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

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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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Abstract (249 words)

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

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

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

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

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

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

105

Introduction

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

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

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

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

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

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

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

Methods

Study population

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

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

Results

Steatosis prevalence and associated risk factors

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

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

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

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

Fibrosis prevalence and associated risk factors

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

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

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

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

Discussion

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

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

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

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

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

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

Beyond these limitations, our IPDMA approach had several strengths unique in the field. Using this methodology, we were able to use consistent inclusion and exclusion criteria together with OSA and COPD severity indices across studies; missing data were accounted for at the individual level; and results for specific subgroups of participants were assessed across individuals, which reduced between-dataset heterogeneity [16]. Moreover, we used causal mediation analysis to 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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336

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

	No steatosis n=536	Steatosis n=1,584	<i>p</i> - 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

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

Table 2. Characteristics of the population with pulmonary function tests with and without steatosis

	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

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

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

	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

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

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

	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

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

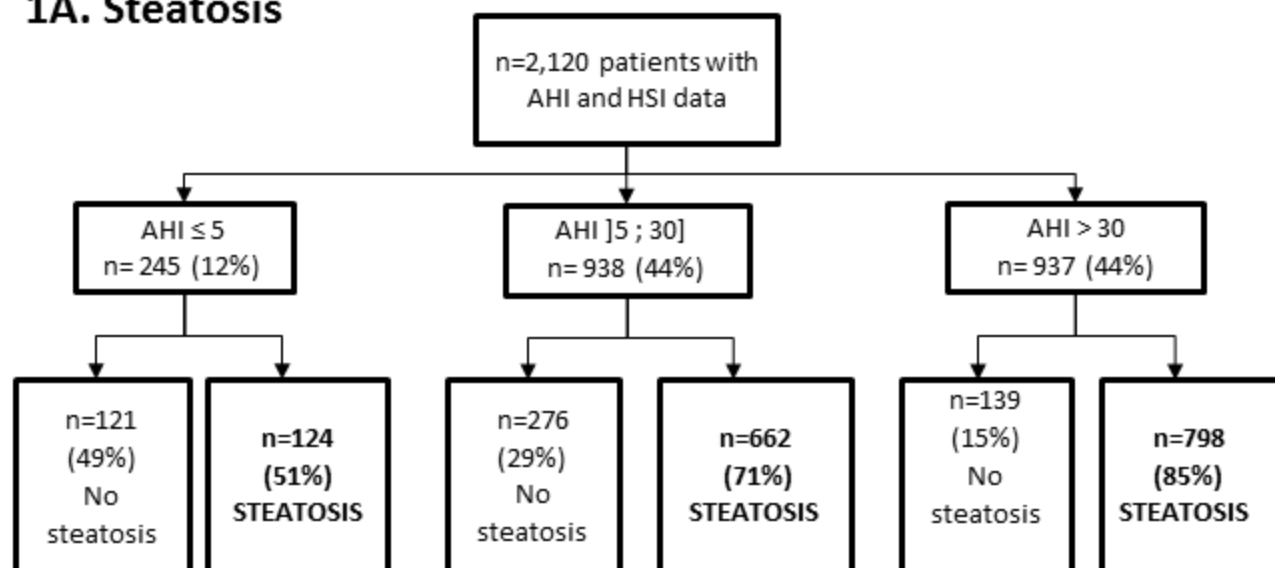
Figure legends

Figure 1. Flow-chart for steatosis (A) and fibrosis (B).

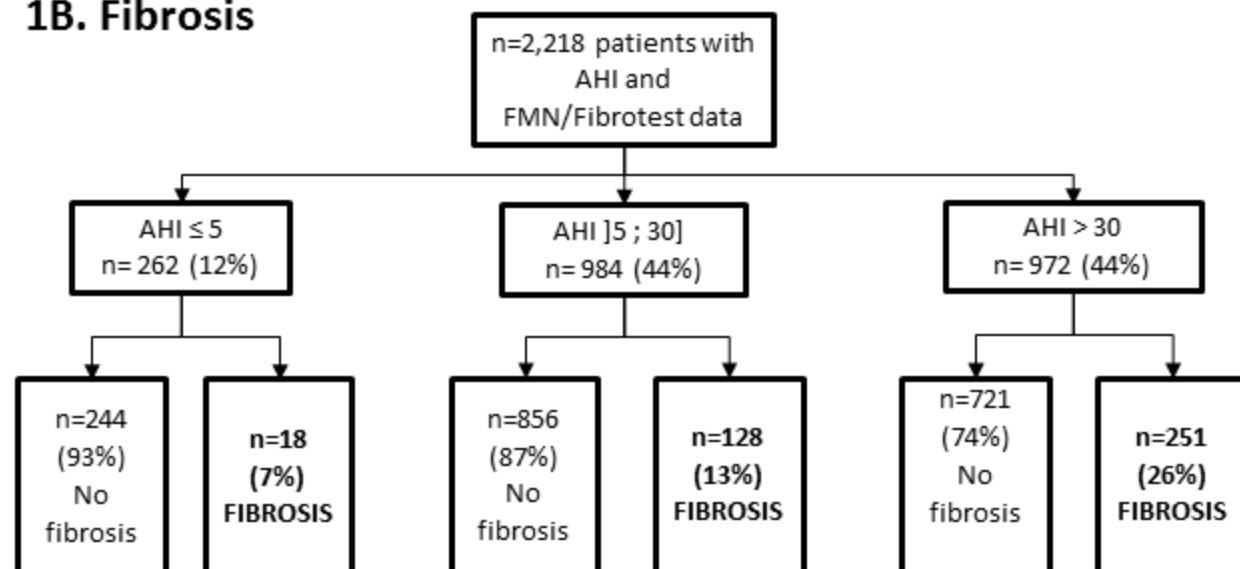
Figure 2. Multivariable analysis for steatosis in OSA (A), mediation analysis (B), COPD (C) and overlap (D).

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

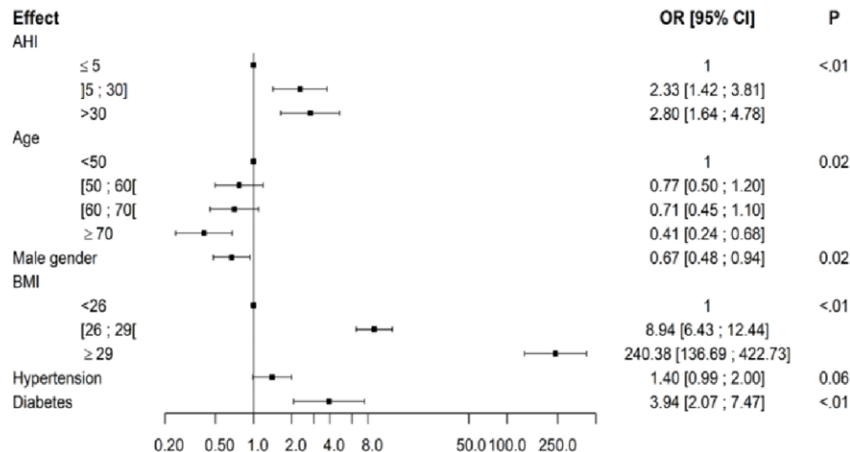
1A. Steatosis



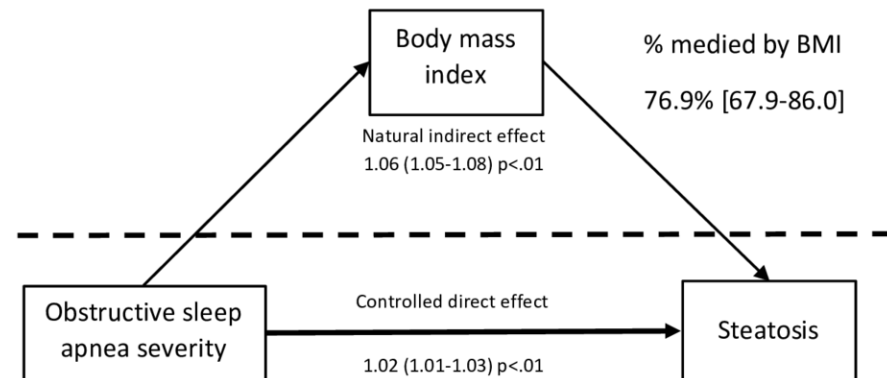
1B. Fibrosis



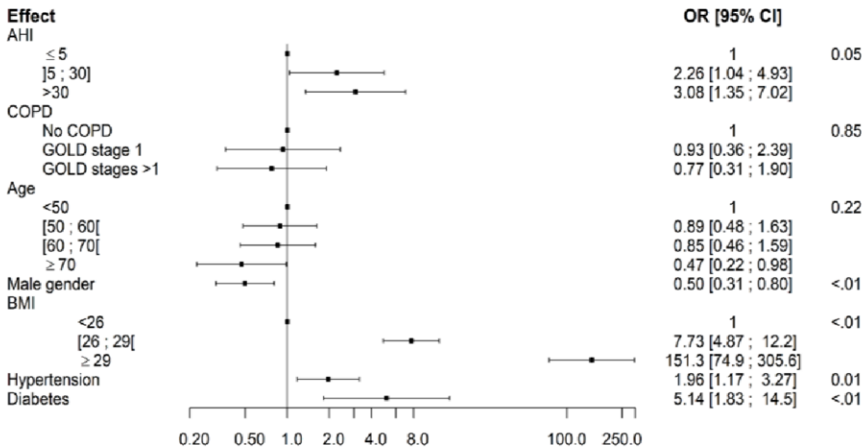
2A



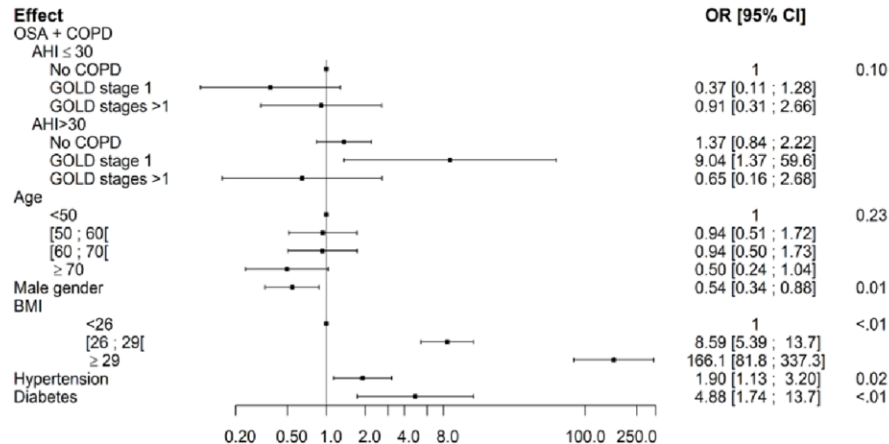
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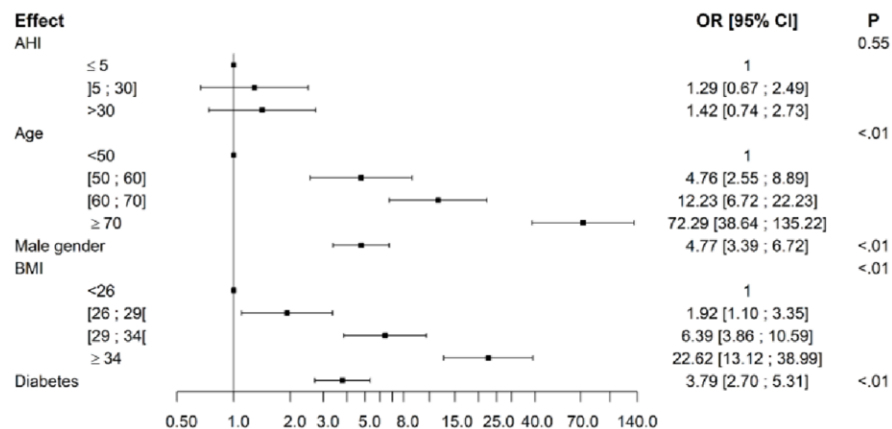
2C



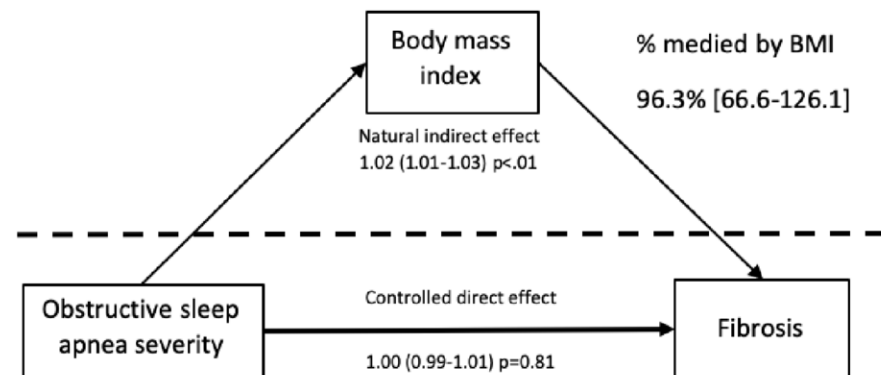
2D



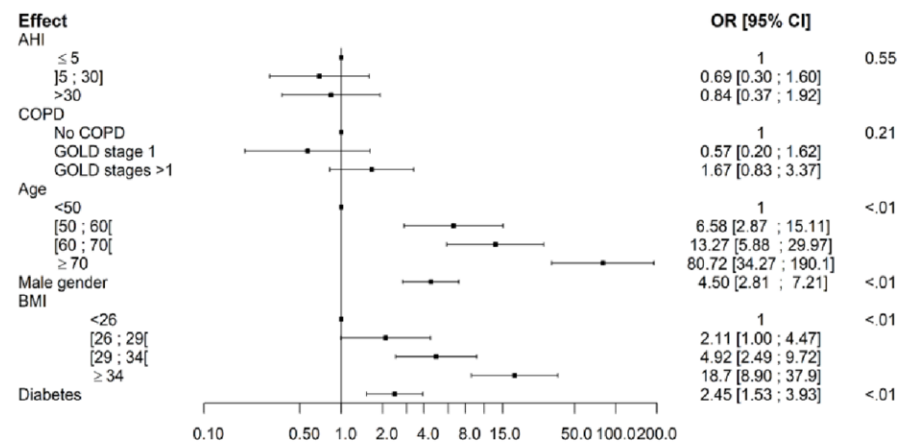
3A



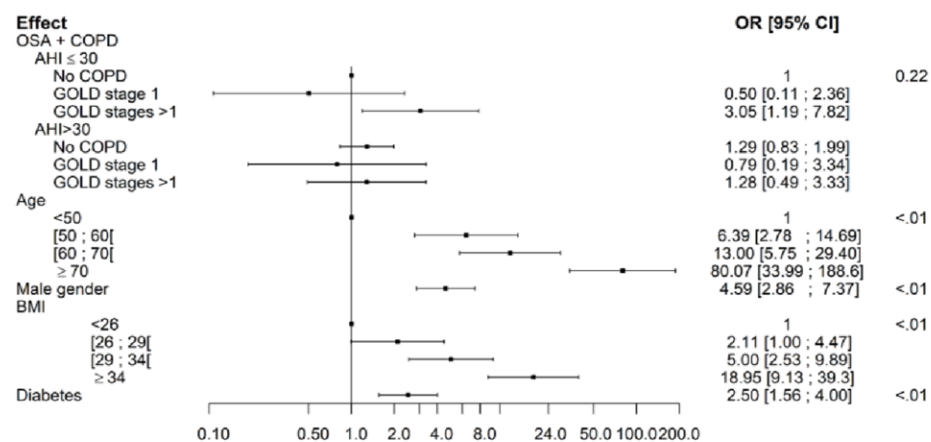
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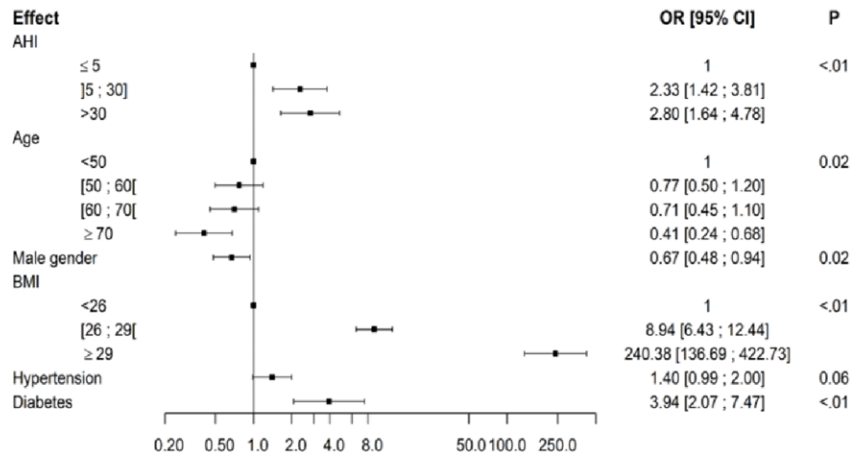
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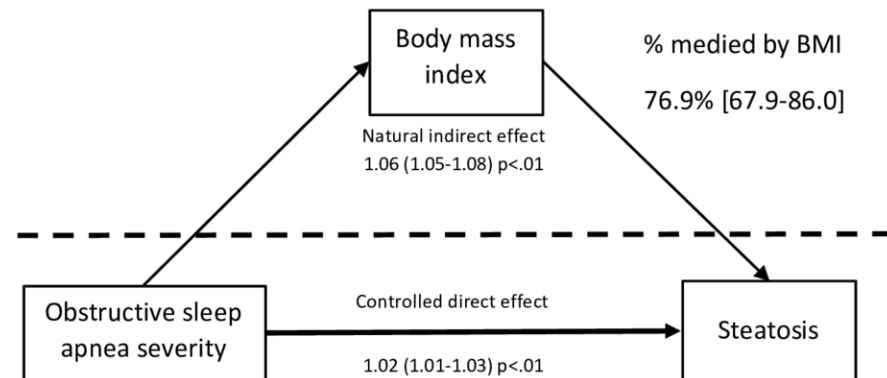
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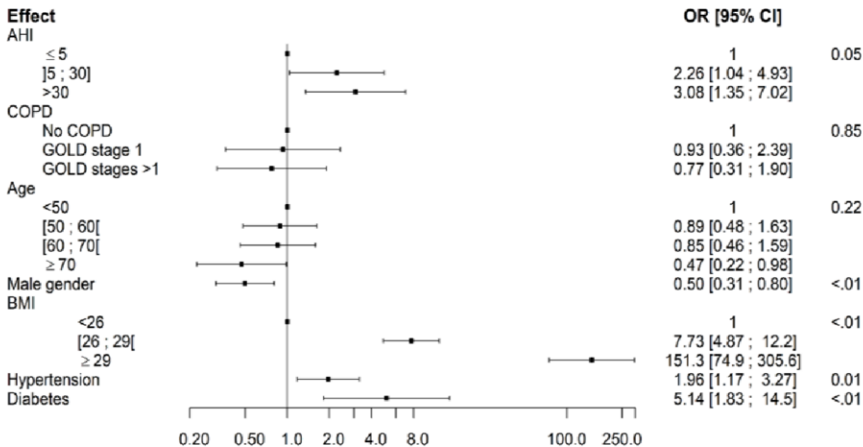
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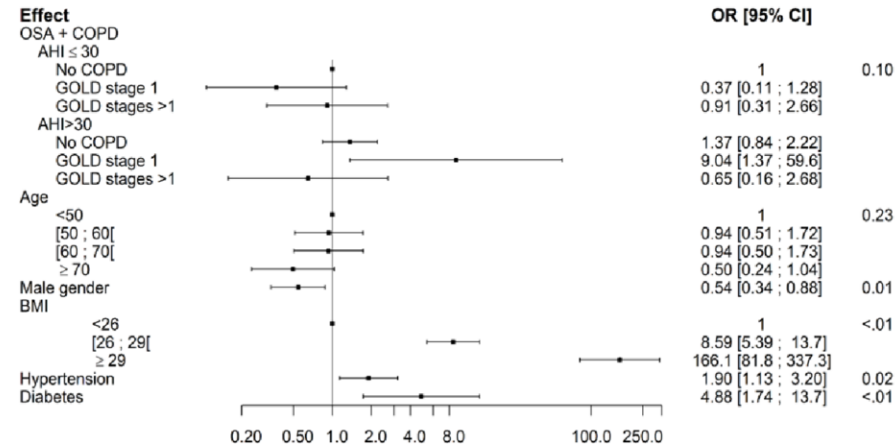
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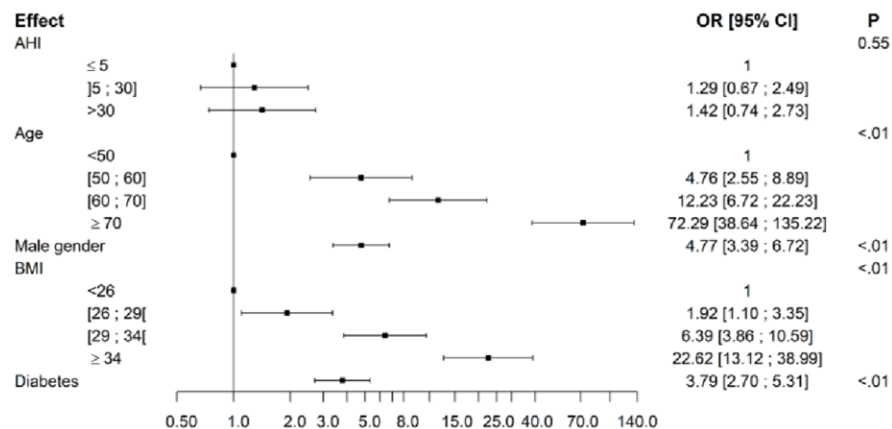
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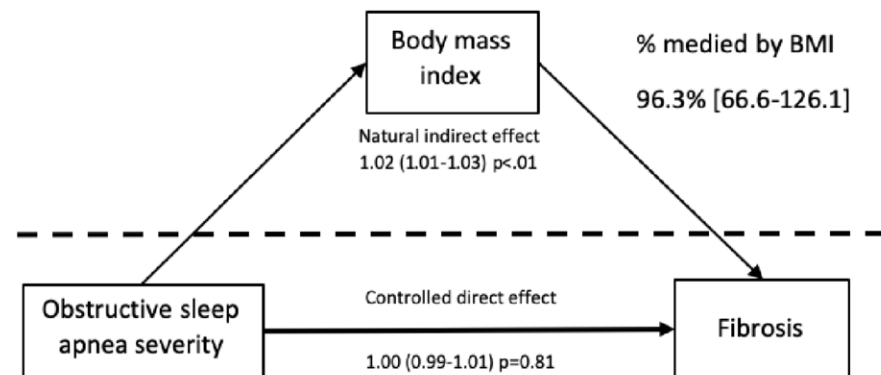
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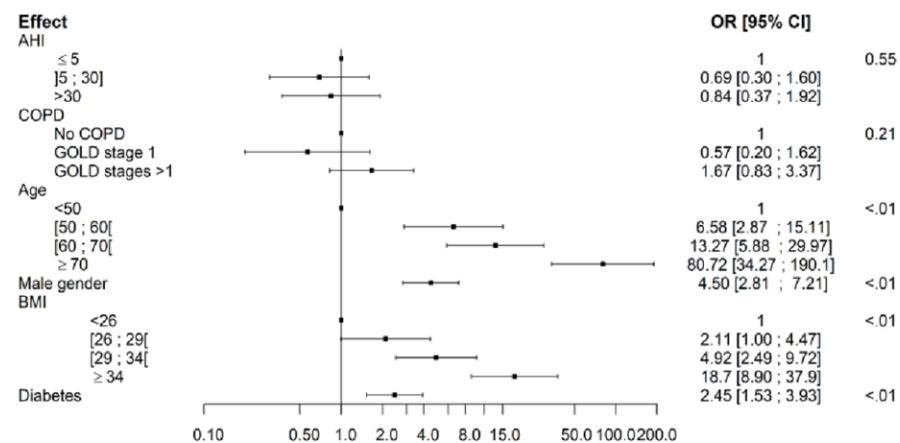
3A



3B



3C



3D

