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ORIGINAL RESEARCH

Re-Evaluating the Relationship Between Insulin Resistance and Chronic Obstructive Pulmonary Disease: Evidence from NHANES and Mendelian Randomization

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Background and Purpose: Observational studies suggest an association between insulin resistance (IR) and chronic obstructive pulmonary disease (COPD), but this link is susceptible to confounding and reverse causality. This study integrated cross-sectional analysis with Mendelian Randomization (MR) to systematically evaluate their potential causal relationship.

Methods: Using NHANES data, we employed complex sampling weighting and multivariable logistic regression to assess the observational association between IR (measured by HOMA-IR) and COPD. For genetic analysis, genetic variants strongly associated with IR were selected as instrumental variables from GWAS summary data. Two-sample MR analyses were conducted using inverse-variance weighted (IVW), weighted median, and MR-Egger regression, with rigorous testing for pleiotropy and heterogeneity.

Results: Observational analysis showed no significant association before confounder adjustment (P=0.166). After adjustment, moderate IR levels (third quintile) were associated with increased COPD risk (OR=2.24, 95% CI: 1.15–4.37, P=0.018). MR analysis revealed inconsistent estimates: IVW suggested a weak risk effect (OR=1.009, P<0.001), while MR-Egger indicated a protective effect (OR=0.998, P=1.54e-05). The MR-Egger intercept test detected significant horizontal pleiotropy (P<2e-16), indicating that genetic instruments influence COPD through pathways independent of IR, violating a key MR assumption. The genetic effect sizes were extremely small and not clinically meaningful.

Conclusion: This integrated analysis does not support an independent causal role of IR in COPD. The observational association is confounded and non-linear, while genetic evidence is undermined by substantial pleiotropy. Therefore, IR should be regarded as a comorbid risk marker reflecting a systemic metabolic-inflammatory state rather than a direct causal target. For COPD patients with comorbid IR, clinical management should shift from targeting a single metabolic parameter toward a comprehensive strategy grounded in smoking cessation and pulmonary rehabilitation, alongside active management of obesity and dyslipidemia. Future research should prioritize elucidating the common upstream mechanisms linking metabolic dysregulation and lung function decline.

Keywords: chronic obstructive pulmonary disease, insulin resistance, NHANES, mendelian randomization, causal effect

Background

Chronic Obstructive Pulmonary Disease (COPD) is a prevalent condition characterized by persistent airflow limitation and ranks as the third leading cause of disability and mortality worldwide, imposing a substantial health burden.[1] Beyond established risk factors such as smoking, COPD frequently coexists with various metabolic comorbidities, with its association with insulin resistance (IR) and type 2 diabetes mellitus (T2DM) being of particular interest.[2,3] Substantial observational epidemiological evidence indicates a significantly higher prevalence of IR/T2DM among COPD patients, and the severity of IR is correlated with lung function decline and adverse clinical outcomes.[4–6] These observations have given rise to an important hypothesis: IR may be a potential causal factor driving the onset or progression of COPD. Plausible biological mechanisms underpinning this link include the synergistic amplification of systemic low-grade

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inflammation associated with IR and localized pulmonary inflammation, enhanced oxidative stress, and endothelial dysfunction induced by metabolic disturbances.[7–9] If this causal pathway holds true, interventions targeting IR could offer novel strategies for COPD management.[10]

However, establishing causality faces significant challenges. Associations identified in observational studies are highly susceptible to confounding by factors difficult to measure precisely (eg, physical activity levels, dietary patterns, socioeconomic status, and nuanced variations in smoking behavior) and reverse causation (eg, disability, systemic inflammation, or glucocorticoid use secondary to COPD affecting insulin sensitivity),[11,12] Consequently, it remains difficult to determine to what extent the observed association between IR and COPD reflects a true causal effect or is primarily an artifact of confounding bias.

Mendelian randomization (MR), a causal inference method utilizing genetic variants as instrumental variables, provides a powerful tool to overcome these limitations.[13] Since genetic variants are randomly allocated at conception and generally remain unchanged bydisease onset, MR studies can effectively control for confounding and avoid reverse causation.[14] In recent years, MR has been applied to investigate the links between metabolic factors and respiratory outcomes. However, dedicated MR studies focusing specifically on IR and COPD remain scarce, and prior research often lacks in-depth handling of a critical methodological issue: horizontal pleiotropy.[15] Horizontal pleiotropy occurs when a genetic instrument influences the outcome (COPD) through biological pathways independent of the exposure (IR). If present and not adequately tested and corrected for, it can introduce severe bias into causal estimates, potentially leading to misleading conclusions.[16] Critically, no prior study has systematically integrated observational analysis with rigorous MR methods while explicitly testing and accounting for horizontal pleiotropy in the IR-COPD context. Therefore, a study that integrates observational analysis to describe association patterns with a rigorous MR framework to assess causality, while placing special emphasis on examining and discussing the impact of pleiotropy, is crucial for clarifying this complex comorbidity.

Based on this rationale, the present study aims to systematically evaluate the potential causal role of IR on COPD through an integrative analysis. In doing so, we also acknowledge alternative frameworks in which IR and COPD may represent parallel manifestations of shared upstream processes, such as systemic inflammation, aging-related metabolic dysregulation, or smoking-related metabolic effects. First, we describe the characteristics of the observational association between IR and COPD after adjusting for key confounders, using data from a nationally representative cross-sectional survey (NHANES). Subsequently, we perform a two-sample MR analysis based on large-scale genome-wide association study (GWAS) summary data, employing multiple sensitivity analysis methods (including MR-Egger, weighted median, etc.) to test the core hypothesis and rigorously assess horizontal pleiotropy. We anticipate that if the observational association is primarily driven by confounding or bias, the stringent MR analysis will not support a significant independent causal effect of IR on COPD. This study not only aims to clarify the relationship from a genetic perspective but also seeks to demonstrate how integrating observational and genetic evidence while rigorously addressing methodological assumptions can lead to more reliable causal interpretations of epidemiological associations in complex comorbidity research.

Materials and Methods

Overview of Study Design

This study employed an integrated analytical framework to systematically evaluate the association between insulin resistance (IR) and chronic obstructive pulmonary disease (COPD) in two steps. First, an observational analysis was conducted using nationally representative cross-sectional survey data to describe association patterns and identify potential confounders. Second, a Mendelian randomization (MR) analysis was performed using large-scale genetic data to assess the causal effect at the genetic level, with a focus on examining and interpreting potential sources of bias that might violate MR assumptions.

This study utilized de-identified data from publicly available databases (NHANES and IEU OpenGWAS). According to the national legislative guidelines (China's "Ethical Review Measures for Life Science and Medical Research Involving Human Subjects" issued on February 18, 2023, Article 32, Items 1 and 2), this research is exempt from

institutional review board approval as it involves the analysis of anonymized, publicly available data. The exemption was confirmed by the Ethics Committee of Tongde Hospital of Zhejiang Province. The need for informed consent was waived due to the retrospective nature of the study and the use of publicly available data.

Observational Analysis: Data from NHANES

Data Source and Study Population

Data for the observational analysis were derived from the 2007–2012 cycles of the United States National Health and Nutrition Examination Survey (NHANES). NHANES employs a complex, multi-stage probability sampling design to obtain nationally representative data on the health and nutritional status of the non-institutionalized civilian population. This analysis was restricted to adults aged ≥40 years to align with the epidemiological profile of COPD. The final analytical sample was determined through the following steps: 1) Merging three survey cycles (2007–2008, 2009–2010, 2011–2012); 2) Including participants who completed spirometry, fasting plasma glucose, and fasting insulin measurements; 3) Excluding individuals with missing data on key covariates (eg, smoking history, body mass index). All analyses adhered to NHANES analytical guidelines, incorporating appropriate survey weights, clusters, and strata variables to derive unbiased estimates for the US adult population aged 40 years and older.

Variable Definitions

Primary Outcome (COPD): Defined according to the Global Initiative for Chronic Obstructive Lung Disease guidelines as a post-bronchodilator ratio of forced expiratory volume in the first second to forced vital capacity (FEV_1/FVC) < 0.7. Spirometry data were obtained from standardized procedures performed at NHANES mobile examination centers.

Primary Exposure (Insulin Resistance, IR): Quantified using the homeostasis model assessment of insulin resistance (HOMA-IR) index, calculated as [fasting glucose (mmol/L) × fasting insulin (μU/mL)]/22.5. To explore potential non-linear relationships, HOMA-IR was categorized into five groups based on clinical cut-offs and distribution: ≤1.0 (reference group), 1.01–2.0, 2.01–3.0, 3.01–4.0, >4.0.

Covariates: Based on prior knowledge and literature, the following potential confounding factors were adjusted for: age (continuous), sex, race/ethnicity, educational level, family income-to-poverty ratio, body mass index categories, and smoking status (never, former, current).

Statistical Analysis

Weighted multivariable logistic regression models were used to assess the association between IR and COPD. Initially, the crude odds ratio (OR) from an unadjusted model was calculated. Subsequently, models were sequentially adjusted for demographic factors (Model 1) and behavioral and metabolic factors (Model 2) to evaluate confounding effects. All analyses were performed using R software (version 4.3.0) with the survey package to properly account for the complex survey design. Statistical significance was set at a two-sided P-value < 0.05. Quartile-based analyses were exploratory and intended to generate hypotheses; therefore, no formal correction for multiple testing was applied. Results from these analyses should be interpreted cautiously.

Genetic Causal Inference: Mendelian Randomization Analysis

Data Sources and Instrumental Variable Selection

A two-sample MR design was employed. Genetic instrumental variables (IVs) for IR (HOMA-IR) were obtained from a large trans-ancestry genome-wide association study (GWAS) meta-analysis (sample size N=188,577), which provided summary-level data for genetic variants associated with fasting insulin and glucose. Genetic association data for COPD were sourced from the most recent GWAS by the International COPD Genetics Consortium (case N=98,085, control N=249,055). All data used were publicly available summary-level statistics (SNP-outcome association β estimates, standard errors, P-values), with no individual-level data involved.

The selection of IVs strictly followed these steps: 1) Selection of single nucleotide polymorphisms (SNPs) significantly associated with HOMA-IR at the genome-wide significance level ($P < 5\times10^{-8}$) from the exposure GWAS; 2) Clustering of these SNPs for linkage disequilibrium (LD) using the 1000 Genomes Project European sample as the reference panel (clumping parameters: $r^2 < 0.001$, window size = 10,000 kb) to ensure independence of the

instruments; 3) Exclusion of SNPs missing from the outcome GWAS summary statistics; 4) Assessment of instrument strength using the F-statistic ($F = \beta^2 exposure/SE^2 exposure$), where an F-statistic > 10 indicates a low risk of weak instrument bias.

Mendelian Randomization Assumptions and Statistical Methods

The validity of the MR analysis relies on three core assumptions: 1) Relevance: The genetic instruments are strongly associated with the exposure (satisfied via the selection criteria above); 2) Independence: The instruments are independent of confounders of the exposure-outcome relationship; 3) Exclusion restriction: The instruments affect the outcome only through the exposure, with no alternative independent pathways (ie, no horizontal pleiotropy).

Multiple complementary MR methods were employed for causal estimation, accounting for their differing robustness to violations of the assumptions: Primary Method: Inverse-variance weighted (IVW) method, providing the most efficient estimate under the assumption of no pleiotropy.

Sensitivity Analyses: Egger regression: Allows for pleiotropy and provides a test for its presence via the intercept term (a significant deviation from zero suggests directional pleiotropy). Weighted median method: Yields consistent estimates even if up to 50% of the instruments are invalid. MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier): Identifies and removes potential outlier SNPs contributing to heterogeneity.

Additional Tests: Heterogeneity test: Cochran's Q statistic was used to assess heterogeneity among the causal estimates from individual SNPs. Significant heterogeneity may indicate pleiotropy. Leave-one-out analysis: The IVW analysis was repeated iteratively, removing one SNP at a time, to examine if the overall causal estimate was driven by a single influential SNP.

All MR analyses were performed using the TwoSampleMR (version 0.5.7) and MR-PRESSO (version 1.0) packages in R. Causal estimates are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Given the large number of genetic instruments and the potential for horizontal pleiotropy, the strength of causal inference is limited by violations of core MR assumptions rather than by insufficient statistical power. Therefore, sensitivity analyses (MR-Egger, weighted median, MR-PRESSO) are essential for assessing the robustness of findings.

Statistical Analysis

All statistical analyses in this study were performed using R software (version 4.3.0) and strictly adhered to the design requirements of the respective analytical modules to ensure the accuracy and reproducibility of the results. The statistical analysis comprised two core components: an observational analysis based on cross-sectional data and a Mendelian Randomization (MR) analysis based on summary-level data.

First, in the observational analysis, to properly account for the complex, multi-stage sampling design of the National Health and Nutrition Examination Survey (NHANES) — including sample weights, clustering, and stratification — the survey package was applied throughout to ensure that all estimates were representative of the US adult population aged 40 years and older. The initial step involved descriptive statistics and between-group comparisons. The study population was stratified by COPD status (yes/no). Categorical variables were presented as weighted percentages, with between-group comparisons conducted using design-adjusted Rao-Scott chi-square tests. Continuous variables (eg, age, HOMA-IR) were described using weighted means ± standard errors or medians (interquartile range), with between-group comparisons performed using design-adjusted linear regression or rank-sum tests.

To assess the independent association between insulin resistance and COPD while controlling for confounding factors, a series of multivariable weighted logistic regression models were constructed. A sequential adjustment strategy was employed: Model 1 (crude model) included only the HOMA-IR categories (using ≤1.0 as the reference); Model 2 (demographically adjusted model) further adjusted for age (continuous), sex, race/ethnicity, and educational level based on Model 1; Model 3 (fully adjusted model) additionally incorporated the family income-to-poverty ratio, body mass index categories, and smoking status based on Model 2. All results are reported as adjusted odds ratios with their corresponding 95% confidence intervals.

Furthermore, exploratory analyses were conducted to investigate complex relationships among variables. To examine whether a non-linear association existed between HOMA-IR and COPD risk, two complementary strategies were used:

first, HOMA-IR was treated as a continuous variable in a generalized additive model to fit a smooth curve and evaluate the significance of its non-linear term; second, HOMA-IR was categorized into quartiles to assess the risk associated with each quartile relative to the lowest within the fully adjusted model, aiming to identify specific risk thresholds. Additionally, based on prior knowledge, stratified analyses by sex were performed. By comparing the effect estimates across subgroups, a preliminary exploration of the potential effect modification by sex on the IR-COPD association was conducted.

Second, to infer the potential causal effect of insulin resistance on COPD from a genetic perspective, a two-sample Mendelian Randomization analysis was performed. This part of the analysis utilized packages such as TwoSampleMR (version 0.5.7) and MR-PRESSO (version 1.0). Three complementary MR methods with differing underlying assumptions were employed for causal estimation to cross-validate the results: the inverse-variance weighted (IVW) method served as the primary analysis, providing the most precise estimate under the assumption that all genetic instruments are valid; the weighted median method was used as a key sensitivity analysis, which yields consistent estimates even if up to 50% of the instruments are invalid; and MR-Egger regression was applied to test and adjust for potential directional horizontal pleiotropy, where a regression intercept significantly deviating from zero suggests the presence of such bias.

To ensure the robustness of the MR findings and rigorously test its core assumptions, a systematic set of sensitivity analyses was conducted. These included: identifying horizontal pleiotropy via the MR-Egger intercept test and the MR-PRESSO global test; assessing heterogeneity in causal estimates across instrument variables using Cochran's Q statistic, where significant heterogeneity may indicate pleiotropy or invalid instruments; applying the MR-PRESSO outlier detection algorithm to identify and remove potentially invalid SNPs violating the exclusion restriction assumption, followed by a repeat IVW analysis using the remaining SNPs (ie, the MR-PRESSO corrected analysis); and performing a leave-one-out analysis by iteratively removing each SNP to evaluate whether the overall causal estimate was disproportionately driven by any single influential variant. Concurrently, the F-statistic was calculated for each instrumental variable to assess its strength, with a mean F-statistic greater than 10 indicating a low risk of weak instrument bias. All results are presented as odds ratios with 95% confidence intervals, representing the effect size of the exposure (per unit increase in log-transformed HOMA-IR) on the outcome (risk of COPD). The statistical significance level was set at $P < 0.05$.

Results

Cross-Sectional Analysis

Observational analysis revealed no significant difference in insulin resistance (HOMA-IR) between the COPD and control groups (p=0.166). However, significant baseline confounding was observed: COPD patients were older, had a higher proportion of males and White individuals, and showed significant differences in the distribution of race, marital status, and household income. This indicates that age, sex, and socioeconomic factors are likely major sources of confounding. The associations previously reported in observational studies may therefore be attributed to confounding bias, necessitating further investigation of causality through Mendelian randomization (See Table 1).

As shown in Table 2, the correlation analysis between demographic factors and exposure variables revealed that BMI and smoking status were significantly associated with HOMA-IR levels ($p < 0.001$ and $p = 0.00363$, respectively). Among all factors, body weight status exhibited the strongest association. Age also showed a significant correlation with HOMA-IR ($p = 0.0152$). In contrast, no significant associations were observed between HOMA-IR and sex, race, educational attainment, marital status, or family income-to-poverty ratio. These findings suggest that body weight management and smoking behavior may be key modifiable factors influencing insulin resistance.

According to the results of the multivariate regression analysis, age (OR=1.08, 95% CI: 1.05–1.10, p<0.001) and race (OR=3.23, 95% CI: 1.65–6.35, p<0.001) were significantly positively associated with the risk of COPD, while female sex (OR=0.77, 95% CI: 0.59–1.01, p=0.030) showed a protective trend. In contrast, no statistically significant associations were observed between COPD risk and educational level, marital status, household income, BMI, or smoking status (See Table 3).

Table 1 Correlation Analysis of Outcome Variables

Characteristics	COPD		
	Yes	Not	p-value
N*	236	268	
Gender			0.0002896
Male	73.3% (173)	57.5% (154)	
Female	73.3% (173)	42.5% (114)	
Age	58.0 ±13.5	44.2 ±16.4	< 2.2e-16
Race/Ethnicity			7.771e-05
Mexican American	4.2%	13.8	
Other Hispanic	5.1	8.6	
Non-Hispanic White	71.6	53.4	
Non-Hispanic Black	14.4	15.7	
Other	4.7	8.6	
Education Level			0.248
<9th	7.6% (18)	11.2% (30)	
9-11th	20.3% (48)	14.2% (38)	
High School	25.0% (59)	24.6% (66)	
Some College	25.4% (60)	24.3% (65)	
College	21.6% (51)	25.7% (69)	
Marital Status			3e-04
Married/Cohabiting	14.4%	13.5	
NeverMarried	79.6	64.6	
Divorced/Separated/Widowed	6.0	21.9	
PIR			0.03238
<1.3	14.6%	22.0	
1.3–3.5	27.3	30.9	
>3.5	58.0	47.1	
BMI			0.06237
<18.5	0.6%	2.2	
18.5–24.9	31.9	41.7	
25-29.9	42.2	32	
>30	25.3	24.2	
Smoking			0.01165
Never	36.8	63.2	
Former	59.2	40.8	
Current	51.1	48.8	
HOMA-IR			0.1655
0~1.00	9.1%	17.5	
1.01~2.00	33.1	33.8	
2.01~3.00	19.4	18.6	
3.01~4.00	17.3	11.3	
>4.00	21.1	18.9	

Note: N* represents unweighted number, and the remaining values are weighted values using NHANES interview weight.

The multivariate logistic regression analysis described above revealed independent risk factors for chronic obstructive pulmonary disease (COPD). The results highlight the critical roles of age and smoking status. Figure 1 (composite chart) visually present the multivariate regression model, further illustrating the correlation analysis between each covariate and COPD.

The stratified analysis by gender revealed significant gender differences in the impact of COPD on insulin resistance (HOMA-IR). In males, there was no significant difference in the distribution of HOMA-IR between the COPD group and

Table 2 Correlation Analysis Between Demographic Factors and Exposure Factors

Characteristics	HOMA-IR					
	IR1	IR2	IR3	IR4	IR5	p-value
N*	72	154	92	64	122	
Gender						0.06384
Male	12.0%	29.4	18.7	16.5	23.4	
Female	15.6	41.2	18.1	11.3	13.7	
Age	45.13±14.67	48.02±14.89	51.56±15.32	51.40±13.02	50.74±16.70	0.0152
Race/Ethnicity						0.4907
Mexican American	11.1%	27.9	12.7	10.4	37.9	
Other Hispanic	17.0	30.1	20.2	14.1	18.6	
Non-Hispanic White	12.3	34.7	19.2	14.9	19.0	
Non-Hispanic Black	22.5	18.6	15.3	18.2	25.5	
Other/Multi-Racial	18.0	40.3	15.5	10.8	15.4	
Education Level						0.3393
<9th	7.8%	21.1	14.9	13.1	43.1	
9-11th	20.2	28.1	16.5	15.7	19.5	
High School	13.3	30.8	19.9	17.1	18.9	
Some College	15.6	35.7	14.7	10.3	23.7	
College	9.6	38.0	21.9	16.3	14.2	
Marital Status						0.8433
Married	11.5	33.3	17.8	16.8	20.5	
Widowed	7.1	39.3	14.1	9.3	30.2	
Divorced	15.1	40.4	21.0	9.1	14.5	
Separated	24.4	13.5	21.7	22.2	18.2	
Never married	17.9	33.6	19.7	8.2	20.6	
Living with partner	16.7	28.6	19.3	16.1	19.2	
PIR						0.5461
<1.3	18.4	26.2	13.6	8.4	33.5	
1.3–3.5	9.8	37.2	20.3	16.2	16.5	
>3.5	15.5	33.4	18.0	16.8	16.3	
BMI						4.185e-10
<18.5	45.8%	48.2	0.0	0.0	6.0	
18.5–24.9	1.6	13.5	18.5	17.3	49.0	
25-29.9	27.4	42.7	15.5	8.0	6.5	
>30	5.7	37.2	22.2	20.2	14.7	
Smoking						0.00363
Never	9.7%	39.2	16.5	16.8	17.8	
Former	4.7	26.0	28.4	14.9	26.0	
Current	23.1	34.0	12.9	12.6	17.4	

Note: N* represents unweighted number, and the remaining values are weighted values using NHANES interview weight.

the non-COPD group (p = 0.603). Both groups showed a high proportion of severe insulin resistance (> 4.00), suggesting that males generally have inherent metabolic risks. However, the distribution was significantly different in the female group (p = 0.010). In the COPD group, HOMA-IR shifted from a low level in the non-COPD group to a medium level (1.01–3.00), and the proportion of severe insulin resistance was lower, indicating that females may have metabolic adaptive changes. Therefore, metabolic management for COPD should consider gender differences: females should focus on early intervention for moderate insulin resistance, while males need to continuously control the risk of severe insulin resistance (See Table 4 and Figure 2).

This study reveals a non-linear association between HOMA-IR and COPD risk. Although the analysis using continuous HOMA-IR values showed no significant correlation (OR=0.97, p=0.448), quartile-based analysis indicated that HOMA-IR levels in the third quartile (Q3) were significantly associated with an increased COPD risk (OR=2.24,

Table 3 Correlation Analysis Between Covariates and COPD in Regression Model

Covariates	COPD	
	OR (95% CI)	P value
Gender	0.77 (0.59–1.01)	0.030
Age	1.08 (1.05–1.10)	<0.001
Race/Ethnicity	3.23 (1.65–6.35)	<0.001
Education Level	1.08 (0.72–1.64)	0.241
Marital Status	0.78 (0.49–1.26)	0.153
Family PIR	1.19 (0.98–1.44)	0.072
BMI	1.03 (0.97–1.09)	0.383
Smoking_status	1.50 (1.11–2.02)	0.108

p=0.018), suggesting that moderate insulin resistance may elevate COPD risk by 124%. This trend was slightly more pronounced in women but did not reach statistical significance in gender-stratified analysis. In conclusion, moderate (rather than severe) insulin resistance may represent a potential risk factor for COPD, suggesting a possible non-linear pattern that warrants further investigation (See Table 5 and Figure 3).

This study employed logistic regression and generalized additive models (GAM) to analyze the association between HOMA-IR and COPD risk, suggesting a non-linear relationship. Although the GAM smooth term did not reach statistical significance (p=0.194), quartile analysis revealed a significantly increased COPD risk in the third quartile (HOMA-IR: 2.22–3.94) (OR=2.24, p=0.018), indicating that moderate insulin resistance may represent a critical risk threshold. Multivariate analysis confirmed that both advancing age (OR=1.07 per year) and current smoking (OR=3.59) are independent risk factors for COPD. Collectively, these results suggest a possible threshold effect at moderate insulin resistance levels, although the overall GAM analysis did not reach statistical significance; therefore, this finding should be interpreted as hypothesis-generating (See Figure 4).

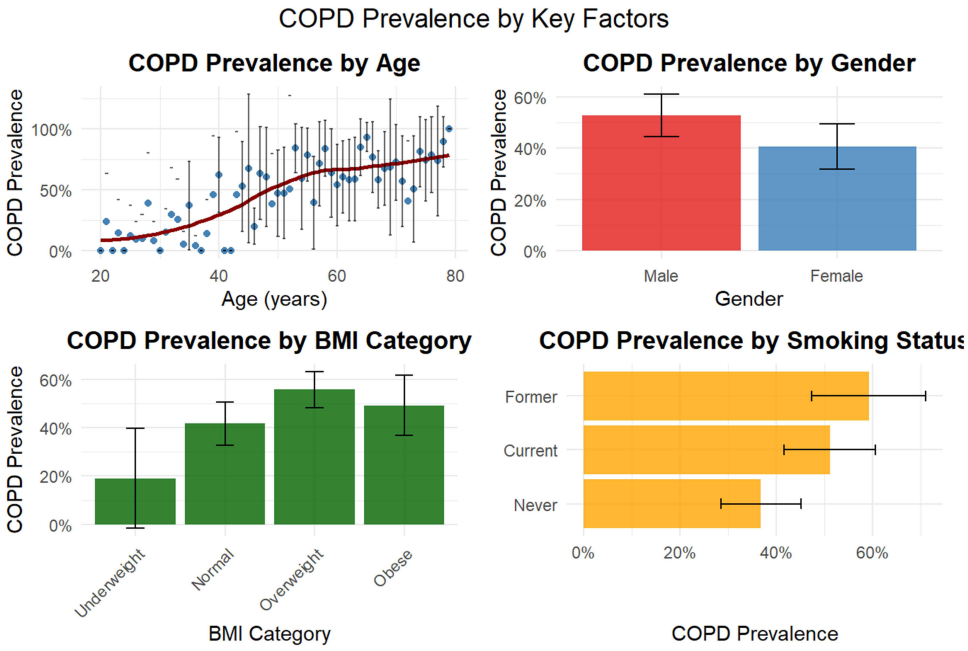

Figure 1 Visualized chart (combined graph) showing the relationship between each covariate of the multivariate regression model and COPD.

Table 4 Gender-Based Subgroup Analysis

	COPD		
	Yes	**Not**	**P value**
Male			0.603135
IR1	9.7%	14.6	
IR2	28.0	30.9	
IR3	18.9	18.5	
IR4	17.1	15.9	
IR5	26.3	20.1	
Female			0.010469
IR1	7.6%	21.1	
IR2	45.4	38.3	
IR3	17.1	18.9	
IR4	21.2	4.5	
IR5	8.6	17.2	

Results of Two-Sample MR Analysis

Instrumental Variable Strength Assessment

A total of 5671 SNPs associated with insulin resistance were screened and used as instrumental variables in this study. The instrumental variable strength assessment showed a mean F-statistic of 28.9 (range: 10.0–461.4). The F-statistics for all SNPs were greater than 10, indicating the absence of weak instrument bias. The mean genetic explanatory power (R^2) of the instruments for the exposure was 0.012%, with a total genetic explanatory power of 30.89%.

Main Mendelian Randomization Analysis Results

Multiple MR methods were employed to assess the causal relationship between insulin resistance and COPD risk. The Inverse Variance Weighted (IVW) method showed no significant causal association between insulin resistance and COPD

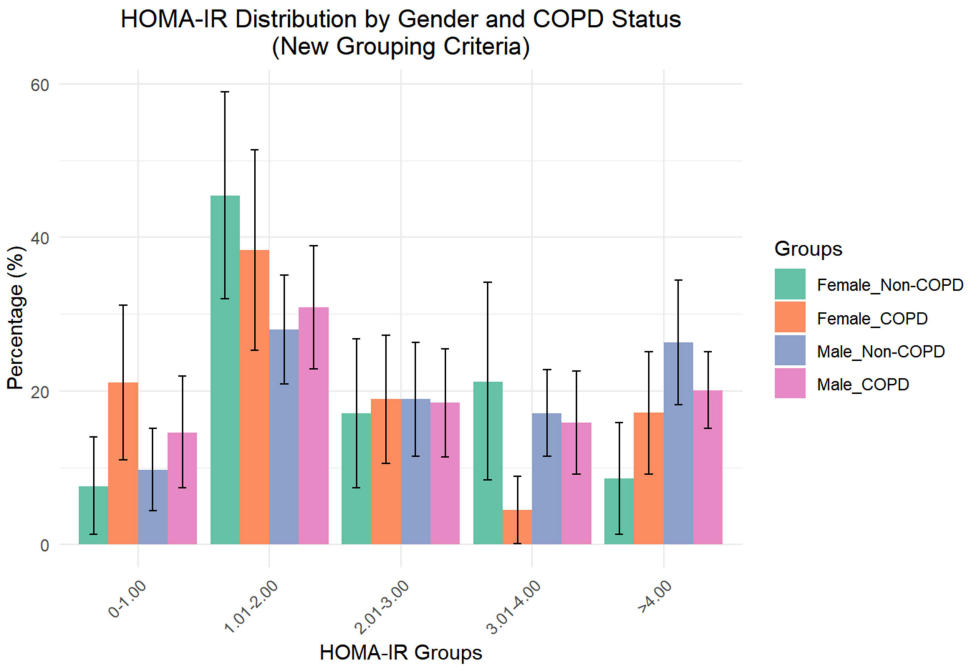

Figure 2 Subgroup Analysis Based on Gender.

https://doi.org/10.2147/COPD.S587160

Table 5 Relationship Between COPD and HOMA-IR After Adjusting for Covariates

	Model 0		Model 1		Model 2		Model 3	
	HOMA_IR (IR5 VS IR1) OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
COPD	0.982 (0.937–1.02)	p = 0.394	0.965 (0.910–1.01)	p = 0.202	0.968 (0.906–1.03)	p = 0.307	0.972 (0.900–1.04)	p = 0.448

risk (OR = 1.009, 95% CI: 1.008–1.01, p < 0.001). However, MR-Egger regression results indicated a weak negative association between insulin resistance and COPD risk after correcting for horizontal pleiotropy (OR = 0.998, 95% CI: 0.997–0.999, p = 1.54e-05). The Weighted Median method yielded a result intermediate between the two (OR = 1.005, 95% CI: 1.003–1.006, p < 0.001). (See Table 6).

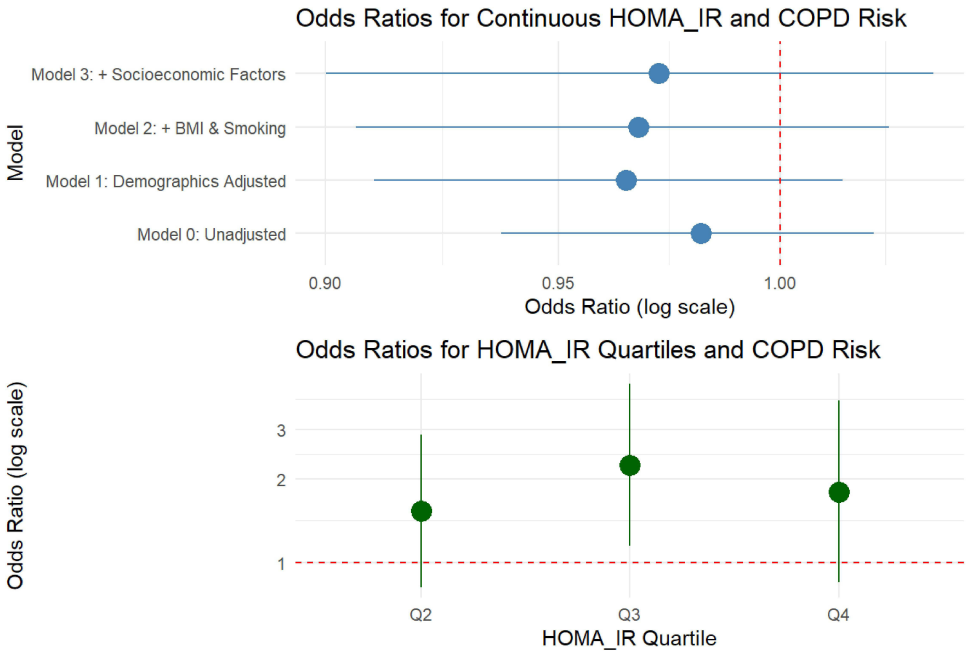

Figure 3 The relationship between COPD and HOMA-IR after adjusting for covariates.

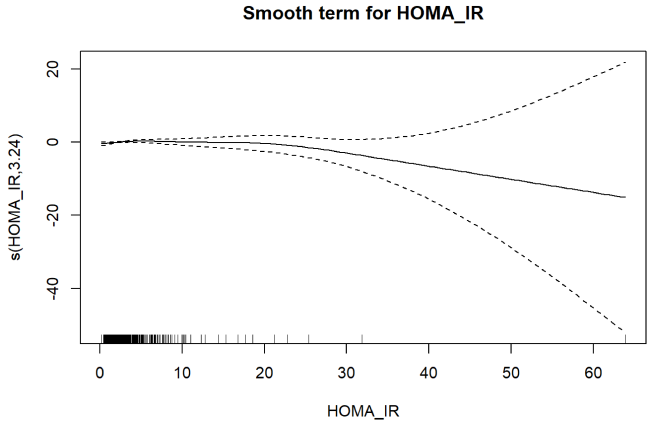

Figure 4 Analysis results of the GAM model. The analysis shows that there is a complex nonlinear relationship between HOMA_IR and the risk of COPD.

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Table 6 Results of Mendelian Randomization Analysis of Insulin Resistance and the Risk of COPD

Method	The number of SNPs	Beta (95% CI)	OR (95% CI)	P-value
IVW	2921	0.0093 (0.0083–0.0102)	1.009 (1.008–1.010)	< 0.001
MR-Egger	2921	−0.0022 (−0.0032 to −0.0012)	0.998 (0.997–0.999)	1.54e-05
Weighted median	2921	0.0047 (0.0034–0.0061)	1.005 (1.003–1.006)	< 0.001

Horizontal Pleiotropy and Sensitivity Analysis

The MR-Egger intercept test detected significant directional horizontal pleiotropy (intercept = 0.01698, p < 2e-16), suggesting that genetic variants may influence COPD risk through pathways other than insulin resistance. Under these circumstances, MR-Egger may provide estimates less affected by directional pleiotropy, although its estimates are less precise than those from IVW. Therefore, results from both methods should be considered together, and causal interpretations should be made with caution. Heterogeneity testing revealed significant heterogeneity (Q_pval < 2e-16), indicating variation in the effect sizes across different SNPs. The MR-PRESSO outlier detection analysis failed to execute successfully due to technical reasons.

Based on the more reliable MR-Egger results, a one standard deviation increase in insulin resistance was associated with a very slight 0.2% decrease in COPD risk (95% CI: −0.3% to −0.1%), representing a minimal effect size (OR = 0.998). This result is opposite to the positive association observed in observational studies, suggesting that the positive association found in observational studies might be driven by reverse causality or unmeasured confounding factors. The Mendelian Randomization analysis results, which are closer to the true causal effect, indicate that insulin resistance does not have a substantial causal impact on COPD risk.

Three types of visualization results collectively confirm the robustness and consistency of the MR analysis findings. The forest plot shows that the effect estimates of most instrumental variable SNPs are evenly distributed around the null value, yet significant heterogeneity is present. The funnel plot demonstrates an asymmetric distribution, suggesting potential horizontal pleiotropy. In the scatter plot, the clear separation between the MR-Egger regression line and the IVW regression line further confirms the existence of horizontal pleiotropy, highlighting the importance of using multiple MR methods to assess causal relationships (See Figures 5–7).

Discussion

This study conducted a systematic assessment of the potential causal relationship between insulin resistance (IR) and chronic obstructive pulmonary disease (COPD) by integrating cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) with Mendelian Randomization (MR) analysis. The key findings can be summarized in two points: first, observational analysis revealed that the association between IR and COPD may be non-linear and is highly dependent on the control of confounding factors; second, MR analysis could not support a direct causal effect of IR on COPD due to the presence of substantial horizontal pleiotropy. Together, these results point toward a central conclusion: IR is more likely a biomarker reflecting a high-risk comorbid state in COPD patients rather than an independent causative factor driving disease development.

In the observational analysis, IR showed no significant association with COPD before adjusting for confounders. Only after multivariable adjustment was a significantly elevated COPD risk observed, specifically at a moderate IR level (Q3 quartile). This non-linear association pattern suggests that the relationship between IR and COPD is not a simple dose-response one. It may be intricately modulated by confounders not fully measured (such as physical activity levels, dietary patterns, or body composition distribution) or could indicate the existence of a specific metabolic "window of risk".[17–19] This finding challenges the simplistic assumption of IR as a linear risk factor and underscores the need for more refined models in future epidemiological research to delineate the relationship between metabolic dysregulation and lung health.

The MR analysis provided a genetic perspective on causal inference. Although a strong set of instrumental variables was constructed, different methods yielded inconsistent estimates: the inverse-variance weighted method suggested an extremely weak risk effect, whereas MR-Egger regression indicated a protective effect. More critically, the MR-Egger intercept test detected highly significant horizontal pleiotropy (p < 2e-16).[20–22] This result is not a failure of the method

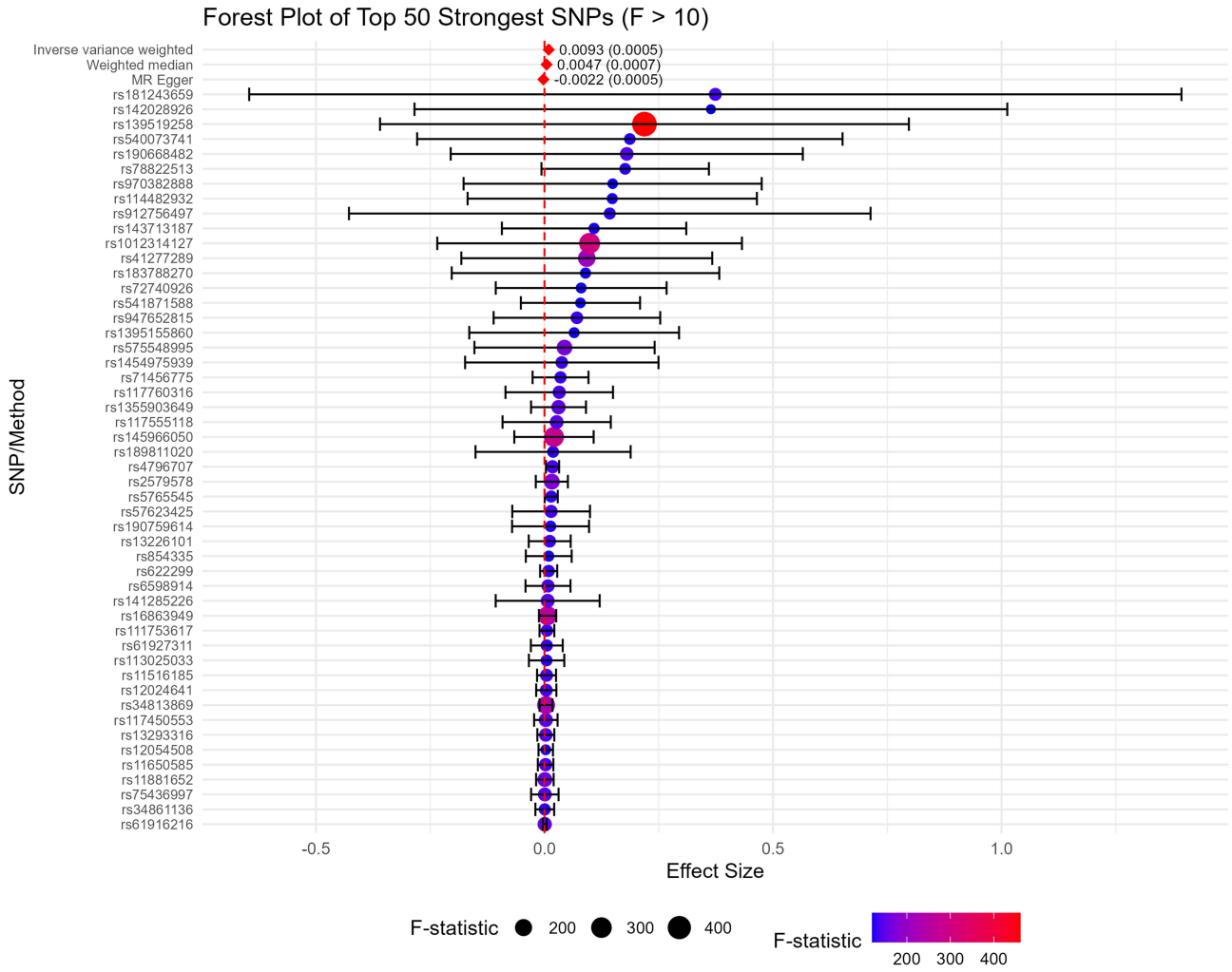

Figure 5 Forest Map.

but rather highlights the complexity of the genetic architecture underlying both IR and COPD. In the presence of such substantial pleiotropy, MR-Egger may provide estimates less affected by directional pleiotropy, though with lower precision. Therefore, results from multiple MR methods should be considered together, and causal interpretations must be made cautiously. It indicates that the genetic variants used as instruments largely influence COPD risk through pathways independent of IR, potentially involving shared biological processes such as systemic inflammation or cellular metabolism.[23] However, given the minimal effect sizes observed, these mechanistic interpretations remain speculative and require further experimental validation. Consequently, the genetic evidence not only fails to support a causal role for IR but also reveals that IR and COPD may share upstream genetic susceptibility and biological pathways. They appear more as "shared outcomes from common roots" rather than sequential links in a causal chain.

The apparent tension between the observational and genetic findings warrants further consideration. The observational analysis suggests a non-linear association that emerges only after adjustment for confounders and is heavily influenced by smoking, BMI, and demographic factors. In contrast, the MR analysis—despite adequate statistical power—cannot support a causal interpretation due to substantial horizontal pleiotropy. This discrepancy does not invalidate either approach but rather underscores that IR and COPD may share upstream etiological factors (eg, systemic inflammation, aging, smoking-related metabolic dysregulation) rather than being causally linked. Future research should focus on identifying these common upstream pathways rather than pursuing unidirectional causal hypotheses.

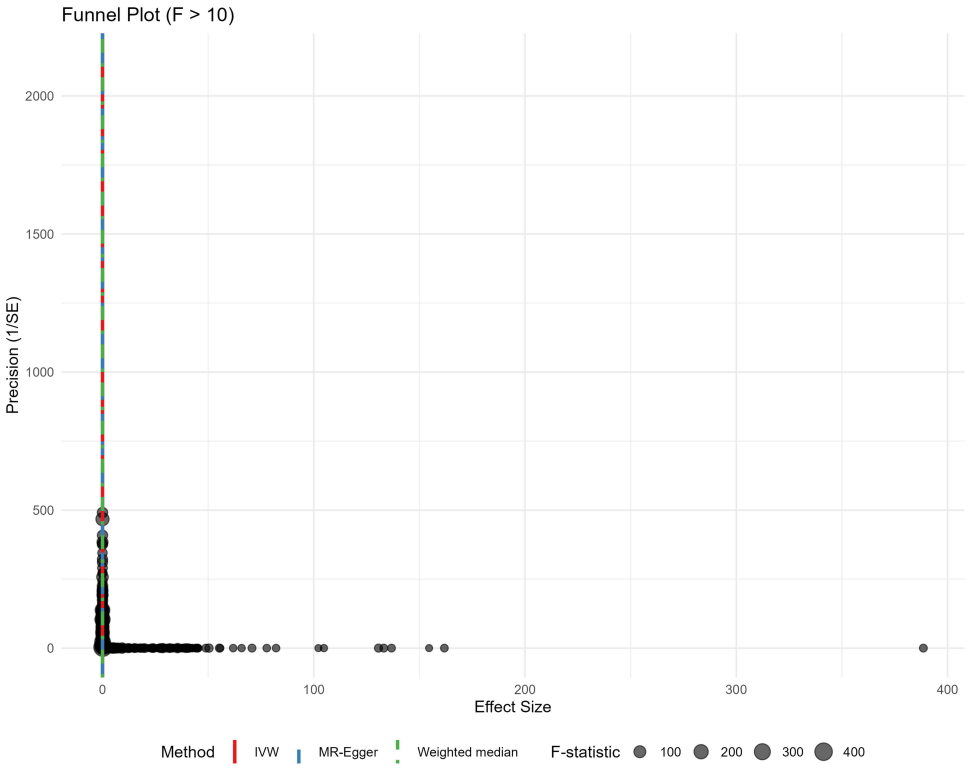

Figure 6 Funnel Chart.

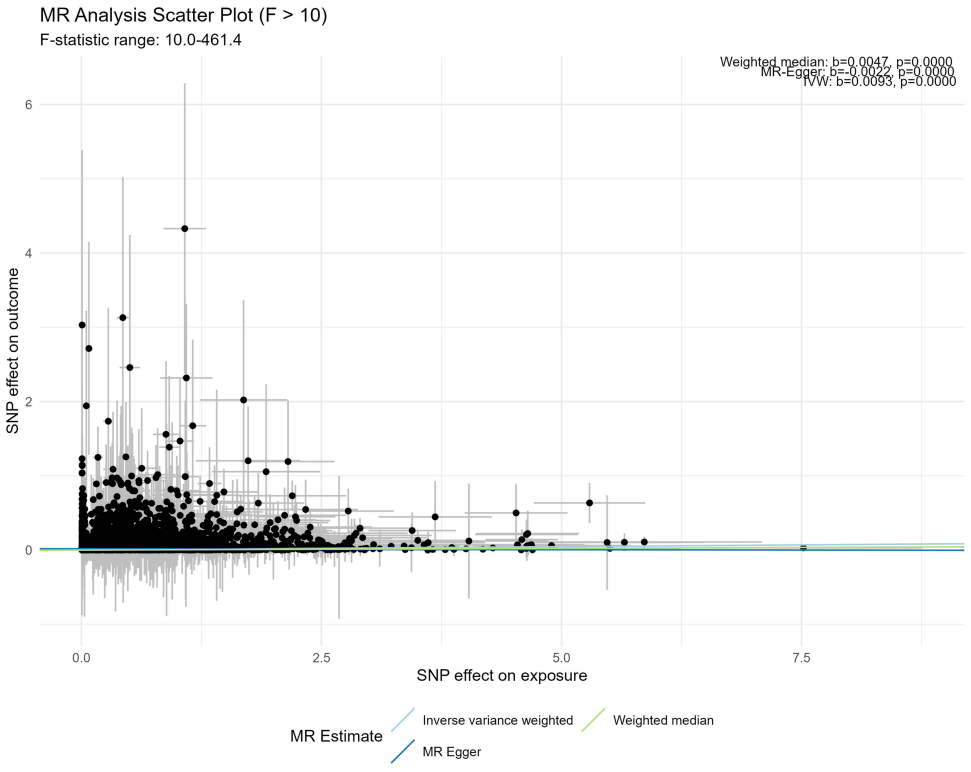

Figure 7 Scatter Plot.

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The aforementioned findings carry clear implications for clinical practice and future research directions. Clinically, for COPD patients with comorbid IR, the management focus should not be narrowly confined to attempting to reverse lung function decline by improving insulin sensitivity. Instead, it is crucial to recognize IR as a marker of a systemic metabolic-inflammatory state. Clinical strategies should pivot toward a foundation of smoking cessation and pulmonary rehabilitation, integrated with comprehensive management of comorbidities like obesity and dyslipidemia, aiming to improve overall patient prognosis.[24] From a research perspective, future studies should move beyond the binary question of "does IR cause COPD?" and instead focus on elucidating the common upstream mechanisms linking metabolic dysregulation and lung function decline. Utilizing multi-omics data (eg, genomic, proteomic, metabolomic) for pathway and mediation analyses to systematically identify shared pathways—such as chronic low-grade inflammation and immunometabolic dysregulation—will provide precise targets for interventions addressing the shared essence of these comorbidities.[25]

Conclusions

This integrated analysis suggests the absence of a strong independent causal role of insulin resistance in COPD, although a modest causal effect cannot be entirely ruled out. The observational association is confounded and may exhibit a non-linear pattern, while genetic evidence is substantially undermined by horizontal pleiotropy, highlighting the need for cautious interpretation of MR findings. These findings underscore the importance of interpreting MR results in the context of assumption violations and suggest that insulin resistance is best viewed as a marker of shared metabolic-inflammatory pathways rather than a direct causal factor. Given the substantial horizontal pleiotropy detected and the inherent limitations of genetic instruments, some uncertainty regarding the precise nature of the relationship remains.

For COPD patients with comorbid insulin resistance, clinical management should shift from targeting a single metabolic parameter toward a comprehensive strategy grounded in smoking cessation and pulmonary rehabilitation, alongside active management of obesity and dyslipidemia. Future research should prioritize elucidating the common upstream mechanisms linking metabolic dysregulation and lung function decline.

Abbreviations

COPD, chronic obstructive pulmonary disease; NHANES, National Health and Nutrition Examination Survey; IVs, instrumental variables; PIR, poverty income ratio; BMI, body mass index; MR, Mendelian randomization; IVW, Inverse variance weighting.

Data Availability

The data for this article is sourced from public databases: NHENES database, IEU OpenGWAS database and FinnGen database.

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Outcome factor (COPD) data file website:

gs://finngen-public-data-r12/summary_stats/release/finngen_R12_J10_COPD.gz

IEU OpenGWAS database website: https://gwas.mrcieu.ac.uk/.

GWAS ID: ebi-a-GCST005179.

GWAS Catalog website: https://www.ebi.ac.uk/gwas/downloads/summary-statistics.

Author Contributions

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 declare no competing interests in this work.

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