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

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

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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

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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/m<sup>2</sup>,  
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/m<sup>2</sup>,  
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  $\alpha$ 2-macroglobulin, apolipoprotein  
168 A1, haptoglobin,  $\gamma$ -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 SaO<sub>2</sub>  
211 and minimum nocturnal SaO<sub>2</sub> 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 SaO<sub>2</sub>, 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<sup>®</sup> algorithm developed by Biopredictive<sup>™</sup> 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<sup>®</sup> 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

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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 <sup>2</sup> )	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 <sub>2</sub>	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

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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.  
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483 **Table 2. Characteristics of the population with pulmonary function tests with and without**  
 484 **steatosis**  
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	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 <sup>2</sup> )	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 <sub>2</sub>	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**

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	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 <sup>2</sup> )	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 <sub>2</sub>	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.  
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499 **Table 4. Characteristics of the population with pulmonary function tests with and without**  
 500 **fibrosis**

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	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 <sup>2</sup> )	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 <sub>2</sub>	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

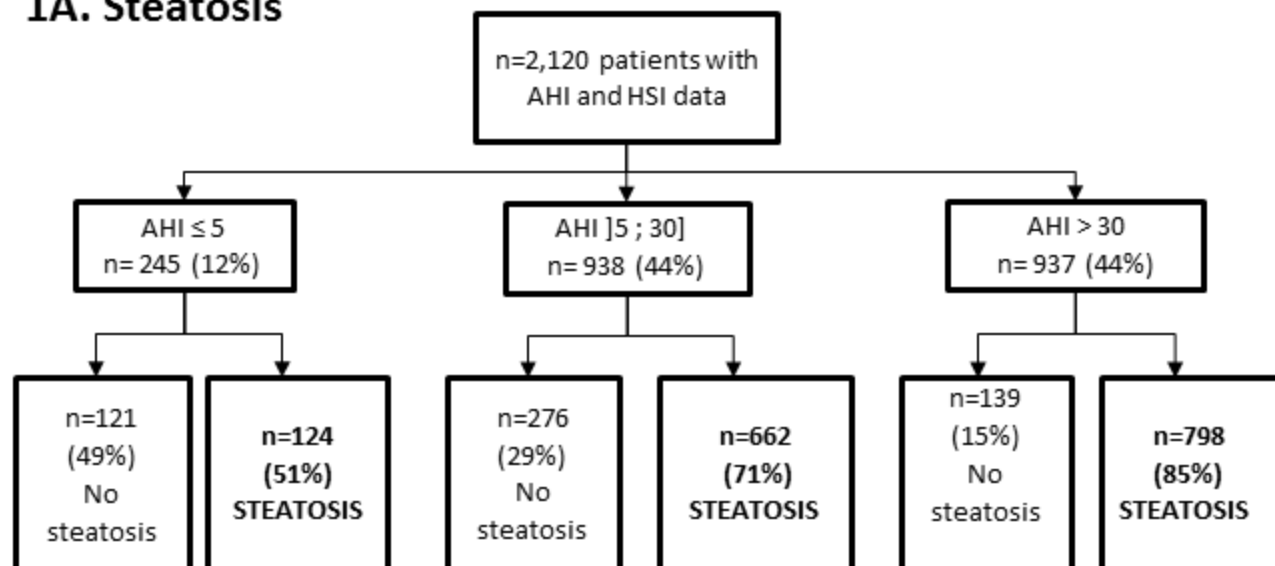
502  
 503 Data are presented as median [interquartile range] or number (percentage). AHI, apnea hypopnea  
 504 index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global  
 505 Initiative for Chronic Obstructive Lung Disease; HDL, high density lipoprotein.  
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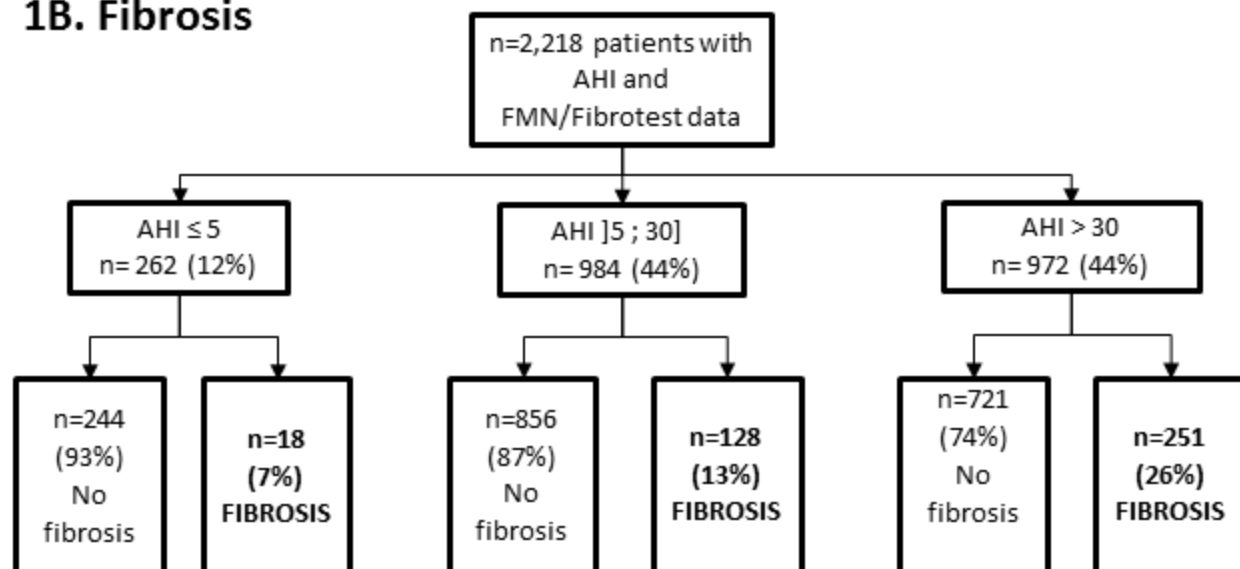
507 **Figure legends**

- 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).
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- 514 Figure 3. Multivariable analysis for fibrosis in OSA (A), mediation analysis (B), COPD (C) and overlap
- 515 (D).
- 516

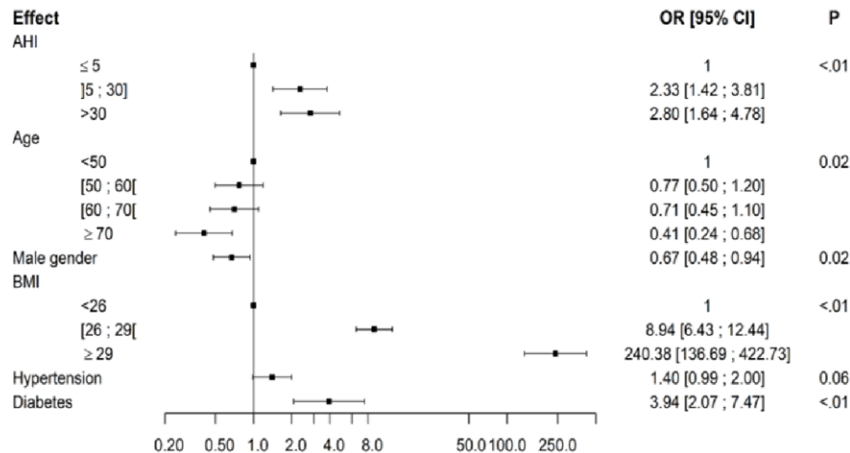
## 1A. Steatosis



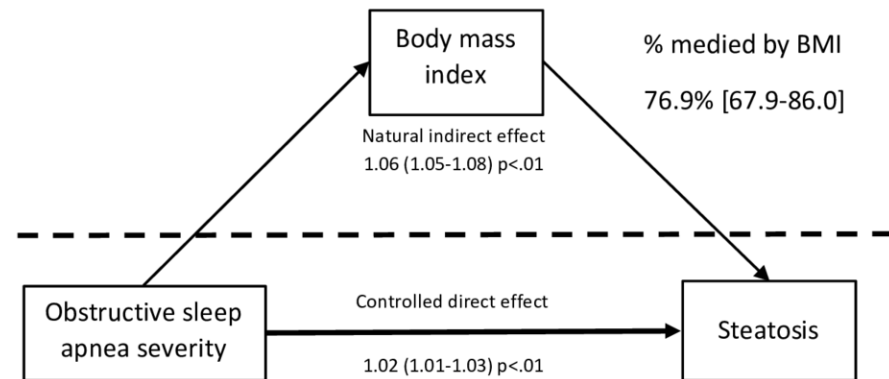
## 1B. Fibrosis



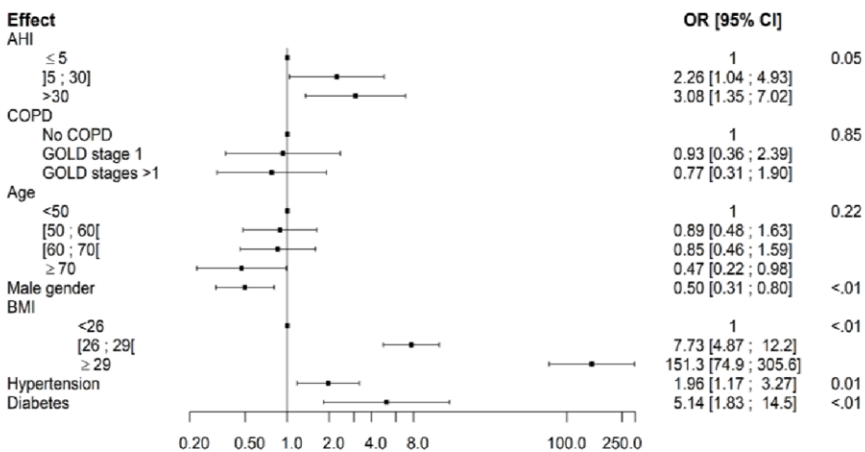
2A



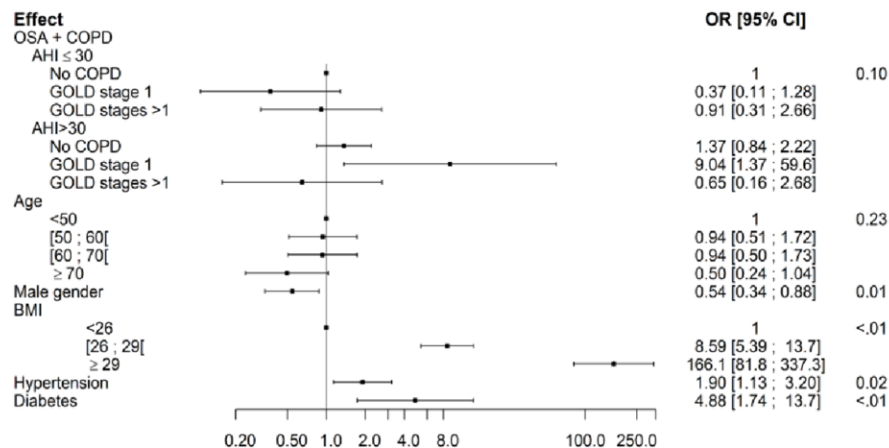
2B



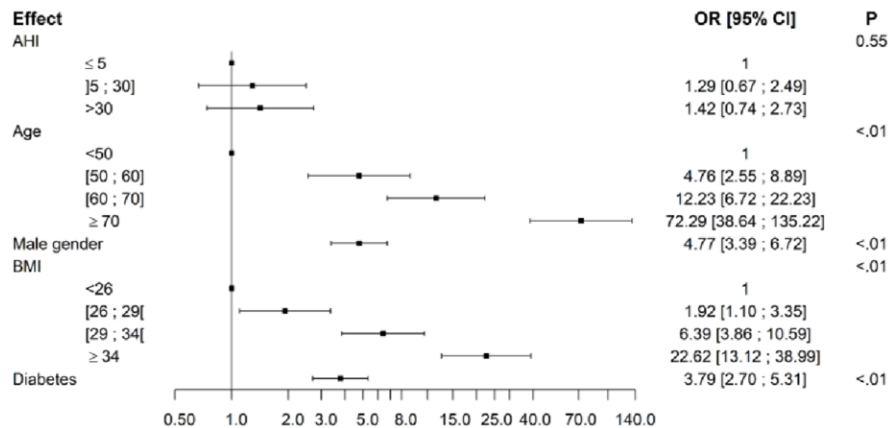
2C



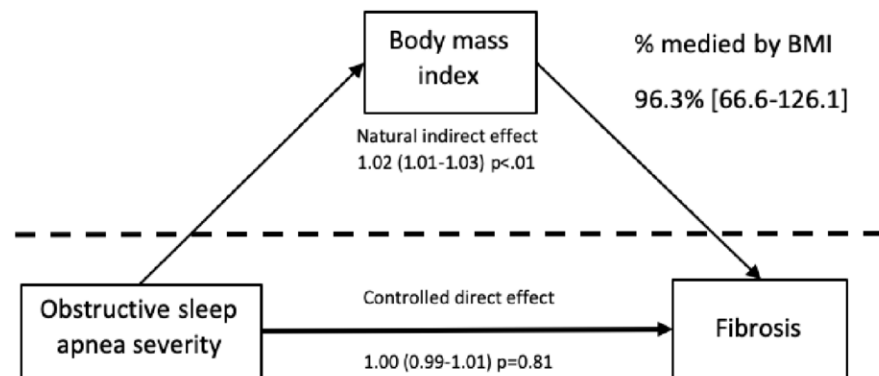
2D



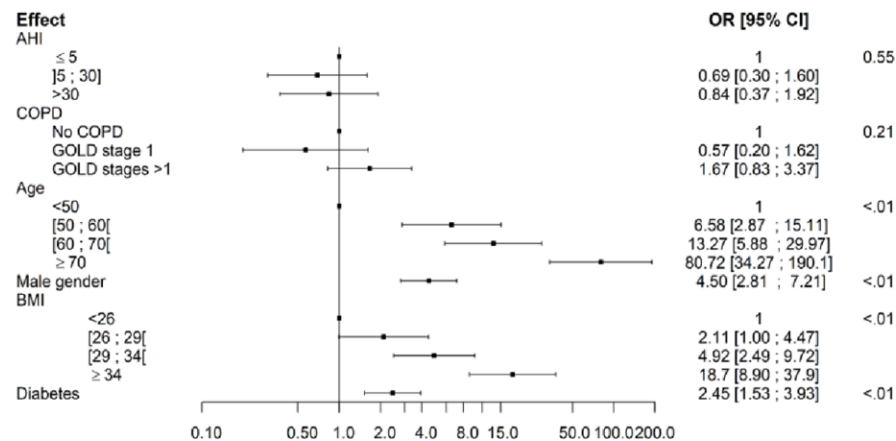
3A



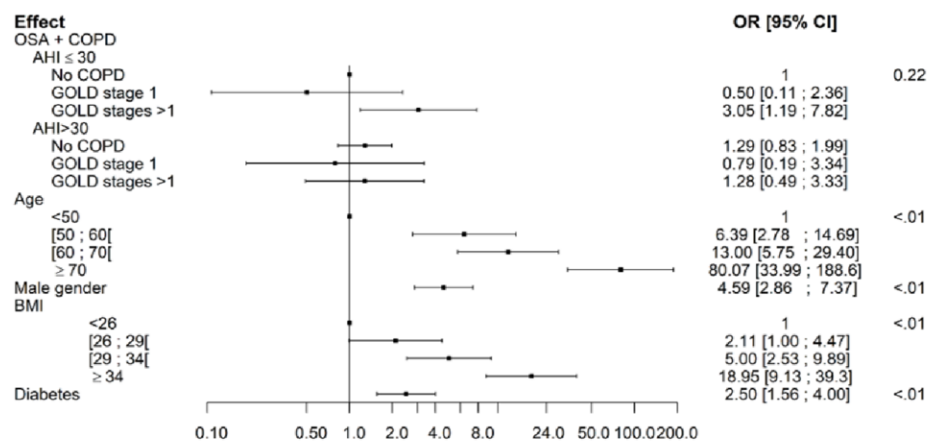
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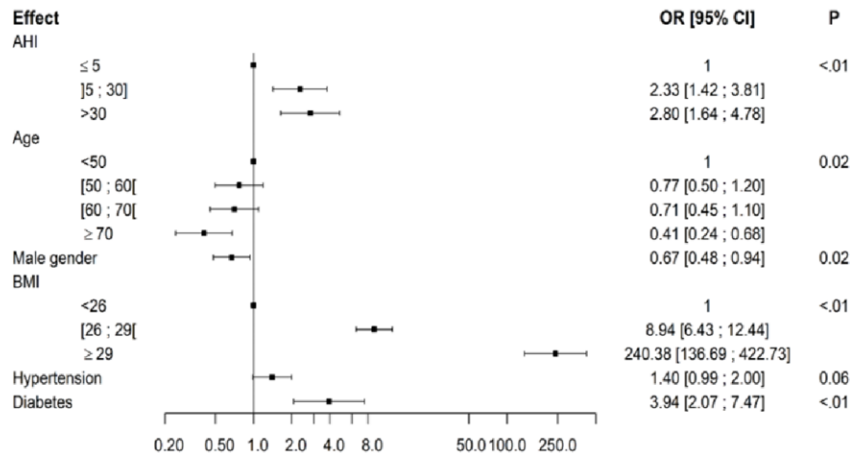
3C



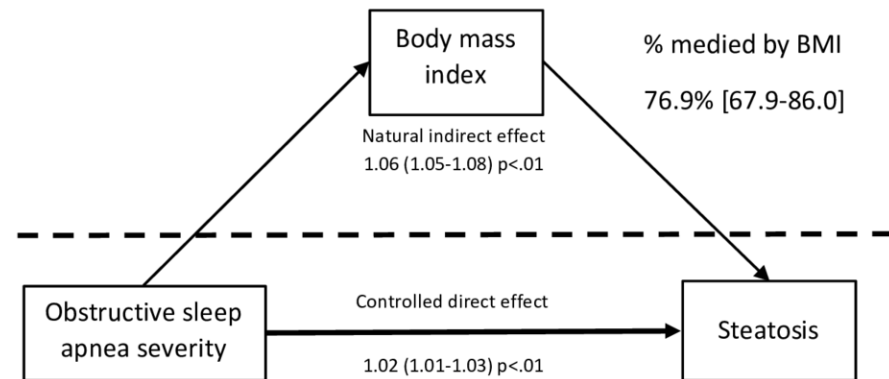
3D



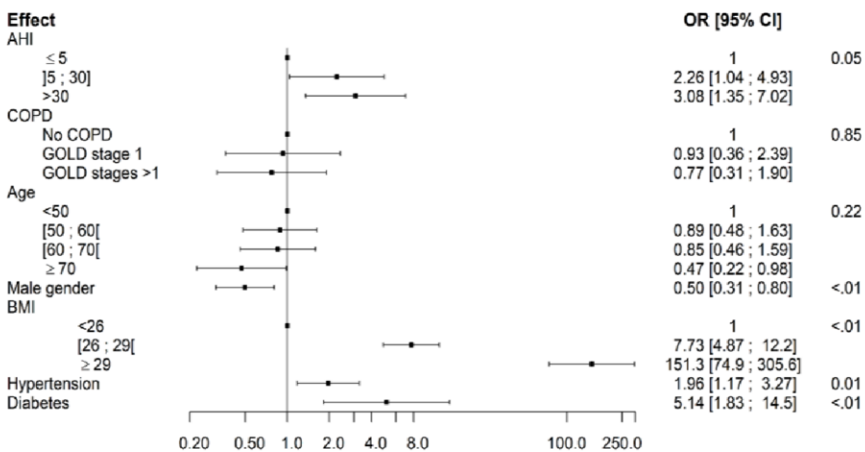
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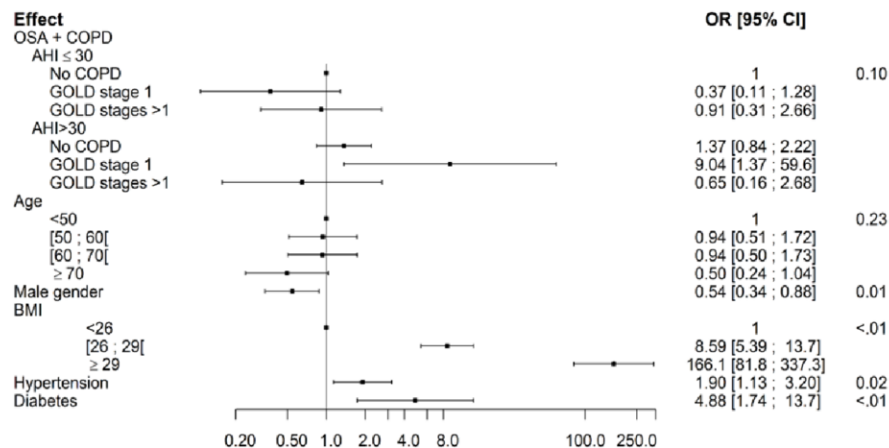
2B



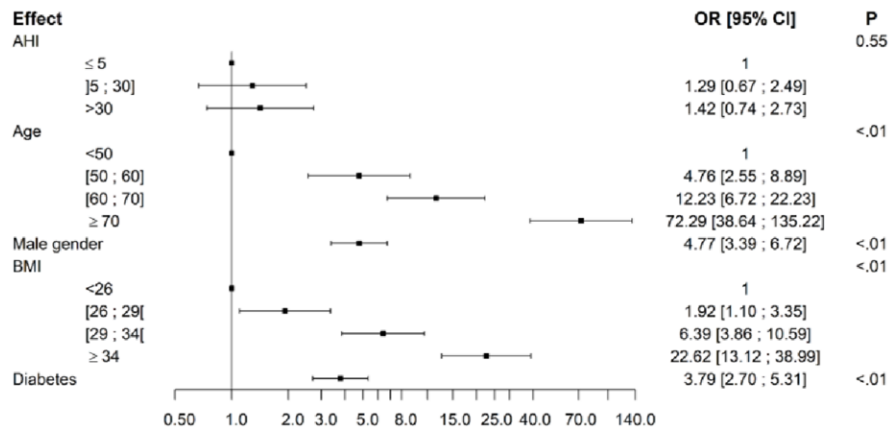
2C



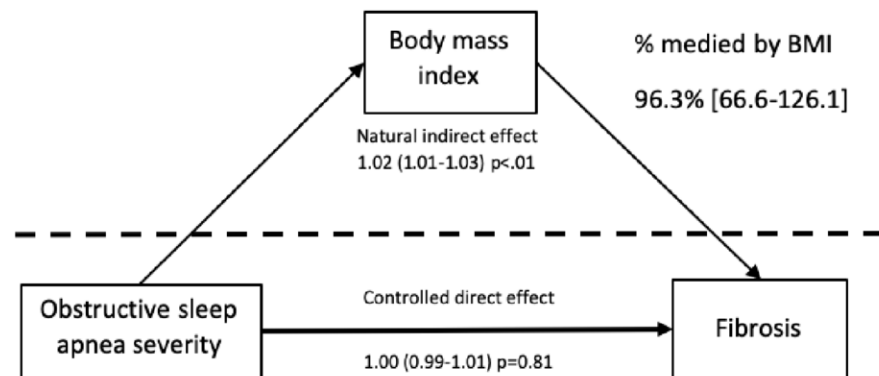
2D



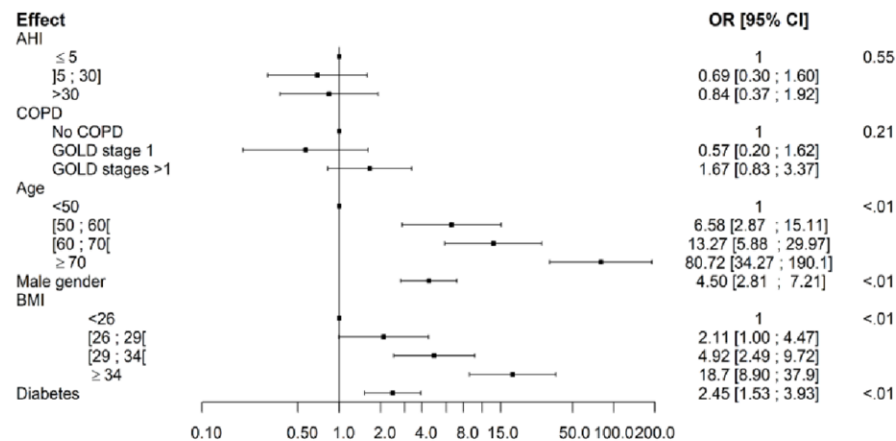
3A



3B



3C



3D

