



HAL
open science

Obstructive sleep apnea, chronic obstructive pulmonary disease and NAFLD: an individual participant data meta-analysis

Ingrid Jullian-Desayes, Wojciech Trzepizur, Jérôme Boursier, Marie Joyeux-Faure, Sébastien Bailly, Meriem Benmerad, Marc Le Vaillant, Sandrine Jaffre, Thierry Pigeanne, Acya Bizieux-Thaminy, et al.

► To cite this version:

Ingrid Jullian-Desayes, Wojciech Trzepizur, Jérôme Boursier, Marie Joyeux-Faure, Sébastien Bailly, et al.. Obstructive sleep apnea, chronic obstructive pulmonary disease and NAFLD: an individual participant data meta-analysis. *Sleep Medicine*, 2020, 10.1016/j.sleep.2020.04.004 . hal-03001812

HAL Id: hal-03001812

<https://hal.science/hal-03001812v1>

Submitted on 13 Feb 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **Obstructive sleep apnea, chronic obstructive pulmonary disease and** 2 **NAFLD: an individual participant data meta-analysis**

3
4 Ingrid Jullian-Desayes^{1,2,§}, Wojciech Trzepizur^{3,4,§}, Jérôme Boursier^{5,6}, Marie Joyeux-Faure^{1,2},
5 Sébastien Bailly^{1,2}, Meriem Benmerad^{1,2}, Marc Le Vaillant⁷, Sandrine Jaffre⁸, Thierry Pigeanne⁹,
6 Acya Bizieux-Thaminy¹⁰, Marie-Pierre Humeau¹¹, Claire Alizon¹², François Goupil¹³, Charlotte
7 Constantin^{14,15}, Jonathan Gaucher¹, Renaud Tamisier^{1,2}, Frédéric Gagnadoux^{3,4,§}, Jean-Louis
8 Pépin^{1,2,§}

- 9
10
11 1. HP2 laboratory, INSERM U1042, Grenoble Alpes University, Grenoble, France
12 2. EFCR Laboratory, Pole Thorax et Vaisseaux, Grenoble Alps University Hospital, Grenoble, France
13 3. Department of Respiratory Diseases, Angers University Hospital, Angers, France
14 4. INSERM U1063, SOPAM, Angers University, F-49045, Angers, France
15 5. Hepato-Gastroenterology Department, Angers University Hospital, Angers, France
16 6. HIFIH Laboratory, UPRES 3859, SFR 4208, Angers University, Angers, France
17 7. Institut Recherche en Santé Respiratoire des Pays de la Loire, Beaucouzé, France
18 8 Institut du Thorax, Department of Respiratory Diseases, Nantes University Hospital, Nantes,
19 France
20 9. Respiratory Unit, Pôle santé des Olonnes, Olonne sur Mer, France
21 10. Department of Respiratory Diseases, General Hospital, La Roche sur Yon, France
22 11. Department of Respiratory Diseases, Nouvelles Cliniques Nantaises, Nantes, France
23 12. Department of Respiratory Diseases, General Hospital, Cholet, France
24 13. Department of Respiratory Diseases, General Hospital, Le Mans, France
25 14. Hepatogastroenterology Department, Grenoble Alpes University Hospital, Grenoble, France
26 15. INSERM U823, IAPC Institute for Advanced Biosciences, University Grenoble Alpes, Grenoble,
27 France

28
29
30 § These co-first authors contributed equally to this work

31 § These co-senior authors contributed equally to this work

32
33 **Running title:** NAFLD and sleep apnea

34 **Corresponding author:**

35 **Pr Jean-Louis PEPIN**

36 Laboratoire EFCR

37 CHU de Grenoble

38 CS10217

39 38043 Grenoble Cedex 9, France

40 Email: JPepin@chu-grenoble.fr

41 Phone: +33 476768766

42
43 *Word count: 2,678: Number of figures and tables: 3 figures and 4 tables*

44 **Author contributions:** IJ-D, WT, MJ-F, RT, SJ, TP, AB-T, M-PH, CA, FGo, FGa, VL and J-LP contributed
45 substantially to the study design, data collection and interpretation. MB, ML and SB performed the
46 statistical analysis. IJ-D, WT, MJ-F, JB, FGa and J-LP wrote the article and SB, MB, RT critically
47 revised the manuscript.

48

49 **Conflict of interest:** None of the authors has a conflict of interest with respect to this study.

50

51 **Funding:** JLP, RT and SB are supported by the French National Research Agency in the framework
52 of the "Investissements d'avenir" program (ANR-15-IDEX-02) and the "e-health and integrated
53 care and trajectories medicine and MIAI artificial intelligence" Chairs of excellence from the
54 Grenoble Alpes University Foundation. This work has been partially supported by MIAI @
55 Grenoble Alpes, (ANR-19-P3IA-0003) and the Institut de Recherche en Santé Respiratoire des Pays
56 de la Loire (Loire region Respiratory Health Research Institute).

57

58 **Abbreviations**

59

60 **ALT:** alanine aminotransferase

61 **AST:** aspartate aminotransferase

62 **BMI:** body mass index

63 **COPD:** chronic obstructive pulmonary disease

64 **FMN:** FibroMeter NAFLD Score

65 **GOLD:** Global Initiative for Chronic Obstructive Lung Disease

66 **HSI:** Hepatic Steatosis Index

67 **IPDMA:** individual participant data meta-analysis

68 **NAFLD:** nonalcoholic fatty liver disease

69 **NASH:** nonalcoholic steatohepatitis

70 **OSA:** obstructive sleep apnea

71

72

73

74

75

76

77

78

79

80

81 **Abstract (249 words)**

82 Rationale: Chronic intermittent hypoxia occurring in obstructive sleep apnea (OSA) is
83 independently associated with nonalcoholic fatty liver disease (NAFLD). Chronic obstructive
84 pulmonary disease (COPD) has also been suggested to be linked with liver disease.

85 Objective: In this individual participant data meta-analysis, we investigated the association
86 between liver damage and OSA and COPD severity.

87 Methods and measurements: Patients suspected of OSA underwent polysomnography or home
88 sleep apnea testing (HSAT). Non-invasive tests were used to evaluate liver steatosis (Hepatic
89 Steatosis Index) and fibrosis (Fibrotest or FibroMeter). An individual participant data meta-analysis
90 approach was used to determine if the severity of OSA/COPD affects the type and severity of liver
91 disease. Results were confirmed by multivariate and causal mediation analysis. Sub-group analyses
92 were performed to investigate specific populations.

93 Main results: Among 2,120 patients, 1,584 had steatosis (75 %). In multivariable analysis, risk
94 factors for steatosis were an apnea-hypopnea index (AHI) >5/h, body mass index (BMI) >26 kg/m²,
95 age, type 2 diabetes (all p-values <0.01) and male gender (p=0.02). Concerning fibrosis, among
96 2,218 patients 397 had fibrosis (18 %). Risk factors associated with fibrosis were BMI>26kg/m²,
97 age, male gender, and type 2 diabetes (all p-values <0.01). AHI severity was not associated with
98 fibrosis. A combination of AHI >30/h and COPD stage 1 was associated with an increased risk of
99 steatosis.

100 Conclusion: This meta-analysis confirms the strong association between steatosis and the severity
101 of OSA. The relation between OSA and fibrosis is mainly due to BMI as shown by causal mediation
102 analysis.

103 **Keywords:** Obstructive sleep apnea; chronic obstructive pulmonary disease; liver diseases; NAFLD;

104 liver fibrosis

105

106 **Introduction**

107 Nonalcoholic fatty liver disease (NAFLD) is characterized by the accumulation of hepatic
108 triglycerides (steatosis) in patients without significant alcohol consumption or viral hepatitis [1]. A
109 significant percentage of patients develop additional inflammatory infiltration (nonalcoholic
110 steatohepatitis [NASH]) and can eventually develop liver fibrosis leading to an increased risk of
111 hepatocellular carcinoma and/or cirrhosis [2,3].

112 NAFLD is becoming epidemic in the general population with its prevalence increasing in
113 parallel with obesity and type-2 diabetes; reaching 25% in the worldwide general population and
114 75% in the morbidly obese population [1–3]. NAFLD, and in particular liver fibrosis, are strongly
115 associated with a higher risk of cardiovascular diseases and early mortality [4,5]. Improvement in
116 NAFLD integrated care requires the better identification of associated conditions and diseases that
117 trigger its progression from steatosis to NASH and liver fibrosis.

118 Obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD) are also
119 among the most disabling and frequent chronic diseases, causing considerable health-related
120 costs and increased premature mortality [6,7]. These two diseases share underlying intermediary
121 mechanisms such as low grade inflammation, oxidative stress, insulin resistance and lipotoxicity
122 that are recognized as being involved in the initiation and progression of NAFLD [8,9]. These
123 intermediary mechanism are known to be triggered by intermittent hypoxia [10,11].

124 Studies of the link between COPD and NAFLD are scarce [12,13] and require confirmation.
125 Rodent and human data are by far more consistent concerning the relationship between OSA and
126 NAFLD [8,9].

127 The two existing meta-analyses [14,15] addressing an association between OSA and NAFLD
128 are based on heterogeneous aggregated data assembled from studies using different NAFLD
129 diagnosis techniques. Moreover, the bulk of the datasets is characterized by studies of morbidly

130 obese women that do not reflect the epidemiology of OSA and COPD. Approaches using individual
131 participant data meta-analysis (IPDMA) do not aggregate summary data but address study
132 questions by including actual participant data from different data sources [16]. Using data from all
133 participants with individual data for OSA and COPD indices of severity overcomes limitations
134 related to the selective cut-offs used in previous publications and allows specific subgroup
135 analyses. Information at the participant level regarding confounders permits proper adjustment.

136 The primary objective of this IPDMA was to investigate the dose response relationship
137 between NAFLD and OSA or COPD severity indices after appropriate adjustment for confounders.

138

139 **Methods**

140 *Study population*

141 Patients were included by two French university expert sleep and respiratory disease centers
142 (Angers and Grenoble) and affiliated general or private hospitals participating in the “Institut de
143 Recherche en Santé Respiratoire des Pays de la Loire” sleep cohort (Nantes University Hospital,
144 Pôle santé des Olonnes, Nouvelles Cliniques Nantaises, La Roche sur Yon, Cholet, and Le Mans
145 General Hospitals) [17]. Individual patient data were generated from previous studies in Angers
146 and Grenoble including non-invasive tests for assessment of NAFLD. These assessments were
147 conducted in OSA patients with or without abnormalities in liver enzymes. Depending on the
148 design of the original studies generating individual patient data, sleep studies were conducted by
149 HSAT or in lab-polysomnography. Included patients reporting a daily alcohol intake of < 20 g/day
150 in women and < 30 g/day in men (in order to exclude liver damage induced by alcohol
151 consumption) were initially investigated for clinical suspicion of OSA. All studies furnishing patients
152 for the individual data meta-analysis were approved by Angers or Grenoble ethical committees
153 and all patients had provided their written informed consent.

154

155 *Sleep and Respiratory parameters*

156 All patients had been assessed by an overnight polysomnography or HSAT. OSA severity was
157 classified as follows: less than 5 events/h (no OSA), 5-30 (mild to moderate OSA), 30 or greater
158 (severe OSA) [18]. Pulmonary function tests had been performed to evaluate the severity of COPD
159 and graded according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD): I (mild),
160 II (moderate), III and IV (severe) [19].

161

162 *Characterization of NAFLD*

163 All patients had a diagnosis of liver steatosis or fibrosis by non-invasive biomarkers. In the “Institut
164 de Recherche en Santé Respiratoire des Pays de la Loire” sleep cohort, all patients had undergone
165 fasting blood tests including blood glucose, glycated hemoglobin, serum lipids, ferritin, alanine
166 aminotransferase (ALT), aspartate aminotransferase, glutamyl transpeptidase, and platelets. In
167 Grenoble Alpes University Hospital, fasting blood tests including α 2-macroglobulin, apolipoprotein
168 A1, haptoglobin, γ -glutamyltransferase (GGT), total bilirubin, ALT, aspartate aminotransferase
169 (AST), fasting blood glucose, triglycerides and total cholesterol had been performed. Steatosis was
170 evaluated on the hepatic steatosis index (HSI) for all subjects. HSI was calculated from body mass
171 index (BMI, the AST/ALT ratio (AAR), sex, and the presence or absence of diabetes mellitus.
172 Steatosis was defined by a HSI > 36 [20]. Concerning fibrosis evaluation, the FibroMeter NAFLD
173 (FMN), as previously used by Trzepizur et al. [21], was kindly calculated by Echosens (Paris, France)
174 for patients in the “Pays de la Loire” sleep cohort. In Grenoble Alpes University Hospital a
175 Fibromax® test was calculated for each patient as previously described in Jullian-Desayes et al. [22]
176 and liver fibrosis was evaluated by the Fibrotest. A FMN or a Fibrotest score > 0.49 was considered
177 to indicate the presence of liver fibrosis [21,22].

178

179 *Statistical analysis*

180 An IPDMA approach was chosen to increase statistical power, better adjust for confounders and
181 perform sub-group analyses. Datasets were checked for accuracy and merged to constitute a
182 single dataset with individual data for all outcome and confounders of interest. Variables were
183 described by using number and percent for qualitative variables and median and interquartile
184 range for quantitative variables.

185 To account for missing values, a multiple imputation method was used by applying the Monte-
186 Carlo Markov Chain (MCMC) method for quantitative variables and Fully Conditional Specification
187 (FCS) method for qualitative variables. Ten datasets were obtained and Rubin's rules for multiple
188 imputations were applied when combining the ten datasets. Details on missing values and
189 imputation are presented in Table S1 in the online data supplement.

190 A one stage random effect meta-analysis was performed by using a mixed logistic regression
191 model including a random effect of hospital, to account for inter-hospital variability. To select the
192 confounders in the final model, a univariable logistic regression analysis was performed. The
193 multivariable logistic regression model was adjusted for confounders, including BMI. The
194 assumptions of the statistical models were verified. Subgroup analyses were performed to
195 determine if there were some differences between patient subgroups according to OSA or COPD
196 severity. Interactions between covariates and events (liver disease) were assessed.

197 The relation between liver damage and OSA or COPD severity was assessed by using a
198 multivariable multinomial logistic regression mixed model. Finally, we performed a causal
199 mediation analysis because OSA and liver disease have common risk factors such as being over-
200 weight. Indeed, BMI is a collider, ie, a factor that is associated with both sleep apnea and liver

201 diseases such as fibrosis and steatosis studied in this meta-analysis. Briefly, causal mediation
202 analysis allows one to study the impact of a third variable, a named mediator, on the association
203 between an exposure (independent variable X) and an outcome (dependent variable Y) [23,24].
204 The interest of mediation analysis associated with the counterfactual framework is to decompose
205 the total effect into direct and indirect effects of the exposure on the outcome by considering the
206 mediator [25]. To perform this analysis, BMI and AHI were considered as continuous variables and
207 liver disease (steatosis or fibrosis) was considered as a dichotomous outcome variable. Other
208 confounders were added: age, gender and hypertension, dyslipidemia, diabetes mellitus and they
209 were introduced as covariates in the causal mediation process. Hypoxia parameters were included
210 in the analysis. However, they were significantly linked with AHI (TST<90%, mean nocturnal SaO₂
211 and minimum nocturnal SaO₂ with correlation coefficient of 0.60, 0.45 et 0.47 respectively). As
212 they were covariables, only AHI was included in the multivariate analysis. Causal mediation
213 analyses were performed by using the CAUSALMED procedure. All statistical analyses were
214 performed by using SAS V9.4 (SAS Institute Inc., Cary, NC, USA). A p-value <0.05 was considered as
215 significant.

216

217 **Results**

218 *Steatosis prevalence and associated risk factors*

219 Indices of steatosis (HSI) and sleep apnea (AHI) were available for 2,120 patients (Figure 1A). The
220 baseline characteristics of this population are shown in Table 1. Among them, 1,584 (75%) had
221 steatosis (defined by an HSI>36). Steatosis prevalence ranged from 51% in the non-OSA group to
222 85% in patients with severe OSA (AHI>30/h). Patients with steatosis had a higher AHI but also
223 more comorbidities (hypertension, dyslipidemia, diabetes, and a higher BMI). In univariable

224 analysis, BMI, hypertension, dyslipidemia, type 2 diabetes, AHI, mean nocturnal SaO₂, cholesterol
225 (total and HDL), triglycerides and fasting glucose (Table S2) were associated with steatosis. In
226 multivariable analysis, age, male gender, BMI, diabetes and AHI were significantly associated with
227 steatosis (Figure 2A). The prevalence of steatosis decreased with age and increased with OSA
228 severity (OR: 2.33 [1.42; 3.81] for AHI between 5 and 30 events per hour versus OR: 2.80 [1.64;
229 4.78] for AHI > 30 events per hour, p<0.01).

230 In the causal mediation analysis, assuming that all important confounders were taken into
231 account, the OR of the total effect was 1.09 [1.07-1.11] and corresponds to a significant
232 association between OSA severity (AHI) and steatosis. The decomposition of the total effect
233 showed that although the direct effect of OSA severity on steatosis remained significant, 76.9% of
234 the total effect was mediated by the BMI (Figure 2B).

235 Of 1,033 patients with HSI and pulmonary function test data, 121 (12%) had COPD, mainly of mild
236 to moderate severity (34 GOLD stage 1, 42 stage 2, 10 stages 3-4) as shown in Table 2. There was
237 no association between COPD stages and steatosis either in univariable (p=0.34) or in
238 multivariable analyses (p=0.85) (Figure 2C). Concerning “overlap syndrome”, the combination AHI
239 >30/h and COPD stage 1 was associated with an increased risk of steatosis, whereas AHI >30/h and
240 COPD stages 2-3-4 failed to show significance (Figure 2D).

241 *Fibrosis prevalence and associated risk factors*

242 Fibrosis data were available for 2,218 patients (Figure 1B). Among them, 397 (18%) patients had
243 liver fibrosis. Fibrosis prevalence went from 7% in the non-OSA group to 26% in the severe OSA
244 (AHI>30/h) group. Baseline characteristics are given in Table 3 showing that patients with fibrosis
245 were significantly older, mainly men with higher BMI and with more comorbidities than patients
246 without fibrosis. The univariable analysis showed age, male gender, BMI, hypertension,

247 dyslipidemia, diabetes, and AHI as fibrosis associated risk factors (Table S3). In multivariable
248 analysis age, male gender, BMI and type 2 diabetes remained significantly associated with fibrosis
249 (Figure 3A). There was no relationship between AHI and fibrosis ($p= 0.55$). In contrast to steatosis,
250 older age was associated with fibrosis.

251 Here again, in the causal mediation analysis, assuming that all important confounders were taken
252 into account, the OR of the total effect was 1.02 [1.01-1.03] and represents a significant effect of
253 OSA severity on fibrosis. The decomposition of the total effect showed that 96.3% of the total
254 effect was mediated by the BMI, and the controlled direct effect (effect directly associated with
255 OSA) was not significant. The association between OSA severity and fibrosis is almost entirely due
256 to obesity (Figure 3B).

257 Concerning COPD, 1,067 patients had pulmonary function test and fibrosis data. These 1,067
258 patients are compared to patients without pulmonary function test data in Table S4. Among them,
259 52 were GOLD stage 1, 65 stage 2 and 12 stages 3-4 as shown in Table 4. There was significant
260 association between fibrosis and COPD stages in univariable analysis ($p=0.02$). However, in
261 multivariable analysis there is no significant association between fibrosis and COPD ($p=0.21$)
262 (Figure 3C) or overlap syndrome ($p=0.22$) (Figure 3D).

263

264 **Discussion**

265 This IPDMA conducted with more than 2,000 patients referred for suspicion of OSA
266 demonstrated a significant influence of male gender, age, BMI and diabetes on steatosis as
267 estimated by non-invasive blood tests, with a correlation between OSA severity and steatosis.
268 While steatosis occurred earlier in life, fibrosis was associated with older age, male gender but

269 predominantly with BMI. In our dataset, which is the largest studied to date for COPD, the
270 combination of AHI >30/h and COPD stage 1 was associated with an increased risk of steatosis and
271 COPD was associated with liver fibrosis only in the univariable analysis.

272 Our IPDMA provides a truly original dataset to analyze the association between COPD and
273 NAFLD. In a previous population of 111 COPD patients with more severe stage disease, we
274 reported the liver fibrosis prevalence to be 61% [12]. One limitation was the absence of a non-
275 COPD control group in that study [26]. The current meta-analysis, including a large non-COPD
276 subgroup and mainly mild to moderate COPD patients, extended previous results showing an
277 association between liver fibrosis and the most severe COPD GOLD stages [13]. The significance in
278 univariable analysis was lost in multivariable analysis. This might be explained by a lack of power,
279 justifying additional investigations.

280 The association between OSA and NAFLD has been demonstrated previously [14,15]. Their
281 conclusions could be challenged due to some methodological considerations. The majority of
282 patients, particularly those with liver biopsies, were morbidly obese and enrolled by bariatric
283 surgery clinics. Also, the authors themselves acknowledged that diagnosis techniques for NAFLD
284 and the cut-offs for OSA definitions varied substantially across studies. Our IPDMA used a
285 homogeneous OSA definition thus surmounting this limitation and allowing us to demonstrate a
286 correlation between OSA severity and steatosis. In obstructive sleep apnea, animal and clinical
287 studies are now in full agreement [8] and the next question is to further evaluate the impact of
288 OSA treatment on NAFLD evolution. Two systematic reviews including one meta-analysis
289 [22,27,28] have addressed this question. They summarized randomized controlled trials, of which
290 there are only a few (n=3) of small sample size, that used surrogate outcomes for NAFLD
291 characterization (ie, liver enzymes or Fibromax) to evaluate a few months of effective versus sham
292 continuous positive airway pressure (CPAP). Owing to the limited amount of data, the level of

293 evidence remains low but suggests no effect of a CPAP treatment used in isolation. This might be
294 explained by the need for longer exposure to CPAP or the necessity to combine CPAP with lifestyle
295 interventions and exercise to improve OSA metabolic outcomes including NAFLD [29–31]. Large
296 randomized controlled trials comparing different modalities of lifestyle interventions combined
297 with CPAP are ongoing in obese populations with both OSA and NAFLD.

298 Our study had several limitations. There was potentially an inclusion bias as all participants were
299 referred for a sleep study in the context of suspicion of OSA. The cross-sectional nature of included
300 studies prevented any definitive causal inference between OSAS/COPD and NAFLD. To date, liver
301 biopsy remains the reference for the evaluation of liver lesions in NAFLD. However, this
302 assessment was weakened by sample bias and suboptimal inter-observer reproducibility [32–34].
303 Non-invasive tests have been developed and validated to diagnose liver steatosis and fibrosis. For
304 example, the hepatic steatosis index (HSI) evaluates steatosis with acceptable sensitivity and
305 specificity [35]. The Fibromax[®] algorithm developed by Biopredictive[™] is a combination of three
306 tests Steatotest, Nashtest and Fibrotest that respectively evaluate the stages of steatosis,
307 nonalcoholic steatohepatitis (NASH) and fibrosis [36,37]. FibroMeter[®] NAFLD (FMN) is another
308 non-invasive test with a high performance and provides reliable diagnosis of significant fibrosis
309 [38,39].

310 Beyond these limitations, our IPDMA approach had several strengths unique in the field. Using
311 this methodology, we were able to use consistent inclusion and exclusion criteria together with
312 OSA and COPD severity indices across studies; missing data were accounted for at the individual
313 level; and results for specific subgroups of participants were assessed across individuals, which
314 reduced between-dataset heterogeneity [16]. Moreover, we used causal mediation analysis to
315 assess the direct and indirect effects of OSA mediated by BMI on liver diseases.

316

317 **Conclusion**

318 Our results are robust enough to accept a significant association between COPD, OSA and
319 NAFLD. Personalized medicine is one of the main challenges in chronic diseases. To better define
320 the appropriate treatment for a single patient there is a need for a better phenotyping and
321 validation of combinations of biomarkers in order to characterize consequences at the level of
322 organ damage that are linked to hard outcomes and prognosis. The question for clinical practice is
323 how aggressively should the clinician screen for NAFLD in OSA and COPD patients, and vice-versa
324 [9,26] ? Which is the most simple and most reliable technique to do that? There are currently no
325 validated medications to treat NAFLD, although several promising drugs may be on the horizon
326 [40].

327 Weight reduction and exercise are universally recommended in NAFLD but are also the main
328 targets of COPD and OSA therapies. In multimorbid patients combining several chronic diseases, a
329 focus on the liver is probably important for assessing end-organ target damage and evaluating the
330 efficacy of single disease treatments.

331

332

333 **Acknowledgements**

334 We thank Alison Foote (Research division, Grenoble Alpes University Hospital, France) for critical
335 reading and editing.

336

337 **References**

338 1. Younossi ZM. Non-alcoholic fatty liver disease - A global public health perspective. *J. Hepatol.* 2018;

- 339 .
- 340 2. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of
341 nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatol.*
342 *Baltim. Md* 2016; 64: 73–84.
- 343 3. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ, American
344 Association for the Study of Liver Diseases, American College of Gastroenterology, American
345 Gastroenterological Association. The diagnosis and management of non-alcoholic fatty liver disease:
346 Practice guideline by the American Association for the Study of Liver Diseases, American College of
347 Gastroenterology, and the American Gastroenterological Association. *Am. J. Gastroenterol.* 2012; 107: 811–
348 826.
- 349 4. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease
350 or cirrhosis. *Nat. Rev. Gastroenterol. Hepatol.* 2013; 10: 330–344.
- 351 5. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of
352 incident cardiovascular disease: A meta-analysis. *J. Hepatol.* 2016; 65: 589–600.
- 353 6. Lévy P, Kohler M, McNicholas WT, Barbé F, McEvoy RD, Somers VK, Lavie L, Pépin J-L. Obstructive
354 sleep apnoea syndrome. *Nat. Rev. Dis. Primer* 2015; 1: 15015.
- 355 7. Vanfleteren LEGW. Does COPD stand for “COMorbidity with Pulmonary Disease”? *Eur. Respir. J.*
356 2015; 45: 14–17.
- 357 8. Aron-Wisnewsky J, Clement K, Pépin J-L. Nonalcoholic fatty liver disease and obstructive sleep
358 apnea. *Metabolism.* 2016; 65: 1124–1135.
- 359 9. Mesarwi OA, Loomba R, Malhotra A. Obstructive Sleep Apnea, Hypoxia, and Nonalcoholic Fatty
360 Liver Disease. *Am. J. Respir. Crit. Care Med.* 2018; .
- 361 10. Labarca G, Gower J, Lamperti L, Dreyse J, Jorquera J. Chronic intermittent hypoxia in obstructive
362 sleep apnea: a narrative review from pathophysiological pathways to a precision clinical approach. *Sleep*
363 *Breath. Schlaf Atm.* 2019; .
- 364 11. Ding H, Huang J-F, Xie H-S, Wang B-Y, Lin T, Zhao J-M, Lin Q-C. The association between
365 glycometabolism and nonalcoholic fatty liver disease in patients with obstructive sleep apnea. *Sleep Breath.*
366 *Schlaf Atm.* 2019; 23: 373–378.
- 367 12. Viglino D, Jullian-Desayes I, Minoves M, Aron-Wisnewsky J, Leroy V, Zarski J-P, Tamisier R, Joyeux-
368 Faure M, Pépin J-L. Nonalcoholic fatty liver disease in chronic obstructive pulmonary disease. *Eur. Respir. J.*
369 2017; 49.
- 370 13. Viglino D, Plazanet A, Bailly S, Benmerad M, Jullian-Desayes I, Tamisier R, Leroy V, Zarski J-P,
371 Maignan M, Joyeux-Faure M, Pépin J-L. Impact of Non-alcoholic Fatty Liver Disease on long-term
372 cardiovascular events and death in Chronic Obstructive Pulmonary Disease. *Sci. Rep.* 2018; 8: 16559.
- 373 14. Musso G, Cassader M, Olivetti C, Rosina F, Carbone G, Gambino R. Association of obstructive sleep
374 apnoea with the presence and severity of non-alcoholic fatty liver disease. A systematic review and meta-
375 analysis. *Obes. Rev. Off. J. Int. Assoc. Study Obes.* 2013; 14: 417–431.

- 376 15. Jin S, Jiang S, Hu A. Association between obstructive sleep apnea and non-alcoholic fatty liver
377 disease: a systematic review and meta-analysis. *Sleep Breath. Schlaf Atm.* 2018; 22: 841–851.
- 378 16. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct,
379 and reporting. *BMJ* 2010; 340: c221.
- 380 17. Trzepizur W, Le Vaillant M, Meslier N, Pigeanne T, Masson P, Humeau MP, Bizieux-Thaminy A,
381 Goupil F, Chollet S, Ducluzeau PH, Gagnadoux F, Institut de Recherche en Santé Respiratoire des Pays de la
382 Loire (IRSR) Sleep Cohort Group. Independent association between nocturnal intermittent hypoxemia and
383 metabolic dyslipidemia. *Chest* 2013; 143: 1584–1589.
- 384 18. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S,
385 Quan SF, Redline S, Strohl KP, Davidson Ward SL, Tangredi MM, American Academy of Sleep Medicine.
386 Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and
387 Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of
388 Sleep Medicine. *J. Clin. Sleep Med. JCSM Off. Publ. Am. Acad. Sleep Med.* 2012; 8: 597–619.
- 389 19. Song JH, Lee C-H, Um S-J, Park YB, Yoo KH, Jung KS, Lee S-D, Oh Y-M, Lee JH, Kim EK, Kim DK, KOLD,
390 KOCOSS, and SNU airway registry investigators. Clinical impacts of the classification by 2017 GOLD guideline
391 comparing previous ones on outcomes of COPD in real-world cohorts. *Int. J. Chron. Obstruct. Pulmon. Dis.*
392 2018; 13: 3473–3484.
- 393 20. Trzepizur W, Boursier J, Le Vaillant M, Ducluzeau P-H, Dubois S, Henni S, Abraham P, Aubé C, Calès
394 P, Gagnadoux F, on the behalf of the METABOL group. Increased liver stiffness in patients with severe sleep
395 apnoea and metabolic comorbidities. *Eur. Respir. J.* 2018; 51.
- 396 21. Trzepizur W, Boursier J, Mansour Y, Le Vaillant M, Chollet S, Pigeanne T, Bizieux-Thaminy A,
397 Humeau M-P, Alizon C, Goupil F, Meslier N, Priou P, Calès P, Gagnadoux F, Institut de Recherche en Santé
398 Respiratoire des Pays de la Loire Sleep Cohort Group. Association Between Severity of Obstructive Sleep
399 Apnea and Blood Markers of Liver Injury. *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol.*
400 *Assoc.* 2016; .
- 401 22. Jullian-Desayes I, Tamisier R, Zarski J-P, Aron-Wisnewsky J, Launois-Rollinat SH, Trocme C, Levy P,
402 Joyeux-Faure M, Pepin J-L. Impact of effective versus sham continuous positive airway pressure on liver
403 injury in obstructive sleep apnoea: Data from randomized trials. *Respirol. Carlton Vic* 2016; 21: 378–385.
- 404 23. Lange T, Hansen KW, Sørensen R, Galatius S. Applied mediation analyses: a review and tutorial.
405 *Epidemiol. Health* 2017; 39: e2017035.
- 406 24. VanderWeele TJ. Mediation Analysis: A Practitioner’s Guide. *Annu. Rev. Public Health* 2016; 37: 17–
407 32.
- 408 25. VanderWeele TJ. A three-way decomposition of a total effect into direct, indirect, and interactive
409 effects. *Epidemiol. Camb. Mass* 2013; 24: 224–232.
- 410 26. Lonardo A, Nascimbeni F, Ponz de Leon M. Nonalcoholic fatty liver disease and COPD: is it time to
411 cross the diaphragm? *Eur. Respir. J.* 2017; 49.
- 412 27. Jullian-Desayes I, Joyeux-Faure M, Tamisier R, Launois S, Borel A-L, Levy P, Pepin J-L. Impact of

- 413 obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers:
414 a systematic review from sham CPAP randomized controlled trials. *Sleep Med. Rev.* 2015; 21: 23–38.
- 415 28. Labarca G, Cruz R, Jorquera J. Continuous Positive Airway Pressure in Patients With Obstructive
416 Sleep Apnea and Non-Alcoholic Steatohepatitis: A Systematic Review and Meta-Analysis. *J. Clin. Sleep Med.*
417 *JCSM Off. Publ. Am. Acad. Sleep Med.* 2018; 14: 133–139.
- 418 29. Chirinos JA, Gurubhagavatula I, Teff K, Rader DJ, Wadden TA, Townsend R, Foster GD, Maislin G,
419 Saif H, Broderick P, Chittams J, Hanlon AL, Pack AI. CPAP, weight loss, or both for obstructive sleep apnea.
420 *N. Engl. J. Med.* 2014; 370: 2265–2275.
- 421 30. Vivodtzev I, Tamisier R, Croteau M, Borel J-C, Grangier A, Wuyam B, Lévy P, Minville C, Sériès F,
422 Maltais F, Pépin J-L. Ventilatory support or respiratory muscle training as adjuncts to exercise in obese
423 CPAP-treated patients with obstructive sleep apnoea: a randomised controlled trial. *Thorax* 2018; .
- 424 31. Hudgel DW, Patel SR, Ahasic AM, Bartlett SJ, Bessesen DH, Coaker MA, Fiander PM, Grunstein RR,
425 Gurubhagavatula I, Kapur VK, Lettieri CJ, Naughton MT, Owens RL, Pepin J-LD, Tuomilehto H, Wilson KC,
426 American Thoracic Society Assembly on Sleep and Respiratory Neurobiology. The Role of Weight
427 Management in the Treatment of Adult Obstructive Sleep Apnea. An Official American Thoracic Society
428 Clinical Practice Guideline. *Am. J. Respir. Crit. Care Med.* 2018; 198: e70–e87.
- 429 32. Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T,
430 LIDO Study Group. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology*
431 2005; 128: 1898–1906.
- 432 33. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu Y-C,
433 Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ, Nonalcoholic Steatohepatitis Clinical
434 Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver
435 disease. *Hepatology. Baltim. Md* 2005; 41: 1313–1321.
- 436 34. Boursier J, Anty R, Vonghia L, Moal V, Vanwolleghem T, Canivet CM, Michalak S, Bonnafous S,
437 Michielsen P, Oberti F, Iannelli A, Van Gaal L, Patouraux S, Blanchet O, Verrijken A, Gual P, Rousselet M-C,
438 Driessen A, Hunault G, Bertrais S, Tran A, Calès P, Francque S. Screening for therapeutic trials and treatment
439 indication in clinical practice: MACK-3, a new blood test for the diagnosis of fibrotic NASH. *Aliment.*
440 *Pharmacol. Ther.* 2018; 47: 1387–1396.
- 441 35. Sumida Y, Nakajima A, Itoh Y. Limitations of liver biopsy and non-invasive diagnostic tests for the
442 diagnosis of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J. Gastroenterol.* 2014; 20:
443 475–485.
- 444 36. Morra R, Munteanu M, Imbert-Bismut F, Messous D, Ratziu V, Poynard T. FibroMAX: towards a new
445 universal biomarker of liver disease? *Expert Rev. Mol. Diagn.* 2007; 7: 481–490.
- 446 37. Munteanu M, Ratziu V, Morra R, Messous D, Imbert-Bismut F, Poynard T. Noninvasive biomarkers
447 for the screening of fibrosis, steatosis and steatohepatitis in patients with metabolic risk factors: FibroTest-
448 FibroMax experience. *J. Gastrointest. Liver Dis. JGLD* 2008; 17: 187–191.
- 449 38. Calès P, Lainé F, Boursier J, Deugnier Y, Moal V, Oberti F, Hunault G, Rousselet MC, Hubert I, Laafi J,
450 Ducluzeaux PH, Lunel F. Comparison of blood tests for liver fibrosis specific or not to NAFLD. *J. Hepatol.*

451 2009; 50: 165–173.

452 39. Siddiqui MS, Patidar KR, Boyett S, Luketic VA, Puri P, Sanyal AJ. Performance of non-invasive models
453 of fibrosis in predicting mild to moderate fibrosis in patients with non-alcoholic fatty liver disease. *Liver Int.*
454 *Off. J. Int. Assoc. Study Liver* 2016; 36: 572–579.

455 40. Lassailly G, Caiazzo R, Pattou F, Mathurin P. Perspectives on Treatment for Nonalcoholic
456 Steatohepatitis. *Gastroenterology* 2016; 150: 1835–1848.

457

458

459

460

461

462

463

464

465

466

467

468

469

470

471

472

473

474

475

476

477 **Table 1. Characteristics of the study population with and without steatosis**

	No steatosis n=536	Steatosis n=1,584	p- value
Age	60 [50 ; 68]	59 [49 ; 67]	0.04
Male gender	352 (65.7)	950 (60)	0.02
BMI (kg/m ²)	24.5 [22.6 ; 26.1]	31.6 [28.7 ; 36.2]	<.01
Hypertension	128 (24.1)	705 (44.9)	<.01
Dyslipidemia	104 (19.5)	489 (31.2)	<.01
Diabetes	19 (3.5)	274 (17.3)	<.01
AHI	18 [6 ; 31]	30.8 [16 ; 47]	<.01
Epworth Sleepiness Scale	10 [6 ; 14]	10 [6 ; 13]	0.21
Mean SaO ₂	94 [93 ; 95]	93 [91.4 ; 94]	<.01
Cholesterol total (mmol/L)	5.2 [4.6 ; 6]	5.2 [4.4 ; 5.9]	0.33
HDL (mmol/L)	1.4 [1.2 ; 1.7]	1.2 [0.9 ; 1.4]	<.01
Triglycerides (g/L)	0.9 [0.7 ; 1.2]	1.3 [0.9 ; 1.8]	<.01
Glycemia (mmol/L)	5.1 [4.8 ; 5.5]	5.6 [5.1 ; 6.2]	<.01
ALAT (UI/L)	18 [14 ; 23]	30 [22 ; 41]	<.01
ASAT (UI/L)	20 [17 ; 24]	21 [17 ; 26]	<.01
HSI	32.9 [30.6 ; 34.5]	44.5 [40.2 ; 50.9]	<.01

478
479 Data are presented as median [interquartile range] or number (percentage). AHI, apnea hypopnea
480 index; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BMI, body mass index;
481 HDL, high density lipoprotein; HSI, hepatic steatosis index.
482

483 **Table 2. Characteristics of the population with pulmonary function tests with and without**
 484 **steatosis**
 485

	No steatosis n=245	Steatosis n=788	p-value
Age	59 [50 ; 67]	59 [49 ; 67]	0.41
Male gender	179 (73.1)	479 (60.8)	<.01
BMI (kg/m ²)	24.5 [22.8 ; 26.2]	31.8 [28.8 ; 36.7]	<.01
Hypertension	50 (20.4)	341 (43.6)	<.01
Dyslipidemia	54 (22.2)	234 (30)	0.02
Diabetes	7 (2.9)	129 (16.4)	<.01
AHI	19.1 [9 ; 32]	31 [16 ; 47]	<.01
Epworth Sleepiness Scale	10 [7 ; 14]	10 [6 ; 14]	0.35
Mean SaO ₂	94 [93 ; 95]	93 [91 ; 94]	<.01
COPD	35 (14.3)	86 (10.9)	0.15
GOLD stages			0.74
1	16 (45.7)	34 (39.5)	
2	17 (48.6)	42 (48.8)	
3	2 (5.7)	9 (10.5)	
4	0 (0)	1 (1.2)	
AHI & GOLD stages			<.01
AHI≤30 & No COPD	147 (60)	345 (43.8)	
AHI≤30 & GOLD stage1	14 (5.7)	14 (1.8)	
AHI≤30 & GOLD stage>1	14 (5.7)	27 (3.4)	
AHI>30 & No COPD	63 (25.7)	357 (45.3)	
AHI>30 & GOLD stage1	2 (0.8)	20 (2.5)	
AHI>30 & GOLD stage>1	5 (2)	25 (3.2)	
Cholesterol total (mmol/L)	5.1 [4.4 ; 6]	5.2 [4.4 ; 5.9]	0.91
HDL (mmol/L)	1.4 [1.2 ; 1.7]	1.2 [1 ; 1.5]	<.01
Triglycerides (g/L)	1 [0.7 ; 1.4]	1.3 [1 ; 1.8]	<.01
Glycemia (mmol/L)	5.1 [4.8 ; 5.6]	5.7 [5.2 ; 6.3]	<.01
ALAT	19 [15 ; 23]	29 [21 ; 41]	<.01
ASAT	20 [17 ; 24]	21 [18 ; 27]	<.01
HSI	33.1 [30.9 ; 34.7]	44.1 [40 ; 50]	<.01

486
 487 Data are presented as median [interquartile range] or number (percentage). AHI, apnea hypopnea
 488 index; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BMI, body mass index;
 489 COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung
 490 Disease; HDL, high density lipoprotein; HSI, hepatic steatosis index.
 491

492 **Table 3. Characteristics of the study population with and without liver fibrosis**

493

	No fibrosis n=1,821	Fibrosis n=397	<i>p</i> -value
Age	57 [47 ; 64]	69 [62 ; 76]	<.01
Male gender	1067 (58.6)	300 (75.6)	<.01
BMI (kg/m ²)	28.7 [25.5 ; 33.3]	33.2 [29.7 ; 38.4]	<.01
Hypertension	597 (34.5)	241 (62.9)	<.01
Dyslipidemia	417 (24.1)	183 (48.4)	<.01
Diabetes	149 (8.6)	146 (37.8)	<.01
AHI	24 [11 ; 39]	36 [22 ; 53]	<.01
Epworth Sleepiness Scale	10 [6 ; 14]	8 [5 ; 12]	<.01
Mean SaO ₂	93 [92 ; 95]	92 [91 ; 93]	<.01
Cholesterol total (mmol/L)	5.3 [4.6 ; 6]	4.7 [3.9 ; 5.5]	<.01
HDL (mmol/L)	1.3 [1 ; 1.6]	1.2 [1 ; 1.5]	0.02
Triglycerides (g/L)	1.1 [0.8 ; 1.6]	1.3 [0.9 ; 1.8]	<.01
Glycemia (mmol/L)	5.3 [5 ; 5.8]	6.4 [5.6 ; 8.3]	<.01
Fibro Test	0.2 [0.1 ; 0.3]	0.6 [0.6 ; 0.7]	<.01
FibroMeter	0.1 [0 ; 0.2]	0.7 [0.6 ; 0.9]	<.01

494 Data are presented as median [interquartile range] or number (percentage). AHI, apnea hypopnea
 495 index; BMI, body mass index; HDL, high density lipoprotein.
 496
 497

498

499 **Table 4. Characteristics of the population with pulmonary function tests with and without**
 500 **fibrosis**

501

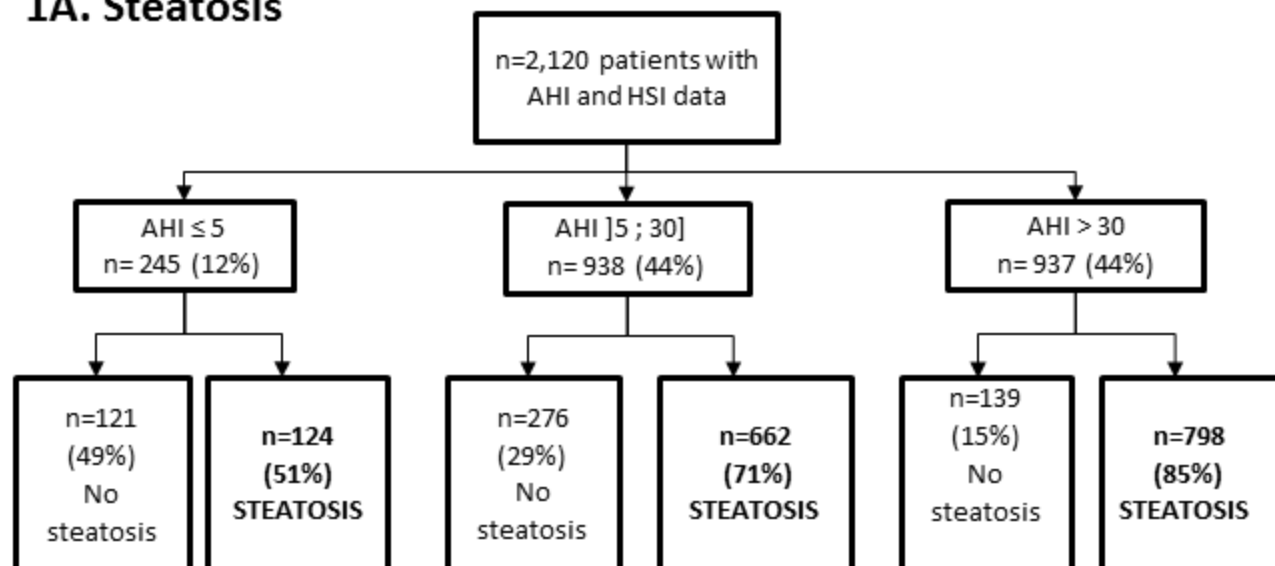
	No fibrosis n=854	Fibrosis n=213	<i>p</i> -value
Age	56.7 [47 ; 64]	69 [61 ; 75]	<.01
Male gender	511 (59.8)	167 (78.4)	<.01
BMI (kg/m ²)	29.3 [26 ; 33.7]	32.9 [29.4 ; 38.7]	<.01
Hypertension	271 (32.7)	123 (59.4)	<.01
Dyslipidemia	196 (23.7)	98 (47.8)	<.01
Diabetes	68 (8.2)	70 (33.7)	<.01
COPD	96 (11.2)	33 (15.5)	0.09
GOLD			
1	45 (46.9)	7 (21.2)	0.06
2	43 (44.8)	22 (66.7)	.
3-4	7 (7.3)	4 (12.1)	.
AHI	26 [14 ; 40]	37 [24 ; 53.5]	<.01
≤5	87 (10.2)	13 (6.1)	<.01
]5 ; 30]	417 (48.8)	65 (30.5)	.
>30	350 (41)	135 (63.4)	.
Epworth Sleepiness Scale	11 [7 ; 14]	9 [5 ; 12]	<.01
Mean nocturnal SaO ₂	93 [92 ; 95]	92 [91 ; 93.5]	<.01
Total cholesterol (mmol/L)	5.2 [4.6 ; 6]	4.8 [4.1 ; 5.6]	<.01
HDL (mmol/L)	1.3 [1 ; 1.6]	1.2 [1 ; 1.5]	<.01
Triglycerides (g/L)	1.2 [0.9 ; 1.7]	1.4 [1 ; 1.9]	<.01
Fasting glucose (mmol/L)	5.4 [5 ; 5.9]	6.3 [5.7 ; 8.1]	<.01
Fibro Test	0.2 [0.1 ; 0.3]	0.7 [0.6 ; 0.8]	<.01
FibroMeter	0.1 [0 ; 0.2]	0.7 [0.6 ; 0.9]	<.01

502
 503 Data are presented as median [interquartile range] or number (percentage). AHI, apnea hypopnea
 504 index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global
 505 Initiative for Chronic Obstructive Lung Disease; HDL, high density lipoprotein.
 506

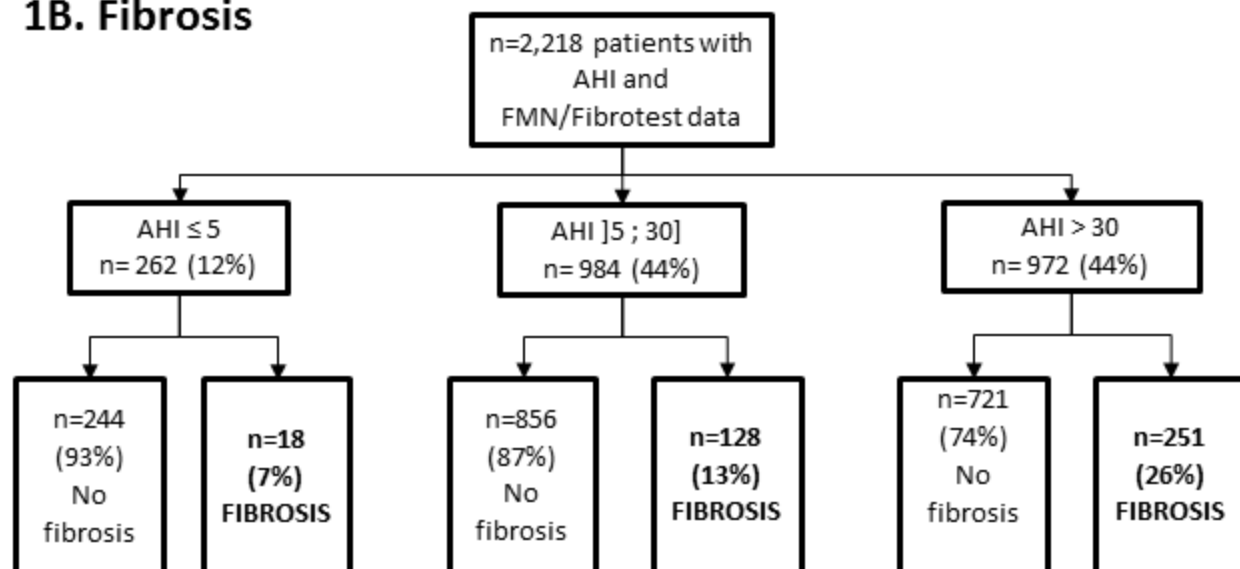
507 **Figure legends**

- 508
- 509 Figure 1. Flow-chart for steatosis (A) and fibrosis (B).
- 510
- 511 Figure 2. Multivariable analysis for steatosis in OSA (A), mediation analysis (B), COPD (C) and
- 512 overlap (D).
- 513
- 514 Figure 3. Multivariable analysis for fibrosis in OSA (A), mediation analysis (B), COPD (C) and overlap
- 515 (D).
- 516

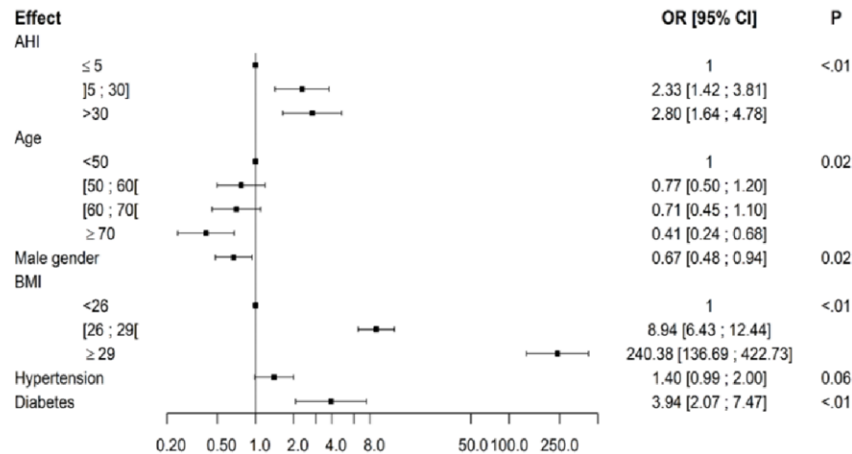
1A. Steatosis



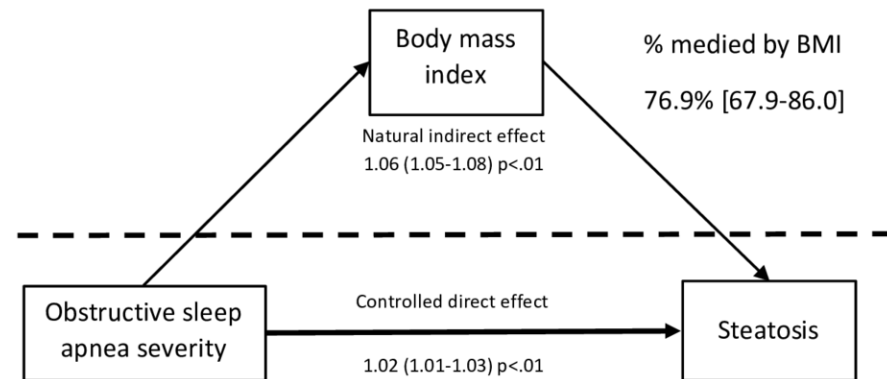
1B. Fibrosis



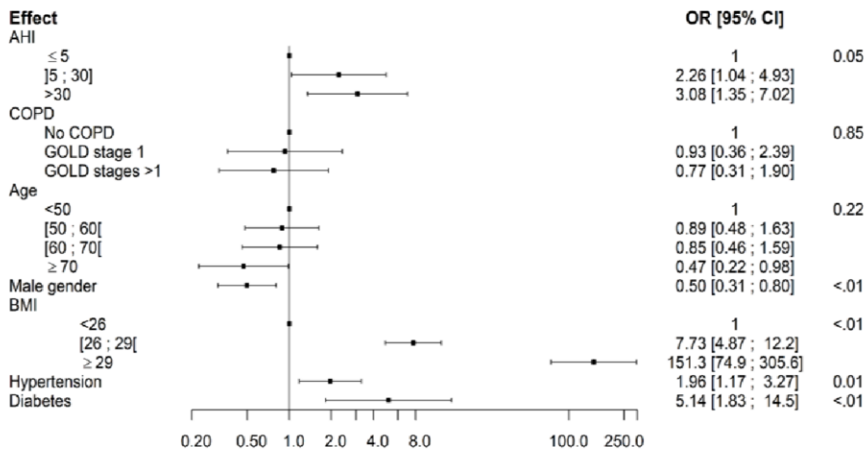
2A



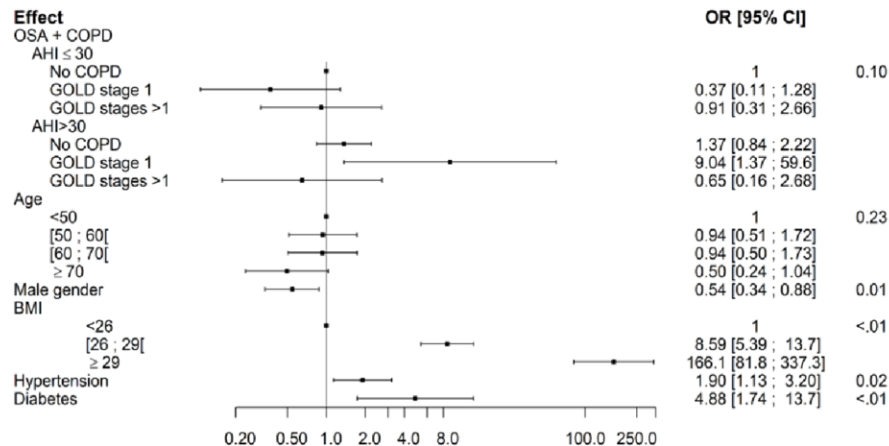
2B



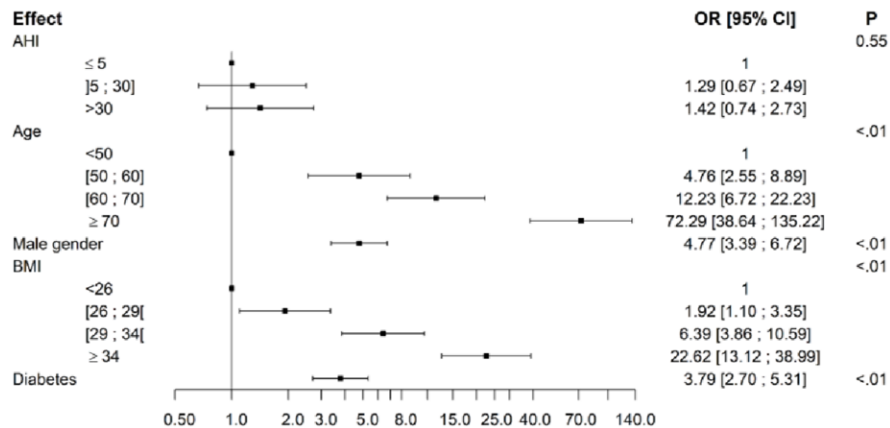
2C



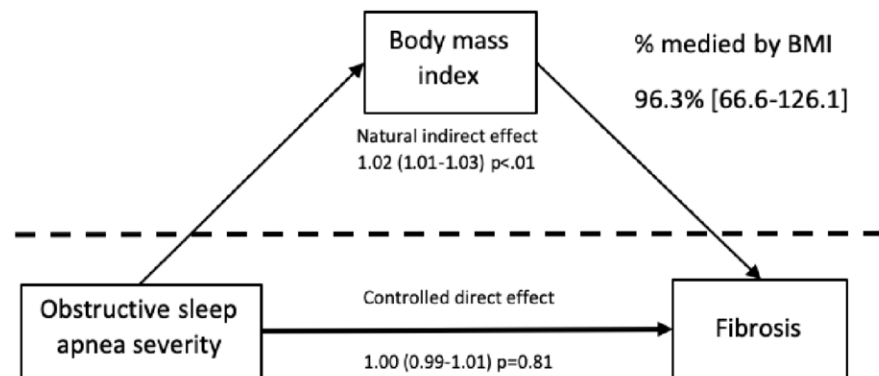
2D



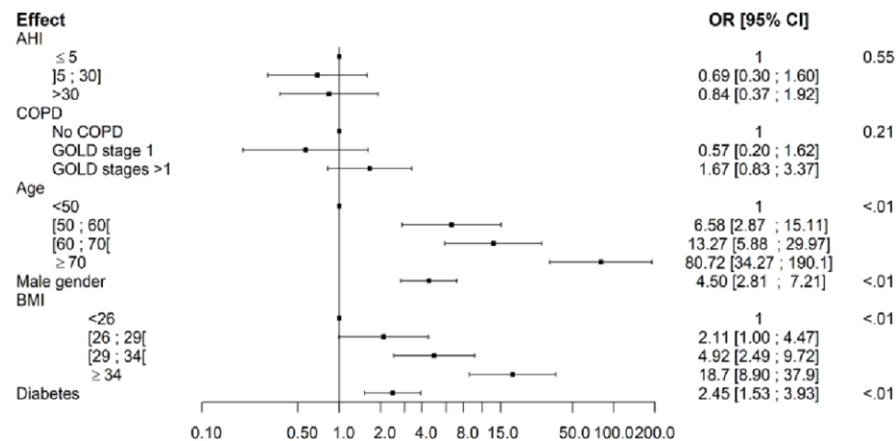
3A



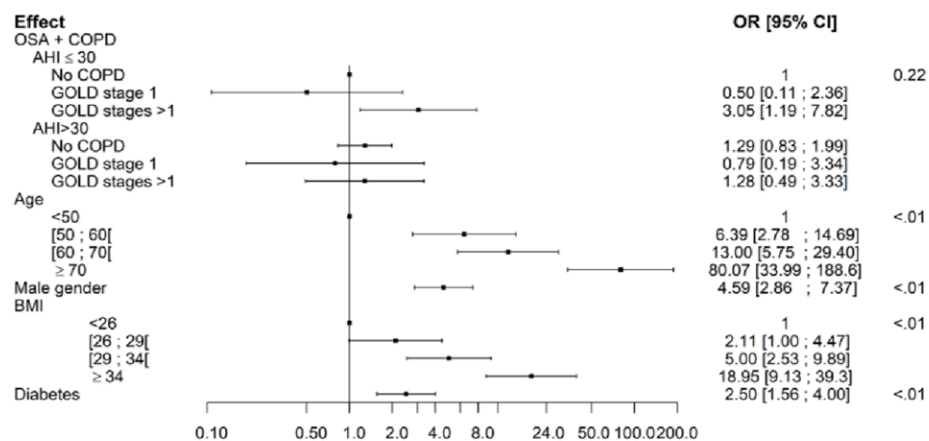
3B



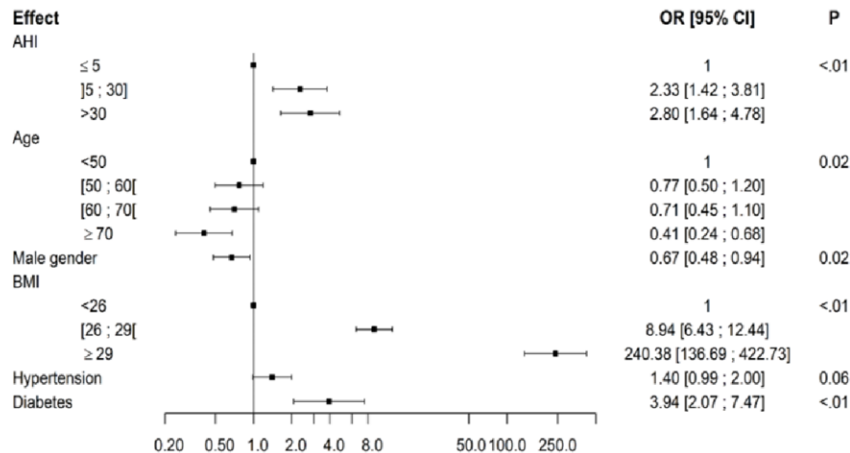
3C



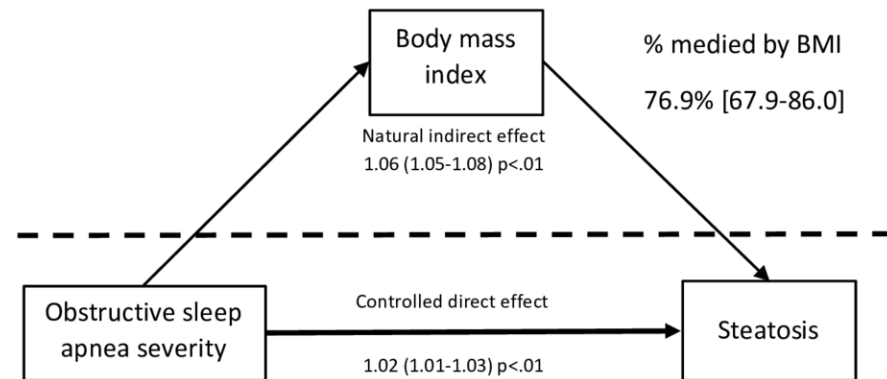
3D



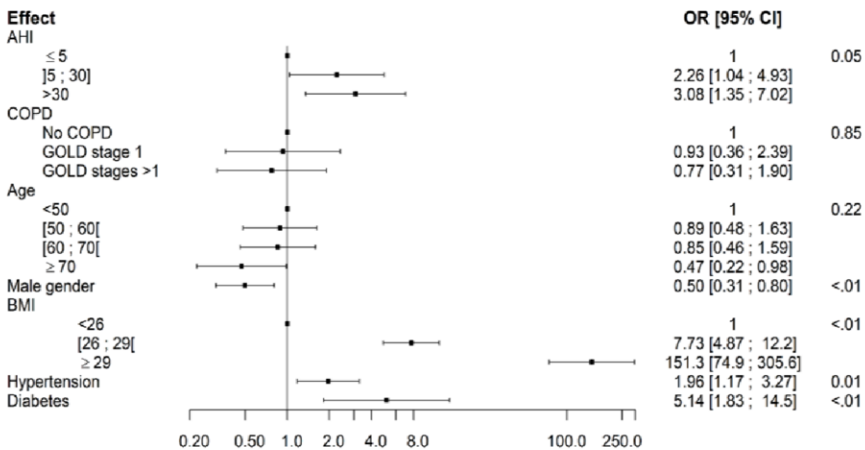
2A



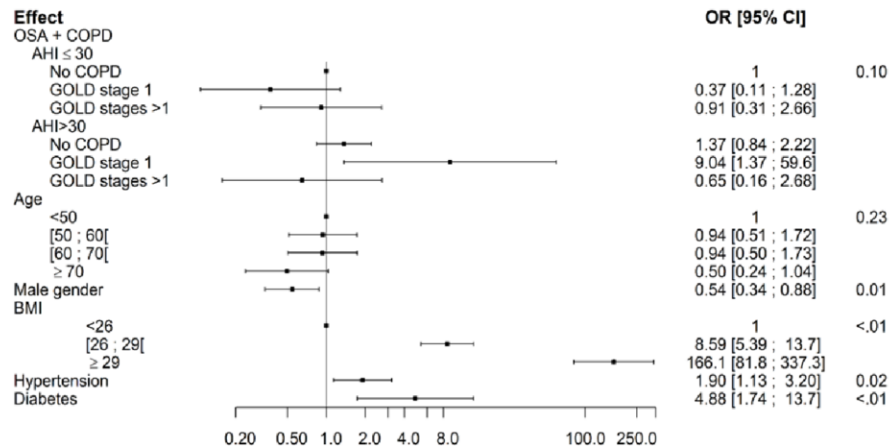
2B



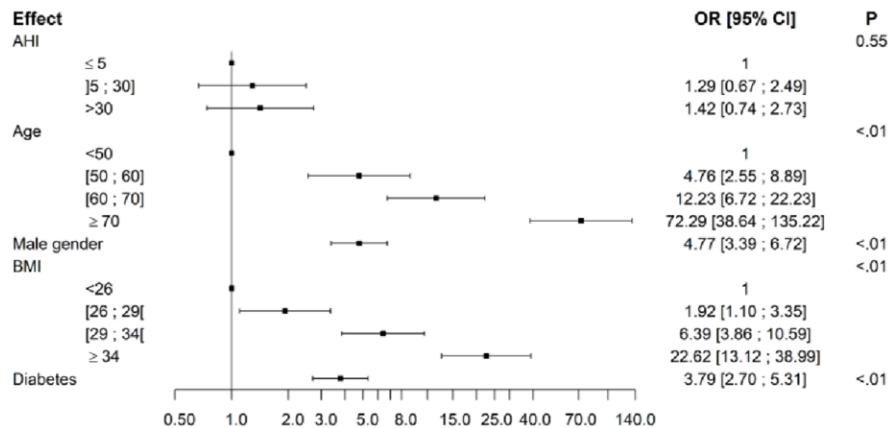
2C



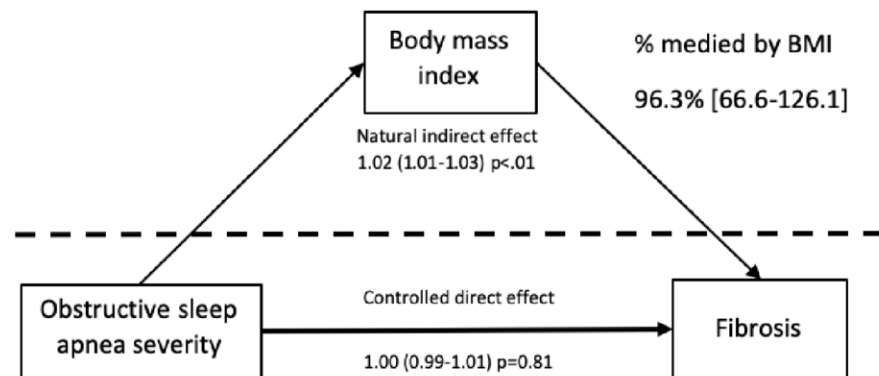
2D



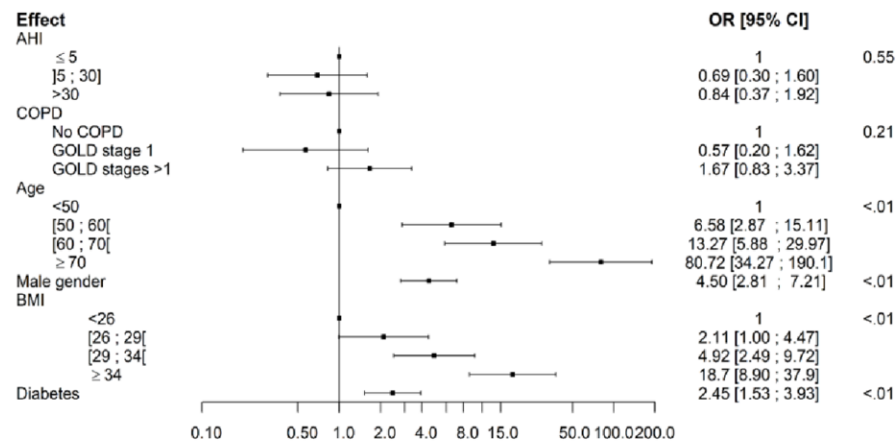
3A



3B



3C



3D

