

# The Nonlinear Relationship Between High-Density Lipoprotein and Changes in Pulmonary Structure Function and Pulmonary Function in COPD Patients in China

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**Background:** The previous findings on the correlation between spirometry and high-density lipoprotein (HDL) cholesterol are intriguing yet conflicting. The aim of this research is to evaluate the relationship between HDL levels and spirometry as well as imaging parameters in patients with chronic obstructive pulmonary disease (COPD) in China.

**Methods:** This study encompasses a total of 907 COPD patients. Participants with complete data from questionnaire interviews, lipid profile examinations, spirometry testing, and computed tomography (CT) scans were included in the analysis. A generalized additive model was employed to identify the non-linear relationship between HDL levels and both spirometry and imaging parameters. In the presence of non-linear correlations, segmented linear regression model was applied to ascertain threshold effects.

**Results:** After adjusting for various factors, we found a non-linear correlation between HDL levels and spirometry/imaging parameters, with an inflection point at 4.2 (66 mg/dL). When Ln (HDL) was below 4.2, each unit increase correlated significantly with reduced post-bronchodilator FEV<sub>1</sub> (0.32L, 95% CI: 0.09–0.55), decreased predicted FEV<sub>1</sub>% (11.0%, 95% CI: 2.7–19.3), and lowered FEV<sub>1</sub>/FVC (8.0%, 95% CI: 4.0–12.0), along with notable increases in Ln (LAA<sub>-950</sub>) by 1.20 (95% CI: 0.60–1.79) and Ln (LAA<sub>-856</sub>) by 0.77 (95% CI: 0.37–1.17). However, no significant associations were observed when Ln (HDL) was greater than or equal to 4.2.

**Conclusion:** A non-linear correlation existed between HDL levels with lung function and CT imaging in COPD patients. Prior to reaching 66 mg/dL, an elevation in HDL was significantly associated with impaired lung function, more severe gas trapping and emphysema.

**Keywords:** COPD, high-density lipoprotein, lung function, computed tomography imaging

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a pulmonary disorder marked primarily by persistent and progressive airflow obstruction stemming from abnormalities in the airways and/or alveoli.<sup>1,2</sup> COPD emerges as a major cause for the escalating rates of incidence and mortality worldwide, imposing significant economic and societal burdens.<sup>3,4</sup> Anticipated trends suggest a considerable rise in COPD cases, with projections indicating an increase of 112 million cases by 2050, culminating in a total of 592 million individuals affected, equivalent to 9.5% of the population. This reflects a 23.3% increase from 2020 to 2050 in relative terms.<sup>5</sup> The burden of COPD in China is notably severe. According to the latest epidemiological survey, the prevalence of COPD among individuals aged 40 and above has risen from 8.2% in 2007 to

13.7%.<sup>6</sup> Predictions suggest that new cases and deaths from COPD in China will increase by approximately 1.5 times over the next 25 years.<sup>7</sup> The economic impact of COPD in China is the highest in the world, amounting to approximately \$1.4 trillion annually. This equates to an additional tax burden of 0.16% on the Chinese economy each year due to COPD.<sup>8</sup>

The relationship between abnormal systemic lipid metabolism and the onset and progression of cardiovascular diseases was well-established.<sup>9,10</sup> However, recent research indicated that changes in the lipid profile may not be confined solely to the cardiovascular system; they may also be relevant to respiratory system health.<sup>11,12</sup> Reportedly, atherosclerotic cardiovascular disease was the most frequent comorbidity in COPD, affecting approximately 13% of COPD patients, compared to 4% among subjects with normal pulmonary function.<sup>11,12</sup> COPD was a disease characterized by the pathophysiological underpinning of chronic airway inflammation.<sup>13</sup> The dysregulation of inflammatory control mechanisms resulted in the chronicization of inflammation and the possibility of systemic inflammation, potentially establishing a link between COPD and various comorbidities.<sup>14,15</sup> An expanding body of research had highlighted the crucial involvement of disturbances in lipid metabolism in the airway inflammation experienced by individuals with COPD. Earlier investigations had indicated a link between reduced low density lipoprotein-cholesterol (LDL) cholesterol levels and a higher likelihood of developing COPD, experiencing COPD exacerbation, and facing mortality specifically related to COPD.<sup>16</sup> A substantial correlation was evident between levels of LDL cholesterol and the deterioration of lung function, alongside an increase in oxidative stress.<sup>17,18</sup> Moreover, there was compelling evidence suggesting a potential correlation between high-density lipoprotein (HDL) and both the development and advancement of COPD.<sup>19,20</sup> Previous studies in the general population or patients with metabolic syndrome had explored the relationship between HDL and spirometry, but contradictory research results had been obtained.<sup>21–25</sup> Some studies found that higher HDL levels were linked to better lung function, while others reported a negative association or no significant correlation. These discrepancies may be due to differences in study populations, methodologies, and measurement techniques.<sup>21–25</sup>

To summarize, the available research on the correlation between lung function and HDL presented inconsistent findings. Moreover, studies conducted earlier on the association between lung function and HDL primarily targeted general populations and individuals diagnosed with metabolic syndrome. Another crucial aspect was the absence of research data exploring the relationship between HDL and computed tomography (CT) imaging in COPD patients. Motivated by these factors, we analyzed data from a survey carried out in Guangdong, China, aiming to explore the relationship between HDL levels and both spirometry and imaging parameters in COPD patients.

## Materials and Methods

### The ECOPD Study

The Early Chronic Obstructive Pulmonary Disease (ECOPD) study (Registration No. ChiCTR 1900024643) is a population-based, multicenter, randomized survey specifically targeting COPD patients, conducted from June 2019 to June 2021 in Wengyuan County, Shaoguan City, and Lianping County, Heyuan City, and Guangzhou City in Guangdong Province, China. The study primarily recruited residents aged 40–80 years from the community. After obtaining written informed consent, participants completed a questionnaire on high-risk factors for COPD, an assessment of respiratory symptoms, pre-bronchodilator and post-bronchodilator spirometry. Based on the spirometry, all COPD patients and a quarter of the participants with normal pulmonary function were scheduled for chest computed tomography (CT) scan. Participants included in the study received annual follow-ups, during which they completed the high-risk factors questionnaire, respiratory symptoms assessment, spirometry testing, and evaluations for acute respiratory events/exacerbations. The detailed procedures and content of this study had been previously published in the literature.<sup>26</sup>

### Study Population

The participants in our study were sourced from the ECOPD study. Inclusion criteria comprised individuals who: (1) were between the ages of 40 and 80; (2) had completed a standard respiratory epidemiological survey questionnaire; (3) possessed quality-controlled and complete lung function and CT data; (4) had complete fasting blood lipid data. Primary exclusion criteria included individuals who: (1) had a respiratory tract infection or worsening symptoms in the 4 weeks prior to screening; (2) experienced malignant arrhythmia or myocardial infarction in the last 3 months; (3) had a history

of pulmonary lobectomy; (4) were newly diagnosed with malignancy undergoing treatment; (5) had a history of pulmonary diseases other than asthma (such as active pulmonary tuberculosis, widespread bronchiectasis, pneumococcosis, pulmonary aspergillosis, lung cancer).

## Questionnaires

The epidemiological survey questionnaire utilized was derived from a comprehensive epidemiological investigation<sup>27</sup> of COPD conducted in China, incorporating key demographic details (gender, age, height, weight, etc.), smoking status and index, passive smoking, occupational history of fumes/gases/dust exposure, family history of respiratory system diseases, biomass exposure, and previous comorbidities.<sup>26,27</sup>

## Spirometry

In the course of our investigation, skilled personnel conducted spirometry utilizing a portable spirometer (CareFusion, Yorba Linda, CA, USA), strictly adhering to the guidelines of spirometry outlined by the European Respiratory Society.<sup>28</sup> After the baseline spirometry measurements before the administration of bronchodilator, participants underwent post-bronchodilator spirometry assessments following the inhalation of 400 µg of salbutamol, with a 20-minute interval. Those identified with COPD were characterized by a post-bronchodilator forced expiratory volume in first second (FEV<sub>1</sub>)/forced vital capacity (FVC) ratio below 0.70. The severity of COPD was assessed by determining the percentage of predicted FEV<sub>1</sub> (FEV<sub>1</sub>% of predicted).<sup>29</sup>

## Imaging

Utilizing multidetector-row CT scanners, we conducted CT scans spanning from the lung apex to the base during full inhalation and deep expiration. The detailed CT protocol employed in our study had been previously published.<sup>26</sup> The analysis of CT images was carried out utilizing software programs.<sup>30</sup> Gas trapping was determined as the percentage of low-attenuation lung area below -856 HU during full expiration CT, denoted as LAA<sub>-856</sub>. Emphysema was identified by determining the percentage of low-attenuation lung area below -950 Hounsfield units (HU) during full inhalation CT, denoted as LAA<sub>-950</sub>.<sup>31</sup>

## Measurement of Serum Lipid

Proficient personnel collected and prepared biological samples from participants, assessing the lipid profile of fasting subjects with a minimum fasting duration of 8.5 hours. Blood samples from participants were stored at temperatures below -20 °C in serum separation tubes. Enzymatic methods were employed to determine the levels of serum lipids.<sup>26</sup>

## Ethical Statement

Ethical clearance for the study was granted by the Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University (No. 2018-53), and all participants provided written informed consent. This present study was in line with the principles of the Declaration of Helsinki.

## Statistical Analysis

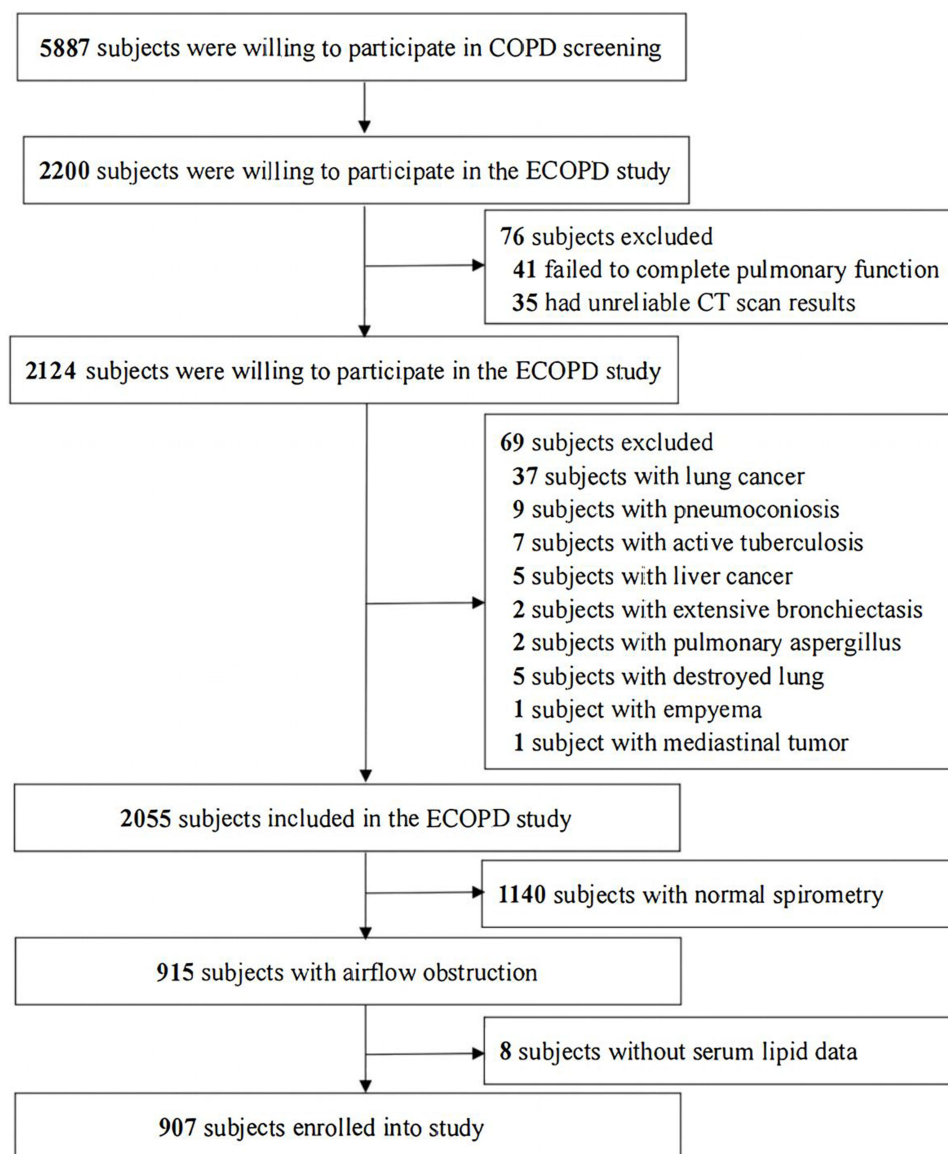
The dataset's normality was appraised utilizing the Kolmogorov-Smirnov test. Continuous variables, denoted as mean ± standard deviation (SD) for normally distributed data, underwent comparison through the analysis of variance. Non-normally distributed continuous variables, characterized by the median within the interquartile range, were subjected to analysis using the Kruskal-Wallis *U*-test. Categorical variables were quantified in frequencies (proportions) and subjected to comparison using either the Pearson's Chi-squared test or Fisher's exact test. Given the non-normal distribution observed in HDL and imaging parameters, a natural logarithm (Ln) transformation was applied. Participants were stratified into four groups based on baseline HDL quartiles. Covariance analysis was employed to explore associations between distinct HDL levels and pulmonary function metrics, emphysema and air trapping. Covariate adjustments encompassed gender, age, body mass index (BMI), smoking index and status, passive smoke, family history of respiratory diseases, biomass exposure,

occupational exposure, triglyceride, total cholesterol, and history of coronary artery disease. Furthermore, a generalized additive model (GAM) was utilized to identify non-linear relationships, with trends visually represented through smoothed plots. In the presence of non-linear correlations, segmented linear regression models were executed to ascertain threshold effects of HDL on pulmonary function and CT parameters. Recursive methodologies automatically computed inflection points, leveraging them to optimize model likelihood. Subgroup analyses were conducted through stratified linear regression models. SPSS (Version 26) and R software (version 4.3.1) were utilized for the statistical analysis. Statistical significance was established with a two-sided p-value below 0.05.

## Results

### Characteristics

A total of 907 participants met the inclusion criteria, possessing comprehensive and reliable data. The detailed procedures for participant inclusion and exclusion can be found in [Figure 1](#). The mean age of the participants was  $64.8 \pm 7.2$  years, with an average BMI of  $22.1 \pm 3.2$  kg/m<sup>2</sup>. Of the participants, 823 (90.7%) were male subjects, and 506



**Figure 1** Study flow chart.

**Abbreviations:** CT, computer tomography; ECOPD, early chronic obstructive pulmonary disease.

(55.8%) were current smokers. Comprehensive clinical characteristics are presented in detail in Table 1. Grouping participants based on quartiles of plasma HDL levels revealed a higher proportion of male patients and an elevated BMI in the first quartile (Q1) compared to the other three groups. Patients in Q1 also exhibited a lower prevalence of biofuel exposure history compared to the second (Q2) and third (Q3) groups. In terms of lipid profiles, participants in Q1 demonstrated higher levels of both total cholesterol and triglycerides than those in the other three groups. No statistically significant variations were detected among the four groups concerning age, smoking status, passive smoking, respiratory symptom, family history of respiratory diseases, complications, and occupational exposure history (Table 1).

## Relationship Between HDL and Lung Function, Imaging Parameters

In terms of pre-bronchodilator lung function, patients in the Q2, Q3, and Q4 groups exhibited a gradual lower in FEV<sub>1</sub> compared to the reference Q1 group. However, a notable difference was only noted in the Q4 group, exhibiting a decrease of 126mL (95% confidence interval 12 to 240) and a p-value of 0.030. Furthermore, the Q4 group demonstrated a 4.92% decrease in FEV<sub>1</sub>% of predicted compared to the Q1 group, with a p-value of 0.018. When contrasted with the Q1 group, patients in the Q2, Q3, and Q4 groups experienced respective decreases in FEV<sub>1</sub>/FVC of 2.07%, 2.93%, and 4.63%. There were no notable variations in FVC across the four groups. Post-bronchodilator lung function results similarly exhibited consistent patterns across the four groups. Detailed data were provided in Table 2.

**Table 1** Clinical Characteristics of COPD Patients Stratified by Quartiles of High Density Lipoprotein-Cholesterol (HDL) Levels

Characteristics	All (n=907)	Q1 (n=227)	Q2 (n=222)	Q3 (n=231)	Q4 (n=227)	P value
Age, years	64.8±7.2	64.0±6.9	64.5±7.1	65.5±7.4	65.1±7.2	0.116
Males, n (%)	823 (90.7)	216 (95.2) <sup>†‡</sup>	200 (90.1)*	210 (90.9)*	197 (86.8)*	0.022
Body mass index, kg/m <sup>2</sup>	22.1±3.2	23.4±3.2 <sup>‡</sup>	22.6±3.2 <sup>‡</sup>	21.6±3.2 <sup>†‡</sup>	20.8±2.9 <sup>†‡</sup>	<0.001
Smoking status, n (%)						0.057
Never smoked	128 (14.1)	21 (9.3)	30 (13.5)	41 (17.7)	36 (15.9)	
Former smoking	273 (30.1)	62 (27.3)	64 (28.8)	73 (31.6)	74 (32.6)	
Current smoking	506 (55.8)	144 (63.4)	128 (57.7)	117 (50.6)	117 (23.1)	
Smoking index, pack ×years	37.4±32.6	38.6±30.0	40.2±34.8	32.0±2.1	33.4±2.2	0.325
Comorbidity, n (%)						
Hypertension	154 (17.0)	48 (21.1)	40 (18.0)	32 (13.9)	34 (15.0)	0.157
Diabetes	31 (3.4)	10 (4.4)	9 (4.1)	9 (3.9)	3 (1.3)	0.248
Coronary artery disease	32 (3.5)	8 (3.5)	9 (4.1)	8 (3.5)	7 (3.1)	0.957
Cerebral stroke	24 (2.6)	6 (2.6)	4 (1.8)	6 (2.6)	8 (3.5)	0.730
Family history of respiratory diseases, n (%)	163 (18.0)	32 (14.2)	37 (16.7)	44 (19.0)	50 (22.0)	0.152
Biomass exposure, n (%)	338 (37.3)	66 (29.1) <sup>‡</sup>	93 (41.9)*	97 (42.0)*	82 (36.1)	0.012
Occupational exposure, n (%)	225 (24.8)	53 (23.3)	51 (23.0)	60 (26.0)	61 (26.9)	0.718
Passive smoke, n (%)	330 (36.4)	75 (33.0)	76 (34.4)	91 (39.6)	88 (38.8)	0.391
Blood eosinophils (10 <sup>9</sup> /L)	0.23±0.21	0.23±0.17	0.23±0.20	0.21±0.20	0.24±0.25	0.369
Blood neutrophils (10 <sup>9</sup> /L)	4.14±1.51	4.25±1.45	4.25±1.57	4.10±1.48	3.95±1.55	0.112
TG, mg/dL	126±93	173±143 <sup>‡</sup>	124±62 <sup>‡</sup>	118±74 <sup>‡</sup>	90±38 <sup>†‡</sup>	<0.001
TC, mg/dL	208±39	198±37 <sup>‡</sup>	201±37 <sup>‡</sup>	213±42 <sup>†‡</sup>	220±36 <sup>†‡</sup>	<0.001
LDL, mg/dL	134±36	138±36	138±37	142±37	134±33	0.109
HDL, mg/dL	56.5±17.8	41.4±5.5 <sup>†‡</sup>	50.9±2.1 <sup>‡</sup>	58.7±2.5 <sup>†‡</sup>	74.7±15.4 <sup>†‡</sup>	<0.001
Respiratory Symptoms, n (%)						
Chronic cough	369 (40.7)	84 (37.0)	81 (36.5)	101 (43.7)	103 (45.4)	0.119
Expectoration of phlegm	445 (49.1)	106 (46.7)	105 (47.3)	113 (48.9)	121 (53.3)	0.490
Dyspnea	385 (42.4)	89 (39.2)	89 (40.1)	99 (42.9)	108 (47.6)	0.268
Wheeze	175 (19.3)	37 (16.3)	49 (22.1)	40 (17.3)	49 (21.6)	0.289
Acute respiratory exacerbations during preceding year						
Total, n (%)	136 (15.0)	24 (10.6)	35 (15.8)	34 (14.7)	43 (18.9)	0.094
Exacerbations	0.29±0.75	0.21±0.63	0.34±0.91	0.28±0.71	0.32±0.71	0.381

**Notes:** Data are mean ± standard deviation or n (%). p < 0.05; \* vs Q1; † vs Q2; ‡ vs Q3; § vs Q4.

**Abbreviations:** Q1-Q4, grouped by quartiles of high-density lipoprotein-cholesterol levels; COPD, chronic obstructive pulmonary disease; HDL, high density lipoprotein-cholesterol; LDL, low density lipoprotein-cholesterol; TC, total cholesterol, TG, triglyceride.

**Table 2** Association Between Pulmonary Function and HDL Levels in COPD Patients

Variable	Group	Before Bronchodilator Use		After Bronchodilator Use	
		Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Spirometry FEV <sub>1</sub> , mL	Q1	0 (Ref.)		0 (Ref.)	
	Q2	-40 (-142, 63)	0.450	-28 (-128, 72)	0.580
	Q3	-80 (-186, 25)	0.140	-81 (-184, 22)	0.120
	Q4	-126 (-240, -12)	0.030	-111 (-221, -2)	0.048
FVC, mL	Q1	0 (Ref.)		0 (Ref.)	
	Q2	40 (-89, 170)	0.538	29 (-93, 150)	0.644
	Q3	2 (-132, 136)	0.976	5 (-120, 130)	0.936
	Q4	17 (-127, 161)	0.814	2 (-132, 137)	0.974
FEV <sub>1</sub> % of predicted, %	Q1	0 (Ref.)		0(Ref.)	
	Q2	-1.92 (-5.60, 1.77)	0.308	-1.43 (-4.99, 2.14)	0.433
	Q3	-2.87 (-6.66, 0.93)	0.139	-2.76 (-6.43, 0.91)	0.141
	Q4	-4.92 (-9.00, -0.84)	0.018	-4.21 (-8.15, -0.26)	0.037
FEV <sub>1</sub> /FVC, %	Q1	0 (Ref.)		0 (Ref.)	
	Q2	-2.07 (-3.88, -0.25)	0.026	-1.35 (-3.11, 0.40)	0.131
	Q3	-2.93 (-4.80, -1.06)	0.002	-2.78 (-4.58, -0.97)	0.003
	Q4	-4.63 (-6.64, -2.61)	<0.001	-3.62 (-5.56, -1.67)	<0.001

**Notes:** Data are estimate (95% CI). Outcomes were adjusted for age, sex, body mass index group, smoking status, pack-years of smoking, family history of respiratory diseases, biomass exposure, occupational exposure, passive smoke, triglyceride, total cholesterol, and history of coronary artery disease.

**Abbreviations:** Q1-Q4, grouped by quartiles of high-density lipoprotein-cholesterol levels; FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; COPD, chronic obstructive pulmonary disease; CI, confidence interval.

Table 3 illustrated the differences in imaging parameters among patients in the four groups. After adjusting for multiple confounding factors, we noticed that individuals in the Q2, Q3, and Q4 categories exhibited more severe gas trapping compared to those in the Q1 category. Furthermore, individuals in the Q3 and Q4 categories displayed a more pronounced degree of emphysema.

## The Analyses of Non-Linear Relationship

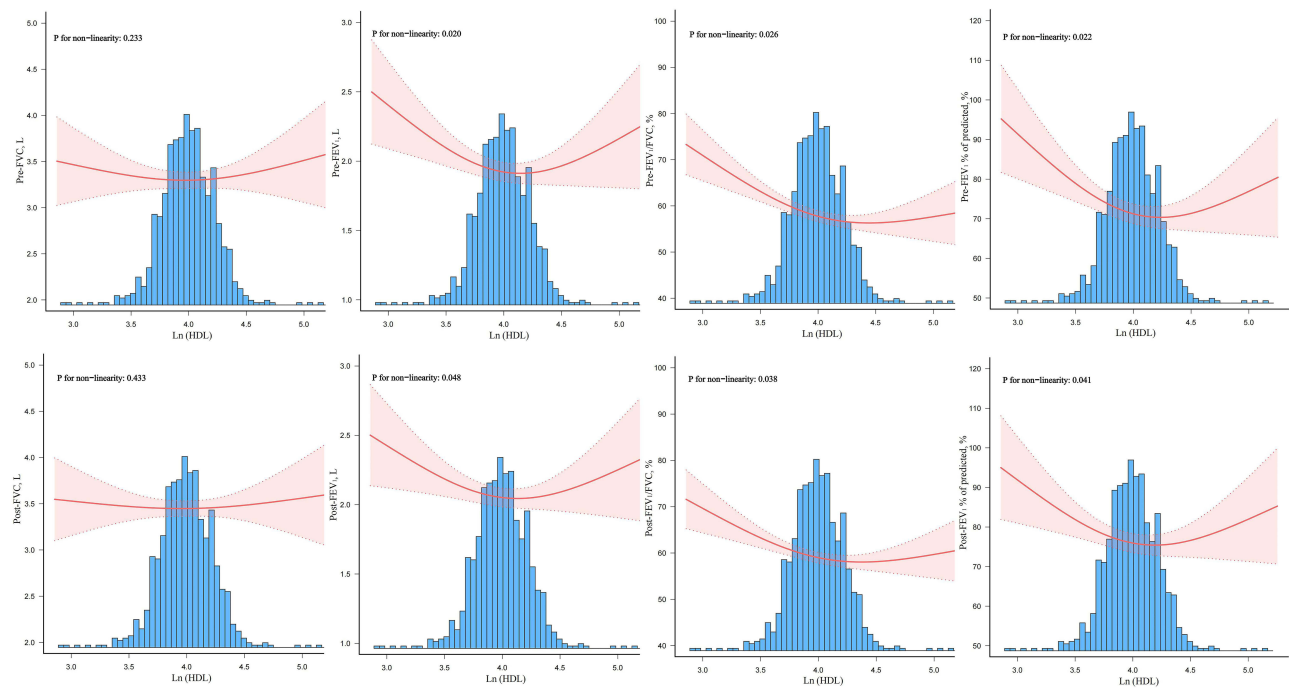
Figures 2 and 3 demonstrated a non-linear correlation between HDL levels and both spirometry and imaging parameters among COPD patients (after adjusting multiple confounding factors). By segmented linear regression models, we

**Table 3** Association Between Imaging Parameters and HDL Levels in COPD Patients

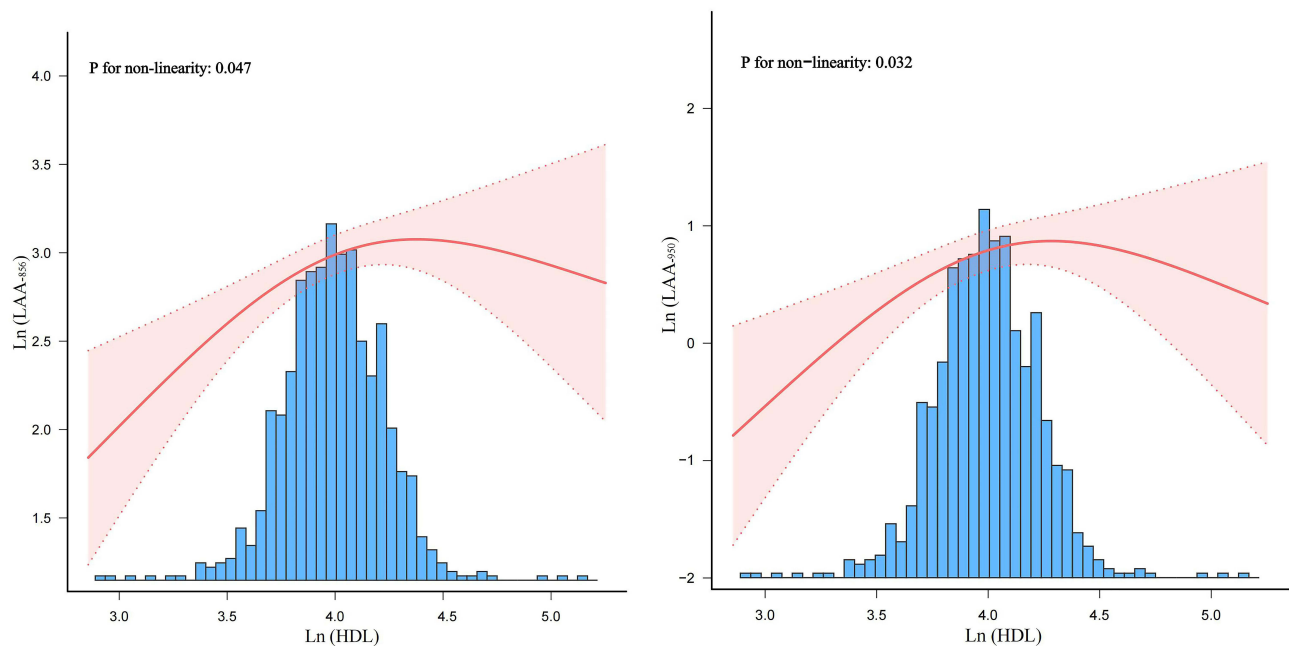
Variable	Group	Unadjusted		Multivariable-Adjusted	
		Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Computed tomography Ln (LAA-856)	Q1	0 (Ref.)		0 (Ref.)	
	Q2	0.21 (0.03, 0.39)	0.022	0.18 (0.01, 0.34)	0.042
	Q3	0.38 (0.20, 0.56)	<0.001	0.25 (0.08, 0.43)	0.004
	Q4	0.54 (0.35, 0.72)	<0.001	0.40 (0.22, 0.59)	<0.001
Ln (LAA-950)	Q1	0 (Ref.)		0 (Ref.)	
	Q2	0.27 (-0.01, 0.56)	0.060	0.24 (-0.02, 0.50)	0.069
	Q3	0.62 (0.33, 0.90)	<0.001	0.45 (0.19, 0.72)	0.001
	Q4	0.66 (0.38, 0.94)	<0.001	0.48 (0.19, 0.77)	0.001

**Notes:** Data are estimate (95% CI). Outcomes were adjusted for age, sex, body mass index group, smoking status, pack-years of smoking, family history of respiratory diseases, biomass exposure, occupational exposure, passive smoke, triglyceride, total cholesterol, and history of coronary artery disease.

**Abbreviations:** Q1-Q4, grouped by quartiles of high-density lipoprotein-cholesterol levels; HDL, high density lipoprotein-cholesterol; COPD, chronic obstructive pulmonary disease; CI, confidence interval. Ln, natural log; LAA-950, low-attenuation area of the lung with attenuation values below -950 Hounsfield units; LAA-856, low-attenuation area of the lung with attenuation values below -856 Hounsfield units.

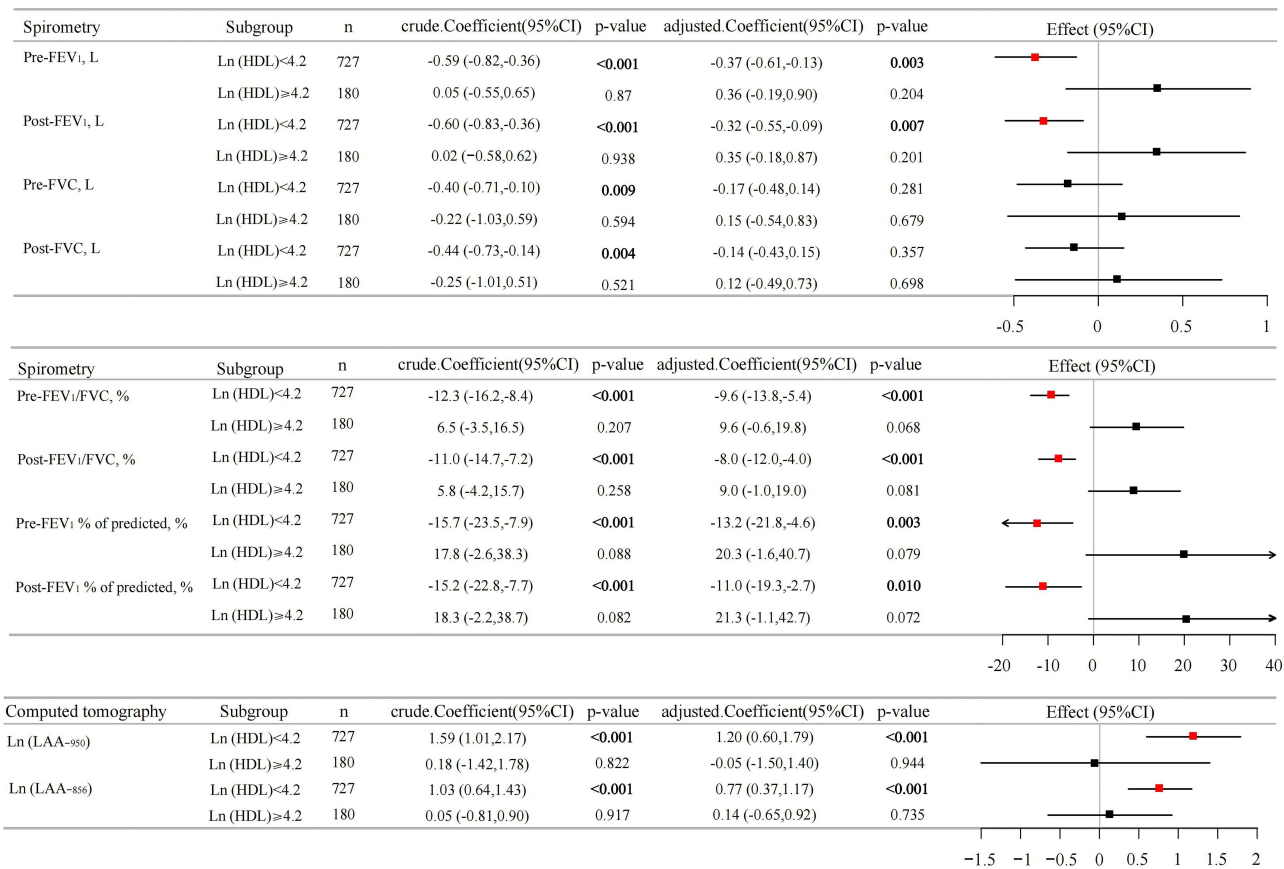


**Figure 2** Nonlinear Relationship Between HDL Levels and Pulmonary Function in Patients with Chronic Obstructive Pulmonary Disease. Outcomes were adjusted for age, sex, smoking status, pack-years of smoking, family history of respiratory diseases, biomass exposure, occupational exposure, passive smoke, triglyceride, total cholesterol, and history of coronary artery disease.



**Figure 3** Nonlinear Relationship Between HDL Levels and Imaging parameters in Patients with Chronic Obstructive Pulmonary Disease. Outcomes were adjusted for age, sex, smoking status, pack-years of smoking, family history of respiratory diseases, biomass exposure, occupational exposure, passive smoke, triglyceride, total cholesterol, and history of coronary artery disease.

calculated the inflection point was 4.2 (66 mg/dL). When Ln (HDL) was less than 4.2 (66 mg/dL), each unit increase in the natural logarithm of HDL (Ln (HDL)) was significantly associated with a reduction in post-bronchodilator FEV<sub>1</sub> of 0.32L (95% CI: 0.09 to 0.55), a decrease in FEV<sub>1</sub>% of predicted by 11.0% (95% CI:2.7 to 19.3), a decline in FEV<sub>1</sub>/FVC by 8.0% (95% CI:4.0 to 12.0), a notable increase in Ln (LAA<sub>-95</sub>) by 1.20 (95% CI:0.60 to 1.79), and a rise in Ln



**Figure 4** Association Between HDL Levels and Pulmonary Function, as well as Imaging parameters in COPD Patients Stratified by Optimal Cut-off Values. Outcomes were adjusted for age, sex, smoking status, pack-years of smoking, family history of respiratory diseases, biomass exposure, occupational exposure, passive smoke, triglyceride, total cholesterol, and history of coronary artery disease. The bold text in the table and the red boxes in the legend both indicate significant statistical differences.

(LAA<sub>-856</sub>) by 0.77 (95% CI:0.37 to 1.17). However, when Ln (HDL) was equal to or greater than 4.2 (66 mg/dL), no significant associations were observed between HDL levels and spirometry or imaging parameters. Detailed data was available in Figure 4.

### Discussion

Our study differed from previous research, revealing a non-linear relationship between HDL levels and spirometry, as well as CT imaging in COPD patients. The observed non-linearity suggested that the impact of HDL on pulmonary function, emphysema, and gas trapping may not have followed a simple linear trend. This finding challenged previous assumptions and emphasized the complexity of the interaction between lipid metabolism and respiratory health. As far as our knowledge extends, this study is the initial comprehensive analysis exploring the correlation between HDL levels and spirometry, as well as CT imaging, in COPD patients.

Our research unveiled relationships between HDL levels and various spirometry and CT imaging parameters, including post-bronchodilator FEV<sub>1</sub>, predicted FEV<sub>1</sub>%, FEV<sub>1</sub>/FVC, as well as LAA<sub>-950</sub> and LAA<sub>-856</sub>. This correlation implied that changes in HDL levels may have had a graded impact on the severity of airflow obstruction. Significantly, the observed associations remained robust even after accounting for established COPD risk factors such as age, sex, BMI, smoking, and other potentially related factors through adjustments. This independence enhanced the validity of our study results, suggesting that HDL may have influenced pulmonary function through mechanisms distinct from those associated with traditional risk factors.

Past investigations into the interplay between HDL and pulmonary function yielded varied and inconclusive outcomes.<sup>21–23,32,33</sup> In a study focused on metabolic syndrome, subjects with low HDL demonstrated enhanced

pulmonary function compared to those with high HDL levels.<sup>32</sup> This included notable metrics such as FEV<sub>1</sub> and FEV<sub>1</sub>/FVC. Park et al observed in male adolescents that each 1.0 mg/dL increase in HDL cholesterol was associated with a 10 mL decrease in both FVC (p=0.013) and FEV<sub>1</sub> (p=0.013). Furthermore, percent predicted values of FVC (p=0.036) and FEV<sub>1</sub> (p=0.017) showed inverse relationships with HDL cholesterol levels.<sup>22</sup> Despite being a small-sample cross-sectional study, it provided insights into the relationship between high-density lipoprotein cholesterol and lung function in the general population.<sup>23</sup> Notably, even after meticulous adjustments for the confounding influence of obesity, HDL cholesterol retained its predictive prowess for the FEV<sub>1</sub>/FVC ratio. Another analysis with a 7-year follow-up indicated an accelerated decline in FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratio with escalating levels of HDL cholesterol.<sup>25</sup> While our study concurred with these outcomes, it delved deeper to uncover a nuanced non-linear relationship between HDL and pulmonary function, with the negative correlation attenuating beyond a certain threshold of HDL levels. However, dissenting perspectives emerged from alternative inquiries. Cirillo et al posited a putative role for HDL cholesterol in mitigating inflammatory tissue damage and closely aligning with improvements in pulmonary function.<sup>34</sup> In analyzing public data from three nationwide surveys, Lee et al discovered a linear positive correlation between HDL cholesterol and lung function. Specifically, for each 1 SD increase in serum HDL levels, FVC and FEV<sub>1</sub> increased by 0.5% to 1.7% (p<0.0001).<sup>21</sup> The incongruity between our study and these antecedent findings could be attributed to divergent study cohorts. The former encompassed a general demographic aged between 20 and 40, whereas our focus rested exclusively on patients afflicted with COPD. Furthermore, Huang et al had identified the lymphocyte-to-high-density lipoprotein ratio (LHR) as a novel biomarker for assessing the severity of airflow limitation in COPD.<sup>35</sup> Lower levels of LHR were independently associated with poorer lung function, but these findings stemmed from small-sample, retrospective, single-center cross-sectional studies.<sup>35</sup>

Previous studies have indicated significant age-related differences in HDL levels between younger and older populations.<sup>36,37</sup> Furthermore, considering other lipoproteins in the lipid profile became crucial when elucidating the intricate relationship between pulmonary function and HDL, given the correlations established in previous research.<sup>17,18</sup>

In the realm of CT imaging, we observed a close correlation between HDL and pulmonary emphysema and gas trapping in COPD patients. There was relatively limited research on this aspect in the past, findings from the MESA Lung Study discovered that a rise of 10 mg/dL in HDL cholesterol resulted in a 0.4% increase in the risk of emphysema.<sup>19,38</sup> This aligned with our study results. We noted that an elevation in HDL was linked to greater emphysema severity and more severe gas trapping before the HDL levels fell below the cutoff value. The reason for this could be clarified by the notable influence of the oxidation of proteins related to HDL on their capacity to withstand inflammation and facilitate the movement of cholesterol.<sup>39,40</sup> Even dysfunctional HDL may have a pro-inflammatory effect, leading to the exacerbation of emphysema. Studies at the genetic and molecular levels by Burkart et al suggested that alterations in expression of the apolipoprotein M gene, associated with HDL-C, could influence the quality and functionality of HDL-C, consequently leading to emphysema.<sup>19</sup> Notably, the expression of APOM-related genes was found in two ethnicities (African Americans and European Americans), and whether similar conclusions existed in other ethnic groups required further confirmation in future studies.

Historical research had underscored the pivotal role played by HDL in regulating lipid homeostasis—a process of paramount importance for the normal functioning of pulmonary cells.<sup>41,42</sup> Beyond its role in lipid transport, HDL was also recognized for its regulatory impact on inflammatory processes, a function dictated by its composition, involvement in maintaining cellular cholesterol composition, and participation in specific signaling pathways.<sup>43–45</sup> HDL was implicated in both the inflammatory activation of alveolar macrophages and the induction of neutrophil proliferation, significantly contributing to the onset of pulmonary inflammation and emphysema. Furthermore, recent investigations shed light on the ability of elevated HDL levels to modulate the functionality of type II lung cells and alter the surface characteristics of pulmonary surfactant, which is a complex blend of lipids and proteins.<sup>42</sup> This modulation prevented the collapse of alveolar structures during expiration, thereby facilitating the respiratory process.<sup>46</sup> The observed decline in lung function appeared to be associated with modifications in the surface tension of HDL cholesterol and an increase in the rigidity of the polar regions of surfactant. In the intricate regulation of type II alveolar cell processes by HDL through the p38MAPK signaling pathway, the ATP-binding cassette transporter family (specifically, ABCA1 and ABCA7) played a pivotal role.<sup>47,48</sup> These proteins were crucial in saturating HDL and shielding cells from the detrimental effects of sterol overload.<sup>49,50</sup> Importantly, the number of key proteins and factors involved in these inflammation-regulating processes was inherently limited. Moreover, HDL reached a steady state after reaching a certain threshold, elucidating,

in part, the apparent lack of correlation between HDL levels beyond the inflection point and changes in lung function, emphysema, and small airway lesions. This phenomenon underscored the intricacies of the interplay between HDL and pulmonary dynamics, paving the way for a more nuanced understanding in the context of scientific inquiry.

This study demonstrated several notable strengths. Firstly, the inclusion of COPD patients through a community-based random screening process ensured a robust statistical foundation. Additionally, the analysis incorporated adjustments for multiple confounding factors, thereby enhancing the methodological rigor of the study. Thirdly, in exploring the role of HDL, the evaluation extended beyond the sole consideration of lung function, encompassing a comprehensive assessment of imaging changes in the pulmonary structures of COPD patients. This comprehensive approach contributed to a more holistic comprehension of the implications of HDL in the context of COPD. However, the study also presented certain limitations. Firstly, its cross-sectional design constrained our ability to establish a causal link between HDL and the decline in lung function or the occurrence of emphysema. Longitudinal cohort studies were essential to validate the genuine causal impact of HDL on the progression of lung function decline and its potential influence on pulmonary diseases. Secondly, although our study adjusted for numerous confounding factors, it might not have comprehensively addressed all potential confounders, such as the past use of lipid-lowering medications and dietary factors. These unaccounted variables could potentially have affected the outcomes of our research.

Our study had revealed a significant non-linear correlation between HDL levels and COPD. Specifically, when HDL levels were below 66 mg/dL, increases in HDL were significantly associated with impaired lung function, exacerbated gas trapping, and increased severity of emphysema. Dyslipidemia was a common comorbidity in COPD, and these findings contribute to understanding the role of lipid profiles in COPD patients. Given the substantial global impact of COPD on health, a deeper understanding of the relationship between HDL and COPD holds important public health significance and may offer new interventions to improve patient prognosis.

## Conclusion

In COPD patients, we observed a non-linear correlation between HDL levels and both lung function and CT imaging. Below 66 mg/dL, increases in HDL were notably linked to impaired lung function, exacerbated gas trapping, and increased severity of emphysema. Further investigation is warranted to elucidate the potential role of HDL in the development of COPD.

## Abbreviations

ATS, American Thoracic Society; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ERS, European Respiratory Society; FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; HDL, high-density lipoprotein; LAA<sub>-950</sub>, low-attenuation area of the lung with attenuation values below -950 Hounsfield units; LAA<sub>-856</sub>, low-attenuation area of the lung with attenuation values below -856 Hounsfield units; LDL, low density lipoprotein-cholesterol; Ln, natural log; TC, total cholesterol; TG, triglyceride.

## Data Sharing Statement

The information provided in this research can be obtained by contacting the corresponding authors overseeing the research (Pixin Ran, MD, PhD; Yumin Zhou, MD, PhD).

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## 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 report no conflicts of interest in this work.

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