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**PUBLISHED ABSTRACT**

# The Association of Impaired Lung Function and Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis

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## Background

Insulin resistance and ensuing systematic inflammation are central to the pathogenesis of Nonalcoholic Fatty Liver Disease (NAFLD). Increased insulin resistance causes an increase in hepatic lipogenesis and decreased lipolysis. As a consequence, the production of inflammatory cytokines and reactive oxidative species (ROS) are affected and increased, which further contributes to hepatic inflammation and progression of liver disease. Studies have shown that impaired lung function, measured by forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), is associated with diabetes, insulin resistance, and metabolic syndrome. Given similar risk factors, it was proposed that reduced lung function maybe linked to the progression of NAFLD. Recent studies have looked into this association but the results were inconclusive whether there was an association with obstructive, restrictive, or both lung patterns. The aim of this study was to conduct a meta-analysis evaluating the association between lung function and NAFLD and the possible association with obstructive, restrictive, or mixed lung patterns.

## Methods

Multiple databases (PEBMED, EMBASE and Scopus) were searched through September 2018, with the mention of NAFLD as defined by American Association of Study of Liver Diseases (AASLD) and lung function (or pulmonary function testing). 229 abstracts were identified and underwent screening, out of which 10 underwent full text review. Full texts were not available for 3 abstracts, 1 article did not provide relevant data, and 3 articles did not meet inclusion criteria upon further examination of the full text. Therefore, 3 articles were use to gather data to compare restrictive vs. obstructive pattern and predicted FEV1% and FVC%. A limited pooled meta-analysis was performed on crude data from the studies using Comprehensive Meta-Analysis (USA, NJ, Ver 3).

## Results

All 3 articles supported a relationship between decreased pulmonary function testing and NAFLD even after controlling for BMI or waist circumference, smoking status and age. These studies did not reveal a relationship with obstructive lung function. The limited meta-analysis revealed a pooled difference in means of FVC of -3.54% (95% CI: -6.75 to -0.328%) and FEV1 of -3.33% (95% CI: -5.33 to -1.33%) in the lung function of NAFLD patients when compared to non-NAFLD patients. The first longitudinal study of this relationship by Lee et al. (median follow-up 6.6 years) revealed no difference in the rate of decrease in lung function between NAFLD and non-NAFLD patients. When NAFLD patients with indeterminate to advanced fibrosis (estimated by Fibrosis-4 (FIB4) score  $\geq 1.30$  were examined separately however, there was a statistical difference in the rate of lung function decline compared to propensity matched controls (-27.4 vs -21.7 P = .001 in males, -27.9 mL/y vs -22.4 mL/y, P = .016 in females).

## Conclusions

This meta-analysis to examines the relationship between NAFLD and decreased lung function, and it supports an association with restrictive lung impairment. The mediators and pathophysiological pathways of which still remain unclear. The estimated severity of fibrosis in NAFLD patients also correlates with the rate of progression of restrictive lung function. Unfortunately adjusted data could not be pooled due to the variation in the methodology between studies and so our meta-analysis is unable to control for age, BMI and smoking status. Given the sparse data, additional studies, are warranted to determine these associations.

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