Diabetes & Metabolism 45 (2019) 536–544

Available online at ScienceDirect www.sciencedirect.com

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Original article

Association between non-alcoholic fatty liver disease and decreased lung function in adults: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 18 March 2019
Received in revised form 25 April 2019
Accepted 28 April 2019
Available online 5 May 2019

Keywords:
Lung function
Meta-analysis
NAFLD
Pulmonary fibrosis
Spirometry

ABSTRACT

Aim. – Recent observational studies assessed the association between non-alcoholic fatty liver disease (NAFLD) and lung function in adults, but the magnitude of this association remains uncertain. We estimated the magnitude of the association between NAFLD and lung function on spirometry (predicted forced expiratory volume in 1 s [FEV_1] and forced vital capacity [FVC]).
Methods. – We searched publication databases using predefined keywords to identify studies (published up to October 4, 2018), in which NAFLD was diagnosed by imaging or biochemistry (no studies with biopsy-proven NAFLD were available). Data from selected studies were extracted, and meta-analysis was performed using random-effects modelling.
Results. – Six observational studies (5 cross-sectional and 1 longitudinal) with aggregate data on 133,707 individuals (27.8% with NAFLD) of predominantly Asian ethnicity (74.6%) were included in the final analysis. There were significant differences in predicted FEV_1 (n = 5 studies; pooled weighted mean difference [WMD]: −2.43%, 95% CI: −3.28 to −1.58; I^2 = 69.7%) and predicted FVC (pooled WMD: −2.96%, 95% CI: −4.75 to −1.17; I^2 = 91.7%) between individuals with and without NAFLD. Decreased FEV_1 and FVC at baseline were also independently associated with a ∼ 15% increased risk of incident NAFLD (n = 1 study in Korean individuals). Subgroup analyses did not materially modify these findings.
Conclusions. – NAFLD is associated with significant reductions of both FEV_1 and FVC in Asian and United States adults, and such small, but significant, reductions of lung volumes at baseline may be also associated with increased NAFLD incidence in Asian individuals. Further research is needed to better elucidate the link between NAFLD and impaired lung volumes.

Introduction

Non-alcoholic fatty liver disease (NAFLD) has reached epidemic proportions and is estimated to affect up to 25% of the general adult population worldwide [1–3]. Convincing evidence indicates that NAFLD is a multisystem disease affecting multiple extrahepatic organ systems and interacting with the regulation of several metabolic/endocrine and pro-inflammatory pathways [4,5]. Indeed, the adverse effects of NAFLD extend far beyond the liver, with a large body of evidence showing that NAFLD is associated with an increased risk of developing cardiovascular disease and other extrahepatic diseases (such as type 2 diabetes, chronic kidney disease and colorectal tumours) [6–9].

Some epidemiological studies have shown that chronic respiratory diseases, and particularly chronic obstructive pulmonary disease (COPD), may be variably associated with metabolic disorders, such as obesity, diabetes and metabolic syndrome [10–12], and that

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https://doi.org/10.1016/j.diabet.2019.04.008
1262-3636/

decreased lung function may predict the development of these metabolic conditions [13,14]. A small meta-analysis of observational studies also reported a significant association between NAFLD and obstructive sleep apnoea syndrome (OSAS) [15]. Notably, recent observational studies have explored the association between NAFLD and lung function parameters (largely within the normal range values) both in community-based cohorts of adults and in large cohorts of Asian individuals participating in health check-up programs [16–21]. However, the nature and the extent to which NAFLD is associated with impaired lung function in these cohorts of predominantly healthy, middle-aged individuals remain uncertain.

Therefore, we carried out a comprehensive meta-analysis of observational studies in order to provide a quantitative estimate of the magnitude of the association between NAFLD and lung function parameters (assessed by standard spirometry) in middle-aged individuals. Clarification of the nature and magnitude of the association between NAFLD and lung function might have clinical implications for the screening and management of both patients with NAFLD and those with chronic pulmonary diseases, which are two common pathologic conditions responsible for a considerable burden of morbidity, mortality and healthcare expenditure worldwide [1,3,4,22–24].

Materials and methods

Registration of review protocol

We registered in advance the protocol for this systematic review and meta-analysis in PROSPERO (International Prospective Register of Systematic Reviews, No. CRD42018111957).

Data sources and searches

We conducted a systematic literature search in PubMed, Scopus and Web of Science databases for identifying all observational studies (published up to October 4, 2018) that examined the association between NAFLD and lung function tests on standard spirometry in adults. The search free text terms were "fatty liver" (OR "non-alcoholic fatty liver" OR "non-alcoholic steatohepatitis") AND "lung function" OR "pulmonary function" OR "lung function tests" OR "spirometry". We also searched for MeSH (Medical Subject Headings) terms. Searches were restricted to human studies. No language restrictions were applied. Additionally, we reviewed references from relevant original papers and review articles for identifying further eligible studies not covered by the original database searches. We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix A, see check list; see supplementary material associated with this article on line). Because the included studies were observational in design, we followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for the meta-analysis of these studies [25].

Study selection

Original studies were included if they met the following criteria:

- cross-sectional, case-control or longitudinal studies examining the association between NAFLD and lung function in adults;
- all studies that reported data of predicted forced expiratory volume in 1 s [FEV_1], predicted forced vital capacity [FVC] or the FEV_1/FVC ratio that were expressed (or that could be calculated) as means ± SD in individuals with and without NAFLD;
- all studies in which NAFLD was diagnosed with imaging techniques, serum liver enzyme levels or other surrogate markers of NAFLD (e.g., the NAFLD liver fat score) [26], in the absence of excessive alcohol consumption (< 30 g/day for men and < 20 g/day for women, respectively) and other competing causes of chronic liver disease. No studies using liver biopsy for diagnosing NAFLD were available for the analysis.

Study participants included in the meta-analysis were adult individuals (aged ≥ 18 years) of either sex without any restriction in terms of age, race or ethnicity.

Exclusion criteria were as follows:

- congress abstracts, theses, case reports, reviews, practice guidelines, commentaries and editorials;
- studies which did not exclude individuals with excessive alcohol consumption and other known causes of chronic liver disease;
- studies which did not specifically report any means ± SD for lung function tests;
- studies in cohorts of either patients with established COPD, OSAS and cirrhosis of any etiology or candidates for liver transplantation;
- studies performed in paediatric population.

Two investigators (AM and GT) independently reviewed the titles and abstracts of all studies identified using the previously described search criteria to identify studies meeting the inclusion criteria. Each study meeting the requirements of the first-round inclusion criteria then underwent a full-text independent review by both investigators. Disagreements about inclusion of studies between investigators were resolved by a third clinical investigator.

Data extraction and quality assessment

For all eligible studies, we extracted information on study design, study size, publication year, study country, participants' characteristics, methods used for diagnosing or staging NAFLD, outcomes of interest, and list of covariates adjusted in multivariable regression analyses. In the case of multiple publications, the most up-to-date or comprehensive information was included.

Two investigators assessed the risk of bias independently. Any discrepancies were addressed by a re-evaluation of original articles by a third author. Quality assessment was performed according to the Newcastle-Ottawa Quality Assessment Scale (NOS), which is a validated scale for non-randomized studies in meta-analyses [27]. A NOS scale adapted for the cross-sectional studies was also used [28]. Briefly, the NOS scale uses a star system to assess the quality of a study in three domains: selection, comparability, and outcome/exposure. The NOS assigns a maximum of five stars for selection (or four stars in the case of longitudinal studies), two stars for comparability, and three stars for outcome/exposure. We judged studies that received a score of at least eight stars to be at low risk of bias (i.e., thus reflecting the highest quality).

Data synthesis and analysis

The outcome measures were predicted FEV_1, predicted FVC or the FEV_1/FVC ratio that were expressed as means ± SD. When the eligible studies reported only mean values of these lung function parameters but not also SD, we calculated this value from either 95% confidence intervals (CI) or range values that were related to the differences between means in two groups by using validated formulas [27]. When studies had several adjustment models, we extracted those values reflecting the maximum extent of adjustment for potentially confounding factors.

The effect size of the meta-analysis was expressed as weighted mean difference (WMD) and 95% CI. The overall estimate of effect size was calculated using a random-effects model, as this methodology considers any differences between studies even in the absence of statistically significant heterogeneity [29].

Visual inspection of the forest plots was used to investigate the possibility of statistical heterogeneity. The statistical heterogeneity among studies was assessed by the I^2 statistic, which provides an estimate of percentage of variability across studies that is due to heterogeneity rather than chance alone [30]. The proportion of heterogeneity accounted for by between-study variability was estimated using the I^2-index and adjudicated to be significant if I^2 was $> 50\%$. A Chi^2 test P-value < 0.10 was used to determine statistical significance.

To explore the possible sources of the heterogeneity among the eligible studies and to test the robustness of the associations, we conducted subgroup analyses, stratifying the studies according to socio-demographic factors (e.g., age, sex, body mass index [BMI], smoking and preexisting diabetes), study country, methods used for diagnosing NAFLD, or whether the studies had eight or nine stars on the NOS scale (i.e., the "high-quality" studies).

The possibility of publication bias was evaluated using the funnel plot and the Egger's regression asymmetry test; the trim and fill method was also used for further examining the possibility of publication bias [27,29]. STATA® 14.2 (StataCorp, College Station, Texas) was used for all statistical analyses.

Results

Literature search and study characteristics

Fig. 1 shows the PRISMA flow diagram of the meta-analysis. After excluding duplicates, based on titles and abstracts of 265 citations and in accordance with the aforementioned exclusion criteria of the meta-analysis, we identified eight potentially relevant studies [16–21,31,32] from publication databases prior to October 4, 2018 (last date searched). After examining the full-text of these eight articles, we further excluded two studies [31,32], because of unsatisfactory inclusion criteria or unavailability of extractable data for lung volumes, as specified in the flow diagram.

Table 1 summarizes the main characteristics of the included studies. Most of these studies had a cross-sectional design [16–19], one study had both a cross-sectional and longitudinal design [20], whereas one was only longitudinal [21]. The diagnosis of NAFLD was mainly based on ultrasonography in the absence of excessive alcohol intake and other known causes of chronic liver disease

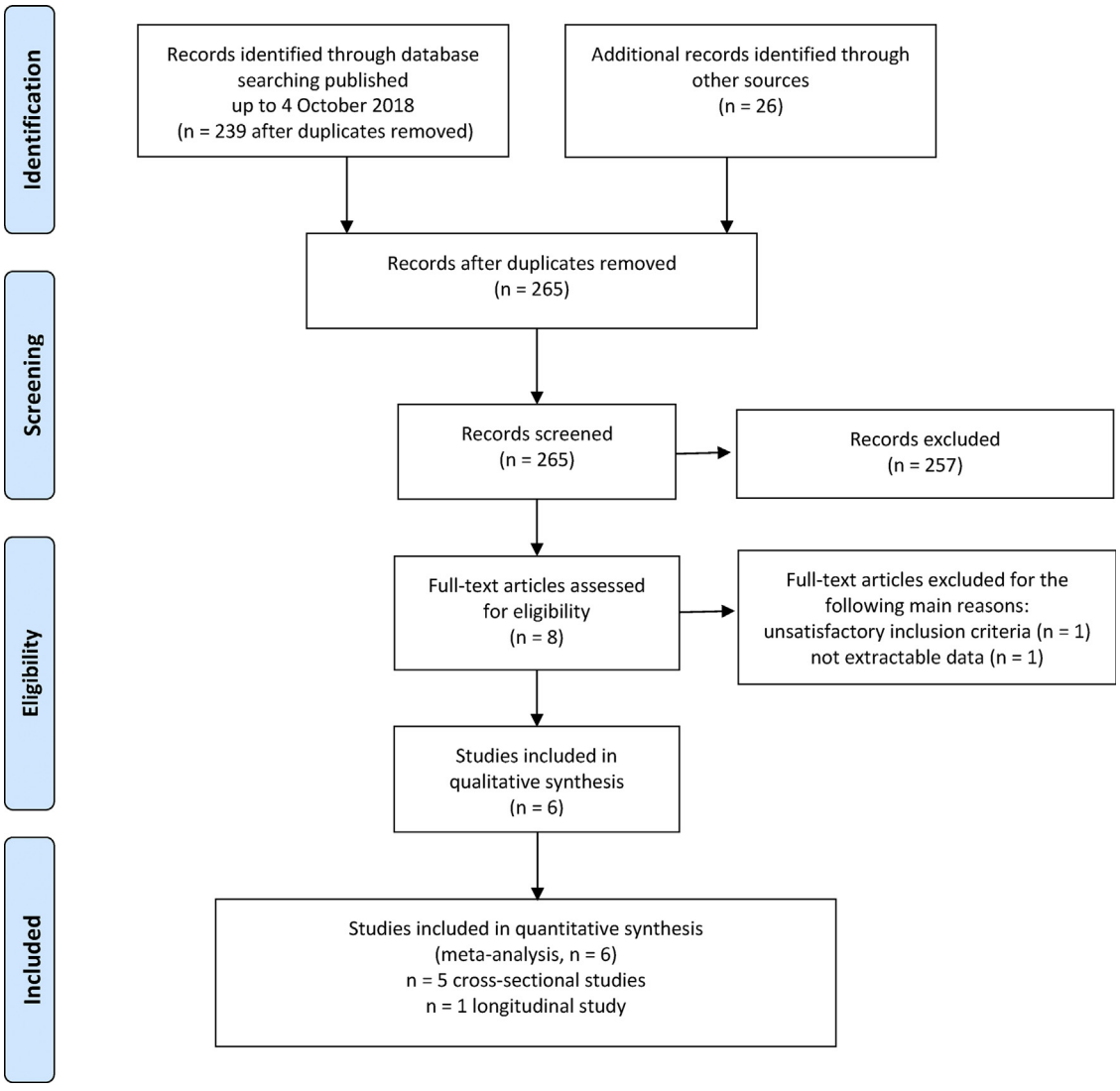

Fig. 1. The PRISMA flow diagram for search and selection processes of the meta-analysis.

Table 1
Principal observational, cross-sectional and longitudinal, studies examining the association between NAFLD and spirometric lung function parameters in adult individuals (ordered by publication year).

Author, year [Ref.]	Study design, sample size, population characteristics	Diagnosis of NAFLD, prevalence of NAFLD	Lung function tests on standard spirometry	Mean ± standard deviation of lung function tests in no-NAFLD vs. NAFLD group	Covariate adjustment(s)	Main findings
Cross-sectional studies (n = 5)						
Jung et al., 2012 [16]	Cross-sectional study: 2119 South Korean men (mean age 48.9 years; mean BMI 24.2 kg/m^2; 36.6% current smokers and 8% diabetics)	Ultrasonography; 1014 subjects (47.8%) with NAFLD	Predicted FVC and predicted FEV_1	Predicted FVC: 93.5 ± 11.2% vs. 91.6 ± 10.2%; P = 0.01 Predicted FEV_1: 100.5 ± 13.3% vs. 98.3 ± 12.1%; $P < 0.05$	Age, BMI, smoking, systolic/diastolic blood pressure, fasting glucose, plasma lipid profile, preexisting diabetes, hypertension	NAFLD was independently associated with decreased pulmonary function tests. In addition, both predicted FVC and FEV_1 progressively decreased across the ultrasonographic severity of hepatic steatosis
Peng et al., 2015 [17]	Cross-sectional population-based study (NHANES 1988–1994): 9976 United States individuals (mean age 44 years; mean waist circumference 93 cm; 48.7% men; 26.8% current smokers and 7.2% diabetics)	Ultrasonography; 3636 subjects (36.4%) with NAFLD	Predicted FVC and predicted FEV_1	Predicted FVC: 99.8 ± 27% vs. 94.9 ± 38%; $P < 0.001$ Predicted FEV_1: 97.8 ± 31% vs. 93.6.1 ± 42.7%; $P < 0.001$	Age, sex, race, waist circumference, smoking, physical activity, alcohol intake, plasma lipid profile, C-reactive protein, uric acid, preexisting diabetes, hypertension	NAFLD was independently associated with decreased pulmonary function tests, especially with a restrictive pulmonary pattern (i.e. defined as FEV1/FVC ratio > 70% and FVC < 80%), but not with an obstructive pulmonary pattern
Qin et al., 2017 [18]	Cross-sectional study: 1842 Chinese individuals (mean age 56 years; mean BMI 24.5 kg/m^2; mean waist circumference 85 cm; 31.9% men; 24.6% current smokers)	Ultrasonography; 678 subjects (36.8%) with NAFLD	Predicted FVC and predicted FEV_1	Predicted FVC: 90 ± 28% vs. 85 ± 26%; $P < 0.001$ Predicted FEV_1: 98 ± 34% vs. 93 ± 29%; $P < 0.001$	Age, sex, BMI, waist circumference, smoking, family history of diabetes, systolic/diastolic blood pressure, plasma lipid profile, fasting glucose, haemoglobin A1c, 2-h OGTT glucose, HOMA-IR score	NAFLD was independently associated with decreased pulmonary function tests
Moon et al., 2018 [19]	Cross-sectional population-based study (KNHANES 2007–2010): 11,738 Korean adults (mean age 48 years; mean BMI 24 kg/m^2; 39.6% men; 33.7% current smokers; 8.7% diabetics)	NAFLD liver fat score; 3570 subjects (30.4%) with NAFLD	Predicted FEV_1 and FEV_1/FVC ratio	Predicted FEV_1: 92.6 [95% CI: 92.1–93.1]% vs. 91.1 [95% CI: 90.4–91.7]%; $P < 0.001$ FEV_1/FVC ratio: 80 [95% CI: 80–81]% vs. 79 [95% CI: 79–80]%; $P < 0.001$ Prevalence of obstructive pulmonary disease: 8.5 [95% CI: 7.7–9.4]% vs. 10.0 [95% CI: 8.8–11.4]%; $P < 0.001$	Age, sex, smoking	NAFLD was independently associated with decreased pulmonary function tests and a greater prevalence of obstructive pulmonary disease (i.e. defined as predicted FEV_1 < 70%)
Lee et al., 2018 [20]	Cross-sectional and longitudinal study: 11,892 South Korean individuals (mean age 47.7 years; mean BMI 23 kg/m^2; mean waist circumference 84 cm; smoking: mean 7.3 pack-years; 47.2% men; 4.1% diabetics) without baseline hepatic and respiratory diseases who underwent regular health exams with at least 3 years' follow-up	Ultrasonography; 3815 subjects (32.1%) with NAFLD	Predicted FVC, predicted FEV_1 and FEV_1/FVC ratio	Cross-sectional analyses: predicted FVC: 96.4 ± 11% vs. 95.4 ± 10.7%; $P < 0.001$; predicted FEV_1: 105.4 ± 12.1% vs. 103.5 ± 12.5%; $P < 0.001$; FEV_1/FVC ratio: 83.3 ± 6.1 vs. 81.5 ± 5.1; $P < 0.001$ Longitudinal analyses: during the mean follow-up of 6.6 years, there were no significant differences in the annual rates of both FEV_1 and FVC decline between the two groups in a propensity score-matched cohort (n = 4558)	Age, sex, BMI, waist circumference, smoking pack-years, plasma lipid profile, preexisting diabetes, hypertension	NAFLD was independently associated with decreased pulmonary function tests in both sexes at baseline. However, NAFLD was not independently associated with faster rates of pulmonary function decline in longitudinal analyses. However, those patients with high NAFLD fibrosis score or high fibrosis-4 had a significantly faster decline in predicted FVC (but not in FEV_1 and FEV_1/FVC ratio) compared to those with low fibrosis scores over the follow-up

Table 1 (*Continued*)

Author, year [Ref.]	Study design, sample size, population characteristics	Diagnosis of NAFLD, prevalence of NAFLD	Lung function tests on standard spirometry	Mean ± standard deviation of lung function tests in no-NAFLD *vs.* NAFLD group	Covariate adjustment(s)	Main findings
Longitudinal studies (n = 1)						
Song et al., 2019 [21]	Retrospective longitudinal study: 96,104 South Korean individuals (mean age 35.7 years; mean BMI 22 kg/m^2; 44.7% men; 20% current smokers), free from hepatic steatosis at baseline, who were followed-up from 2002 to 2015	Ultrasonography; 24,450 (25.4%) subjects developed incident fatty liver on ultrasonography during a mean follow-up period of 5.9 ± 3.4 years	Predicted FVC and predicted FEV_1	Regardless of smoking history, the risk for incident NAFLD increased progressively with decreasing quartiles of predicted FEV_1 and FVC ($P < 0.001$). In never smokers, the adjusted HRs (95% CI) for incident NAFLD were 1.15 (1.08–1.21), 1.11 (1.05–1.18), and 1.08 (1.02–1.14) in quartiles 1–3 for FEV_1 and 1.12 (1.06–1.18), 1.11 (1.05–1.18), and 1.09 (1.03–1.15) in quartiles 1–3 for FVC, compared with the highest quartile reference. Almost identical results were observed for smoke-exposed individuals	Age, sex, BMI, alcohol intake, smoking, physical activity, education level, study centre, year of test	Decreased FVC and FEV_1 at baseline were independently associated with an increased risk of developing NAFLD

BMI: body mass index; CI: confidence interval; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; HR: hazard ratio; HOMA-IR score: homeostasis model assessment-insulin resistance; NAFLD: non-alcoholic fatty liver disease; KNHANES: Korea National Health and Nutrition Examination Survey; NHANES: National Health and Nutrition Examination Survey; OGTT: oral glucose tolerance test.

(n = 5 studies), whereas the NAFLD liver fat score was used in a single study. The outcome measure for the eligible studies was the predicted FEV_1 (n = 6 studies), the predicted FVC (n = 5 studies) or the FEV_1/FVC ratio (n = 2 studies) between patients with and without NAFLD. Five studies were carried out in Asian countries (mostly from South Korea), whereas only one community-based study was carried out in the United States.

Overall, this meta-analysis included 133,707 (unique) middle-aged individuals (mean age: 46.7 years), predominantly women (55%) and non-obese (mean BMI: 23.4 kg/m^2). Most of these subjects were of Asian ethnicity (74.6%). Nearly 22% of them were current smokers and 27.8% had NAFLD.

As shown in Appendix A, Tables S1–S3 (see supplementary materials associated with this article on line), four studies received at least eight stars on the NOS (indicating that those studies had a low risk of bias), and two studies received seven stars (indicating that those studies had an unclear risk of bias). No studies received five stars or lower (i.e., being at high risk of bias).

Effect of NAFLD on lung function parameters

Fig. 2 shows the distribution of the five cross-sectional studies (involving a total of 37,567 individuals) by effect size of the association between NAFLD and predicted FEV_1 or predicted FVC values.

Overall, the meta-analysis showed that there were significant differences in both predicted FEV_1 (panel A; pooled WMD: −2.43%, 95% CI: −3.28 to −1.58%; I^2 = 69.7%) and predicted FVC (panel B; pooled WMD: −2.96%, 95% CI: −4.75 to −1.17%; I^2 = 91.7%) between individuals with and without NAFLD. As specified in Table 1, the association between NAFLD and lung volumes remained statistically significant in those studies where analysis was adjusted for age, sex, smoking history, measures of adiposity (BMI or waist circumference), dyslipidaemia, hypertension or diabetes. Similar results were also observed for the FEV_1/FVC ratio (Appendix A, Figure S1; see supplementary materials associated with this article on line).

As shown in Appendix A, Figure S2 (see supplementary materials associated with this article on line), the Egger's regression test did not reveal any statistically significant asymmetry of the funnel plot for predicted FEV_1 (P = 0.13), thus suggesting that publication bias was unlikely, although it should be noted that the numbers of included studies was small. Almost identical results were found for predicted FVC (data not shown). These results were also confirmed by the trim and fill method (data not shown).

Subgroup analyses

Stratifying by study country, the observed differences in predicted FEV_1 and FVC values between individuals with and without NAFLD were consistent for studies performed in both Asian and non-Asian populations (Table 2). Similarly, there were significant differences in both predicted FEV_1 and FVC values between individuals with and without NAFLD even after stratifying by the methods used for diagnosing NAFLD, or whether the studies had a NOS scale $\geq$ 8 stars (Table 2). We also performed a sensitivity analysis using the one-study remove (leave-one-out) approach in order to examine the influence of each study on the overall effect size. The exclusion of each of these studies from the analysis did not show any significant effect on the observed differences in predicted FEV_1 and FVC values between individuals with and without NAFLD (data not shown).

Effect of lung function parameters on risk of incident NAFLD

Fig. 3 shows the distribution of the only available longitudinal cohort study (involving a total of 96,104 South Korean individuals

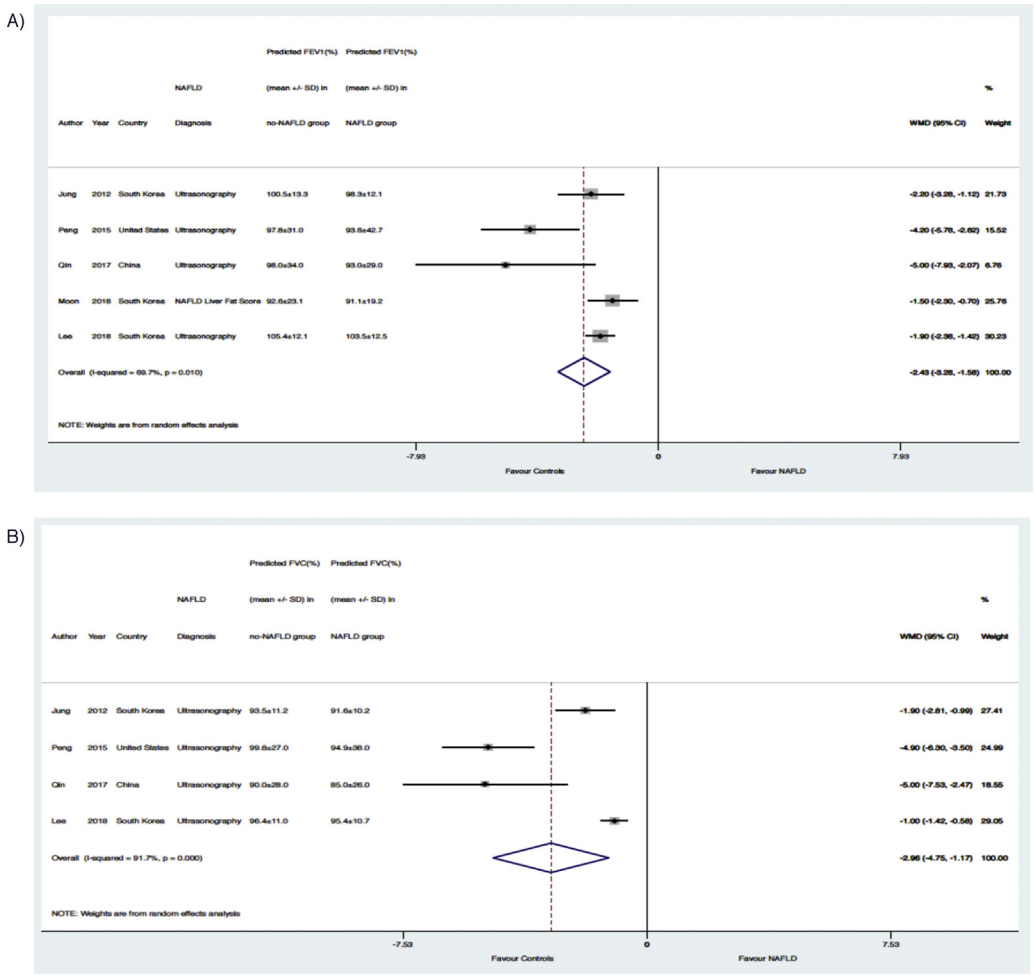

Fig. 2. Forest plot of comparison of lung function tests on standard spirometry (i.e., predicted FEV_1 [panel A] and predicted FVC [panel B]) between NAFLD and control groups. The effect size was expressed as weighted mean difference (WMD) and 95% confidence interval for all studies included (n = 5 cross-sectional studies).

free from hepatic steatosis at baseline; mean age 35.7 years; 44.7% men; 20% current smokers) by effect size of the association between baseline lung volumes and risk of developing incident NAFLD.

Regardless of smoking history, the risk for incident NAFLD increased progressively with decreasing quartiles of both predicted FEV_1 (panel A) and predicted FVC (panel B) values over a mean follow-up of 5.9 years. Notably, these results were independent of age, sex, BMI, smoking, alcohol consumption, physical activity, education level, study centre and year of test. However, it should be noted that there is only one published study, and that no other longitudinal studies involving non-Asian individuals are available for this latter analysis, thus limiting the generalizability of these findings to other ethnic populations.

Discussion

The main findings of our meta-analysis are as follows:

- NAFLD was significantly associated with similar reductions of predicted FEV_1 and predicted FVC in both Asian and United States middle-aged individuals;
- these results were generally consistent in most subgroups analysed and, most importantly, remained significant in those studies where analysis was adjusted for age, sex, smoking history, measures of adiposity (BMI and/or waist circumference), dyslipidaemia, hypertension or diabetes;
- small, but significant, reductions in lung volumes at baseline were found to be independently associated with a ~ 15% increased long-term risk of developing incident NAFLD among Asian individuals (n = 1 study involving ~ 96,000 middle-aged South Korean adults).

Notably, only a few of the eligible studies provided data on the prevalence of either restrictive or obstructive pulmonary pattern [17,19], probably because most individuals included in these cohorts were of relatively young age (mean age: ~ 47 years) and often had spirometric values of lung volumes within the normal ranges. That said, the findings derived from these two studies have been controversial. In fact, Peng et al. showed that imaging-defined NAFLD was associated mainly with a restrictive pulmonary pattern in a nationally representative cohort of 9976 United States middle-aged individuals [17]. In contrast, Moon et al. reported NAFLD to be associated mainly with an obstructive pulmonary pattern in a community-based cohort of South Korean individuals [19]. This latter study also confirms the findings of some studies reporting a high prevalence of NAFLD and other chronic liver diseases in patients with established COPD [33,34].

Regarding the possible association between decreased lung volumes and the severity of NAFLD, it should be noted that no studies using liver biopsy for diagnosing and staging NAFLD were available for the analysis. This does not allow drawing any conclusion

Table 2
Subgroup analyses – Comparison of lung function measurements on standard spirometry between individuals with and without NAFLD, stratified by category of Newcastle-Ottawa quality assessment Scale (NOS), diagnostic methods for NAFLD or study country. The effect size was expressed as pooled weighted mean difference (WMD) and 95% confidence interval for all eligible cross-sectional studies.

	Predicted FEV_1	Predicted FVC
NOS category		
NOS < 8 stars	Pooled WMD −3.26% (95% CI: −5.91 to −0.60) I^2 = 67.6% Number of studies: 2 *n* = 3961	Pooled WMD −3.21% (95% CI: −6.22 to −0.21) I^2 = 80.4% Number of studies: 2 *n* = 3961
NOS ≥ 8 stars	Pooled WMD −2.27% (95% CI: −3.32 to −1.22) I^2 = 77.8% Number of studies: 3 *n* = 33,606	Pooled WMD −2.89% (95% CI: −6.71 to −0.03) I^2 = 96.3% Number of studies: 2 *n* = 21,868
NAFLD diagnosis		
Ultrasonography	Pooled WMD −2.87% (95% CI: −4.05 to −1.69) I^2 = 73.1% Number of studies: 4 *n* = 25,829	Pooled WMD -2.96% (95% CI: −4.75 to −1.17) I^2 = 91.7% Number of studies: 4 *n* = 25,829
NAFLD liver fat score	Pooled WMD −1.50% (95% CI: −2.30 to −0.70) I^2 = not applicable Number of studies: 1 *n* = 11,738	Not available
Study country		
South Korea	Pooled WMD −1.85% (95% CI: −2.23 to −1.46) I^2 = 0% Number of studies: 3 *n* = 25,749	Pooled WMD −1.35% (95% CI: −2.22 to −0.49) I^2 = 67.8% Number of studies: 3 *n* = 25,749
China	Pooled WMD −5.00% (95% CI: −7.93 to −2.07) I^2 = not applicable Number of studies: 1 *n* = 1842	Pooled WMD −5.00% (95% CI: −7.53 to −2.47) I^2 = not applicable Number of studies: 1 *n* = 1842
United States	Pooled WMD −4.20% (95% CI: −5.78 to −2.62) I^2 = not applicable Number of studies: 1 *n* = 9976	Pooled WMD −4.90% (95% CI: −6.30 to −3.49) I^2 = not applicable Number of studies: 1 *n* = 9976

regarding a potential link between lung volumes and severity of NAFLD histology. In our meta-analysis, we included two Asian studies in which the severity of NAFLD was diagnosed either by ultrasonographic scoring systems or by non-invasive markers of liver fibrosis [16,19]. In particular, Jung et al. reported that both predicted FVC and FEV_1 values sharply decreased across the ultrasonographic severity of hepatic steatosis in 2,119 South Korean men [16]. Similarly, in a cohort study involving ∼ 12,000 South Korean people, Moon et al. found that the presence of advanced hepatic fibrosis at baseline (as evaluated by the NAFLD fibrosis score) was associated with a faster decline over time in predicted FVC both in men and women, independently of age, BMI and smoking history [19]. That said, we consider that this question remains largely unresolved, and future studies in large cohorts of well-characterized patients with NAFLD (as diagnosed by magnetic resonance-proton density fat fraction and magnetic resonance elastography, which are rapidly being recognized as being as good as liver biopsies) [2,35] are needed to prove whether the severity of NAFLD (especially the severity of liver fibrosis) may adversely affect lung function.

Another issue is whether the association between NAFLD on ultrasonography and reduced lung volumes could be mainly driven by obesity. Obesity, especially with an excess of intra-abdominal or visceral adipose tissue, has long been recognized as having adverse effects on lung function [36]. It is important to underline that all studies included in the meta-analysis, except one [19], have adjusted their results at least for BMI, and three studies also adjusted their results for waist circumference [17,18,20]. Although we are inclined to believe that the significant association between NAFLD and reduced lung volumes is not just a consequence of being obese, however, we also consider that the lack of statistical adjustment for waist circumference (or other more accurate measures of intra-abdominal fat accumulation) represents one of the major weaknesses of these studies.

Collectively, the findings of our meta-analysis support the existence of a complex and bi-directional relationship between NAFLD and impaired lung function. Understanding how and why even small reductions of lung volumes may be associated with risk of NAFLD is beyond the scope of our meta-analysis. Although the underlying mechanisms relating impaired lung function to NAFLD are poorly understood, emerging evidence now suggests a significant association between OSAS and risk of NAFLD [15,37,38]. Experimentally, it has been demonstrated that chronic intermittent hypoxia may be a major trigger for NAFLD [37,39]. In addition, it is also plausible to assume that NAFLD, especially in its more histologic severe forms (i.e. NASH with increasing amounts of liver fibrosis), exacerbates insulin resistance and causes the release of several pro-inflammatory, prooxidant and profibrogenic mediators, which may contribute to worsening lung function [1–5,40]. However, more research is required to better understand the pathophysiological interconnections between NAFLD and impaired lung function.

Our meta-analysis has some important limitations (strictly inherent to the nature of the included studies) that should be mentioned. First, the observational design of the eligible studies does not allow establishing temporal or causal relationships between NAFLD and decreased lung volumes. Second, although almost all studies included in the meta-analysis have adjusted the results for age, sex, adiposity measures, smoking, hypertension and diabetes, the possibility of residual confounding by some unmeasured factors cannot be ruled out. Third, most studies originate from Asian countries, where large populations undergo regular health check-up programs, including liver ultrasonography and spirometry. Although the NHANES-III study showed an independent association between NAFLD and decreased lung function in United States adults [17], the generalizability of these findings to European populations remains untested. In addition, as Asian and

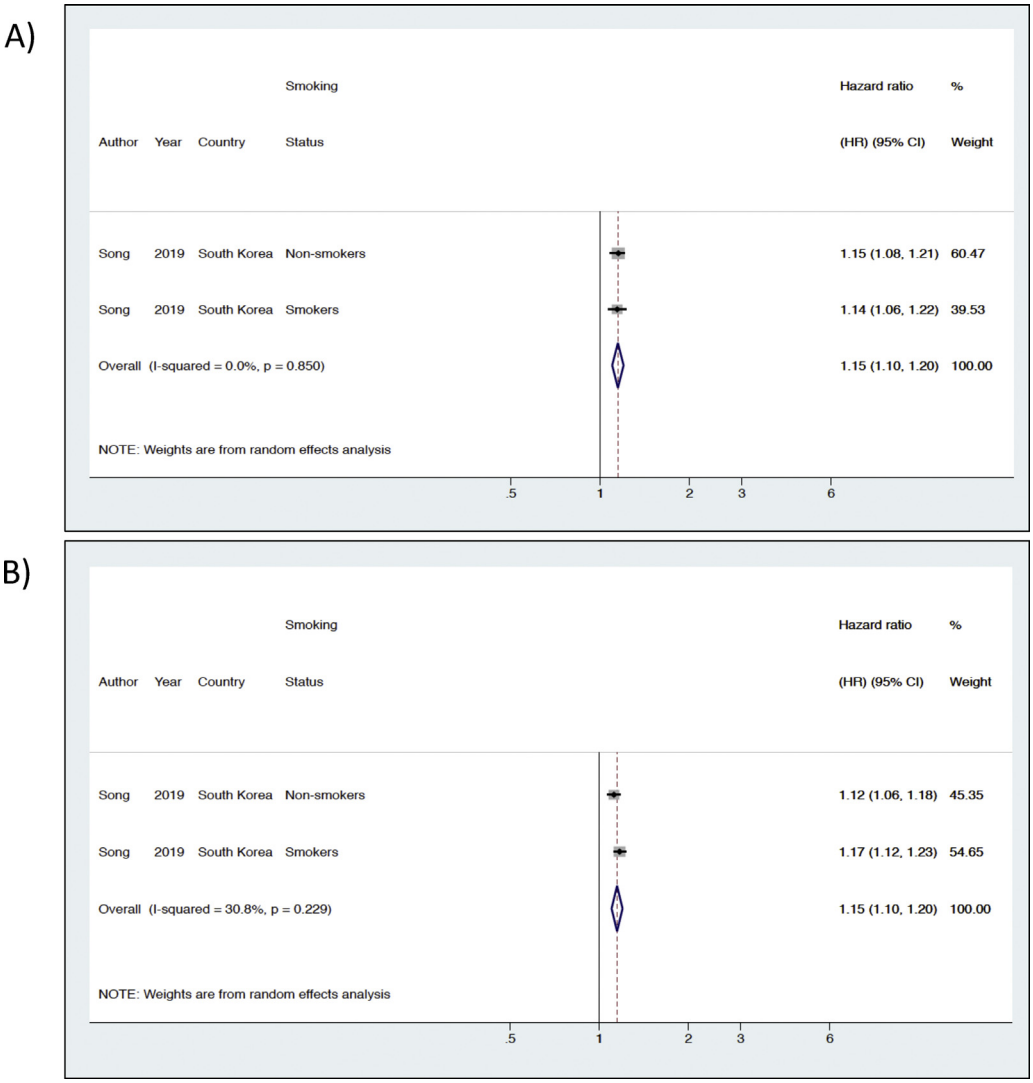

Fig. 3. Forest plot and pooled estimates of the effect of lung function tests (i.e., predicted FEV_1 [panel A] and predicted FVC [panel B]; 1st quartile vs. other quartiles combined) on risk of developing incident NAFLD, stratified by smoking status (n = 1 longitudinal study).

non-Asian populations have different genetic/cultural backgrounds, dietary habits and adipose tissue distributions, further studies should also be conducted in non-Asian populations. Fourth, although we used a random-effects model, the interpretation of some results of our meta-analysis should be made cautiously, given the medium-high heterogeneity observed in the pooled primary analysis of cross-sectional studies (I^2 = 69.7%). However, our subgroup analyses showed that this medium-high heterogeneity most likely reflected differences in race/ethnicity among the included studies (as shown in Table 2). Another limitation of our meta-analysis was that no published studies with biopsy-proven NAFLD were available for the analysis. Conversely, most of the eligible studies used liver ultrasonography, which is the recommended first-line imaging method for detecting hepatic steatosis in clinical practice, and it enables a reliable and accurate detection of mild-to-moderate steatosis compared with liver biopsy [1,2]. Finally, standard spirometry cannot give an accurate picture of the lung function, which should be completed by the plethysmographic measures of lung volumes.

Notwithstanding these limitations, our meta-analysis has also important strengths. This meta-analysis provides the most comprehensive and updated assessment on the nature and magnitude of the association between lung function and NAFLD in large-scale cohort studies of predominantly healthy adults. Moreover, we have used standardized risk estimates from all eligible studies to allow consistent combination of estimates across studies. The overall quality of the studies included in this meta-analysis appears to be relatively high, being a low risk of bias according to the NOS scale. The large number of individuals with NAFLD has also provided high statistical power to quantitatively assess the association between lung function parameters and NAFLD. Finally, although a selective reporting bias of eligible studies could be not definitely excluded (because we did not include 'grey' literature in the meta-analysis, i.e., unpublished studies and studies published outside widely available journals), we think our comprehensive search have made it unlikely that any published report was missed, whilst visual inspection of the funnel plot and formal statistical tests did not show any significant publication bias (although the interpretation of the Egger's regression test should be viewed cautiously because the number of studies included was low).

In conclusion, this is the first meta-analysis of observational studies (involving middle-aged individuals of predominantly Asian ethnicity) suggesting that imaging-defined NAFLD is associated with significant reductions of both predicted FEV_1 and FVC in Asian and United States middle-aged individuals, and that such small, but significant, reductions of lung volumes at baseline may also predict subsequent development of NAFLD in middle-aged healthy

Korean individuals. These associations remained significant in those studies where analysis was adjusted for age, sex, smoking, adiposity measures, diabetes and other metabolic risk factors. However, more prospective studies, particularly in non-Asian populations, and mechanistic studies are certainly needed to better elucidate the association between NAFLD and decreased lung volumes.

Funding sources

GT is supported in part by grants from the University School of Medicine of Verona, Verona, Italy. CDB is supported in part by grants from the Southampton National Institute for Health Research Biomedical Research Centre.

Authors' contributions

Study concept and design: AM, GT; acquisition of data: AM, GT; statistical analysis of data: AM, GT; analysis and interpretation of data: AM, AL, GV, GZ, GL, EB, RL, HT, CDB, LF and GT; drafting of the manuscript: GT; critical revision of the manuscript for important intellectual content: AL, GV, GZ, GL, EB, RL, HT, CDB and LF. GT is the guarantor who takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript. All authors have approved the submitted manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary material (Checklist, Figures S1, S2 and Tables S1, S2, S3) related to this article can be found, in the online version, at https://doi.org/10.1016/j.diabet.2019.04.008.

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