

The Association Between Stomach Disease and Chronic Obstructive Pulmonary Disease: A Cross–Sectional Analysis of the 2018 China Health and Retirement Longitudinal Study (CHARLS)

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Purpose: Chronic obstructive pulmonary disease (COPD) has become a global epidemic and is the third leading cause of death worldwide. However, its diagnostic rate is low. Based on the 2018 wave of China Health and Retirement Longitudinal Study (CHARLS) database, this cross–sectional study aimed to investigate the association between stomach disease and COPD using a nationally representative sample.

Patients and Methods: A total of 9119 CHARLS subjects were divided into COPD and non–COPD groups using the DA007_5 questionnaire. Both COPD and stomach disease were identified based on participants' self–reported physician diagnoses from the standardized CHARLS questionnaire. Baseline characteristics were compared between groups, and multivariate logistic regression analysis was used to analyze the association between stomach diseases and COPD. Receiver operating characteristic (ROC) curve assessment of Model 3's predictive capacity for COPD and stratified analysis verified correlation stability.

Results: In baseline comparisons, multiple covariates differed significantly between COPD and non–COPD groups ($p < 0.05$). However, the core regression analysis showed that stomach disease was significantly associated with COPD in Model 3 (OR = 1.95, 95% CI = 1.46–2.57, $p = 3.61E-06$), after full adjustment for potential confounders. Model 1 (odds ratio (OR) = 3.12, 95% confidence interval (CI) = 2.43–3.98, $p = 1.95E-19$), Model 2 (OR = 3.21, 95% CI = 2.49–4.1, $p = 3.65E-20$), and Model 3 (OR = 1.95, 95% CI = 1.46–2.57, $p = 3.61E-06$) revealed that stomach disease was a risk factor for COPD. Furthermore, the ROC curve indicated a good prediction performance for Model 3. Stomach disease remained significantly associated with COPD in all three models ($P < 0.05$). In addition to stomach disease, sex (male), health status, dyslipidemia, liver disease, heart attack, kidney disease, and asthma were significantly associated with COPD.

Conclusion: In this cross–sectional analysis of a nationally representative Chinese cohort, stomach disease was significantly associated with COPD, extending prior evidence and suggesting its role in risk assessment. Causality cannot be inferred; prospective spirometry–confirmed studies are needed.

Keywords: chronic obstructive pulmonary disease, stomach disease, China health and retirement longitudinal study, cross–sectional study

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease and is the third leading cause of death worldwide.¹ According to the Global Burden of Disease Study from 1990 to 2021, the crude incidence and prevalence rates of COPD in China were 311.68 and 3555.69 cases per 100,000 population, respectively.^{2,3} These cases account for nearly one-quarter of global COPD cases and are characterized by persistent respiratory symptoms and progressive airflow obstruction.⁴ COPD is a syndrome caused by multiple mechanisms.⁵ It is commonly observed in the elderly population, where patients often have multiple concurrent diseases.⁶ When COPD worsens, it can cause cardiovascular diseases.⁷ At present, the treatment of COPD includes drug therapy, oxygen therapy, respiratory rehabilitation, and other measures. Although COPD is very common, its diagnostic rate is relatively low, and many patients are not diagnosed until advanced stages of the disease. Therefore, early screening is of clinical significance. Identifying new factors related to COPD is crucial to improve its prevention, diagnosis, and treatment.

⁸ The China Health and Retirement Longitudinal Study (CHARLS) is a nationally representative prospective cohort study that employs probability proportionate to size sampling (PPS). The standardized questionnaire collects multidimensional data, such as socioeconomic factors and physiological health, which include self-reported diagnoses of lung function and a self-reported history of stomach disease. Biological samples were tested for various biomarkers.⁹ Quality control was ensured using a CAPI system. Previous CHARLS studies have demonstrated significant methodological strengths in revealing associations between diseases across different organ systems.¹⁰ For example, Wang et al found that the association between plasma atherogenic index and incident stroke depends on glucose metabolism.¹¹ Additionally, Zhang et al further confirmed a dose-response relationship, showing that increasing levels of sarcopenic obesity are associated with a higher risk of cardiovascular events. However, the definition of exposure needs to be clarified. In CHARLS, “stomach disease (excluding tumors or cancers)” is a self-reported diagnosis made by doctors. In the elderly population in China, this diagnosis mainly includes chronic gastritis, peptic ulcers, and gastroesophageal reflux disease (GERD).^{12,13} Although this definition is rather broad, combining these diseases for analysis has biological and clinical significance because they share common pathophysiological pathways, including chronic systemic inflammation, autonomic nerve dysfunction, and potential adverse reactions from long-term medication. These pathways may affect lung health. Therefore, studying this composite exposure factor helps to understand the “gastrointestinal-lung axis” at a macro level.^{14,15} Notably, the prevalence of comorbid stomach disease such as gastroesophageal reflux disease in patients with COPD ranges from 19% to 78%. These stomach disease are also listed as important comorbidities to be managed according to GOLD guidelines. The potential biological link between stomach disease and chronic obstructive pulmonary disease (COPD) is likely to be bidirectional. On one hand,¹⁶ stomach disease (especially gastroesophageal reflux disease, GERD) may trigger airway inflammation and remodeling by allowing minute amounts of gastric contents to accidentally enter the airways;¹⁷ activate vagal nerve reflexes leading to bronchial contraction;¹⁸ and cause systemic inflammation from the affected intestines, thereby exacerbating lung damage. On the other hand, COPD may also make individuals more prone to stomach disease.^{19,20} Chronic hypoxia and hypercapnia caused by impaired lung function can damage the integrity and motility of the gastrointestinal mucosa. Moreover,^{21,22} certain COPD medications (such as corticosteroids and bronchodilators) may have side effects that can lead to gastric mucosal injury or reflux. Importantly, multiple factors are known to be associated with both stomach disease and COPD, including aging, smoking, low socioeconomic status, and metabolic abnormalities such as dyslipidemia. Ignoring these common risk factors may lead to residual confounding, highlighting the need for cautious adjustment in multivariate analyses. However, high-quality evidence regarding the association between stomach disease and COPD in large populations remains scarce. In particular, there is a lack of systematic adjustment for confounding factors (such as age and metabolic comorbidities) and quantitative assessment of predictive efficacy. This highlights the importance of CHARLS as a valuable platform for exploring the relationship between stomach disease and COPD.

Previous studies have suggested a correlation between stomach disease and COPD, but there is still a lack of high-quality evidence, especially a lack of research results based on large-scale populations with national representativeness. At the same time,^{23,24} most existing studies have not systematically corrected for key confounding factors such as age and metabolic comorbidities, nor have they quantitatively evaluated the predictive efficacy of the association. Therefore, this study fills the research gap by leveraging the nationally representative Chinese middle-aged and elderly CHARLS

cohort. It controls for covariates through weighted multivariate logistic regression and uses ROC curves to analyze the model's predictive efficacy, providing an ideal research platform for robustly exploring the association between stomach disease and COPD. However, the outcome variable of this study is self-reported and diagnosed COPD by doctors, rather than COPD confirmed by pulmonary function tests. Although this approach is practical and feasible in large-scale epidemiological surveys, its detection sensitivity is lower than that of pulmonary function tests, and there may be a certain degree of misclassification bias.

Materials and Methods

Study Participants and Design

CHARLS is a longitudinal survey, but the present analysis uses only the 2018 cross-sectional data; therefore, no longitudinal follow-up or causal inference is intended. The study focused on individuals aged 45 years and above in mainland China, and informed consent was obtained from all subjects. The collected data encompassed both urban and rural respondents, ensuring the representation of China's middle-aged and elderly populations. The study selected all the subjects (n=19816) collected in this database for the year 2018 and excluded subjects with missing data on Chronic obstructive pulmonary disease (COPD) (n=528), age (n=322), gender (n=0), health status (n=1458), hearing problem (n=2428), alcohol consumption (n=14), dyslipidemia (n=1903), liver disease (n=427), heart attack (n=1099), kidney disease (n=459), asthma (non-lung disease) (n=266), stomach disease (n=1793), and finally recruited 9119 subjects (Figure 1). The substantial number of exclusions is acknowledged as a limitation.

Assessment of Stomach Disease and COPD

The outcome variable for this study was COPD, which was assessed by self-report in the 2018 survey. Participants were asked, "Has a doctor ever told you that you have a chronic lung condition such as chronic bronchitis or emphysema, or cor pulmonale (not including tumors or cancer)?" Participants who answered "yes" to the question were identified as having COPD. Stomach disease was defined based on the question "Have you been diagnosed with stomach or other digestive diseases (except for tumor or cancer) by a doctor?" (Code DA007_10_). Participants answering "yes" were classified as having stomach disease.

Covariates

Ten covariates were selected based on clinical and epidemiological evidence to adjust for potential confounding in the analysis of stomach disease outcomes: age (BA004_W3), gender (BA000_W3_2), health status (DA002), hearing problems (DA005_4), alcohol consumption (DA067), dyslipidemia (DA007_2), liver disease (DA007_6), heart attack (DA007_7), kidney disease (DA007_9), and asthma (non-lung disease) (DA007_14) (Table 1). Health status captures systemic inflammation and functional reserve. Liver, kidney, and heart diseases share common inflammatory pathways

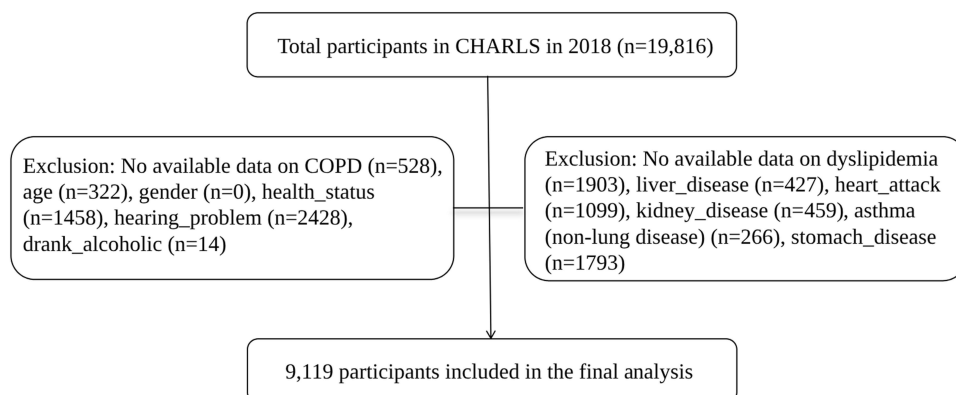


Figure 1 Flow diagram of study participants.

Abbreviations: COPD, chronic obstructive pulmonary disease; CHARLS, The China Health and Retirement Longitudinal Study.

Table 1 Information Sheet on Covariates

Variable	Categorical Variable/Continuous Variable	Dataset
Age	Continuous Variable	BA004_W3
Gender	Categorical Variable (Male, Female)	BA000_W3_2
Health status	Categorical Variable (very good, good, average, not good, very bad)	DA002
Hearing problem	Categorical Variable (Yes, No)	DA005_4_
Alcohol consumption	Categorical Variable (Yes, No)	DA067
Dyslipidemia	Categorical Variable (Yes, No)	DA007_2_
Liver disease	Categorical Variable (Yes, No)	DA007_6_
Heart attack	Categorical Variable (Yes, No)	DA007_7_
Kidney disease	Categorical Variable (Yes, No)	DA007_9_
Asthma (non-lung disease)	Categorical Variable (Yes, No)	DA007_14_

(eg., the lung-kidney axis); asthma was included to avoid phenotype misclassification. Alcohol use and dyslipidemia are shared modifiable risk factors, while hearing problems serve as a proxy for aging-related frailty and health behavior differences. Important potential confounders such as smoking status, body mass index (BMI), education level, and household income are known to be associated with both stomach disease and COPD. However, these variables were not included in the primary models due to high rates of missing data in the 2018 CHARLS wave (eg., smoking: >30%, BMI: >15%).

Statistical Analysis

²⁵ Baseline characteristics were summarized using the tableone package (v 0.13.2). Categorical variables were presented as percentages and compared using the χ^2 -test. Continuous variables were tested for normality using the Shapiro–Wilk test; as all continuous variables deviated from normality, they were compared between groups using the Mann–Whitney *U*-test (for two groups) or Kruskal–Wallis test (for three or more groups). Age was treated as a continuous variable in regression models but was categorized as <62 years vs. ≥ 62 years in baseline tables based on the median split for descriptive purposes only. Multivariable logistic regression was performed using the glm() function in R (v 4.3.1), and three hierarchical models were constructed: Model 1 (unadjusted): COPD ~ Stomach disease; Model 2 (adjusted for age and sex): COPD ~ Stomach disease + Age + Sex; and Model 3 (fully adjusted): COPD ~ Stomach disease + health status + hearing problem + alcohol consumption + dyslipidemia + liver disease + heart attack + kidney disease + asthma. Collinearity was assessed using variance inflation factors (VIF); all VIF values were <2, indicating no significant multicollinearity.²⁶ For ROC analysis, the receiver operating characteristic (ROC) curves for model 3 were plotted using the pROC package (v 1.18), and the area under the curve (AUC) was reported as a descriptive measure of model fit. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

General Characteristics of Participants

Table 2 contains information on the baseline characteristics of the subjects according to the presence of COPD, with “Yes” being subjects with a particular disease or underlying condition and “No” being control subjects without a particular disease or underlying condition. A total of 9119 participants were selected from the CHARLS cohort, of which 380 exhibited COPD. As shown in Table 2, all covariates and stomach disease showed significant differences ($p < 0.05$) for COPD, except for alcohol consumption.

Strong Association Between Stomach Disease and COPD

To further understand the relationship between COPD and stomach disease, correlation analyses between COPD and stomach disease were performed to construct three successive multifactorial glm regression models. As shown in Table 3, the results were as follows: Model 1 (OR = 3.12, 95% confidence interval (CI) = 2.43–3.98, $p = 1.95\text{E}^{-19}$), Model 2 (OR =

Table 2 Baseline Characteristics of Subjects by Presence of COPD

	Level	No	Yes	p
n		8739	380	
Age (%)	18–61	5331 (61.0)	197 (51.8)	<0.001
	≥62	3408 (39.0)	183 (48.2)	
Gender (%)	Female	4576 (52.4)	165 (43.4)	<0.001
	Male	4163 (47.6)	215 (56.6)	
Health status (%)	Average	4353 (49.8)	190 (50.0)	<0.001
	Good	1483 (17.0)	36 (9.5)	
	Not good	1102 (12.6)	96 (25.3)	
	Very bad	259 (3.0)	40 (10.5)	
Hearing problem (%)	Very good	1542 (17.6)	18 (4.7)	0.004
	No	8372 (95.8)	352 (92.6)	
Alcohol consumption (%)	Yes	367 (4.2)	28 (7.4)	0.38
	No	5474 (62.6)	247 (65.0)	
Dyslipidemia (%)	Yes	3265 (37.4)	133 (35.0)	<0.001
	No	7896 (90.4)	303 (79.7)	
Liver disease (%)	Yes	843 (9.6)	77 (20.3)	<0.001
	No	8537 (97.7)	348 (91.6)	
Heart attack (%)	Yes	202 (2.3)	32 (8.4)	<0.001
	No	8222 (94.1)	311 (81.8)	
Kidney disease (%)	Yes	517 (5.9)	69 (18.2)	<0.001
	No	8490 (97.2)	344 (90.5)	
Asthma (%)	Yes	249 (2.8)	36 (9.5)	<0.001
	No	8684 (99.4)	310 (81.6)	
Stomach disease (%)	Yes	55 (0.6)	70 (18.4)	<0.001
	No	790 (9.0)	90 (23.7)	
	No	7949 (91.0)	290 (76.3)	

Notes: Age was treated as a continuous variable in regression models but was categorized as <62 years vs. ≥62 years in this baseline table based on the median split for descriptive purposes only.

3.21, 95% CI = 2.49–4.1, $p = 3.65\text{E-}20$), and Model 3 (OR = 1.95, 95% CI = 1.46–2.57, $p = 3.61\text{E-}06$). COPD had a p -value of less than 0.05 in all three models, indicating that the effect of stomach disease on COPD was not significantly confounded by other covariates and was strongly correlated with stomach disease.

Stratified Analysis

To assess the impact of stomach disease and other covariates on COPD, this study analyzed the association between stomach disease, other covariates, and COPD using logistic regression. The results are shown in [Figure 2](#), which shows that stomach disease is still strongly associated with COPD, with an odds ratio (95% CI: 1.46–2.57), which is a risk factor for COPD ($p < 0.05$). Gender (male), health status (very good, good, not good, or bad), dyslipidemia (yes), liver disease (yes), heart attack (yes), kidney disease (yes), and asthma (yes) were also significantly correlated with COPD ($p < 0.05$).

ROC Curve for the Full Model

A risk prediction ROC curve was used to assess the discriminatory ability of the prediction models. The results of Model 3 are shown in [Figure 3](#). The AUC of Model 3 for COPD risk prediction was 0.76, indicating that the full model—which includes stomach disease along with all covariates—has moderate discriminative ability for identifying COPD.

Discussion

^{27–29} COPD is the third leading cause of death worldwide and is characterized by irreversible airflow limitation and diverse systemic comorbidities. We utilized CHARLS data to explore the association between stomach disease and

Table 3 Relationship Between Stomach Disease and COPD

Model	OR (95% CI)	p_value
Model 1	3.12(2.43–3.98)	1.95E–19
Model 2	3.21(2.49–4.1)	3.65E–20
Model 3	1.95(1.46–2.57)	3.61E–06

Notes: Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: further adjusted for health status, hearing problems, alcohol consumption, dyslipidemia, liver disease, heart attack, kidney disease, and asthma.

Abbreviations: COPD, chronic obstructive pulmonary disease; CHARLS, China Health and Retirement Longitudinal Study; PPS, probability proportionate to size sampling; ROC, receiver operating characteristic; OR, odds ratio; CIs, confidence interval; HR, hazard ratio; AUC, area under the curve; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AKI, acute kidney injury; FEV1, forced expiratory volume in the first second; HDL-C, high-density lipoprotein cholesterol; TyG, triglyceride–glucose; GERD, gastroesophageal reflux disease; PPIs, proton pump inhibitors; H2RAs, H2 receptor antagonists.

COPD. Although previous studies, primarily from Western populations, have reported an association between Gastroesophageal reflux disease (GERD) and COPD, our study provides supplementary evidence through a large nationally representative Chinese cohort with survey weights. The prevalence of stomach disease and heart attack was significantly higher in the COPD group than in the control group ($p < 0.05$). Multimodel regression showed that stomach

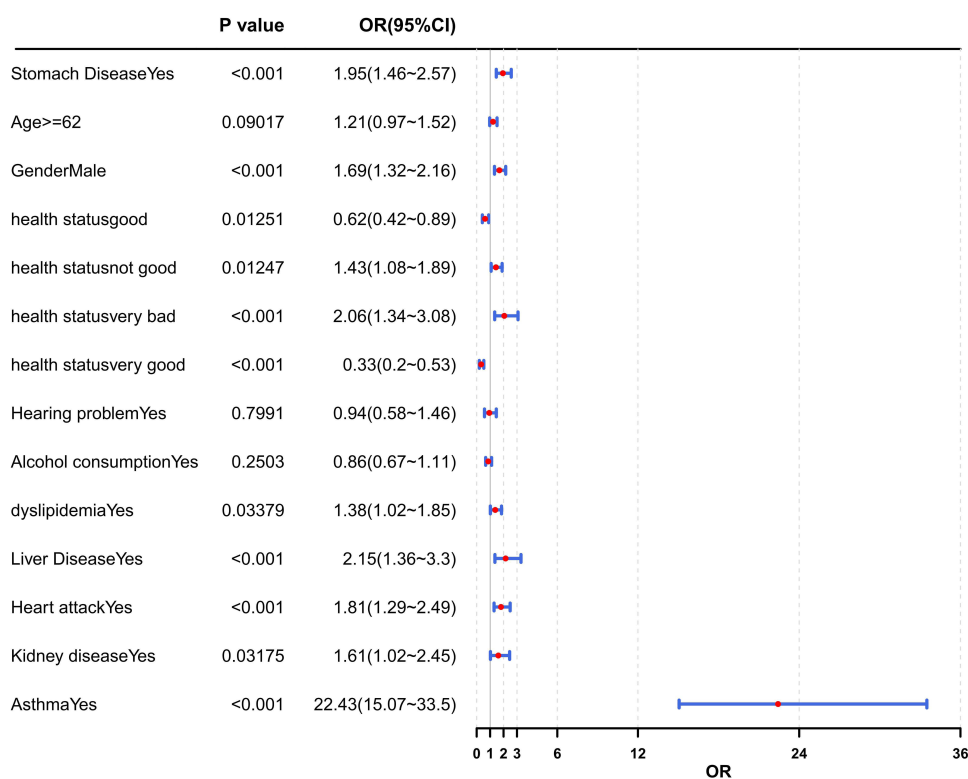


Figure 2 Association between covariates and COPD risk. The forest plot shows odds ratios (ORs) and 95% confidence intervals (CIs) from a logistic regression model (Model 3) that included stomach disease and all covariates. Reference categories are as follows: Stomach disease (No), Age (<62 years), Gender (Female), Health status (very good), Hearing problem (No), Alcohol consumption (No), Dyslipidemia (No), Liver disease (No), Heart attack (No), Kidney disease (No), and Asthma (No). P-values indicate statistical significance.

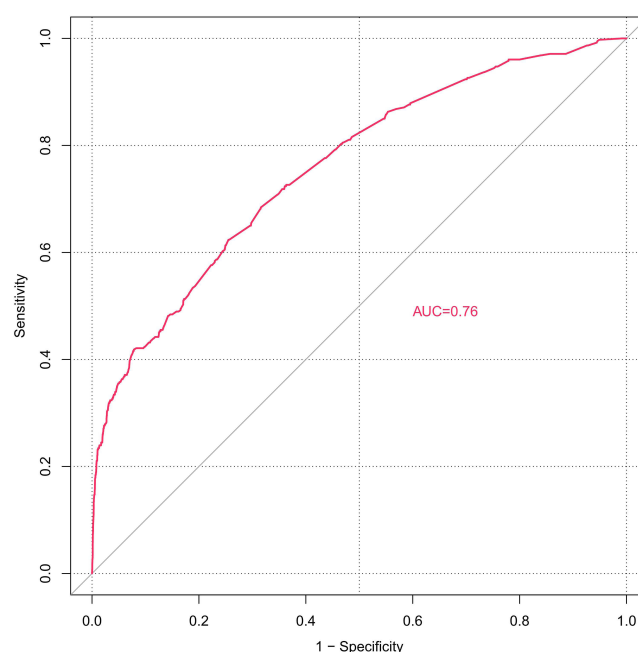


Figure 3 ROC curve for the risk prediction of COPD. The x-axis represents 1 – Specificity, while the y-axis represents Sensitivity. The AUC (Area Under the Curve) of 0.76 indicates moderate discriminative ability of the multivariable model as a whole ($AUC > 0.7$).

disease was independently associated with COPD ($OR = 1.95$, $95\% \text{ CI} = 1.46\text{--}2.57$, $p = 3.61\text{E}\text{--}06$), an estimate consistent with the biologically plausible range reported in the literature. Stratified analyses reflected the presence of associations in all the subgroups. Male sex, dyslipidemia, liver and kidney diseases, and asthma significantly increased the risk of COPD. The ROC curve yielded an AUC of 0.76 for the fully adjusted model, indicating that the combination of stomach disease and all covariates has moderate discriminative ability. This AUC should not be overinterpreted as evidence that stomach disease alone has strong screening utility for COPD; rather, it reflects the collective performance of the multivariable model.

The main contribution of this study is to provide population-level epidemiological evidence supporting an association between stomach disease in general and COPD, using a nationally representative sample of middle-aged and older Chinese adults.^{17,30} While previous studies have primarily focused on gastroesophageal reflux disease (GERD) as a specific gastric condition, this study broadens the scope of research by examining a more practical, self-reported composite stomach disease indicator that reflects real-world clinical complexity. However, it is important to note that this work mainly provides confirmatory evidence at the general population level, rather than achieving breakthrough mechanistic or clinical advances. The observed odds ratio was 1.95 (95% confidence interval: 1.46–2.57), which aligns with biologically plausible pathways but does not establish causality.

The risk of COPD increases significantly with the development of kidney disease.³¹ Mendelian randomized analysis revealed that genetically predicted lowering of the estimated glomerular filtration rate (eGFR) directly enhances the risk of COPD.³² Large clinical cohort study confirmed that the risk of COPD was 61% higher in individuals with chronic kidney disease (CKD) than in those without CKD, suggesting that kidney dysfunction is an independent associated factor for COPD. Moreover, the risk of COPD increases after acute kidney injury (AKI). 10.7% dialysis patients acquire new COPD within one year after recovering from AKI.³³ AKI patients with COPD exhibited a 52% higher risk of ischemic stroke ($sHR=1.52$) and 61% higher risk of heart failure ($sHR=1.61$).^{34,35} Kidney injury aggravates COPD via various mechanisms. Uremic toxins in CKD trigger inflammation and oxidative stress, injuring the lungs. Kidney tubular mitochondrial disorders cause autophagy, and inflammatory markers induce destruction of alveolar membranes. In addition, metabolic acidosis, which promotes dynamic hyperinflation in COPD, a higher concentration of urinary DKK3 delays restoration of the lungs and accelerates the decline in forced expiratory volume in the first second (FEV1).^{31,33,34,36} Thus, the care of patients with reduced eGFR should be considered an integral aspect in COPD risk

evaluation by closely monitoring patients with low eGFR, expanding the monitoring for the low eGFR level (<60 mL/min/1.73 m²), and implementing bicarbonate as a first-choice drug for acidosis correction. Efforts should be made to understand the benefits of autophagy inhibitors in such patients. In dialysis patients, in addition to proper vaccination for any indications such as influenza or pneumococcal vaccination, we should not only prevent the development or aggravation of COPD (occurring within the first year after an episode of AKI) but also lower the risk of future stroke or heart failure.

^{37–39} It has been demonstrated that some liver diseases (including non-alcoholic fatty liver disease, liver fibrosis and hepatitis C-associated liver damage) are highly correlated with COPD among COPD patients, with the incidence of hepatic fat deposition in non-alcoholic fatty liver disease between 41.4%–58.3%, and that in liver fibrosis 45.8%–61.3%. Hepatitis C infection can also accelerate the loss of lung function in aging COPD smokers with COPD.^{39–41} The underlying pathogenesis of this clinical correlation is likely to be characterized by three mechanisms: 1) free fatty acid (FFA) and ceramide(s) exchange from the liver to lung-induced lung injury; 2) hepatocyte-derived Leptin, TNF- α , and so on, which induce lung inflammation; and 3) persistent hypoxia that accompanies COPD impairs HIF-1 α -regulated liver cell regeneration, leading to a pathogenic loop to these mechanisms. We recommend that a physician should adopt the following management strategies: routinely screen liver enzymes and evaluate liver fibrosis with FIB-4 and APRI indices in COPD patients, to use PPAR γ agonists for controlling lipid metabolism, to use TNF- α inhibitors and antioxidant therapy to control inflammation, to optimize COPD management, including oxygen therapy, to handle hypoxia. These approaches have the potential to improve patient outcome.

Based on existing evidence, we observed a significant epidemiological association and bidirectional pathological interaction between hyperlipidemia and COPD.^{42,43} Large cohort studies have shown that patients with hyperlipidemia have a 48% increased risk of developing COPD compared with those without hyperlipidemia (aHR=1.48). This risk was dose dependent. Individuals who did not take lipid-lowering medications faced an additional risk of 9.1%. In contrast, long-term use of statins or fibrates (more than 361 DDDs) can significantly reduce the risk of COPD by 52.6%.^{44–47} Regarding the pathological effects, patients with COPD showed significant changes in their lipid profiles. These include elevated high-density lipoprotein cholesterol (HDL-C) levels and significantly reduced atherogenic markers (such as AIP and CRI-I/II). Additionally, a higher triglyceride-glucose index (TyG) correlated with chronic bronchitis (aOR=1.21), respiratory symptoms such as cough (aOR=1.28), and restrictive ventilatory impairment. Additionally, every time the hs-CRP/HDL ratio increases by 1 unit, the risk of COPD increases by 64%, and cholesterol damages the mitochondria through the STARD3 protein, which induces cholesterol to migrate to the mitochondria and suppresses the expression of MFN2.^{44,48,49} These changes damage fatty acid breakdown and activate mTOR phosphorylation, which augments the secretion of cytokines IL-6 and IL-8 induced by cigarette smoke, whereas dyslipidemia increases the general inflammation associated with insulin resistance (TyG index), aggravating lung tissue damage caused by inflammatory factors (CRP and fibrinogen).^{42,48} Statins are lipid-lowering drugs whose pulmonary protective effects may be mediated by two major mechanisms. First, they directly modulate cholesterol metabolism; second, they attenuate neutrophil infiltration and oxidative stress through negative regulation of the Rho GTPase pathway. These findings highlight the dominant roles of cholesterol imbalance and metabolic inflammation. Therefore, lipid-lowering drugs can be an effective way to prevent and cure COPD.

Analysis of the relationship between COPD and stomach diseases confirmed a significant association between these conditions. Although the exposure variable in this study is a broad, self-reported composite measure of “stomach disease” (encompassing GERD, gastritis, and peptic ulcer), the most thoroughly studied gastric condition related to COPD is gastroesophageal reflux disease (GERD). Therefore, the following discussion leverages the GERD literature to generate mechanistic hypotheses that may partially explain the observed associations. Studies have shown that the prevalence of GERD in COPD patients ranges from 19% to 78%, and GERD is associated with an increased risk of acute exacerbations. However, notably, this study cannot distinguish between specific stomach disease subtypes, and the mechanistic inferences discussed below should be considered speculative and hypothesis-generating rather than definitive. For example,⁵⁰ a case-control study from the ECLIPSE cohort found that COPD patients with self-reported GERD who did not use acid suppression medications had a hazard ratio (HR) of 1.58 (95% CI: 1.35–1.86) for moderate to severe acute exacerbations. This was compared to patients treated with proton pump inhibitors (PPIs) or H₂ receptor

antagonists (H2RAs), highlighting the negative impact of GERD on acute COPD events. Furthermore, GERD is an independent associated factor for ICU admission and mechanical ventilation in COPD patients.⁵¹ A nationwide cohort study in Taiwan showed that COPD patients with GERD had a 1.75-fold higher ICU admission rate (HR_{adj} = 1.75, 95% CI: 1.28–2.38) and 1.92-fold higher risk of requiring mechanical ventilation (HR_{adj} = 1.92, 95% CI: 1.35–2.72), indicating that GERD exacerbates respiratory failure and serious complications.^{52–54} GERD can mask the early symptoms of acute exacerbations through an unusual presentation. GERD frequently occurs in conjunction with gastric ulcers and heart disease, and these conditions significantly impair patients' quality of life and elevate the BODE index.⁵³ In spite of the strong relationship between GERD and poor prognosis in COPD, conventional acid-reducing medications, including proton pump inhibitors (PPIs), have not yielded positive lung function outcomes, indicating that lung damage due to GERD may be a result of mechanisms other than acid reflux, which include neuroreflexes triggered by bile reflux or microaspiration. Current treatments cannot block the primary pathways to prevent this “gastric–lung connection.” Future plans should consider more of a customized approach. This would involve, for example, 24 h pH–impedance studies of older adults and frequent acute exacerbators to detect patients with “silent reflux” needing detection and treatment of reflux; examining non-pharmacological treatments such as vagus nerve treatment or anti-reflux surgery; and recognizing the role of stomach contents on the lung tissue. Treatment directed at specific phenotypes (ie., nighttime refluxers) could be used to provide more targeted clinical care.

Several limitations are worth noting. First, this is a cross-sectional study that only uses the 2018 data from CHARLS and cannot infer causal or temporal relationships between stomach disease and COPD. The observed association between stomach diseases and COPD may be bidirectional. Second, the sample size of COPD cases is limited (n=380), and no sample size estimation was conducted in advance, which excluded a large proportion of participants, potentially limiting the statistical power of some stratified analyses and increasing the risk of Type II errors. Third, important confounding variables such as smoking, BMI, education, income, occupational exposure, and medication have a missing rate of >15% or are unavailable in the 2018 data, which may lead to residual confounding. Fourth, both the exposure and the outcome are based on self-reported doctor diagnoses. COPD lacks confirmation of lung function, and stomach disease lack verification through medical records. There may be misclassification bias. Fifth, the definition of stomach disease is broad and is a combined category, making it impossible to analyze specific stomach disease. The discussion on the mechanism of GERD in the text is only as a background and does not represent the GERD-specific findings of this study. Future studies need to conduct longitudinal follow-ups, use lung function tests to confirm COPD, and conduct more detailed classification of stomach disease (such as endoscopic examination) to verify and expand our findings.

Conclusion

In this cross-sectional analysis of a nationally representative Chinese sample, self-reported stomach disease was positively associated with COPD (OR = 1.95, 95% CI: 1.46–2.57). However, due to the cross-sectional design, single-wave data, self-reported diagnoses without spirometric confirmation, and a broad “stomach disease” definition that does not distinguish specific gastric conditions, no causal inference can be made. Key confounders such as smoking and BMI were not fully adjusted because of missing data. The AUC of 0.76 reflects the full model's performance, not the predictive utility of stomach disease alone. Therefore, these findings are hypothesis-generating rather than practice-changing. They suggest stomach disease as an associated factor and warrant prospective studies with spirometry-confirmed COPD and detailed gastric phenotyping. No clinical screening or therapeutic recommendations are made.

Ethics Approval and Consent to Participate

This study was a secondary analysis of data from the China Health and Retirement Longitudinal Study (CHARLS). The CHARLS study was approved by the Institutional Review Board (IRB) of Peking University (IRB00001052–11015). All participants provided written informed consent. The present study utilized publicly available, anonymized data. As per Item 1 and 2 of Article 32 of the “Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects” (China, effective February 18, 2023), research using publicly available, anonymized data that does not involve personal privacy or sensitive information is exempt from ethical review by the authors' own IRB. Consequently, no additional ethical approval was required for this analysis.

Disclosure

The author(s) report no conflicts of interest in this work.

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