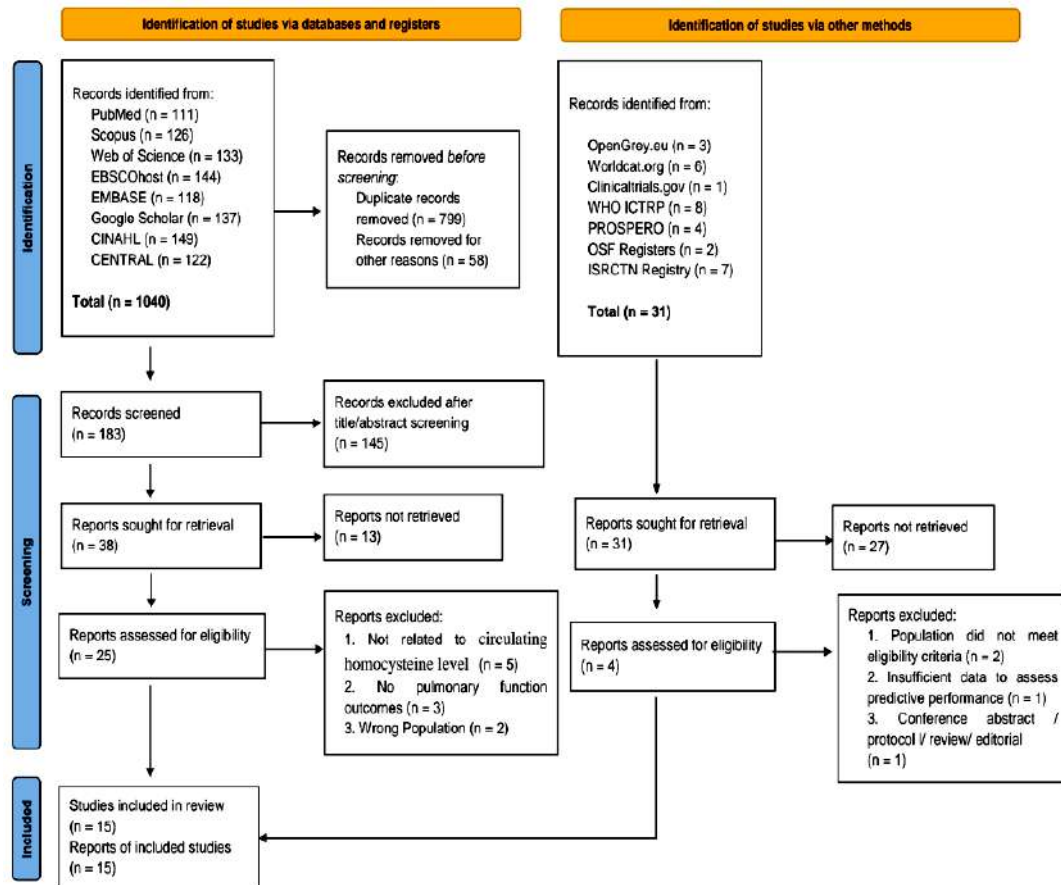


Fig. 1: PRISMA flow diagram of the study selection process.

The PRISMA-guided selection process identified 15 studies for the qualitative synthesis, all of which were eligible for quantitative meta-analysis (Fig. 1). The studies were predominantly cross-sectional, case-control, and cohort studies involving adults, including healthy populations, older adults, smokers, and patients with respiratory or other clinical conditions. Circulating homocysteine was assessed using serum or plasma samples and related to objective pulmonary function measures. Pulmonary function was primarily assessed using spirometry, including FEV₁, FVC, and FEV₁/FVC, with PEF and other parameters reported in some studies. Homocysteine was analyzed as a continuous variable or categorized using study-specific cut-offs, quartiles, or tertiles. Reported effect measures included correlation and regression coefficients, mean differences, odds ratios, and other estimates. Considerable variation existed in participant characteristics, study settings, measurement methods, exposure categorization, statistical approaches, and confounder adjustment. [5-8,11, 16-25]

The 15 studies were published between 2001 and 2025 across eight countries, with sample sizes ranging from 44 to more than 3,000 participants, alongside one large multinational genetic analysis. Most studies were cross-sectional or case-control (12/15), with one prospective cohort, one pilot pre-post study, and one Mendelian randomization analysis. Eleven studies focused on COPD, examining homocysteine in relation to disease presence, severity, exacerbation, or spirometric decline. One study assessed asthma, while another examined COPD with cardiovascular comorbidity. Most observational studies reported higher homocysteine levels with poorer pulmonary function or greater airway disease severity, whereas the asthma and Mendelian randomization studies reported null or discordant findings, indicating heterogeneity in the observed and causal associations.

Table 1: Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Size	Primary Focus	Key Findings
Andersson <i>et al.</i> ^[16]	Sweden	Case-control	48	Plasma homocysteine and thiol redox status in COPD vs controls.	Homocysteine was significantly higher in COPD, with altered thiol redox status.
Kai <i>et al.</i> ^[6]	Japan	Prospective cohort	47	Smoking-related homocysteine and spirometric decline in elderly COPD patients.	Higher homocysteine was associated with faster spirometric decline, particularly in smokers.
Seemungal <i>et al.</i> ^[5]	Trinidad/England	Case-control	54	Plasma homocysteine in COPD and its relationship with lung function.	Homocysteine was higher in COPD and inversely correlated with FEV ₁ % predicted.
Abdallah <i>et al.</i> ^[17]	Egypt	Case-control	44	Serum homocysteine and antioxidant status in COPD.	Homocysteine was higher in COPD and inversely related to antioxidant status.
Fimognari <i>et al.</i> ^[18]	Italy	Case-control	71	Homocysteine and vitamin B status in COPD.	COPD patients had higher homocysteine and poorer vitamin B status.
Khan <i>et al.</i> ^[8]	India	Pilot pre-post study	80	Effect of folic acid supplementation on homocysteine and lung function in COPD.	Folic acid reduced homocysteine and modestly improved pulmonary function.
Moayyedkazemi & Rahimirad ^[19]	Iran	Case-control	91	Serum homocysteine and COPD severity.	Homocysteine was higher in COPD and increased with disease severity.
Abdel-Aziz <i>et al.</i> ^[20]	Egypt	Case-control	80	Homocysteine, asthma severity, and spirometry.	Homocysteine was lower in asthma than controls, with no significant association with spirometry.
He <i>et al.</i> ^[21]	China	Cross-sectional/case-control	106	H ₂ S/homocysteine balance and lung function in COPD with/without CVD.	Homocysteine increased with COPD severity; H ₂ S/Hcy ratio correlated positively with FEV ₁ /FVC.
Wei <i>et al.</i> ^[22]	China	Retrospective case-control	250	Homocysteine in COPD occurrence and acute exacerbation.	Homocysteine was higher in COPD and increased with GOLD severity; it showed diagnostic value for COPD/AECOPD.
Zinellu <i>et al.</i> ^[23]	Italy	Case-control	108	Thiol pathway markers, including	Homocysteine was higher in COPD and

				homocysteine, in COPD.	associated with disease severity.
Nunomiya <i>et al.</i> [7]	Japan	Prospective cohort	3,257 (147 follow-up)	Homocysteine and spirometric decline in healthy male smokers.	Higher homocysteine was associated with lower baseline FEV ₁ /FVC measures and faster FEV ₁ decline.
Hu <i>et al.</i> [11]	China	Two-sample Mendelian randomization	GWAS-derived	Causal relationship between genetically predicted homocysteine and COPD.	No significant causal association was found between homocysteine and COPD risk.
Adarsh <i>et al.</i> [24]	India	Comparative cross-sectional	200	Homocysteine in stable COPD vs AECOPD.	Homocysteine was significantly higher in AECOPD than stable COPD.
Li <i>et al.</i> [25]	China	Cross-sectional with 1-year follow-up	230	Homocysteine, COPD severity, lung function, and prognosis.	Homocysteine correlated positively with CAT/mMRC and negatively with FEV ₁ % and FEV ₁ /FVC; it also predicted 1-year outcomes.

Each square represents a study-specific mean difference in homocysteine (COPD minus control), with horizontal lines indicating 95% CIs; the coral diamond represents the pooled random-effects estimate as depicted in Fig. 2. All nine studies showed higher homocysteine in COPD, with eight CIs excluding the null. The pooled mean difference was 2.90 $\mu\text{mol/L}$ (95% CI 1.97–3.84; $p < 0.001$), with substantial heterogeneity ($I^2 \approx 64\%$), mainly

influenced by differences in study precision and sample size. This estimate closely matches the published Zinellu *et al.* [23] meta-analysis (WMD 2.91 $\mu\text{mol/L}$), providing an internal consistency check. Because COPD and asthma showed opposite-direction associations, a subgroup-style comparison of the pooled COPD estimate with the available asthma study is informative.

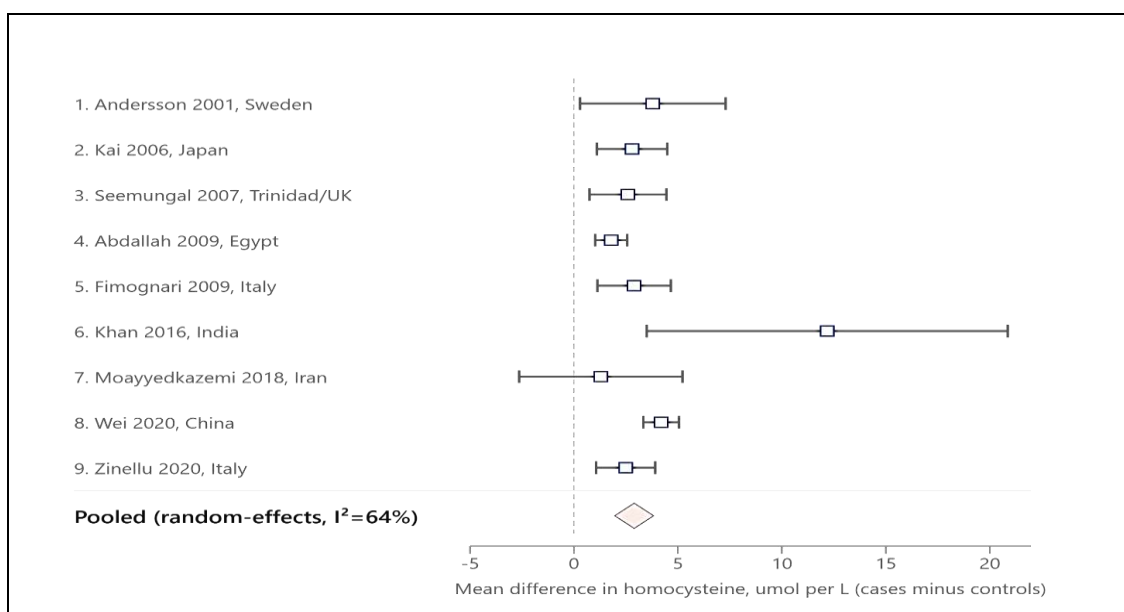


Fig. 2: Mean Difference in Circulating Homocysteine Levels between COPD Patients and Non-COPD Controls

Fig. 3 shows opposing associations: the pooled COPD estimate was +2.90 (95% CI 1.97–3.84), indicating higher homocysteine, whereas Abdel-Aziz *et al.* (2018)^[20] reported –2.90 (95% CI –3.21 to –2.59) in asthma, indicating lower homocysteine. Neither CI crossed zero. Disease phenotype therefore represents an important source of heterogeneity. The COPD findings generally

support elevated homocysteine, while the single asthma study showed the opposite pattern. Given the limited asthma evidence, this finding should be considered hypothesis-generating. The scarcity of studies in asthma, ILD, and general-population spirometry limits quantitative pooling, supporting narrative synthesis for these subgroups.

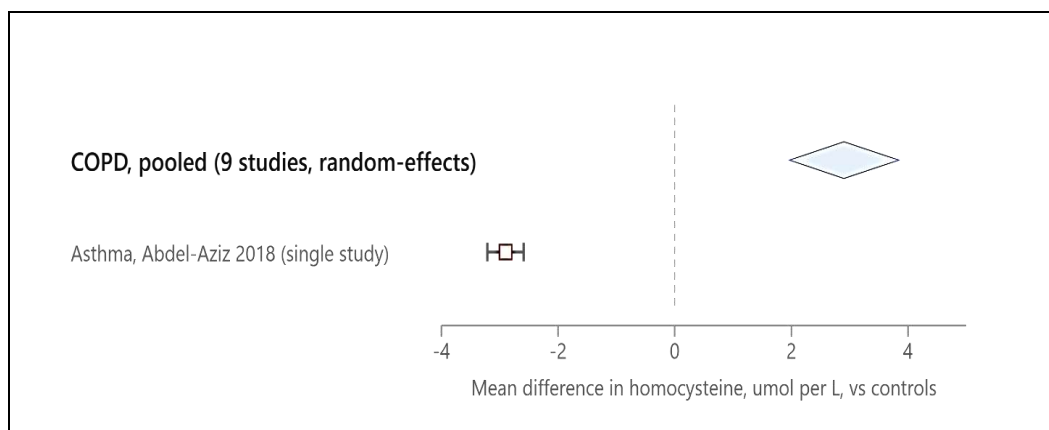


Fig. 3: Disease Phenotype as a Source of Heterogeneity in the Association between Homocysteine and Pulmonary Disease

DISCUSSION

This systematic review and meta-analysis found a significant association between elevated circulating homocysteine and COPD. The pooled mean difference in homocysteine between COPD patients and non-COPD controls was 2.90 $\mu\text{mol/L}$ (95% CI 1.97–3.84; $p < 0.001$), with substantial heterogeneity ($I^2 \approx 64\%$). The direction of effect was consistent across the included COPD studies, suggesting that elevated homocysteine is associated with COPD and impaired pulmonary function. However, because most included studies were observational, these findings should be interpreted as an association rather than evidence of causality.

Our findings are closely consistent with the previous systematic review and meta-analysis by Zinellu *et al.*, which included nine studies and reported a weighted mean difference of 2.91 $\mu\text{mol/L}$ (95% CI 2.00–3.82; $p < 0.001$) between COPD patients and controls. The similarity between the two estimates provides an important consistency check for the present analysis.^[9] In a subsequent meta-analysis of metabolites involved in the arginine, transsulfuration, and folic acid pathways, Zinellu and Mangoni also reported significantly higher homocysteine concentrations in patients with stable COPD (SMD 0.78, 95% CI 0.48–1.07).^[10]

Several individual studies further support this association. Seemungal *et al.* reported significantly higher plasma homocysteine in COPD patients and an inverse relationship with $\text{FEV}_1\%$ predicted, suggesting an association between hyperhomocysteinemia and poorer pulmonary function.^[5] Similarly, Kai *et al.* reported an association between smoking-related hyperhomocysteinemia and accelerated spirometric decline in elderly patients with COPD.^[6] In a community-based cohort of healthy male smokers, Nunomiya *et al.* found that hyperhomocysteinemia predicted subsequent decline in pulmonary function, suggesting that elevated homocysteine may be associated with lung-function deterioration even before clinically established COPD.^[7] Several biological mechanisms may explain this relationship. Homocysteine is involved in the transsulfuration and folate metabolic pathways and may influence oxidative stress, endothelial dysfunction, inflammation, and nitric oxide bioavailability. These processes are also relevant to COPD pathophysiology. The meta-analysis by Zinellu and Mangoni demonstrated concurrent alterations in homocysteine, folate, methionine, cysteine, and other metabolites involved in these pathways, supporting the possibility that elevated homocysteine reflects a broader metabolic disturbance in COPD rather than an isolated abnormality.^[18,23]

Nutritional factors may also contribute to elevated homocysteine. Folate and vitamin B deficiencies can impair homocysteine metabolism. In the pilot study by Khan *et al.*, folic acid supplementation significantly reduced plasma homocysteine concentrations in COPD patients; however, it did not produce a significant improvement in FEV₁.^[8] This finding is important because it suggests that although homocysteine may be associated with COPD, lowering circulating homocysteine alone may not necessarily improve pulmonary function.

An important source of heterogeneity in the present review was disease phenotype. While the COPD studies generally demonstrated elevated homocysteine, the single available asthma study by Abdel-Aziz *et al.* reported lower homocysteine concentrations in patients with asthma than in controls and found no significant relationship with spirometric parameters.^[20] Given that this observation is based on only one study, it should be considered hypothesis-generating rather than evidence of a definitive difference between COPD and asthma. The limited number of studies evaluating asthma, interstitial lung disease, and general-population pulmonary function also prevents reliable quantitative comparisons across respiratory phenotypes.

The distinction between association and causality is particularly important. Although most observational studies demonstrated higher homocysteine concentrations in COPD, a two-sample Mendelian randomization study by Hu *et al.* found no significant causal association between genetically predicted plasma homocysteine and COPD.^[11] This discrepancy suggests that elevated homocysteine could represent a marker of disease-related metabolic, inflammatory, nutritional, or smoking-related changes rather than a direct causal determinant of COPD. Residual confounding, particularly from smoking, nutritional status, renal function, age, and cardiometabolic comorbidities, may also contribute to the observed associations.

The clinical implications of these findings should therefore be interpreted cautiously. Although homocysteine may have potential value as a biomarker of systemic metabolic disturbance in COPD, current evidence is insufficient to support its routine use for COPD diagnosis, severity assessment, or treatment selection. Similarly, the reduction in homocysteine following folic acid supplementation without significant improvement in FEV₁ does not currently support

homocysteine-lowering therapy as a strategy for improving pulmonary function.^[6]

Overall, the available evidence indicates that circulating homocysteine is significantly elevated in COPD and is associated with poorer pulmonary function. However, the absence of consistent causal evidence means that homocysteine should currently be regarded as an associated biomarker rather than an established causal factor. Larger prospective studies with standardized measurements and well-designed intervention trials are required to determine whether homocysteine has independent prognostic or therapeutic relevance.

STRENGTHS

This review has several strengths. It used a comprehensive literature search across multiple major databases and supplementary sources and followed PRISMA-based methodology. The inclusion of 15 studies enabled quantitative synthesis of comparable data, while subgroup and sensitivity analyses allowed potential sources of heterogeneity to be explored. The review also incorporated observational, longitudinal, interventional, and Mendelian randomization evidence, providing a broader perspective on the association between homocysteine and pulmonary function.

LIMITATIONS

Several limitations should be considered. Most included studies were observational, limiting causal inference and leaving the findings vulnerable to residual confounding and reverse causation. Considerable heterogeneity was observed in participant characteristics, smoking exposure, homocysteine measurement methods, pulmonary-function assessment, exposure categorization, and statistical adjustment. Evidence for non-COPD respiratory conditions, particularly asthma and other pulmonary diseases, was limited, restricting meaningful subgroup comparisons. Differences in study designs and reported effect measures also reduced comparability across some outcomes. Finally, the available interventional and genetic evidence remains limited, and further well-designed studies are required to clarify causality.

Conclusion

This systematic review and meta-analysis demonstrates a significant association between elevated circulating

homocysteine and COPD, with a pooled mean difference of 2.90 $\mu\text{mol/L}$ (95% CI 1.97–3.84). The findings are consistent with previous meta-analytic and observational evidence and suggest that higher homocysteine is associated with poorer pulmonary function. However, substantial heterogeneity and the absence of consistent causal evidence indicate that homocysteine should currently be considered an associated biomarker rather than an established causal factor. Further large-scale prospective and interventional studies are needed to determine its prognostic significance and potential therapeutic relevance.

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