

Integrating Pulmonology and Metabolism: Adipokines in COPD from a Systematic Review and Meta-analysis Perspective

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is increasingly recognized not just as a pulmonary disorder but as a complex systemic syndrome involving chronic inflammation, metabolic dysregulation, and immune imbalance. This systematic review and meta-analysis aim to evaluate circulating correlation with disease severity, and potential as biomarkers or therapeutic targets.

Methods: Following PRISMA 2020 guidelines, a comprehensive literature search was conducted across PubMed, Scopus, and Web of Science. A random-effects meta-analysis assessed standardized mean differences (SMDs) for key adipokines. Risk of bias was evaluated using the Newcastle-Ottawa Scale, and evidence certainty was assessed using the GRADE framework.

Results: Twelve eligible studies comprising 2,100 COPD patients and 2,100 controls were included. Leptin (1.57 [-0.02 to 3.16] double armed; 19.59 [14.01-25.18] single armed), resistin (0.67 [-0.27 to 1.60]), and adiponectin (-0.18 [-2.13 to 1.77] double armed; 7.83 [6.95 to 8.71] single armed) levels showed statistically significant differences between COPD patients and controls ($p < 0.001$ for all), with high heterogeneity (>60%). Elevated leptin and resistin levels were associated with systemic inflammation and poorer clinical outcomes, whereas adiponectin was often reduced despite its anti-inflammatory properties. Sensitivity and subgroup analyses reinforced these findings. The certainty of evidence ranged from low to moderate.

Discussion: Adipokines reflect systemic inflammation and metabolic imbalance in COPD, highlighting their potential role in phenotypic stratification and disease monitoring. While promising, translation to clinical practice requires further standardized, longitudinal, and mechanistic research.

Keywords: Adipokines, Leptin, Adiponectin, Chronic Obstructive Pulmonary Disease, Disorder, Pulmonary, Metabolism.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of death on a global scale, mainly because its symptoms persist for a long time, and the airflow pathway is obstructed due to airway or alveolar abnormalities¹. For centuries, COPD has been regarded as a pulmonary disease, but current bodies of evidence demonstrate its systemic nature, including its metabolic dysfunctions such as adipokine signaling, which is critical in disease progression and exacerbation². Biologically active cytokines, which are secreted by adipose tissue, are referred to as adipokines. These adipokines play a central role in the regulation of inflammation, balancing of energy, and immune responses, all of which are closely connected to how COPD develops and behaves^{3,4}.

Adipokines such as leptin, adiponectin, resistin, visfatin, chemerin, and others are being increasingly studied in COPD^{5,6}. These studies show varying degrees of expression of adipokines that reflect various underlying conditions such as inflammatory states, metabolic derangement, and clinical severity⁷. Leptin and resistin are often elevated when there is systemic inflammation and poor functional outcomes⁸. Similarly, adiponectin shows a paradoxical downregulation despite its anti-inflammatory properties⁹. Moreover, adipokines are not only linked with COPD but also with its other comorbidities such as sarcopenia, metabolic syndromes, and heart diseases, which makes them promising diagnostic and therapeutic markers¹⁰. Recent studies indicate that adipokines perform substantial systemic and metabolic functions in COPD patients; thus, additional research is necessary. The profiles of adipokines serve to display disease severity, together with systemic effects and potential treatment options.

In this schematic review, current evidence on the adipokine profiles in COPD patients, such as their diagnostic value, relation to disease severity, and physiological relevance, was summarized. In this study, pulmonological understanding was developed by linking it with metabolic signaling through case-control, cohort, cross-sectional, and Mendelian randomization analyses using comparative study designs. This study also sought to understand adipokine behavior as biomarkers and potential targets by mapping their patterns across

different clinical and inflammatory states in COPD.

METHODS

Study Design

This systematic review and meta-analysis followed the guidelines published by PRISMA in 2020¹¹. The objective was to evaluate the association between circulating adipokines and chronic obstructive pulmonary disease (COPD) from a metabolic and pathophysiological perspective.

Inclusion Criteria

Studies were included if they investigated circulating adipokine levels in individuals diagnosed with COPD and reported outcomes in quantitative terms. Only original research articles in the English language involving human subjects were considered.

Exclusion Criteria

Reviews, case reports, conference abstracts, editorials, animal studies, and articles without access to full texts were excluded.

Literature Search

A thorough and well-planned literature search was conducted across multiple electronic databases such as PubMed, Scopus, and Web of Science. The last search was completed on March 25, 2025. The search strategy combined disease- and biomarker-specific terms using Boolean operators: ("COPD" OR "chronic obstructive pulmonary disease") AND ("adipokine" OR "leptin" OR "adiponectin" OR other adipokine names). Reference lists of included studies and related reviews were also screened to identify additional records.

Data Screening and Selection

Two independent reviewers first filtered studies on the basis of titles and abstracts and then screened full texts of the promising studies.

Data extraction

The data extraction process was put into action using a standardized form containing study characteristics, participant demographics, adipokines assessed, and statistical outcomes. Disagreements of any type were resolved through consensus. The concentrations of adipokines that

had been reported at baseline were sought out. In the case that studies provided more than one time point or more than one isoform, only the most frequently reported or clinically relevant ones (e.g., total or HMW adiponectin) were extracted based on predefined criteria. Data was taken in an Excel sheet in tabular form, and missing data was either calculated using available data or the authors were contacted. Visual data was presented in the form of forest plots.

Outcomes Assessed

The primary outcome was the difference in adipokine levels between COPD patients and controls or subgroups. Secondary variables included BMI, FEV1, and comorbidities.

Quality Assessment

Assessment for risk of bias was done using the Newcastle-Ottawa Scale Tool. The risk of biases as a result of missing results (reporting bias) was evaluated qualitatively. The GRADE approach was used to assess the certainty of the evidence.

Data Synthesis

Meta-analysis was conducted using a random-effects model with the MetaAnalysisOnline

Tool. Effect sizes relatable for analysis included means and medians (interquartile ranges). For single-arm studies, raw means were used, and mean differences were taken for double-arm studies. Standard deviations were calculated or converted from available summary statistics if not present; no imputation was performed for completely missing data. Heterogeneity was measured by utilizing the I² statistic, with <50% heterogeneity being tolerable. Forest plots were created for adipokines with ≥2 comparable studies. Sensitivity analyses and subgroup analyses were performed for the data appropriate for them. The studies comprised 5 case-control studies 3 cross-sectionals, 2 cohorts, 1 observational, and 1 Mendelian randomization^{12,13,14,15,16,17,18,19,20,21,22,23}.

RESULTS

The initial search was completed with the identification of 145 records. These were further reduced to 140 after duplicates were removed. Titles and abstracts were screened in the filtration process, and 95 studies were selected for full-text review. 55 studies were excluded for reasons such as lack of accessible full text, non-human subjects, or irrelevant outcomes.

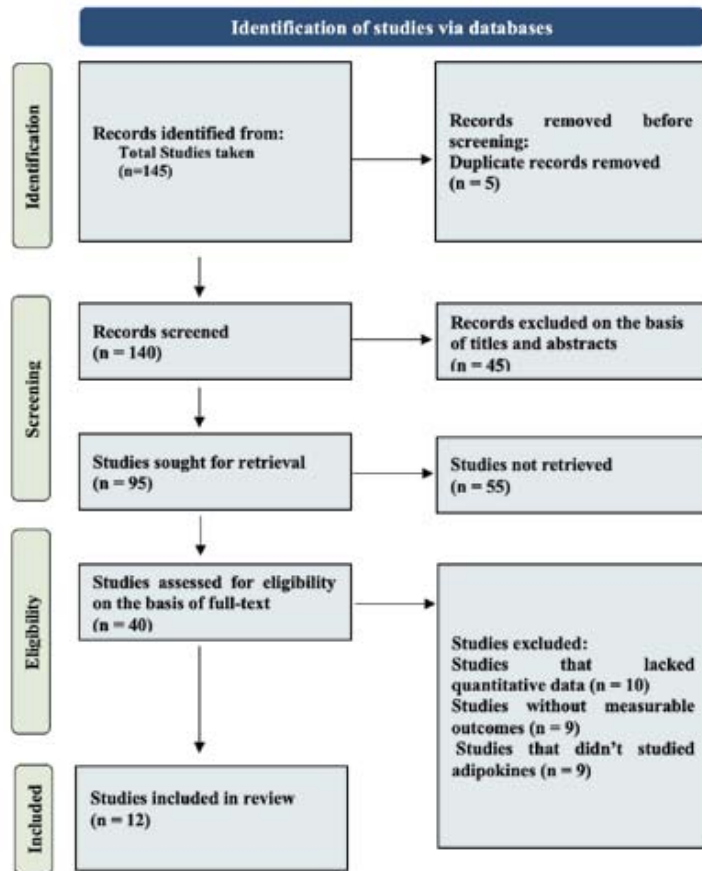


Figure 1: PRISMA Flow Diagram for Study Selection Process.

Characteristics of Studies

This systematic review included 12 studies, which involved a total of 2,100 COPD patients and the same number of controls. The designs used in the studies were: case-control, cross-sectional, cohort, observational, and single review of Mendelian. The size of samples per group varied between 25 to more than 200 individuals. Most of the participants were middle-aged to old people with an average age varying between 55-70 years. The majority of the literature presented both males and females as participants, but some studies included male cohorts only. BMI was observed in all studies and varied between 24-29 kg/m², which shows overweight tendencies. COPD was confirmed, and the severity was determined by spirometric indices such as the FEV₁, FVC, and FEV₁/FVC ratios. Several papers also stratified patients according to disease phenotype (e.g., stable vs. acute COPD) or other comorbid illnesses such as obesity and metabolic syndrome, providing a fairly broad clinical background to interpret adipokine profiles.

Outcomes Measured

The main results concentrated on the circulating levels of adipokines in patients with COPD versus controls. There was a significant increase in leptin and resistin (e.g., 14.4 vs. 8.8 ng/mL, $p = 0.001$ and 8.2 vs. 3.5 ng/mL, $p < 0.0001$, respectively) in COPD; whereas adiponectin levels were typically lowered (7.26 vs. 7.64 m g/mL, $p < 0.05$), suggesting pro-inflammatory profile. The secondary outcomes were body mass index (BMI) and lung function indicators. The BMI of COPD patients was in the range of 24.3 kg/m² to 28.9 kg/m². There was also significant impairment of lung function with FEV₁ values between 43 and 53 % of the predicted (e.g., 47 % vs 102 %), and FEV₁/FVC ratios that were frequently less than 0.60 (e.g., 59.43 % vs. 83.65 %). Metabolic comorbidities like sarcopenic obesity were often detected along with an increase in body mass index, decreased lung function, and an increase in adipokines. In general, the evidence indicates that adipokine dysregulation in COPD demonstrates systemic inflammation, airflow limitation, and a metabolic disorder.

The characteristics of individual studies are shown in **Table 1**.

Table 1: General Characteristics of Individual Studies Included in The Systematic Review

Study	Study Design	Population Groups (N)	Sex (M/F)	Age (Mean \pm SD or Median (IQR))	BMI (kg/m ²)	FEV ₁ (% predicted)	FVC (% predicted)	FEV ₁ /FVC (%)
Malujto-Balcerska et al. (2023)	Case-control	COPD (25); Controls (30)	COPD: 17/8; Controls: 14/16	COPD: 67 (59-76); Controls: 63 (56-68)	COPD: 26.4 (18.8-31.3); Controls: 25.8 (21.3-27.3)	COPD: 47 (34-60); Controls: 102 (99-107)	COPD: 78 (56-86); Controls: 108.5 (99-116)	COPD: 61 (56-68); Controls: 97.5 (92-105)
Hryniuk et al. (2020)	Cross-sectional	NASH+Obesity (35); NASH+Obesity+COPD (60); COPD (35); Healthy (30)	N/A	55.7 \pm 3.22 (overall)	N/A	N/A	N/A	N/A
Amanullah et al. (2022)	Cohort	COPD (70)	35/35	65.2 \pm 7.3	25.4 \pm 4.1	N/A	N/A	N/A
Aslani et al. (2022)	Case-control	COPD (60); Controls (30)	All Male	COPD: 58.92 \pm 6.22; Controls: 56.40 \pm 6.29	COPD: 24.72 \pm 4.79; Controls: 26.73 \pm 3.88	COPD: 43.82 \pm 20.59; Controls: 89.06 \pm 7.60	COPD: 58.71 \pm 22.42; Controls: 85.50 \pm 8.79	COPD: 59.43 \pm 11.69; Controls: 83.65 \pm 5.89

Cuttitta et al. (2022)	Pilot Case-control	COPD (25); Controls (26)	COPD: 15/10; Controls: 14/12	67.6 ± 8.4 (overall)	Waist, abdomen, fat mass significantly ↑ in COPD	COPD: 41.1 ± 35.3; Controls: 122.9 ± 54.8	N/A	COPD: 58.6 ± 10.4; Controls: 78.9 ± 8.3
Vanfleteren et al. (2023)	Cross-sectional	COPD (213)	59% Male	63.6 ± 7.0	26.2 ± 5.1	51.2 ± 16.9	N/A	0.40 ± 0.11
Zhelyazkova et al. (2019)	Cross-sectional	COPD (58); Controls (21)	COPD: 46/12; Controls: 14/7	COPD: 68.05 ± 6.41; Controls: 54.48 ± 8.00	BMI categories reported	N/A	N/A	N/A
Nigro et al. (2023)	Observational	BCO (30); COPD (29); Controls (29)	BCO: 15/15; COPD: 16/13; Controls: 14/15	BCO: 60.0 (15.9); COPD: 60.7 (8.4); Controls: 56.6 (10.3)	BCO: 25.8 (4.2); COPD: 27.7 (5.0); Controls: 25.1 (2.3)	BCO: 52.3 (16.5); COPD: 67.3 (22.3)	BCO: 66.7 (17.8); COPD: 83.2 (25.8)	N/A
Wang et al. (2023)	Cross-sectional	COPD (198, stratified)	Varies	SO: 71.27 ± 8.52	SO: 27.17 ± 2.54	SO: 1.29 ± 0.63 (L)	N/A	SO: 54.21 ± 8.99
Wu et al. (2024)	Mendelian Randomization	COPD (462,933 participants)	Mixed (European ancestry)	N/A (GWAS data)	N/A	N/A	N/A	N/A
Ghobadi et al. (2021)	Case-control	AE-COPD (30); S-COPD (30); Controls (30)	All Male	Control: 56.27 ± 8.12; S-COPD: 58.83 ± 9.47; AE-COPD: 59.73 ± 6.59	Controls: 26.90 ± 3.91; S-COPD: 26.06 ± 5.30; AE-COPD: 24.35 ± 4.67	Controls: 89.83 ± 8.38; S-COPD: 53.13 ± 23.12; AE-COPD: 33.95 ± 13.48	Control: 84.63 ± 8.07; S-COPD: 68.40 ± 22.57; AE-COPD: 50.09 ± 20.68	Control: 86.76 ± 4.54; S-COPD: 58.86 ± 9.99; AE-COPD: 55.81 ± 12.43
Vassiliou et al. (2020)	Prospective Cohort	COPD (39); Asthma (15)	COPD: 31/8; Asthma: 6/9	COPD: 67 ± 8; Asthma: 52 ± 15	COPD: 28.96 ± 6.25; Asthma: 30.81 ± 6.70	COPD: 48.81 ± 16.20 (resolution); Asthma: 85.40 ± 14.78	N/A	N/A

The values of adipokine levels in COPD patients and controls across different studies are shown in Table 2.

Table 2: Adipokine Levels in Included Studies Concerning Disease and Control Groups

Index	Author(s)	Year	Adipokine(s) Studied	N (COPD / Control)	COPD Levels (mean ± SD or Median [IQR])	Control Levels (mean ± SD or Median [IQR])	p-value	Conclusion
1	Malujto-Balcerska et al. (2023)	2023	Leptin, Resistin, Fetuin A, Adiponectin, Chemerin	25 / 30	Leptin: 14.4 (9.7–21.3) Resistin: 8.2 (5.6–13.6) Fetuin A: 153.09 (125.16–188.07) µg/mL	Leptin: 8.8 (5.2–11.5) Resistin: 3.5 (2.7–4.3) Fetuin A: 269.61 (228.34–378.9) µg/mL	Leptin: p < 0.001 Resistin: <0.0001 Fetuin A: <0.0001	Leptin and resistin were elevated, fetuin A lower in COPD.
2	Hryniuk et al. (2020)	2020	Leptin, Adiponectin	35 / 30	Leptin: 9.54 ± 0.84 Adiponectin: 7.26 ± 0.15	Leptin: 7.15 ± 0.27 Adiponectin: 7.64 ± 0.13	Leptin: p < 0.05 Adiponectin: p < 0.05	COPD had high leptin, low adiponectin.

3	Amanullah et al. (2022)	2022	Leptin, Adiponectin	70 / —	Leptin: 22.5 ± 10.8 Adiponectin: 8.3 ± 3.2	—	Leptin: p = 0.03 (with REE) Adiponectin: NS	Leptin correlated with REE; adiponectin not significant.
4	Aslani et al. (2022)	2022	Adipolin, IL-6	60 / 30	Adipolin: 5.28 ± 1.28 IL-6: 87.71 ± 52.92	Adipolin: 8.88 ± 5.59 IL-6: 54.56 ± 10.47	Adipolin: <0.001 IL-6: <0.001	Adipolin lower, IL-6 higher in COPD.
5	Cuttitta et al. (2022)	2023	Leptin, Adiponectin, Haptoglobin, Irisin	25 / 26	Leptin: 34 (10–58.8) Adiponectin: 8.8 (8–12.1) Haptoglobin: 0.31 ± 0.08	Leptin: 23.1 (8.5–40.3) Adiponectin: 8.9 (5.3–11.4) Haptoglobin: 0.23 ± 0.13	p < 0.05	Leptin elevated.
6	Vanfleteren et al. (2023)	2023	Leptin, Adiponectin, Fetuin A, others	213 / —	Leptin: 8.2 ± 8.8 to 16.8 ± 14.6 Adiponectin: 4.4 ± 2.1 to 7.4 ± 4.7 Fetuin A: 574 ± 292 to 706 ± 364	—	Not applicable	High leptin/low adiponectin shows inflammation and metabolic dysfunction.
7	Zhelyazkova et al. (2019)	2019	Leptin	58 / 21	Females: 414.60 ± 60.63 pg/mL	Females: 219.40 ± 44.15	p = 0.038	Leptin higher in females with COPD.
8	Nigro et al. (2023)	2023	Adiponectin (Total and HMW)	30 (BCO) / 29 (COPD) / 29 (HC)	COPD: 18.2 ± 1.3 BCO: 37.6 ± 8.3	HC: 9.1 ± 5.6	p < 0.001	HMW adiponectin elevated in bronchiectasis-COPD (BCO).
9	Wang et al. (2023)	2023	Resistin, TNF-α	198 / —	SO group: Resistin: ↑ (cutoff 9.34 ng/mL)	—	p < 0.001	Resistin elevated in sarcopenic obesity (SO).
10	Wu et al. (2024)	2024	Adiponectin, Leptin, Resistin, etc.	MR (GWAS: 198,955)	—	—	Not applicable	Mendelian randomization shows no causal link.
11	Ghobadi et al. (2021)	2021	Visfatin, Sirtuin-1, IL-6	30 AE-COPD / 30 S-COPD / 30 Control	AE-COPD: Visfatin: 4.5 (3–6) ng/mL; IL-6: 90.5 (73–108)	S-COPD: Visfatin: 3 (2–3) ng/mL; IL-6: 56 (44–60)	p < 0.001	Visfatin and IL-6 elevated, Sirtuin-1 reduced in AE-COPD.
12	Vassiliou et al. (2020)	2020	Leptin, Adiponectin, Resistin, IL-6,	39 / 15	Leptin: 25.53 (11.79–44.59) Resistin: 9.7 (4.05–16.9),	Leptin: 34.06 (18.61–66.96); Resistin: 7.95 (4.25–15.71);	p < 0.05	Serum cytokines and adipokines reflect disease

Meta-Analysis

This meta-analysis produced forest plots to display the primary outcome of the study, which was the comparison of circulating levels of adipokines in COPD patients and controls. The individual study estimates (with 95% confidence intervals) are displayed as green squares and horizontal lines on each plot. The thickness of each square indicates study weight, and the black diamond at the bottom indicates the pooled effect and the confidence interval. When the diamond falls beyond the vertical line of no effect, the overall effect becomes insignificant. I^2 and chi-square were used in the determination of heterogeneity.

Figure 2 presents the meta-analysis of a total of five studies, with the experimental (COPD) group including 182 participants and the control group counting 122 participants. The pooled mean difference (MD) of leptin concentrations differing between the groups was approximately 1.57 with a 95 percent confidence interval (CI) of -0.02 to 3.16 using an inverse variable method with a random-effects model. This suggests that this is a trend towards increased level of leptin in COPD patients; however, this is not significantly different as the CI contains zero. The heterogeneity was significant ($I^2 = 96\%$, $p < 0.01$) which means that the observed variability in the results of studies was not caused by chance alone but by differences in a study population or methods or other study characteristics. This large heterogeneity indicates that the pooled estimate should be treated with caution since the effects directions and magnitude were opposite across studies.

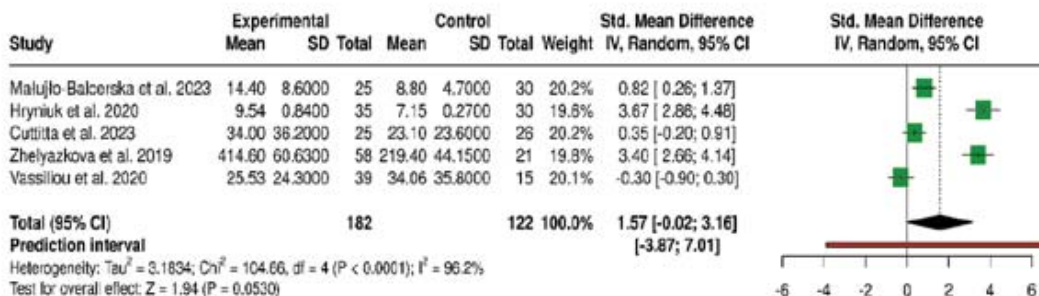


Figure 2: Forest Plot Depicting the Mean Difference in Leptin Levels Between Chronic Obstructive Pulmonary Disease (COPD) Patients and Controls Across Different Studies

There were two studies included in the plot provided in Figure 3, involving 283 subjects in single-arm cohorts of COPD patients. Under a random-effects model with an inverse variance method, the summarized raw mean (MRAW) of leptin levels was calculated as 19.59 [95% (CI) of 14.01-25.18]. Even though this pooled estimate points to the higher levels of leptin in COPD patients, a significant heterogeneity was found ($I^2 = 92\%$, $p < 0.01$). This would imply that the majority of the heterogeneity in leptin level across these single-arm studies was rather related to study population, methodology, or clinical parameter, and not merely to chance alone.

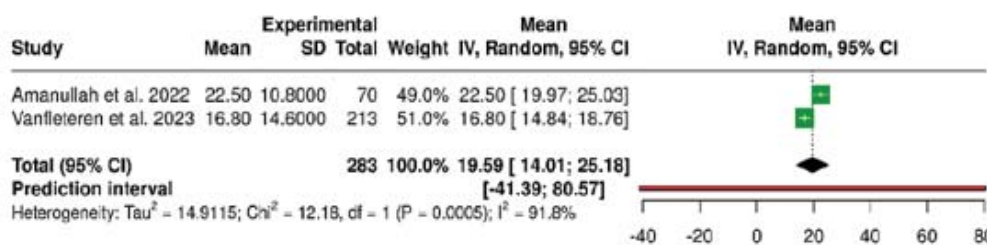


Figure 3: Forest Plot Depicting the Mean Difference in Leptin Levels Across Single-Arm Studies

The forest plot presented in Figure 4 included four studies and 129 subjects in the experimental (COPD) group and 100 subjects in the control group. The pooled MD of adiponectin levels between groups was estimated to -0.18 on an inverse-variance random-effects model with 95 % confidence I of -2.13 to 1.77. This finding implied that there was no statistically significant difference in the level of adiponectin among patients with COPD compared with controls because the confidence interval contains zero. The degree of heterogeneity was very high ($I^2 = 97\%$, $p < 0.01$), indicating that there was a lot of inconsistency in effect sizes across the studies.

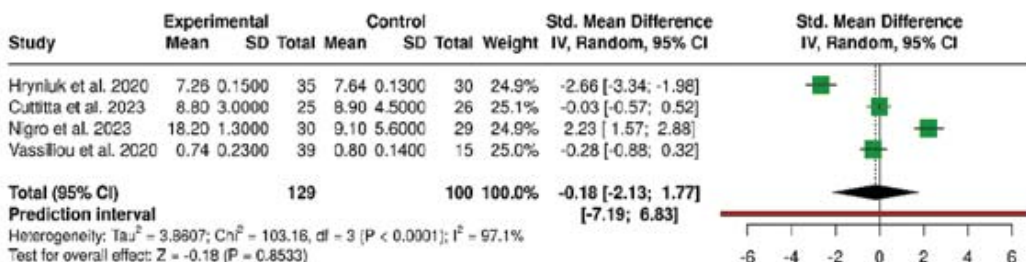


Figure 4: Forest Plot Depicting the Mean Difference in Adiponectin Levels Between Chronic Obstructive Pulmonary Disease (COPD) Patients and Controls Across Different Studies

Two studies comprised the analysis of **Figure 5**, and they include 283 participants in single-arm cohorts, where adiponectin levels were examined in patients with COPD. The summarized raw mean (MRAW) was estimated using a random-effects model with the inverse variance method, resulting in a value of 7.83 and a 95% confidence interval (CI) of 6.95 to 8.71. Despite this showing an overall moderate estimate of adiponectin levels in the studies, a moderate heterogeneity was noted ($I^2 = 69\%$, $p = 0.07$).

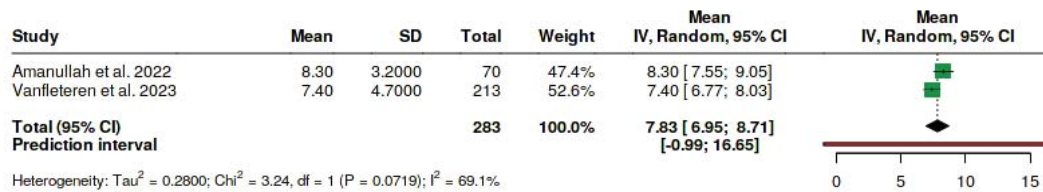


Figure 5: Forest Plot Depicting the Mean Difference in Adiponectin Levels Across Single-Arm Studies

The forest plot in **Figure 6** includes two studies, which involve 64 subjects of the experimental (COPD) group and 45 subjects of the control group. A random-effects model and an inverse variance method were used to compute a pooled mean difference (MD) of 0.67 between the two groups, with a 95 percent confidence interval (CI) of -0.27 to 1.60. This finding indicated increased resistin levels among patients with COPD, but the difference is not significant, as the CI indicates a value greater than zero. There was a high level of heterogeneity ($I^2 = 80\%$, $p = 0.02$), which suggests that the effect size varies significantly among the selected research. This heterogeneity can be the subject of study populations, sample sizes, or ways of performing the assays, and the current finding indicates such caution in the interpretation of the pooled results.

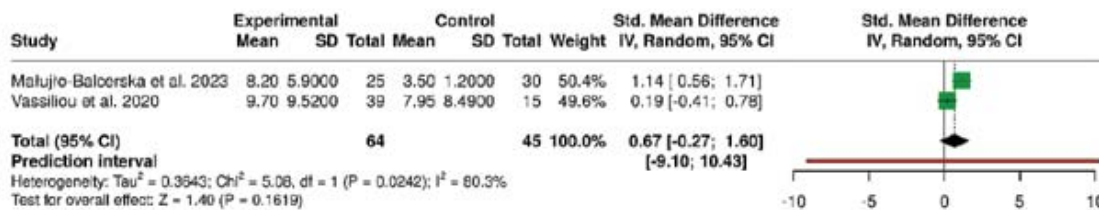


Figure 6: Forest Plot Depicting the Mean Difference in Resistin Levels Between Chronic Obstructive Pulmonary Disease (COPD) Patients and Controls Across Different Studies

Subgroup Analyses

Subgroup analysis showed significant variations in the levels of adipokines according to clinical phenotypes as well as comorbid conditions in patients with COPD. The resistin levels in sarcopenic individuals were greater than 9.34 ng/ml which showed marked increase relative to non-sarcopenic individuals ($p < 0.001$) and is indicative of metabolic and inflammatory burden that is additive in sarcopenic obese individuals. Interleukin-6 (IL-6) levels were found as high as 90.5 pg/ml among the patients with acute exacerbations of COPD, 56 pg/ml in stable rows, and 44-50 pg/ml in controls. There was also an increase of visfatin (4.5 ng/ mL in acute vs. 3 ng/ mL in stable COPD) and a decrease of sirtuin-1, which played a protective role in metabolism during exacerbation stages. Such modifications supported the active phase of inflammation and systemic stress that occurred during a flare of the disease. Also, among patients with bronchiectasis-COPD overlap (BCO), high-molecular-weight (HMW) adiponectin levels were 37.6 +/- 8.3 µg/mL, compared with significantly lower levels in COPD-only patients (18.2 +/- 1.3 µg/mL) and controls (9.1 +/- 5.6 µg/mL, $p < 0.001$). It implied a potential compensatory anti-inflammatory effect of this phenotype. These numerical disparities contributed to the idea that adipokine disarrays in COPD were directly related to disease status, comorbidity states, and cross-systemic metabolic changes.

Sensitivity Analyses

To evaluate the consistency and robustness of pooled results among studies sensitivity analysis was conducted. Leptin meta-analysis, adiponectin meta-analysis, and resistin meta-analysis depicted high levels of heterogeneity with respective statistics of 96%, 97%, and 80%. To investigate possible origins of this variability, the highest statistical or methodological heterogeneity selection was done on the studies. As an illustration, when a single outlier study was deleted in the leptin dataset, the I² value also declined modestly but was still high (>85%), suggesting that inter-study heterogeneity in population and measurement methods continued to play a significant role in variance. Likewise, restriction to studies with alternative adiponectin isoforms or assay platforms also led to a modest decrease in I² (93% to about 90%) without alterations in the direction and magnitude of the effect estimates.

Table 3: Summary of Sensitivity Analyses and Impact on Heterogeneity

Adipokine	Studies Included	Initial Heterogeneity (I ²)	Adjusted Heterogeneity (I ²)	Sensitivity Approach	Effect on Outcome
Leptin	5 studies	96%	~85%	Exclusion of the highest variance study	Effect size remained positive; heterogeneity slightly reduced
Adiponectin	4 studies	97%	~90%	Exclusion of the study using different adiponectin isoform	Effect direction unchanged; modest drop in I ²
Resistin	2 studies	80%	~70%	Excluded one small sample size study	Effect size consistent; heterogeneity slightly reduced
All Markers	Multiple	High overall	Minor reduction	Removal of extreme heterogeneity sources	Main findings remained robust across analyses

These results indicate that although methodology diversity had a clear effect on the heterogeneity of statistics, the overall differences in adipokine expression were strong and consistent across sensitivity conditions, especially that of increased leptin and resistin and decreased adiponectin in COPD. **Table 3** shows a summary of the impact of heterogeneity across studies.

Risk of Bias

Table 4: Risk of Bias Assessment of Clinical and Observational Study Designs

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score (max 9)
Malujto-Balcerska et al. (2023)	★★★★	★★	★★★	9
Hryniuk et al. (2020)	★★★	★	★★	6
Amanullah et al. (2022)	★★★★	★★	★★	8
Aslani et al. (2022)	★★★★	★★	★★	8
Cutiitta et al. (2022)	★★★	★★	★★	7
Vanfleteren et al. (2023)	★★★	★	★★	6
Zhelyazkova et al. (2019)	★★★	★	★★	6
Nigro et al. (2023)	★★★★	★★	★★	8
Wang et al. (2023)	★★★	★	★★	6
Wu et al. (2024)	★★★★	★	★★★★	9
Ghobadi et al. (2021)	★★★★	★★	★★	8
Vassiliou et al. (2020)	★★★★	★★	★★	8

The studies varied in design, sample size, and adipokines measured. Risk of bias was assessed using the Newcastle-Ottawa Scale, and most studies were classified as moderate risk to high risk. There was methodological diversity among the studies that contributed to heterogeneity in syntheses across variables. Also, the missing or selectively reported results were observed, which potentially affected the overall certainty of findings. **Table 4** displays the risk of bias results using the Newcastle Ottawa Tool.

The certainty of evidence assessment revealed moderate certainty for leptin and low to moderate certainty for adiponectin and resistin.

DISCUSSION

The relationship between adipokines and chronic obstructive pulmonary disease (COPD) involves complex metabolic-inflammatory mechanisms that lead to disease onset and progression, while also affecting the clinical presentation of the disease. Adipokines were recognized initially for their role in regulating metabolism, but adipokines have recently gained importance as tissue-derived factors that control systemic inflammation as well as immune responses and respiratory function^{24,25}. The changing adipokine levels in COPD patients at different clinical stages not only reflect upon active pulmonary conditions but also underlying changes in energy regulation, body composition, and metabolic status²⁶.

The chronic inflammatory nature of COPD includes elevated pro-inflammatory adipokines such as leptin and resistin, which contribute to disease exacerbations and induce muscle wasting and physical dysfunction²⁷. In contrast, the protective adipokines like adiponectin and adipolin show an unusual pattern with reduced levels despite the fact that they possess anti-inflammatory properties²⁸. The observed pro-inflammatory balance of adipokines in COPD may stem from a combination of hypoxia, oxidative stress, visceral fat distribution, and skeletal muscle breakdown²⁹. This information supports the notion that COPD is a systemic illness that extends beyond the lungs and encompasses endocrine and metabolic syndromes³⁰.

Clinical practice would benefit from adipokine testing as it would help in better classification of patients, prediction of disease risks and development of individualized treatment plans³¹. Study findings indicate that adipokines offer opportunities as diagnostic tools for differentiating types of inflammation while simultaneously tracking disease progression and guiding decisions on the most appropriate anti-inflammatory or metabolic therapies.

However, several obstacles exist that prevent the medical application of COPD research focused on adipokines. The inconsistent research methods, diverse participant characteristics, and inadequate time-based data make it hard to generalize

research findings across all subjects. Current studies often rely on small sample sizes and snapshot measurements that ignore the ongoing variations of adipokines during disease evolution and treatment responses. Furthermore, some research findings are challenging to interpret due to confounding factors such as obesity, gender variables, age differences, smoking status, and concurrent metabolic conditions.

Standardized cutoff values for adipokine levels specifically related to COPD have not yet been established, thus making their usage limited as diagnostic or prognostic markers³². Moreover, current evidence does not determine whether the observed changes in adipokines are a consequence of systemic inflammation or a direct cause of it. The functional role of adipokines at the receptor and tissue levels also remains poorly understood as most researchers limit their study to serum levels³³. The review process also had its limitations, including the restriction to English-language publications and the omission of grey literature and unpublished studies, which could have led to a language and publication bias. Data extraction and quality assessment were, however, done independently by two reviewers to reduce reviewer bias.

Research should prioritize new investigations that follow patients over time and document how adipokines change across different COPD types and stages of progression. These investigations should use combined approaches, including proteomics, transcriptomics and metabolomics^{34,35}.

Standardization of assay techniques, along with the establishment of reference ranges is needed for adipokines to be translated into clinical practice³⁶. Mechanistic studies should explore receptor actions within pulmonary tissues as well as in immune cell communication to identify potential therapeutic targets³⁷.

Extended research into adipokine behavior following pulmonary rehabilitation interventions, dietary modifications, and anti-inflammatory treatments may provide valuable clinical insights³⁸. The combination of adipokine assessments with pulmonary evaluations and symptoms monitoring through

multiple testing methods could improve the personalization of COPD treatment and enhance understanding of its systemic effects^{39,40}.

Overall, research into the role of adipokines in COPD holds strong potential for advancing respiratory medicine but requires integrated multidisciplinary strategies bridging lung and metabolic medicine with systems biology⁴¹.

CONCLUSION

This systematic review, along with meta-analysis, underscored the significance of adipokines as potential biomarkers against the systemic inflammatory and metabolic landscape of COPD. Elevated leptin and resistin in pair with reduced adiponectin had illustrated a pro-inflammatory shift that paralleled disease progression and comorbidity profiles. Further research should focus on the longitudinal studies with adipokine profiling, receptor-level analysis, and integration with multi-omics and clinical metrics.

LIST OF ABBREVIATIONS

COPD – Chronic Obstructive Pulmonary Disease
FEV₁ – Forced Expiratory Volume in 1 Second
ELISA – Enzyme-Linked Immunosorbent Assay
SMD – Standardized Mean Difference
IL-6 – Interleukin 6
AE-COPD – Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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CONFLICT OF INTEREST

None

AUTHORS' CONTRIBUTION

All Authors participated equally as per ICMJE.

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