OPEN

Association Between Pulmonary Function and Nonalcoholic Fatty Liver Disease in the NHANES III Study

Tao-Chun Peng, MD, Tung-Wei Kao, MD, Li-Wei Wu, MD, Ying-Jen Chen, MD, Yaw-Wen Chang, MD, Chung-Ching Wang, MD, Yu-Tzu Tsao, MD, and Wei-Liang Chen, MD

Abstract: Emerging evidence indicates that nonalcoholic fatty liver disease (NAFLD) is associated with a wide variety of extrahepatic complications. However, the potential association between impaired pulmonary function and NAFLD has been less investigated.

This study examined the relationship between pulmonary function and hepatic steatosis in 9976 adults participating in a cross-sectional analysis of the Third National Health and Nutrition Examination Survey (NHANES III). NAFLD was defined as hepatic steatosis presented on ultrasound examinations in the absence of other known liver diseases. The associations between predicted forced expiratory volume in 1 second (FEV_1)% or predicted forced vital capacity (FVC)% and NAFLD were examined using multivariable linear regression while controlling for confounders. The association between obstructive or restrictive spirometry patterns and NAFLD was also evaluated using multivariable logistic regression analysis.

After adjustment for multiple covariates, predicted FEV_1% and FVC% were significantly and inversely associated with the degree of hepatic steatosis (P for trend <0.001 for both). The restrictive lung pattern was significantly related to participants with moderate and severe hepatic steatosis as compared with those without steatosis (OR 1.65, 95% CI 1.14–2.39 and OR 1.85, 95% CI 1.13–2.82), whereas the obstructive lung pattern was not associated with the presence of hepatic steatosis.

Individuals with a greater degree of hepatic steatosis were at greater risk for poor pulmonary function, especially in restrictive pattern. These novel findings demonstrate that impaired pulmonary function is also an extrahepatic complication of NAFLD.

(*Medicine* 94(21):e907)

Abbreviations: CRP = C-reactive protein, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HDL = high-density lipoprotein, NAFLD = nonalcoholic fatty liver disease, NHANES III = Third National Health and Nutrition Examination Survey.

Editor: Jen Jung Pan.
Received: February 24, 2015; revised: April 6, 2015; accepted: April 20, 2015.
From the Division of Family Medicine (T-CP, T-WK, L-WW, Y-WC, C-CW, W-LC); Division of Geriatric Medicine, Department of Family and Community Medicine, Tri-Service General Hospital; School of Medicine, National Defense Medical Center, Taipei (T-WK, L-WW, Y-WC, W-LC); Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei (Y-JC, W-LC); and Department of Medicine, Taoyuan General Hospital, Taoyuan City, Taoyuan County, Taiwan (Y-TT).
Correspondence: Wei-Liang Chen, Division of Geriatric Medicine, Department of Family and Community Medicine, Tri-Service General Hospital, National Defense Medical Center, Number 325, Section 2, Chang-gong Rd, Nei-Hu District, 114 Taipei, Taiwan (e-mail: weiliang0508@gmail.com).
The authors have no funding and conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000907

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is characterized by the presence of hepatic steatosis without secondary causes for hepatic fat accumulation.[1] NAFLD is the most common liver condition affecting 19% of the US population.[2] The prevalence of NAFLD has increased overtime. Increasing evidence suggests that NAFLD is associated with numerous extrahepatic complications such as metabolic syndrome,[3,4] type 2 diabetes,[5] cardiovascular diseases,[6] chronic kidney disease,[7] and sarcopenia.[8] However, the potential association between NAFLD and impaired pulmonary function has been less investigated. Most previous studies focused on the fact that pulmonary dysfunction may be observed with hepatopulmonary syndrome, which is a distinctive disorder in cirrhotic patients characterized by impaired oxygenation and diffusion capacity. Although NAFLD may potentially progress to cirrhosis, the pathophysiology and clinical manifestations differ between these conditions. In addition, over recent years, a number of studies reported an association between decreased lung function and metabolic syndrome.[9,10] Despite the fact that the mechanisms regulating these associations remain incompletely understood, the role of insulin resistance was a widely accepted hypothesis.[11,12] However, evidence of the association between NAFLD, as an important cause or effect of insulin resistance, and decreased lung function rarely reported in the literature. To our knowledge, no nationally representative US studies on the relationship between NAFLD and lung function are available. Thus, we investigated the association between NAFLD and lung function using results from the Third National Health and Nutrition Examination Survey (NHANES III).

METHODS

Study Population

Data were obtained from the NHANES III, which was conducted in the United States between 1988 and 1994, using a stratified, multistage, clustered probability sample design, by the National Center for Health Statistics of the Centers for Disease Control and Prevention.[13] A total of 14,797 participants aged 20 to 74 years received a hepatic steatosis assessment. Of this group, participants who were pregnant, positive for serum hepatitis B surface antigen, or positive for serum hepatitis C antibody were excluded from the analyses. In addition, patients with excessive alcohol consumption (average >21 drinks/week for men and >14 drinks/week for women), iron overload (transferrin saturation >50%), a self-reported history of asthma, a self-reported history of bronchitis, a self-reported history of emphysema, or missing hepatic steatosis data and lung function data were excluded from the analyses. In total, 9976 patients

were included in this analysis (Figure 1). The survey was approved by the National Center for Health Statistics Institutional Review Board, and all participants provided written informed consent prior to the study.

Nonalcoholic Fatty Liver Disease

NAFLD was assessed by ultrasound. Using recorded Gallbladder Ultrasound Examination videotapes previously obtained as a part of the NHANES III (1988–1994), the Hepatic Steatosis Ultrasound Examination (HSUE) was implemented to grade the presence of fat within the hepatic parenchyma between 2009 and 2010.[13] Hepatic steatosis was evaluated using the following parameters: liver to kidney contrast, parenchymal brightness, bright vessel walls, deep beam attenuation, and gallbladder wall definition. With regard to the interpretation of ultrasound images, readers were trained, observed, and approved by an experienced radiologist. The degree of hepatic steatosis was classified as normal, mild, moderate, or severe.

Pulmonary Function Data

Spirometry was performed using procedures based on the 1987 American Thoracic Society recommendations. Each participant performed at least 5 forced vital capacity (FVC) maneuvers to meet the American Thoracic Society acceptability and reproducibility criteria. Forced expiratory volume in 1 second (FEV_1) was measured using a dry rolling-seal spirometer. FEV_1 and FVC measurements are expressed in liters. We also used prediction equations to calculate predicted FEV_1 and FVC values. Predicted FEV_1 and FVC values differ according to the features (age, gender, height, and race/ethnicity) of different populations. For the United States population, predicted FEV_1 and FVC values were calculated using equations derived by Hankinson et al.[14] Furthermore, participants with an $FEV_1/FVC < 70\%$ were defined as having obstructive pulmonary function. Participants with an FEV_1/FVC ratio $\geq 70\%$ and $FVC < 80\%$ of the predicted value were defined as having restrictive pulmonary function.

Assessment of Covariates

The participants were interviewed to collect information on age, gender, race-ethnicity (including non-Hispanic white, non-Hispanic black, and Mexican-American), and physical activity. Hypertension was defined as doctor-diagnosed hypertension and/or the use of antihypertensive medication. Diabetes mellitus was defined as doctor-diagnosed diabetes and/or the use of hypoglycemic agent or insulin and/or fasting blood sugar $\geq$126 mg/dL and/or HbA1c $\geq$6.5%. Smoke status was categorized as ''never smoker'' in subjects who self-reported that they had not smoked at least 100+ cigarettes during their lifetime, ''ex-smoker'' in subjects who self-reported smoked at least 100+ cigarettes during their lifetime and did not smoke currently, and ''current smoker'' in subjects who self-reported smoked at least 100+ cigarettes in life and smoke currently. Alcohol intake was determined through self-reports and was categorized as ''never'' and ''low-moderate''. The ''physically active'' parameter was classified as ideal, intermediate, or poor. Waist circumference was measured from the right side of the body at the iliac crest. The C-reactive protein (CRP) level was measured by latex-enhanced nephelometry. The detection limit of CRP was 0.3 mg/dL, and a level of 0.21 mg/dL was assigned to those subjects with CRP concentrations below the detection limit. Serum high-density lipoprotein (HDL) cholesterol, serum cholesterol, and triglycerides levels were measured by chemical analysis (Hitachi 737 Analyzer; Boehringer-Mannheim Diagnostics, Indianapolis, IN). The serum uric acid level was measured by oxidization with the specific enzyme uricase to form allantoin and H_2O_2 (Hitachi 737 Analyzer; Boehringer-Mannheim Diagnostics, Indianapolis, IN). Details regarding the quality control procedures have been published elsewhere.[15]

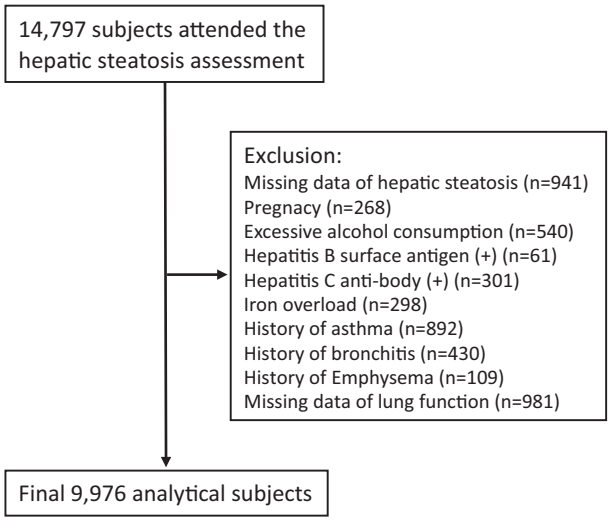

FIGURE 1. Flowchart for subjects selection.

Statistical Analysis

We classified participants according to the degree of hepatic steatosis. Baseline characteristics of participants were compared using chi-squared tests for categorical variables, ANOVA tests for continuous variables with normality, and Kruskal-Wallis tests for continuous variables without normality. The relationships between hepatic steatosis severity and lung function (predicted FEV_1 and FVC values) were assessed using multivariable linear regression. Models were adjusted for pertinent variables as follows: model 1 was adjusted for age, gender, and race/ethnicity; model 2 was additionally adjusted for waist circumference, serum cholesterol, serum HDL cholesterol, serum triglycerides, serum CRP, and serum uric acid; and model 3 was also adjusted for physical activity, alcohol consumption, smoking status, diabetes, and hypertension. Before the analysis, the continuous variables were checked for a linear relationship with the response variable. Variables that were nonlinearly related to the response variable (CRP and triglyceride) were natural log-transformed before analysis. Multivariable logistic regression analysis was also performed to identify the association between hepatic steatosis severity and spirometry patterns, which were defined as obstructive ($FEV_1/FVC < 70\%$) or restrictive ($FEV_1/FVC \geq 70\%$ and $FVC < 80\%$). Tests for trends were used to assess the relationship between the degree of hepatic steatosis and the lung function. A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (Version 18.0 for Windows, SPSS, Inc., Chicago, IL), and the ''Complex Samples'' procedure was performed to account for the study design weights, clusters, and strata.

RESULTS

Baseline Characteristics and Demographic Data

The demographic and clinical characteristics of the 9976 participants are described in Table 1. Compared with the

TABLE 1. Baseline Characteristics and Demographic Data

	Hepatic Steatosis Status				
	Normal (n=6340)	**Mild (n = 1349)**	**Moderate (n = 1541)**	**Severe (n = 746)**	***P***
Age, years	41.05 ± 0.46	42.27 ± 0.67	46.66 ± 0.57	48.29 ± 1.04	<0.001
Male, %	46.8 ± 0.7	47.6 ± 2.1	51.9 ± 2.1	59.8 ± 2.5	<0.001
Race-ethnicity, %					<0.001
Non-Hispanic white	82.1 ± 1.0	82.3 ± 1.3	81.7 ± 1.3	81.4 ± 2.0	
Non-Hispanic black	12.5 ± 0.9	11.4 ± 1.0	9.7 ± 0.9	10.0 ± 1.4	
Mexican American	5.4 ± 0.5	6.3 ± 0.8	8.7 ± 0.9	8.6 ± 1.3	
Waist, cm	88.69 ± 0.28	90.90 ± 0.83	102.10 ± 0.91	104.56 ± 1.00	<0.001
Serum cholesterol, mg/dL	201.07 ± 0.95	202.87 ± 1.57	212.95 ± 2.16	215.44 ± 2.44	<0.001
Serum HDL cholesterol, mg/dL	51.90 ± 0.40	50.12 ± 0.84	44.70 ± 0.64	43.56 ± 1.18	<0.001
Serum triglycerides, mg/dL	100 (72–145)	119 (81–175.25)	152.5 (100–231)	168 (109–257)	<0.001
Serum C-reactive protein, mg/dL	0.21 (0.21–0.33)	0.21 (0.21–0.40)	0.21 (0.21–0.55)	0.21 (0.21–0.60)	<0.001
Serum uric acid, mg/dL	5.08 ± 0.03	5.16 ± 0.07	5.91 ± 0.06	6.19 ± 0.08	<0.001
Smoking status, %					<0.001
Never	47.4 ± 1.3	49.2 ± 2.4	44.2 ± 1.5	41.7 ± 3.0	
Ex-smoker	23.5 ± 1.0	25.1 ± 2.1	35.3 ± 1.8	33.3 ± 3.0	
Current	29.0 ± 1.1	25.4 ± 2.1	20.5 ± 1.5	25.0 ± 2.8	
Alcohol consumption, %					<0.001
Never	10.4 ± 0.7	11.8 ± 1.4	12.4 ± 1.2	12.4 ± 1.7	
Low-moderate	89.6 ± 0.7	88.2 ± 1.4	87.6 ± 1.2	87.6 ± 1.7	
Diabetes, %	3.8 ± 0.4	6.9 ± 1.2	16.0 ± 1.2	20.7 ± 2.0	<0.001
Hypertension, %	17.3 ± 0.8	20.6 ± 2.1	33.8 ± 2.5	36.4 ± 3.5	<0.001
Physically active, %					0.001
Ideal	32.5 ± 1.2	33.7 ± 2.4	25.0 ± 2.3	29.7 ± 3.7	
Intermediate	57.7 ± 1.0	52.7 ± 2.5	59.6 ± 2.6	56.2 ± 3.2	
Poor	9.8 ± 0.9	13.5 ± 1.6	15.4 ± 1.5	14.1 ± 1.9	
Predicted FEV_1, %	97.81 ± 0.39	96.44 ± 0.69	93.71 ± 0.65	90.73 ± 0.86	<0.001
Predicted FVC, %	99.83 ± 0.34	98.08 ± 0.65	94.85 ± 0.57	92.06 ± 0.75	<0.001
FEV_1, mL	3369.08 ± 28.79	3265.80 ± 36.26	3155.85 ± 33.86	3075.42 ± 63.07	<0.001
FVC, mL	4247.59 ± 31.98	4117.05 ± 47.95	4015.21 ± 42.28	3945.74 ± 73.61	<0.001
Obstructive pattern, %	10.4 ± 0.5	12.3 ± 1.2	12.7 ± 1.5	13.6 ± 1.9	0.10
Restrictive pattern, %	5.1 ± 0.4	7.3 ± 1.6	12.7 ± 1.5	16.9 ± 2.6	<0.001

Data are presented as the mean ± standard error, median (inter-quartile range), or percentage ± standard error.
FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HDL = high-density lipoprotein.
* *P* values represent comparisons among the 4 groups using a chi-squared, ANOVA, or Kruskal-Wallis test according to the type of variable.

participants who lacked hepatic steatosis, the patients with mild to severe hepatic steatosis were more likely to be older, male, Mexican American, and physically active. In addition, these patients were more likely to have a greater waist circumference; higher levels of serum cholesterol, serum triglycerides, CRP, and serum uric acid; restrictive pulmonary function; hypertension; diabetes; and reduced serum HDL cholesterol. The predicted FEV_1% and FVC% values gradually decreased as the degrees of hepatic steatosis increased ($P < 0.001$, both).

FEV_1, FVC, and NAFLD

The results from individual comparisons of predicted FEV_1% and FVC% based on the degree of hepatic steatosis are presented in Table 2. The variables were stepwise adjusted in model 3. In the unadjusted model, the β coefficients of the predicted FEV_1% for individuals with mild, moderate, or severe hepatic steatosis were −0.014, −0.041, and −0.071, respectively (*P* for trend <0.001), and the β coefficients of the predicted FVC% for those with mild, moderate, or severe hepatic steatosis were −0.017, −0.050, and −0.078, respectively (*P* for trend <0.001). These significant associations persisted even after adjusting for potential confounding factors in models 1, 2, and 3.

Spirometry Patterns and NAFLD

The results regarding the association between the severity of hepatic steatosis and the obstructive or restrictive spirometry patterns are presented in Table 3. Multiple logistic regression analysis with adjusted model 3 was performed using the degree of hepatic steatosis as an independent variable. The restrictive pattern was a dependent factor associated with moderate and severe hepatic steatosis (OR 1.65, 95% CI 1.14–2.39 and OR 1.85, 95% CI 1.13–2.82, respectively), but not with mild hepatic steatosis (adjusted OR 1.28, 95% CI 0.77–2.13). The obstructive pattern was not significantly associated with mild, moderate, or severe hepatic steatosis (OR 1.15, 95% CI 0.89–1.46; OR 0.95, 95% CI 0.71–1.26; and OR 0.91, 95% CI 0.56–1.47, respectively).

DISCUSSION

Our study revealed that the predicted FEV_1% and FVC% substantially decreased as hepatic steatosis progressed. Notably, an increased risk of a restrictive pulmonary pattern, but not an obstructive pulmonary pattern, was also noted in the moderate and severe hepatic steatosis group. No clear definition is available regarding the grade of hepatic steatosis that can be

TABLE 2. Regression Coefficients (95% CI) According to the Hepatic Steatosis Status for the Predicted FEV_1% and FVC%

	Hepatic Steatosis Status							
	Normal	Mild	*P*	Moderate	*P*	Severe	*P*	*P* for trend
Predicted FEV_1%								
Unadjusted	Reference	−0.014 (−0.027, 0.000)	0.048	−0.041 (−0.053, −0.029)	<0.001	−0.071 (−0.091, −0.051)	<0.001	<0.001
Model 1	Reference	−0.012 (−0.025, 0.002)	0.081	−0.033 (−0.045, −0.020)	<0.001	−0.060 (−0.080, −0.039)	<0.001	<0.001
Model 2	Reference	−0.008 (−0.020, 0.004)	0.187	−0.012 (−0.026, 0.001)	0.070	−0.037 (−0.056, −0.017)	<0.001	0.001
Model 3	Reference	−0.009 (−0.022, 0.004)	0.154	−0.013 (−0.027, 0.000)	0.055	−0.033 (−0.052, −0.013)	0.001	0.002
Predicted FVC%								
Unadjusted	Reference	−0.017 (−0.030, −0.004)	0.010	−0.050 (−0.061, −0.038)	<0.001	−0.078 (−0.094, −0.061)	<0.001	<0.001
Model 1	Reference	−0.016 (−0.029, −0.003)	0.015	−0.045 (−0.056, −0.033)	<0.001	−0.071 (−0.088, −0.054)	<0.001	<0.001
Model 2	Reference	−0.014 (−0.026, −0.002)	0.027	−0.027 (−0.040, −0.015)	<0.001	−0.051 (−0.066, −0.035)	<0.001	<0.001
Model 3	Reference	−0.015 (−0.027, −0.002)	0.021	−0.026 (−0.039, −0.013)	<0.001	−0.044 (−0.060, −0.029)	<0.001	<0.001

FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, CI = confidence interval.

Model 1: adjusted for age, gender, and race-ethnicity; Model 2: adjusted for age, gender, race-ethnicity, waist circumference, serum cholesterol, serum HDL cholesterol, serum triglycerides, serum C-reactive protein, and serum uric acid; Model 3: adjusted for age, gender, race-ethnicity, waist circumference, serum cholesterol, serum HDL cholesterol, serum triglycerides, serum C-reactive protein, serum uric acid, physical activity, alcohol consumption, smoking status, diabetes, and hypertension.

defined as NAFLD, although previous studies used moderate and severe hepatic steatosis as the definition of NAFLD.[2] In our study, the association between hepatic steatosis and reduced lung function was also clearly evident in the cases of moderate or severe hepatic steatosis.

Spirometry parameters such as FEV_1 and FVC were identified as indicators of mortality.[16,17] The link between poor pulmonary function and mortality has often been attributed to other comorbidities, such as cardiovascular disease and diabetes.[18,19] Our study may provide additional data linking reduced pulmonary function to the adverse outcomes attributed to NAFLD.

In contrast to hepatopulmonary syndrome, which is distinguished by intrapulmonary vascular dilatations, as well as increased pulmonary dilated vessels, several mechanisms potentially explain the association between NAFLD and pulmonary function impairment. One possible explanation for this association involves abdominal obesity. Previous studies demonstrated that waist circumference and visceral fat were positively associated with NAFLD severity.[20,21] As NAFLD worsens, the visceral adiposity gradually increases, which may mechanically decrease chest wall compliance. The inverse association between visceral adiposity and FEV_1 and FVC was demonstrated previously.[22,23] In addition, the restrictive spirometry pattern was significantly correlated with NAFLD, whereas the obstructive pattern was not correlated in our study. This result provides further support for the explanation that abdominal obesity may limit lung expansion due to increased thoracic pressure, thereby impeding the descent of the diaphragm and causing restriction.

Recently, Hong et al[8] demonstrated that decreased muscle mass was related to increased NAFLD risk. Reduced lean body

TABLE 3. Odds Ratio (95% CI) for Restrictive Impairment and Obstructive Impairment According to Hepatic Steatosis Status

	Hepatic Steatosis Status							
	Normal	Mild	*P*	Moderate	*P*	Severe	*P*	*P* for Trend
Restrictive								
Unadjusted	1	1.46 (0.90–2.38)	0.13	2.69 (1.95–3.70)	<0.01	3.76 (2.62–5.40)	<0.01	<0.01
Model 1	1	1.42 (0.87–2.34)	0.16	2.26 (1.63–3.14)	<0.01	3.03 (2.09–4.41)	<0.01	<0.01
Model 2	1	1.26 (0.76–2.10)	0.36	1.66 (1.20–2.31)	<0.01	2.01 (1.33–3.04)	<0.01	<0.01
Model 3	1	1.28 (0.77, 2.13)	0.34	1.65 (1.14, 2.39)	0.01	1.85 (1.13–2.82)	0.01	<0.01
Obstructive								
Unadjusted	1	1.21 (0.96–1.52)	0.11	1.26 (0.95–1.67)	0.10	1.37 (0.95–1.96)	0.09	0.02
Model 1	1	1.12 (0.88–1.43)	0.35	0.86 (0.62–1.18)	0.33	0.83 (0.56–1.23)	0.35	0.26
Model 2	1	1.10 (0.86–1.42)	0.45	0.89 (0.66–1.19)	0.41	0.88 (0.56–1.38)	0.57	0.44
Model 3	1	1.15 (0.89–1.46)	0.30	0.95 (0.71–1.26)	0.70	0.91 (0.56–1.47)	0.69	0.69

CI = confidence interval.

Model 1: adjusted for age, gender, and race-ethnicity; Model 2: adjusted for age, gender, race-ethnicity, waist circumference, serum cholesterol, serum HDL cholesterol, serum triglycerides, serum C-reactive protein, and serum uric acid; Model 3: adjusted for age, gender, race-ethnicity, waist circumference, serum cholesterol, serum HDL cholesterol, serum triglycerides, serum C-reactive protein, serum uric acid, physical activity, alcohol consumption, smoking status, diabetes, and hypertension.

mass also leads to a decline in pulmonary function.[24] The restrictive respiratory spirometry pattern, which may be caused by respiratory muscle weakness, was noted in our study. This result may also imply that reduced respiratory muscle mass partly contributes to the association between NAFLD and reduced pulmonary function. Furthermore, Hong et al also reported that the underlying mechanisms associated with both sarcopenia and NAFLD may involve inflammation and insulin resistance. The visceral adipose tissue may act as an important source of inflammation in NAFLD patients, because it correlated positively with circulating levels of hs-CRP, fibrinogen, interleukin-6(IL-6), tumor necrosis factor-α, and leptin.[25–27] Consistent with this observation, Mannino et al[28] demonstrated the impact of inflammation on restrictive and obstructive lung disease, thereby providing a potential mechanism for the association between declined pulmonary function and NAFLD.

No consensus appears to exist regarding whether NAFLD is an initiating event, consequence of insulin resistance, or concurrent event. Nevertheless, insulin resistance plays a key role in NAFLD.[29] Previous studies had examined the relationship between insulin resistance and impaired pulmonary function,[11,12,19,30] but the exact causality is not well defined. In the British Women's Heart and Health Study, FEV_1 and FVC were negatively associated with insulin resistance.[11] In a United States population study by Ford and Mannino,[30] FEV_1, FVC, predicted FEV_1%, predicted FVC%, and the restrictive lung pattern were all inversely associated with the incidence of diabetes. In contrast, insulin resistance potentially precipitates pulmonary function impairment. In the Atherosclerosis Risk in Communities Study, FEV_1, FVC, predicted FEV_1%, and predicted FVC% were decreased by fasting glucose, A1c, and diabetes duration.[19] Therefore, NAFLD, which shares an inseparable pathophysiology with insulin resistance, is potentially related to impaired pulmonary function, as demonstrated in our study.

A previous study by Jung et al[31] demonstrated that NAFLD was associated with reduced pulmonary function in Korea. However, discrepancies in the prevalence of NAFLD, the degree of insulin resistance, and the distribution of adiposity were reported across genders and across racial and ethnic groups,[32] and these factors may interfere with the association between NAFLD and lung function. In addition, only male participants were included in the analysis, and important confounders, such as alcohol consumption, physical activity, and CRP, were not analyzed. Therefore, the Korean result may not be generalized to the United States adult population.

Several limitations of this study should be mentioned. First, NHANES III is a cross-sectional study. Therefore, we were unable to establish a causal relationship between pulmonary function impairment and NAFLD. Second, a restrictive pulmonary pattern was defined as a normal FEV_1/FVC ratio and a low FVC, rather than being determined from a confirmed measurement, such as the total lung capacity and residual volume. Third, no ideal diagnostic tool is available to distinguish nonalcoholic steatohepatitis from hepatic steatosis except for a liver biopsy. Therefore, we only evaluated the relationship between the degree of hepatic steatosis and lung function. Further studies on the association between lung function and nonalcoholic steatohepatitis are warranted.

In conclusion, individuals with a greater degree of hepatic steatosis exhibit increased risk of poor pulmonary function, particularly a restrictive pattern. These novel findings demonstrate that impaired pulmonary function is an extrahepatic complications of NAFLD. Further studies to elucidate the underlying pathophysiological pathways are necessary.

REFERENCES

1. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med.* 2002;346:1221–1231.
2. Lazo M, Hernaez R, Eberhardt MS, et al. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Epidemiol.* 2013;178:38–45.
3. Kotronen A, Yki-Jarvinen H. Fatty liver: a novel component of the metabolic syndrome. *Arterioscler Thromb Vasc Biol.* 2008;28:27–38.
4. Smits MM, Ioannou GN, Boyko EJ, et al. Non-alcoholic fatty liver disease as an independent manifestation of the metabolic syndrome: Results of a US national survey in three ethnic groups. *J Gastroenterol Hepatol.* 2013;28:664–670.
5. Musso G, Gambino R, Cassader M, et al. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med.* 2011;43:617–649.
6. Stepanova M, Younossi ZM. Independent association between nonalcoholic fatty liver disease and cardiovascular disease in the US population. *Clin Gastroenterol Hepatol.* 2012;10:646–650.
7. Armstrong MJ, Adams LA, Canbay A, et al. Extrahepatic complications of nonalcoholic fatty liver disease. *Hepatology.* 2014;59:1174–1197.
8. Hong HC, Hwang SY, Choi HY, et al. Relationship between sarcopenia and nonalcoholic fatty liver disease: the Korean Sarcopenic Obesity Study. *Hepatology.* 2014;59:1772–1778.
9. Leone N, Courbon D, Thomas F, et al. Lung function impairment and metabolic syndrome: the critical role of abdominal obesity. *Am J Respir Crit Care Med.* 2009;179:509–516.
10. Naveed B, Weiden MD, Kwon S, et al. Metabolic syndrome biomarkers predict lung function impairment: a nested case-control study. *Am J Respir Crit Care Med.* 2012;185:392–399.
11. Lawlor D, Ebrahim S, Smith GD. Associations of measures of lung function with insulin resistance and type 2 diabetes: findings from the British Women's Heart and Health Study. *Diabetologia.* 2004;47:195–203.
12. Yeh HC, Punjabi NM, Wang NY, et al. Vital capacity as a predictor of incident type 2 diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care.* 2005;28:1472–1479.
13. Centers for Disease Control and Prevention. Plan and operation of the third National Health and Nutrition Examination Survey, 1988–1994. National Center for Health Statistics; 1994.
14. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med.* 1999;159:179–187.
15. Centers for Disease Control and Prevention. NHANES III reference manuals and reports. National Center for Health Statistics; 1996.
16. Hole DJ, Watt GC, Davey-Smith G, et al. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ.* 1996;313:711–715discussion 715–716.
17. Burney PG, Hooper R. Forced vital capacity, airway obstruction and survival in a general population sample from the USA. *Thorax.* 2011;66:49–54.
18. Sin DD, Wu L, Man SP. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest J.* 2005;127:1952–1959.
19. Yeh HC, Punjabi NM, Wang NY, et al. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care.* 2008;31:741–746.

20. Church TS, Kuk JL, Ross R, et al. Association of cardiorespiratory fitness, body mass index, and waist circumference to nonalcoholic fatty liver disease. *Gastroenterology.* 2006;130:2023–2030.

21. Eguchi Y, Eguchi T, Mizuta T, et al. Visceral fat accumulation and insulin resistance are important factors in nonalcoholic fatty liver disease. *J Gastroenterol.* 2006;41:462–469.

22. Canoy D, Luben R, Welch A, et al. Abdominal obesity and respiratory function in men and women in the EPIC-Norfolk Study, United Kingdom. *Am J Epidemiol.* 2004;159:1140–1149.

23. Ochs-Balcom HM, Grant BJ, Muti P, et al. Pulmonary function and abdominal adiposity in the general population. *Chest.* 2006;129:853–862.

24. Rossi A, Fantin F, Di Francesco V, et al. Body composition and pulmonary function in the elderly: a 7-year longitudinal study. *Int J Obes (Lond).* 2008;32:1423–1430.

25. Fontana L, Eagon JC, Trujillo ME, et al. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes.* 2007;56:1010–1013.

26. van der Poorten D, Milner KL, Hui J, et al. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. *Hepatology.* 2008;48:449–457.

27. Targher G, Bertolini L, Scala L, et al. Non-alcoholic hepatic steatosis and its relation to increased plasma biomarkers of inflammation and endothelial dysfunction in non-diabetic men. Role of visceral adipose tissue. *Diabet Med.* 2005;22:1354–1358.

28. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation: data from the Third National Health and Nutrition Examination. *Am J Med.* 2003;114:758–762.

29. Takamura T, Misu H, Ota T, et al. Fatty liver as a consequence and cause of insulin resistance: lessons from type 2 diabetic liver. *Endocr J.* 2012;59:745–763.

30. Ford ES, Mannino DM. Prospective association between lung function and the incidence of diabetes – Findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study. *Diabetes Care.* 2004;27:2966–2970.

31. Jung DH, Shim JY, Lee HR, et al. Relationship between non-alcoholic fatty liver disease and pulmonary function. *Intern Med J.* 2012;42:541–546.

32. Pan JJ, Fallon MB. Gender and racial differences in nonalcoholic fatty liver disease. *World J Hepatol.* 2014;6:274–283.