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Association of obstructive sleep apnoea with the presence and severity of non-alcoholic fatty liver disease. A systematic review and meta-analysis

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Summary

Obstructive sleep apnoea syndrome (OSAS) and non-alcoholic fatty liver disease (NAFLD) are common in clinical practice. NAFLD encompasses simple steatosis and non-alcoholic steatohepatitis (NASH): both confer an increased risk of cardiovascular disease and diabetes; NASH increases also liver-related risk. Growing experimental evidence connects chronic intermittent hypoxia of OSAS to NAFLD. We reviewed English and non-English articles and international meeting abstracts through December 2012. Observational studies were included if they assessed OSAS by polysomnography and NAFLD by histological, radiological or biochemical criteria. Two reviewers evaluated retrieved articles by appropriate quality scores. Main outcomes were pooled using random- or fixed-effects models. The effect of age, sex and body mass index (BMI) on effect estimates was assessed by meta-regression. Eighteen cross-sectional studies (2,183 participants) were included. Pooled odds ratios (ORs) of OSAS for the presence of NAFLD, as defined by histology, radiology, and AST or ALT elevation, were 2.01(95% CI: 1.36–2.97), 2.99(1.79–4.99), 2.36(1.46–3.82) and 2.60(1.88–3.61), respectively. Pooled ORs of OSAS for NASH, fibrosis-any stage, or advanced fibrosis in biopsy-proven NAFLD patients were 2.37(1.59–3.51), 2.16(1.45–3.20) and 2.30(1.21–4.38). The magnitude and direction of effects were unaffected by age, sex and BMI. In conclusion, OSAS is associated with an increased risk of NAFLD, NASH and fibrosis. OSAS patients should be screened for the presence and severity of NAFLD.

Introduction

Obstructive sleep apnoea syndrome (OSAS) affects over 4% of the general population and 35–45% of obese individuals [1, 2]. Evidence has accumulated that OSAS predisposes to the development of metabolic syndrome, diabetes mellitus and cardiovascular disease (CVD), independent of obesity [3, 4] [5, 6]. An effective treatment for OSAS is available, and continuous positive airway pressure (CPAP) may ameliorate metabolic and cardiovascular outcomes [7-9]. On this basis, a recent report by the International Diabetes Federation has made recommendations to raise awareness of possible OSAS in diabetic patients and also for screening for hypertension, hyperlipidaemia and diabetes in patients with known OSAS [10].

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world, affecting 30% of the general adult population and up to 60–70% of diabetic and obese patients [11]. NAFLD carries a significant burden for the public health: in a 5-year population-based follow-up, the presence of NAFLD increased by 26% overall healthcare costs, after controlling for comorbidities [12].

NAFLD encompasses a histological spectrum ranging from simple steatosis to steatosis plus necro-inflammation (non-alcoholic steatohepatitis, NASH). NASH confers an increased risk of cirrhosis and liver-related complications, which increases most in the presence of fibrosis-any stage and of advanced (stage F3-4) fibrosis [13], and is projected to be the leading cause of liver transplantation by 2020 [14]. Accordingly, recent joint American Association for the Study of Liver Disease(AASLD)/American College of Gastroenterology(ACG)/American Gastroenterological Association(AGA) guidelines recommend early identification and specific treatment of patients with NASH to slow liver disease progression. Furthermore, both simple steatosis and NASH confer an increased risk of CVD and diabetes, independent of metabolic syndrome and traditional risk factors, making all histological subtypes of NAFLD worthwhile of identification, monitoring and treatment [13].

Mechanisms underlying the development of NAFLD and the progression of NAFLD to cirrhosis are incompletely understood. Growing experimental evidence connects chronic intermittent hypoxia caused by

OSAS to the development and progression of NAFLD [15]. However, it is still unclear whether OSAS patients have an increased risk of NAFLD, and if OSAS affects the severity of liver disease in NAFLD, independent of confounders such as age, male gender and obesity. If that was the case, patients with known OSAS should be routinely screened for the presence and severity of NAFLD.

We therefore reviewed the evidence regarding the following research question: does OSAS increase (i) the risk of having NAFLD compared to patients without OSAS and (ii) the severity of liver histology compared to individuals without OSAS in patients with known NAFLD?

Methods

Data sources and searches

We searched English and non-English language publications on MEDLINE, Ovid MEDLINE In-Process, Cochrane Library, EMBASE, PubMed, and abstracts from annual AASLD, AGA, EASL, ATS and DDW meetings through December 2012.

We also contacted authors to acquire information about published studies (see Acknowledgements). Search terms were: obstructive sleep apnoea, OSAS, sleep apnoea, NASH, NAFLD, non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, fatty liver, liver fat, steatosis, liver enzymes, transaminase, ALT, AST, GGT, severity of liver disease, fibrosis.

An example of full electronic search strategy is reported in Supporting Information Appendix S1.

Study selection

Inclusion criteria: observational studies enrolling participant population of any sex or ethnicity, with newly diagnosed OSAS by polysomnography (PSG), cardiorespiratory polygraphy, or nocturnal oximetry [16-18], and a new diagnosis of NAFLD by liver histology, radiology (ultrasound, computer tomography [CT], nuclear magnetic resonance or spectroscopy), and biochemistry (elevation in serum AST, ALT or GGT), together with exclusion of other competing causes of steatosis, according to standard criteria [11].

Time elapse between PSG and liver disease assessment should be <6 months, without any intervening treatment for OSAS (CPAP, oro-facial or bariatric surgery, including adenotonsillectomy and uvulopalatopharyngoplasty, or drugs, including donepezil) or for NAFLD (including regimens inducing a >5% weight loss, use of thiazolidinediones or vitamin E), which could affect severity of OSAS and/or of liver disease in NAFLD [15].

Exclusion criteria: non-human studies, letters/case reports, studies enrolling <10 subjects, articles not reporting outcomes of interest or primary data (editorials, reviews) or using inadequate case definition (in particular, subjects referred for suspicion of OSAS but without a diagnosis by PSG or subjects in whom competing causes of hepatic steatosis, including alcohol, viral hepatitis, etc., were not adequately ruled out according to current guidelines [11].

Outcome measures

Primary outcome was presence of NAFLD, diagnosed on the basis of liver histology, radiology (ultrasound, CT, nuclear magnetic resonance or spectroscopy) and biochemistry (elevation in serum AST, ALT or GGT) [11]. Because of the similar high specificity for steatosis and high sensitivity for mild-to-moderate steatosis (i.e. steatosis involving ≥30% hepatocytes) of ultrasonography and CT [19], studies adopting ultrasound and CT were analyzed together. Liver enzymes were treated as both a dichotomous (elevated or not) and a continuous variable. Secondary outcomes were:

- The severity of liver histology in NAFLD: specifically, the presence of NASH and the presence of fibrosis-any stage and of advanced (stages 3–4) fibrosis, which affect the prognosis of NAFLD, as diagnosed according to standard criteria [11].
- The association of the severity of OSAS with the severity of liver histology, defined by the presence of NASH or advanced (stages 3–4) fibrosis. Specifically, OSAS was defined as severe in the presence of an apnoea–hypopnea index (AHI) ≥50 h^{-1} or a respiratory disturbance index (RDI) >15 h^{-1} and mild to moderate in the presence of AHI <50 h^{-1} or RDI ≤ 15 h^{-1}.

Data extraction and quality assessment

Data were extracted from each study independently and in duplicate by two authors (GM, RG) using a predefined protocol, available at our institution, based on the Cochrane Handbook for Systematic Reviews of Intervention; discrepancies were resolved by mutual discussion. The agreement between the two reviewers for selection and validity assessment of studies was evaluated by kappa coefficient. The analysis was carried out in concordance with the Cochrane Handbook of Systematic Reviews and reported according to PRISMA guidelines [20].

Methodological quality of studies was assessed by the 22-item STROBE score [21], with the following three items specifically incorporated into the checklist: blinding of pathologist reading liver biopsy (if performed); adequate biopsy specimen (fragment length ≥1.5 cm with >6 portal tracts); and liver biopsy processed and scored according to standard criteria [11].

Data synthesis and analysis

We used WinBUGS 1.4 (WinBUGS 1996–2003, Imperial College of Science & MRC, UK). Dichotomous variables were presented as odds ratios (ORs) with 95% CI; continuous variables as weighed mean differences with 95% CI. All measures of dispersion were converted to standard deviations (SDs). When SDs were not reported, estimated baseline and final SDs were derived from data from other studies. The fixed-effect model was used, with significance set at $P = 0.05$. Statistical heterogeneity was assessed using the I^2 statistic: with I^2 values ≥50%, we used a random-effects model and explored individual study characteristics and those of subgroups of the main body of evidence. Sensitivity analysis was performed by removing one study at a time and the meta-analysis was repeated to assess whether any one study significantly affected pooled estimates.

Additionally, subgroup analysis was planned *a priori* to assess the impact of the following items on the association between OSAS and NAFLD: age (adult vs. non-adult population), obesity status (morbidly obese vs. non-morbidly obese subjects), and presence of significant group differences in age/sex/body mass index (BMI) between OSAS and non-OSAS patients.

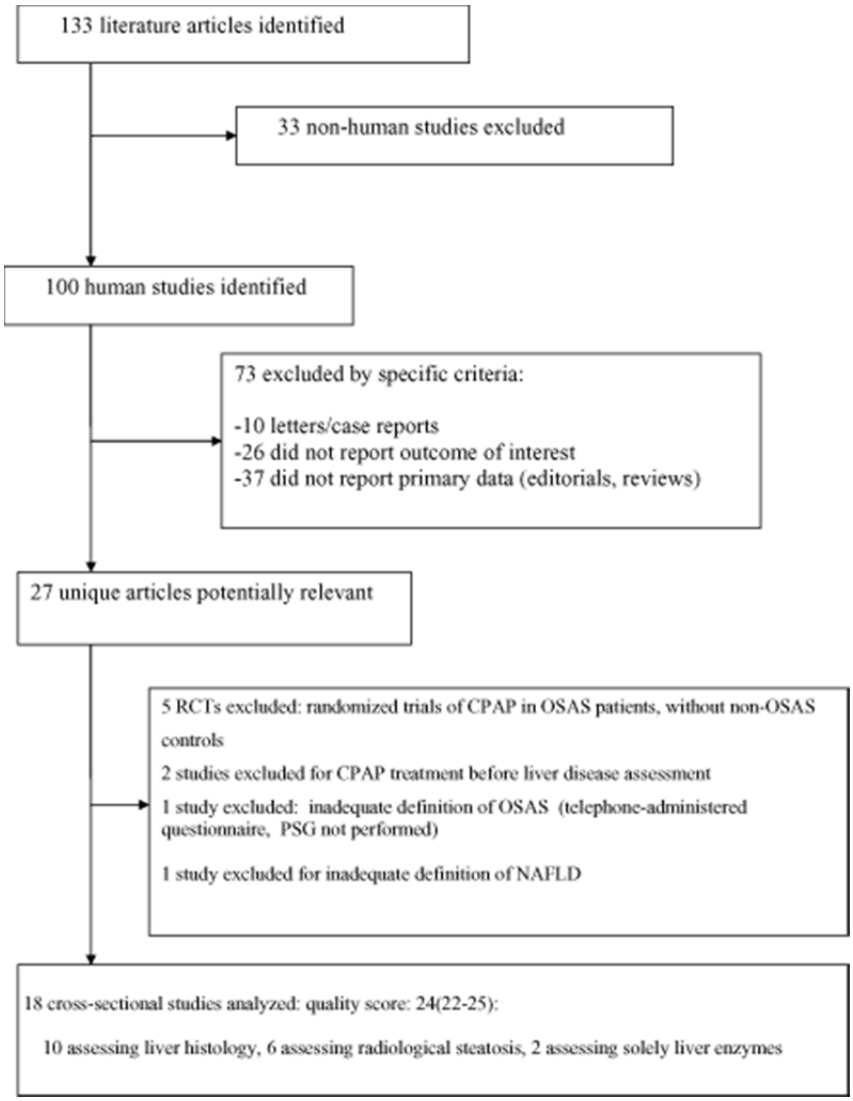
When ≥10 comparisons were available, the effect of potential confounders on the association between OSAS and NAFLD, including age, sex (as % males), BMI, and abdominal obesity (as waist circumference) [15], on each outcome was evaluated by meta-regression analysis (random-effects model, within-study variance estimated with the unrestricted maximum-likelihood method). Publication bias was examined using funnel plots and the Egger test.

Results

The agreement between two reviewers for study selection was 0.88 and for quality assessment of studies was 0.93. The flow of study selection is reported in Fig. 1. Eighteen cross-sectional studies (2,183 participants) were included (Table 1). Fifteen studies used PSG, two studies used ambulatory cardiorespiratory polygraphy, and one study used nocturnal oximetry to define OSAS. Ten studies assessed liver histology (899 subjects with liver biopsy) [22-31]; six studies (478 participants) evaluated NAFLD by

radiology [32-37]: three used ultrasonography, three used CT. Two studies (591 participants) defined NAFLD solely by liver enzyme elevation [38, 39]. AST and ALT levels were available for all studies, while GGT was available in only four studies (Supporting Information Figures S2–S3).

Figure 1.



Evidence acquisition flow diagram. STROBE score of included studies is provided as median (range).

Table 1. Cross-sectional studies on OSAS and NAFLD included in the meta-analysis

Author **Year** **STROBE score (failing items)**	**Population**	**Definitions**	**Correlations**

1. The author name is followed in the same box by the year of publications and by the modified 25-item STROBE score, with the item(s) not satisfied by the study indicated in parentheses:

(A) Title and abstract informative and balanced

(B) Background/rationale stated in the introduction

(C) Objective(s) specified in the introduction

(D) Study design correctly and presented early in the paper

(E) Setting, locations, and relevant dates described

(F) Eligibility criteria, methods of selection and follow-up described

(G) Diagnostic criteria, outcomes, exposures, predictors, potential confounders, and effect modifiers for all variables clearly defined

(H) Sources of data and details of methods of measurement given for each variable of interest

(I) Any efforts to address potential sources of bias described

(J) How the study size was arrived at clearly explained

(K) How quantitative variables were handled in the analyses clearly explained

(L) All statistical methods, how missing data and loss to follow-up were addressed, any sensitivity analyses clearly described

(M) Numbers of individuals at each stage of study reported

(N) Characteristics of study participants, number of participants with missing data, average and total follow-up time clearly described

(O) Outcome events or summary measures over time reported

(P) Unadjusted and confounder-adjusted estimates and their precision (e.g. 95% CI) reported

(Q) Analyses of subgroups and interactions, and sensitivity analyses reported

(R) Key results with reference to study objectives summarized

(S) Limitations of the study discussed

(T) Cautious overall interpretation of results given

(U) Generalizability (external validity) of the study results discussed

(V) Source of funding and role of the funders described

Author Year STROBE score (failing items)	Population	Definitions	Correlations
Acquisition of data regarding liver histology (X) Blinding of pathologist reading liver biopsy (if performed) (Y) Adequate biopsy specimen (fragment length ≥1.5 cm with >6 portal tracts) (Z) Liver biopsy processed and scored according to standard criteria AHI, apnoea/hypopnea index; BS, bariatric surgery; CT, computed tomography; FPG, fasting plasma glucose; LE, liver enzyme; ODI, oxygen desaturation index; OR, odds ratio; OSA, obstructive sleep apnoea; PSG, polysomnography; RDI, respiratory disturbance index (a sum of apnoeas and hypopneas); s_aO2, oxygen saturation; TG, plasma triglycerides.			
Studies assessing NAFLD by liver histology			
Tannè 2005 [22] 23 (S, V)	163 consecutive patients with clinical suspicion of OSAS Age: 51 years Sex: 89% M BMI: 27.8 Diabetes: 4% Mean AHI in OSAS subjects: 45	OSAS (79% of subjects): defined by an AHI ≥ 10 h^{-1} on PSG NAFLD (20% subjects): LE elevation (AST > 30, ALT > 35, GGT > 33) LB performed in 18 out of 32 patients with LE elevation: NASH (defined according to Brunt criteria): 12/18 patients	Age, BMI, male sex and diabetes prevalence higher in OSAS than non-OSAS patients BMI, severe OSAS and AHI independently predicted LE elevation AHI predicted liver histology independently of age and BMI, but not of HOMA
Jouet 2007 [23] 23 (J, V)	62 consecutive morbidly obese patients undergoing BS and systematic intra-operative needle LB Age: 39 years Sex: 13% M BMI: 47.8 Diabetes: 15% Met sy: 56.5% Mean AHI in OSAS subjects: 42	OSAS: (defined by an AHI ≥ 10 h^{-1} on ambulatory cardiorespiratory polygraphy) present in 84% of patients NAFLD (defined by histology) present in 83.6% of patients NASH (Brunt criteria) present in 34% of patients AST was elevated (>45 IU L^{-1}) in 3.3% patients ALT was elevated (>55 IU L^{-1}) in 15% GGT was elevated (>50 IU L^{-1}) in 39% of patients Overall, 46.5% of patients had elevation in at least one liver enzyme	Age and BMI were higher in OSAS group, while gender distribution was similar between OSAS and non-OSAS subjects
Kallwitz 2007 [24] 23 (S, Y)	85 consecutive morbidly obese patients candidate for BS systematically subjected to PSG and intra-operative needle LB if liver appeared abnormal	OSAS defined by an AHI ≥ 15 h^{-1} on PSG, present in 51% of subjects NAFLD by histology present in 99% of patients NASH (Brunt criteria) present in 18% of	Age was similar, while BMI and male gender prevalence was higher in OSAS than non-OSAS patients OSAS independently predicted ALT levels and NASH

Author Year STROBE score (failing items)	Population	Definitions	Correlations
	Age: 44 years Sex: 28% M BMI: 55 Mean AHI in OSAS subjects: 41 h^{-1}	patients LE elevation (cut-off for AST/ALT > 40 IU L^{-1}) present in 9% for AST and in 29% for ALT	
Campos 2008 [25] 25	200 consecutive morbidly obese subjects candidate for BS systematically subjected to PSG and intra-operative needle LB Age: 43 years Sex: 16% M BMI: 48 Diabetes: 26% Mean ODI in OSAS subjects: 23 h^{-1}	OSAS defined by AHI >15 or >5 with symptoms on PSG, present in 14% of patients NAFLD diagnosed by histology was present in 63% of patients NASH (Brunt criteria) was present in 32% of patients LE elevation (cut-off for AST/ALT ≥27 IU L^{-1}) present in 29% for AST and in 42% for ALT	Male gender was more prevalent in OSAS patients, while age and BMI did not differ between OSAS and non-OSAS groups Independent predictors of NASH on multivariate analysis: hypertension, type 2 diabetes, OSAS (OR 4.0; 1.3–12.2), AST > 27 IU L^{-1}, ALT > 27 IU L^{-1}, non-Black race
Mishra 2008 [26] 23 (J, S)	101 consecutive morbidly obese patients candidate for BS systematically subjected to PSG and intra-operative needle LB Age: 43 years Sex: 29% M BMI: 51.6 Diabetes: 33% Mean AHI in OSAS subjects: 32 h^{-1}	OSAS defined by AHI > 5 with symptoms on PSG, present in 81% of patients NAFLD by histology was an inclusion criterion and therefore present in all subjects NASH (Brunt criteria) present in 78% of patients	Gender distribution was similar, while age and BMI were higher in NASH than in non-NASH subjects
Polotsky 2009 [27] 23 (J, S)	90 consecutive morbidly obese patients candidate for BS systematically subjected to sleep study Intra-operative needle LB obtained in 20 randomly selected patients representative of the whole population	OSAS, defined by a RDI ≥ 5 h^{-1} on cardiorespiratory polygraphy with symptoms, present in 81% of patients NAFLD by histology present in 14/20 (70%) of patients who received LB NASH (NASH CRN criteria) present in 36% of patients LE elevation, defined by	Age was higher in OSAS group, while gender distribution and BMI were similar between subjects with and without OSAS

Author Year STROBE score (failing items)	Population	Definitions	Correlations
	Age: 41 years Sex: 18% M BMI: 49 Mean AHI in OSAS subjects: 26 h^{-1}	AST/ALT > 40 IU L^{-1}, present in 0% of patients	
Ulitsky 2010 [28] 25	253 consecutive morbidly obese patients candidate for BS systematically subjected to PSG and intra-operative needle LB Age: 43 years Sex: 14% M BMI: 48.2 Diabetes: 32% Mean AHI in OSAS subjects: 32 h^{-1}	OSAS defined by AHI > 5 h^{-1} on PSG with symptoms, present in 36% of patients NAFLD by histology present in 66% of patients NASH (Brunt criteria) present in 21% of subjects AST elevation(>45 IU L^{-1}) present in 4% of subjects, ALT elevation (>40 IU L^{-1}) present in 10% of subjects	Age, gender distribution and BMI were similar between subjects with and without OSAS
Daltro 2010 [29] 22 (J, P, Y)	40 consecutive morbidly obese patients candidate for BS systematically subjected to PSG and intra-operative needle LB Age: 36 years Sex: 35% M BMI: 41.6 Diabetes: 13% Mean AHI in OSAS subjects: 43 h^{-1}	OSAS defined by AHI ≥ 15 h^{-1}, present in 40% NAFLD by histology was present in 83% of patients NASH (Brunt criteria) was present in 80% of patients AST elevation present in 5% of patients, ALT elevation present in 22% of patients	Male gender was more prevalent in OSAS patients, while age and BMI were similar between OSAS and non-OSAS patients AHI was associated with insulin resistance No association between AHI or oxyhemoglobin desaturation and liver enzymes, hepatic histological features or NASH
Sundaram 2012 [30] 25	19 adolescents with biopsy-proven NAFLD systematically undertaking PSG Age: 13 years Sex: 64% M BMI: *z* score: 2.23 Mean AHI in OSAS subjects: 9 h^{-1}	OSAS, defined by an AHI ≥ 2 h^{-1} with symptoms, present in 63% of subjects NAFLD diagnosed by histology was an inclusion criterion NASH (Brunt criteria) was present in 78% of patients	Age, gender distribution and BMI were similar between patients with and without OSAS
Aron-Wisnewsky 2012 [31] 25	101 consecutive morbidly obese candidates for BS, systematically subjected to sleep study and intra-operative needle LB	OSAS defined by ODI > 6.7 on nocturnal oximetry, with symptoms, present in 67% of subjects NAFLD defined by histology, present in	Age, gender distribution, BMI and fat mass were similar between OSAS and non-OSAS patients

Author Year STROBE score (failing items)	Population	Definitions	Correlations
	Age: 44 years Sex: 9% M BMI: 46.8 Diabetes: 23% Mean ODI in OSAS subjects: 23 h^{-1}	77% of patients NASH (defined by a NAS score ≥5) present in 8% of patients LE elevation (ALT > 30 IU L^{-1}) present in 42% of patients overall, in 75% of patients with NASH, in 33% of patients with fibrosis (any stage)	
Studies assessing NAFLD by radiology			
Tatsumi 2005 [32] 24 (J)	124 non-obese subjects: 83 patients with OSAS and 41 age-, sex-, BMI-matched non-OSAS subjects Age: 50 years Sex: 87% M BMI: 25.6 Mean RDI in OSAS subjects: 4 h^{-1}	OSAS defined by an AHI > 5 h^{-1} on PSG with symptoms NAFLD (diagnosed by CT) present in 15% of subjects	Age, gender distribution and BMI were similar between patients with and without OSAS OSAS patients had higher visceral fat than non-OSAS patients
Acarturk 2007 [33] 23 (S, V)	45 consecutive obese women attending the obesity clinic of a Department of Internal Medicine, systematically subjected to PSG Age: 47 years Sex: 9% M BMI: 39.4 Diabetes: 0% Mean AHI in OSAS subjects: 29 h^{-1}	OSAS defined by an AHI ≥ 10 h^{-1} on PSG, was present in 44% of patients NAFLD (diagnosed by ultrasonography) present in 82% of subjects LE elevation present in 2% of subjects	Similar age, gender distribution, BMI and waist circumference between patients with and without OSAS
Verhulst 2009 [34] 24 (Y)	75 consecutive overweight or obese children and adolescents attending a paediatric obesity clinic, systematically subjected to PSG Age: 10 years (range 6–17 years) Sex: 47% M BMI: *z* score: 2.3 Mean RDI in OSAS subjects: 4 h^{-1}	OSAS defined by RDI ≥ 2 h^{-1} on PSG, with symptoms, present in 58% of patients NAFLD: defined by ultrasound (33% of subjects) LE elevation (AST > 40, ALT > 40) in 16% of subjects	Similar age, gender distribution, BMI and waist circumference between OSAS and non-OSAS group On multivariate analysis, RDI independently predicted ALT levels
Shpirer	47 consecutive subjects referred to a sleep laboratory for suspected	OSAS (AHI > 15 h^{-1} on PSG) present in	Age, gender, BMI and diabetes prevalence did not differ between

Author Year STROBE score (failing items)	Population	Definitions	Correlations
2010 [35] 25	OSAS Age: 55 years Sex: 83% M BMI: 32.8 Diabetes: 32% Mean AHI in OSAS subjects: 51	87% of patients NAFLD: defined by CT (34% of subjects) 17% of subjects had LE elevation (cut-off: ≥40 IU L^{-1} for both AST and ALT)	OSAS and non-OSAS patients
Turkay 2012 [36] 25	106 consecutive patients referred to a sleep unit for clinical suspicion of OSAS Age: 50 years Sex: 75% M BMI: 31.8 Diabetes: 8% Mean AHI in OSAS subjects: 31	OSAS, defined by an AHI ≥ 15 h^{-1} on PSG, was present in 66% of patients NAFLD (diagnosed by ultrasonography) present in 67% of subjects	Similar age, gender distribution and waist circumference between patients with and without OSAS; BMI was higher in OSAS than in non-OSAS group. On multivariate analysis, AHI independently predicted NAFLD after adjustment for BMI and insulin resistance
Kritikou 2012 [37] 25	81 overweight patients systematically subjected to PSG and abdominal CT scan Age: 55 years Sex: 51% M BMI: 28.1 Diabetes: 0% Mean AHI in OSAS subjects: 37 h^{-1}	OSAS defined by AHI > 10 h^{-1} in women and >15 h^{-1} in men, present in 51% of patients NAFLD: defined by CT (17% of subjects) LE elevation (AST > 40, ALT > 60) in 5% of subjects	Similar age, gender distribution, BMI and waist circumference between subjects with and without OSAS
Studies assessing NAFLD solely by liver enzyme elevation			
Kheirandish-Gozal 2008 [38] 25	518 consecutive children evaluated for suspected OSA Age: 8 years (range 4–17 years) Sex: 50% M BMI: *z* score 1.20 Mean AHI in OSAS children: 7.5	OSAS (AHI ≥ 2 h^{-1} on PSG, with symptoms) was present in 66% of subjects NAFLD defined by LE elevation: (ALT or AST ≥ 40 IU L^{-1}) ALT elevation present in 9% of children AST elevation present in 3% of children	Similar age, sex, race, BMI between children with and without OSAS In logistic regression analysis, an AHI > 5 h^{-1} independently predicted ALT levels

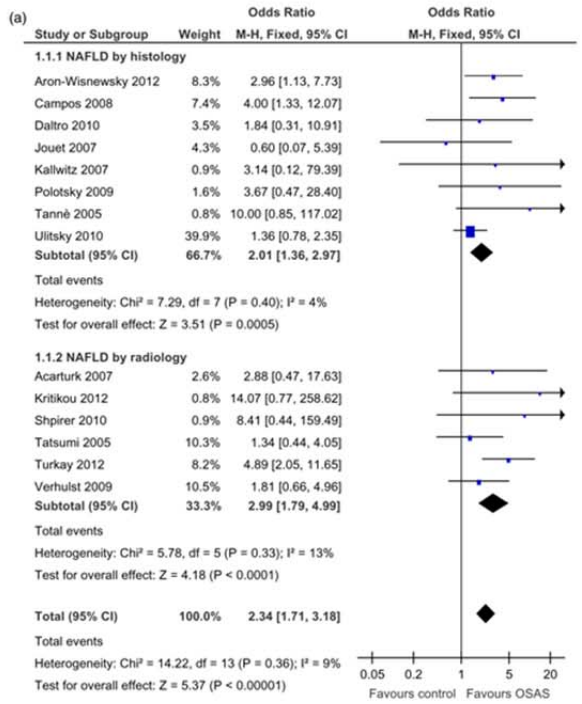
Author Year STROBE score (failing items)	Population	Definitions	Correlations
Byrne 2012 [39] 25	73 consecutive patients referred to a sleep laboratory for suspected OSAS Age: 65 years Sex: 60% M BMI: 32 (58% obese)	OSAS, defined by AHI > 10 h^{-1} on PSG, was present in 66% of subjects NAFLD defined by LE elevation: AST elevation (>29 IU L^{-1}) present in 28% of patients; ALT elevation (>31 IU L^{-1}) present in 23% of patients	Similar age, gender and BMI between patients with and without OSAS

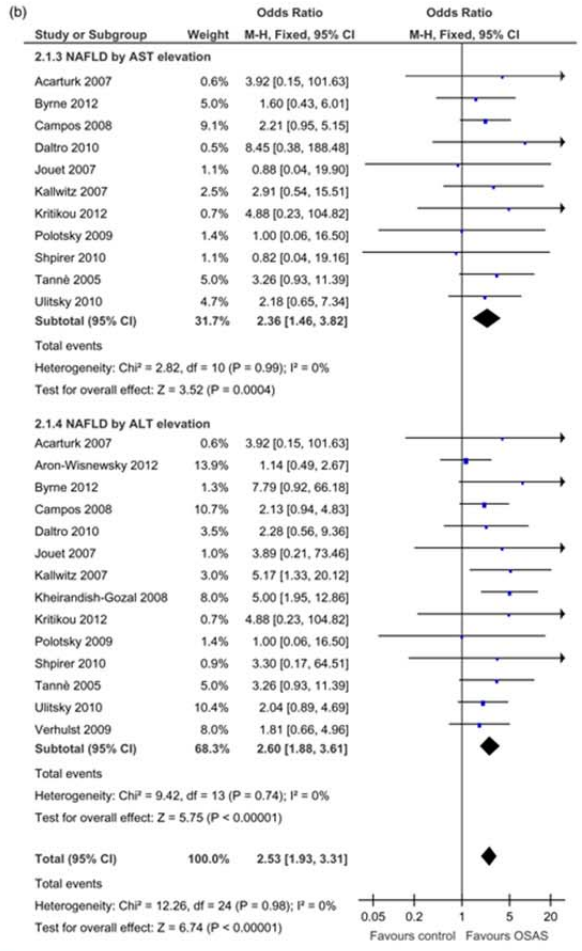
Eight studies enrolled bariatric surgery patients, three studies enrolled children adolescents. The overall methodological quality of the studies was good: the median (range) STROBE score was 24 [22-25]. Five studies did not clearly explain how the study size was arrived at or discuss their limitations, three studies did not disclose the characteristics of liver biopsy specimens, and one study did not adjust outcomes for potential confounders (Table 1, Supporting Information Figure S1).

Association of obstructive sleep apnoea syndrome with non-alcoholic fatty liver disease

Pooled ORs of OSAS for the presence of NAFLD, as defined by histology, radiology, and AST or ALT elevation, were 2.01 (95% CI: 1.36–2.97, I^2 = 4%, P = 0.0005, N comparisons = 8), 2.99 (95% CI: 1.79–4.99, I^2 = 13%, P < 0.0001, N comparisons = 6), 2.36 (95% CI: 1.46–3.82, I^2 = 0%, P = 0.004, N comparisons = 11) and 2.60 (95% CI: 1.88–3.61, I^2 = 0%, N comparisons = 14), respectively (Fig. 2). The difference between OSAS and non-OSAS patients kept significant even when considering liver enzymes as a continuous variable (Supporting Information Figure S3).

Figure 2.





(a) Forest plot of comparison: presence of NAFLD, outcome: NAFLD as defined by liver histology or radiology. (b) Forest plot of comparison: presence of NAFL (liver enzyme elevation), outcome: NAFLD by AST and ALT elevation.

There was little or no heterogeneity in the meta-analysis of overall events, suggesting a consistent disease effect. The magnitude and direction of the effect remained unaltered when the analysis was restricted to studies enrolling adult patients (OR for histological/radiological NAFLD: 2.40, 1.73–3.32, I^2 = 10%, P < 0.001, N comparisons = 13; OR for ALT elevation: 2.36, 1.62–3.43, I^2 = 0%, P < 0.0001, N comparisons = 12), non-morbidly obese patients (OR for histological/radiological NAFLD: 3.16, 1.91–5.21, I^2 = 10%, P < 0.0001, N comparisons = 7; OR for ALT elevation: 3.65, 2.12–6.28, I^2 = 0%, P < 0.0001, N comparisons = 7), or to studies with no differences between OSAS and non-OSAS group in age (OR for histological/radiological NAFLD: 2.33, 1.69–3.21, I^2 = 10%, P < 0.0001; OR for ALT elevation: 2.56, 1.82–3.61, I^2 = 0%, P < 0.0001; N comparisons = 11), sex (OR for histological/radiological NAFLD: 2.12, 1.53–2.95, I^2 = 10%, P < 0.001; OR for ALT elevation: 2.60, 1.79–3.77, I^2 = 0%, P < 0.0001; N comparisons = 11) and BMI (OR for histological/radiological NAFLD: 2.34, 1.70–3.23, I^2 = 10%, P < 0.0001; OR for ALT elevation: 2.40, 1.69–3.41, I^2 = 0%, P < 0.0001; N comparisons = 11). Meta-regression analysis found no association among age, sex, BMI, and waist circumference, and study results (all P values > 0.21). The Egger test and funnel plot analysis found no strong evidence for publication bias (see Supporting Information Figure S4).

Association of obstructive sleep apnoea syndrome with the severity of liver histology in non-alcoholic fatty liver disease

Liver histology was assessed in 10 studies: 80% of studies with liver histology enrolled morbidly obese bariatric surgery candidates, in whom intra-operative liver biopsy was routinely performed.

Obstructive sleep apnoea syndrome and non-alcoholic steatohepatitis

Pooled OR of OSAS for the presence of NASH in biopsy-proven NAFLD patients was 2.37 (95% CI: 1.59–3.51, I^2 = 0%, P < 0.0001, N comparisons = 10).

The magnitude and direction of the effect remained unaltered when the analysis was restricted to studies enrolling non-morbidly obese patients (OR 2.81, 95% CI: 1.18–6.79, I^2 = 0%, P = 0.01, N comparisons = 2) or to studies with no differences between OSAS and non-OSAS group in age (OR 2.53, 1.66–3.86, I^2 = 0%, P < 0.001, N comparisons = 7), sex (OR 2.10, 1.29–3.42, I^2 = 0%, P = 003, N comparisons = 7) or BMI (OR 2.54, 1.64–3.95, I^2 = 0%, P < 0.001, N comparisons = 7).

Obstructive sleep apnoea syndrome and fibrosis-any stage

Pooled OR of OSAS for the presence of fibrosis-any stage was 2.16 (95% CI: 1.45–3.20, I^2 = 0%, P < 0.0001, N comparisons = 10).

The magnitude and direction of the effect remained unaltered when the analysis was restricted to studies enrolling non-morbidly obese patients (OR 2.79, 95% CI: 1.03–3.91, I^2 = 0%, P = 0.02, N comparisons = 2) or to studies with no differences between OSAS and non-OSAS group in age (OR 2.16, 1.42–3.30, I^2 = 0%, P = 0.003, N comparisons = 7), sex (OR 1.82, 1.11–2.99, I^2 = 0%, P = 02, N comparisons = 7) or BMI (OR 2.09, 1.34–3.24, I^2 = 0%, P = 001, N comparisons = 7).

Obstructive sleep apnoea syndrome and advanced (stage F3-4) fibrosis

Pooled OR of OSAS for the presence of advanced fibrosis in biopsy-proven NAFLD patients was 2.30 (95% CI: 1.21–4.38, I^2 = 0%, P = 0.01, N comparisons = 10).

The magnitude and direction of the effect remained unaltered when the analysis was restricted to studies enrolling non-morbidly obese patients (OR 2.98, 95% CI: 1.10–3.77, I^2 = 0%, P = 0.02; N comparisons = 2) or to studies with no differences between OSAS and non-OSAS group in age (OR 2.16, 1.42–3.30, I^2 = 0%, P = 0.003, N comparisons = 7), sex (OR 1.82, 1.11–2.99, I^2 = 0%, P = 02, N comparisons = 7) or BMI (OR 2.11,

1.37–3.26, I^2 = 0%, *P* = 0.01, *N* comparisons = 7). Meta-regression analysis found no association among age, sex, BMI, and waist circumference, and the OR for NASH, fibrosis-any stage or advanced fibrosis (all *P* values > 0.19). The Egger test and funnel plot analysis found no strong evidence for publication bias (see Supporting Information Figure S5).

Association of the severity of obstructive sleep apnoea syndrome with the severity of liver histology in biopsy-proven non-alcoholic fatty liver disease

Pooled OR of severe OSAS vs. mild-to-moderate OSAS for the presence of NASH in biopsy-proven NAFLD was 1.89 (95% CI: 1.15–3.09, I^2 = 0%, *P* = 0.01, *N* comparisons = 9) (Fig. 5a).

Pooled OR of severe OSAS vs. mild-to-moderate OSAS for the presence of advanced fibrosis in biopsy-proven NAFLD was 2.68 (95% CI: 1.23–5.82, I^2 = 0%, *P* = 0.01, *N* comparisons = 9) (Fig. 5b).

Meta-regression analysis found no association among age, sex, BMI, and waist circumference, and the OR for NASH, fibrosis-any stage or advanced fibrosis (all *P* values > 0.23).

Obstructive sleep apnoea syndrome and non-alcoholic fatty liver disease in children/adolescents

Three studies (612 participants) evaluated the association of OSAS with the presence and severity of OSAS in children/adolescents. Pooled OR for NAFLD, as defined by ALT elevation, was 3.41 (1.74–4.67, I^2 = 13%, *P* = 0.0003, *N* comparisons = 3). Only one small study assessed the effect of OSAS on liver histology in NAFLD patients, finding a non-significant increase in the OR for NASH and advanced fibrosis [30].

Discussion

The main results of our analysis are the following:

1. OSAS is associated with an increased prevalence of NAFLD, as defined by histology, radiology or transaminase elevation;
2. In NAFLD patients, OSAS is associated with an increased prevalence of NASH and of fibrosis (any stage and advanced stage). Among patients with OSAS, the severity of OSAS was also associated with the severity of liver disease, as defined by the presence of NASH or advanced fibrosis.

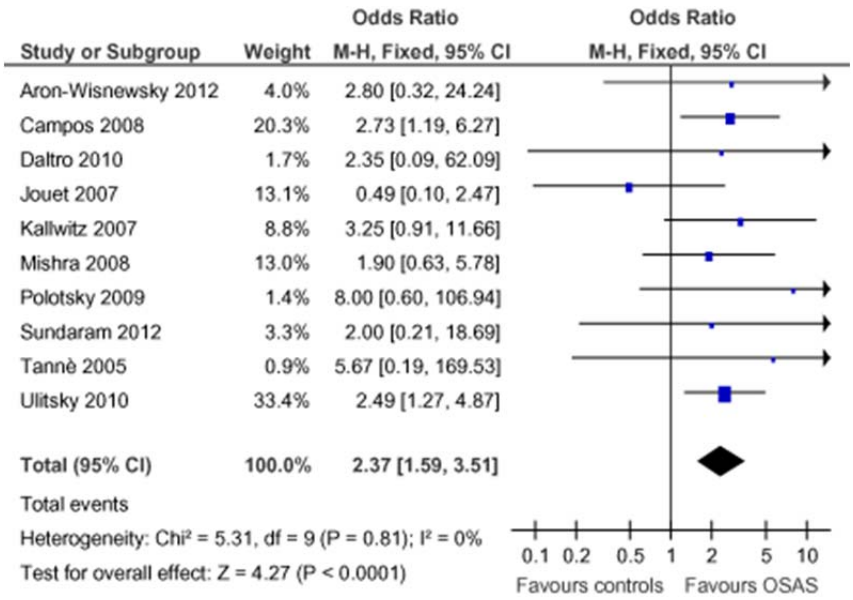
These associations were independent of age, sex, overall obesity (as estimated by BMI) and abdominal obesity (as estimated by waist circumference).

OSAS is increasingly recognized and affects over 4% of general adult population and 35–45% of obese subjects [2, 10]. Its prevalence in the paediatric population is also increasing, together with the obesity epidemic, posing major health issues for cardio-metabolic prevention [40].

OSAS is characterized by episodes of chronic intermittent hypoxia and sleep fragmentation, which increase sympathetic activity and promote oxidative stress, pro-inflammatory cytokine production, platelet aggregation, endothelial dysfunction and metabolic dys-regulation. Collectively, these mechanisms provide the pathophysiological basis for the increased risk of diabetes and CVD observed in these patients [10, 41]. Although OSAS and obesity are epidemiologically linked and converge on overlapping pathways to promote metabolic and CVD, it is increasingly recognized that OSAS *per se* increases cardio-metabolic risk independent of obesity [42], and effective treatment of OSAS by CPAP improves cardio-metabolic outcomes [7-9]. On this basis, the International Diabetes Federation (IDF) recommended that OSAS patients should be thoroughly evaluated for their cardio-metabolic risk, and that the possibility of OSAS should be considered in all patients with type 2 diabetes and the metabolic syndrome [10].

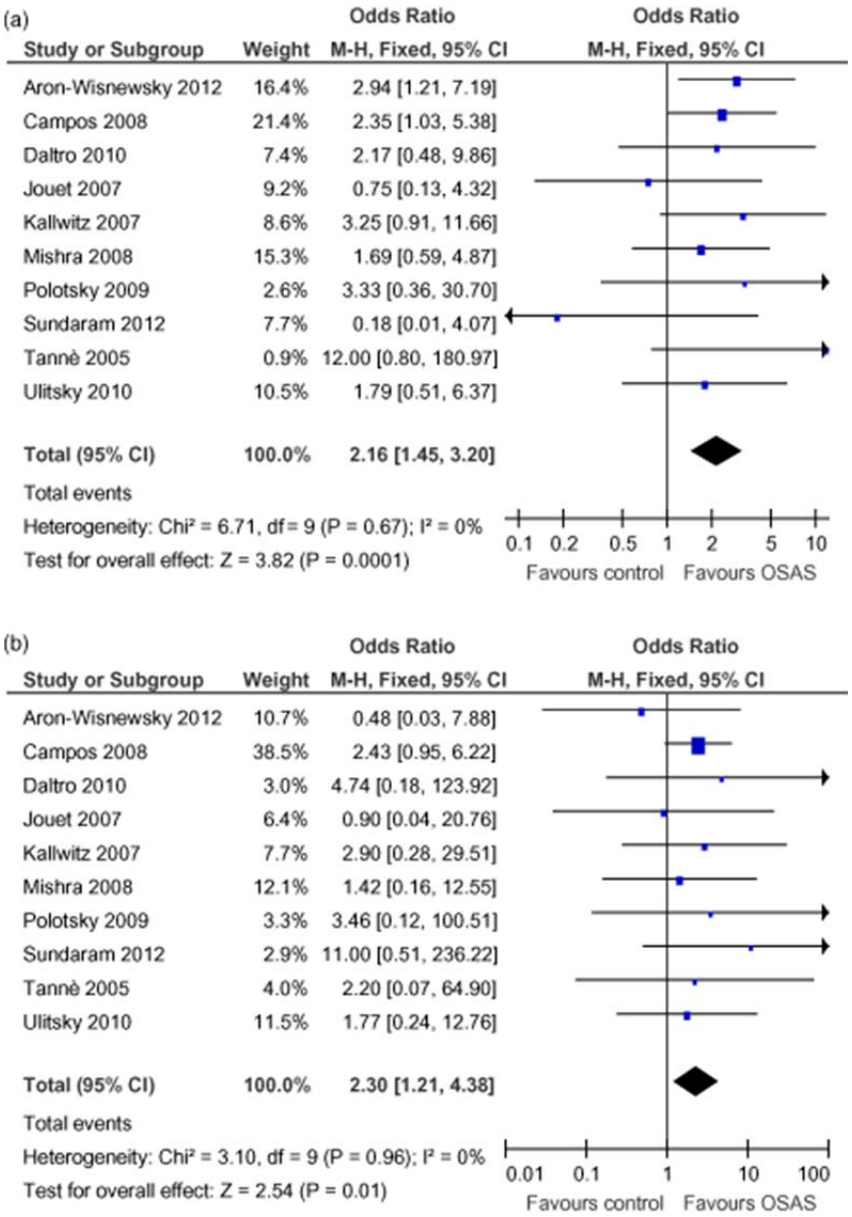
Recent experimental evidence connected OSAS to the pathogenesis and progression of NAFLD, another obesity-related disorder which is associated with an increased cardio-metabolic and liver-related risk [13]: in cellular and animal models chronic intermittent hypoxia promoted hepatic triglyceride accumulation, necro-inflammation and fibrosis through activation of several cellular pathways, including hypoxia-inducible factors, nuclear factor-κB and the unfolded protein response [15]. Furthermore, epidemiological studies documented an association of OSAS with an increased prevalence and severity of NAFLD, and few trials documented the benefit of OSAS treatment on transaminase elevation and radiological steatosis [35, 38, 43]. However, it was so far unclear whether patients with OSAS should be systematically screened for the presence and severity of NAFLD. Our analysis suggests that the presence of OSAS confers an over twofold increased risk of having NAFLD, and a ≅2-fold increased risk of progressive NASH and fibrosis in patients with NAFLD, independent of age, gender, BMI and waist circumference (Figs 2-4). Importantly, we also documented a dose–response relationship between the severity of OSAS and the severity of liver disease in NAFLD patients (Fig. 5). These findings may have potentially relevant clinical implications: based on our analysis, health professionals working in both NAFLD and OSA fields should evaluate a patient presenting with one condition for the presence of the other. Physicians involved with OSAS should be aware of the links between the two conditions, and may want to add a liver workup to the routine cardio-metabolic screening previously recommended for these patients [10].

Figure 3.



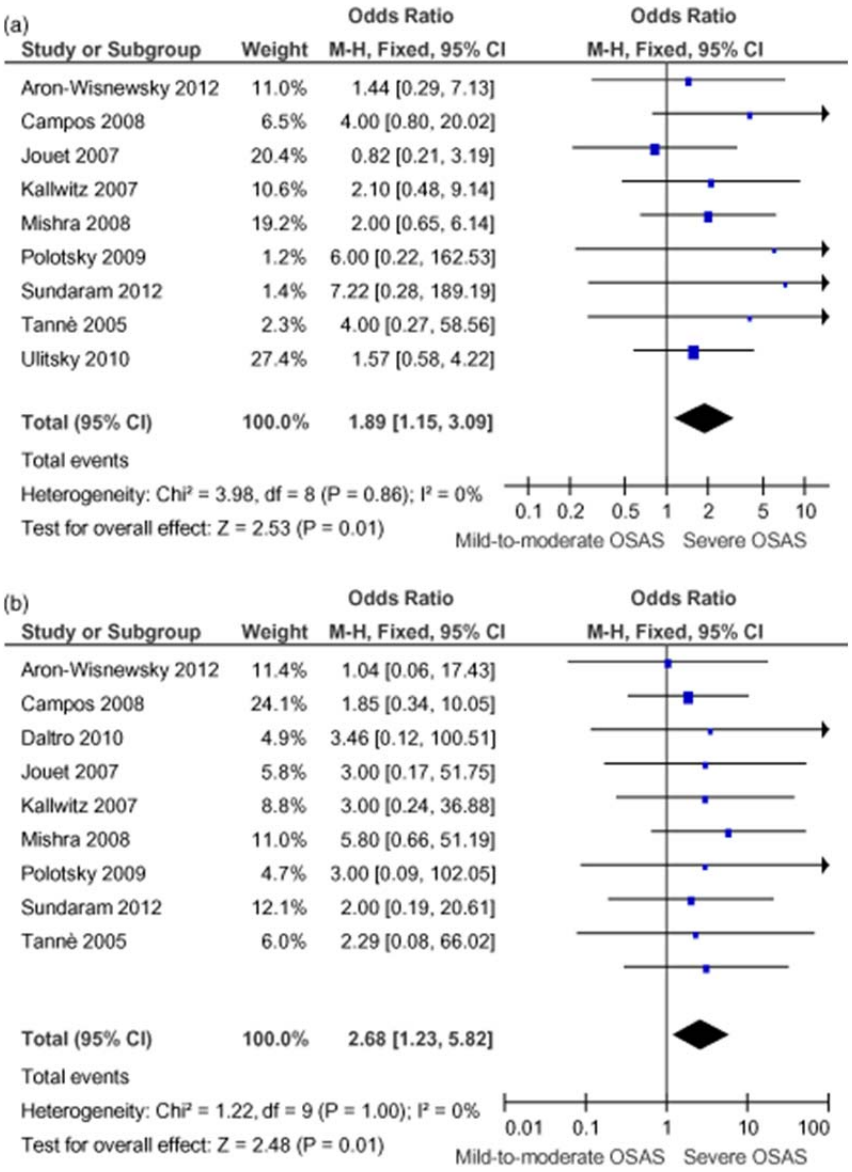
Forest plot of comparison: presence of NASH among biopsy-proven NAFLD, outcome: NASH.

Figure 4.



(a) Forest plot of comparison: presence of fibrosis-any stage among biopsy-proven NAFLD, outcome: fibrosis-any stage. (b) Forest plot of comparison: presence of advanced (F3-4) fibrosis among biopsy-proven NAFLD, outcome: advanced (F3-4) fibrosis.

Figure 5.



(a) Forest plot of comparison: presence of NASH among biopsy-proven NAFLD patients with severe or mild-to-moderate OSAS, outcome: NASH. (b) Forest plot of comparison: presence of advanced (F3-4) fibrosis among biopsy-proven NAFLD patients with severe or mild-to-moderate OSAS, outcome: advanced (F3-4) fibrosis.

Epidemiological evidence indicates both NAFLD overall and its progressive histological subtype, i.e. NASH, warrant early identification in OSAS: while NASH, with or without fibrosis, confers an increased liver-related morbidity and mortality, both NASH and simple steatosis increase the risk of diabetes and CVD, independent of traditional risk factors [13], as liver fat accumulation *per se* adversely affects glucose and lipid metabolism [44, 45]. Furthermore, contrary to traditional belief, even simple steatosis may progress to NASH and fibrosis if metabolic risk factors persist or deteriorate, and therefore warrants early identification and monitoring [46-49].

The optimal method of screening for NAFLD remains to be established: in the studies included in our analysis, the prevalence of NAFLD as defined by ALT elevation was 60% lower than that of radiologically/histologically proven NAFLD, confirming transaminase elevation alone is an insensitive marker of NAFLD, and suggesting an imaging technique like ultrasound should be included at the very least. In NAFLD patients with OSAS, the presence of progressive NASH [22, 25, 26, 30, 31] warrants also early identification for experimental treatments, which can reverse necro-inflammatory changes and stop

disease progression [50], while the presence of advanced fibrosis requires tight monitoring for development of complications of cirrhosis (hepatocellular carcinoma, oesophageal varices, liver failure). The optimal strategy for detecting progressive NASH and fibrosis remains to be defined. Based on the high prevalence of NAFLD in bariatric surgery patients with OSAS, NAFLD staging might be accomplished by routine intra-operative liver biopsy of this population, regardless of liver enzymes or gross liver appearance. In non-bariatric surgery patients with OSAS, a strategy combining non-invasive methods with liver biopsy may help individuate patients at greater risk of having NASH and fibrosis, reducing the need for liver biopsy [11, 13].

In a parallel way, patients with NAFLD should be screened for the presence of OSAS, as this condition increases not only cardio-metabolic risk, but also the risk of having progressive NASH and fibrosis, independent of age, sex and BMI. Screening questionnaires for OSA have relatively poor sensitivity and specificity, and they have not been validated in NAFLD population, where the prevalence of fatigue, troubled sleeping and daytime sleepiness may be increased, even in the absence of OSA [51, 52]. However, as patients with fatigue and symptomatic daytime sleepiness are those who benefit most from treatment of OSA [10], it may be considered worthwhile to target these patients specifically by using a two-stage approach in which a structured questionnaire (i.e. Epworth Sleepiness Scale, Berlin Questionnaire) is used in the first stage to assess the pre-test probability of OSAS. Those at high risk undergo a second stage, with an overnight at home evaluation by portable monitoring devices, which are increasingly validated against the more expensive and less accessible standard, i.e. in-patient PSG [53-58].

Our analysis has some limitations, which are intrinsic to the nature of included studies and provide the basis for future research. The cross-sectional nature of included studies prevents any definitive causal inference between OSAS and NAFLD. However, our findings do suggest that NAFLD is more frequent and severe in OSAS and should be routinely sought in these patients. Secondly, included studies were performed in tertiary care centres for sleep study evaluation or bariatric surgery clinics, where the prevalence and severity of NAFLD may have been overestimated and need confirmation in a population-based setting. Thirdly, the cut-offs for OSAS definition varied quite substantially across several studies, mandating a more homogeneous definition in future studies. Fourthly, most studies assessing liver histology enrolled morbidly obese patients candidate for bariatric surgery; therefore, future research should clarify the impact of OSAS on liver histology in non-morbidly obese subjects, as well as in paediatric population, a major target for prevention of liver-related complications. Finally, the benefit of OSAS treatment by CPAP on liver histology in NASH warrants future evaluation: currently, limited evidence suggests CPAP improves liver enzymes and radiological steatosis, but its impact on liver histology and clinical outcomes remains unknown [35, 38].

In conclusion, our findings support an association of OSAS with the presence and severity of NAFLD, and suggest healthcare providers working in NAFLD and OSAS fields should screen a patient presenting with one condition for the presence of the other; furthermore, the presence of progressive NASH and fibrosis should be considered in NAFLD patients with OSAS.

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