Research Square

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Intermittent Hypoxemia and Sleep Fragmentation Indices in Relation to Nonalcoholic Fatty Pancreas Disease Severity in Adults with Suspected Obstructive Sleep Apnea: A Prospective Cross-Sectional Study

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Abstract

Background

Obstructive sleep apnea (OSA) is associated with ectopic fat deposition in the liver, but its relationship with nonalcoholic fatty pancreas disease (NAFPD) has been explored in few clinical cohorts. Whether polysomnographic indices of intermittent hypoxemia and sleep fragmentation track with ultrasonographic pancreatic steatosis remains unclear.

Methods

In this prospective cross-sectional study, adults with signs and symptoms compatible with OSA underwent full-night polysomnography, abdominal ultrasonography with graded pancreatic steatosis (normal, mild, moderate, severe), and fasting laboratory assessment. Adults with diabetes mellitus were excluded. Associations were tested with chi-square or Fisher exact tests, and prevalence ratios and odds ratios (OR) with 95% confidence intervals (CI) were estimated.

Results

Of 86 adults screened, 72 were analyzed (mean age 44.1 ± 11.4 years; 35 men; mean body mass index 31.4 ± 5.4 kg/m²). An apnea-hypopnea index (AHI) of 5 events/h or higher was present in 58 participants (80.6%), and NAFPD was present in 42 (58.3%). The AHI as a continuous variable (P = 0.013) and an AHI of 5 or higher (P = 0.014) were associated with NAFPD. Prevalence of NAFPD was 65.5% (38 of 58) with an AHI of 5 or higher versus 28.6% (4 of 14) with a normal AHI (OR 4.75; 95% CI, 1.32 to 17.08). Oxygen desaturation to 90% or below was associated with NAFPD (P = 0.001). Normal body mass index was associated with a lower likelihood of NAFPD (OR 0.098; 95% CI, 0.011 to 0.860). Severe OSA was associated with low HDL cholesterol (P = 0.002) and elevated LDL cholesterol (P < 0.001), whereas HOMA-IR showed no association with OSA severity.

Conclusions

In non-diabetic adults with suspected OSA, polysomnographic severity and nocturnal desaturation were associated with ultrasonographic pancreatic steatosis. Because the estimates were unadjusted and the design was cross-sectional, adjusted analyses with quantitative pancreatic fat imaging in multicenter cohorts are warranted to establish independence from adiposity.

1. Introduction

Obstructive sleep apnea (OSA) is a chronic disorder defined by recurrent partial or complete collapse of the upper airway during sleep, producing intermittent hypoxemia, intrathoracic pressure swings, and

arousals. A literature-based analysis estimated that nearly one billion adults aged 30 to 69 years live with the condition worldwide, with Brazil among the countries contributing the largest absolute numbers.[1] In the São Paulo Epidemiologic Sleep Study, which used in-laboratory polysomnography in a probabilistic urban sample, the prevalence reached roughly one third of adults.[2] Beyond cardiovascular consequences, repetitive hypoxemia and sleep fragmentation alter lipid and glucose metabolism through sympathetic activation, adipose tissue lipolysis, and hypoxia-inducible factor signaling.[3]

The metabolic reach of OSA has been best characterized in the liver. Mechanistic reviews and a meta-analysis support an association between OSA and both the presence and the severity of nonalcoholic fatty liver disease,[4,5] and nocturnal hypoxemia has been identified as a major trigger of hepatic steatosis in patients with morbid obesity.[6] These observations raise the question of whether other organs that accumulate ectopic fat under metabolic stress are similarly affected.

Fatty infiltration of the pancreas, termed nonalcoholic fatty pancreas disease (NAFPD), is increasingly recognized as a component of the metabolic syndrome. Ultrasonographic studies have linked pancreatic steatosis to insulin resistance, visceral adiposity, hypertriglyceridemia, and elevated aminotransferases,[7] to older age, higher body mass index, and abnormal glycemic and lipid parameters,[8] and to prediabetes and diabetes, particularly in men.[9] Pancreatic fat is also biologically plausible as a mediator of beta-cell dysfunction, which positions NAFPD at the intersection of obesity, sleep-disordered breathing, and diabetes risk.

A hypothesis article proposed that OSA may act as an additional hit for pancreatic fat deposition, through intermittent hypoxia, sympathetic activation, lipolysis, and local inflammation,[10] and hypoxic injury of pancreatic beta cells has been suggested as a link between sleep apnea and diabetes.[11] Clinical data remain scarce. A recent cohort using modified abdominal ultrasonography reported a higher prevalence of NAFPD in patients with OSA than in controls, with the apnea-hypopnea index (AHI) retaining an association after adjustment for body mass index and hypertension.[12] However, the AHI summarizes event frequency and does not separate the contribution of hypoxemic burden from that of arousal-related sleep fragmentation, and data from Latin American populations with graded pancreatic steatosis in non-diabetic adults are lacking.

This study therefore aimed to evaluate the association between ultrasonographic pancreatic steatosis and polysomnographic indices of OSA severity, oxygen desaturation, and arousals in non-diabetic adults with clinical suspicion of OSA, and to examine anthropometric and metabolic correlates of both conditions.

2. Methods

2.1 Study design and setting

A prospective, observational, cross-sectional study was conducted in outpatient services in Itabuna, Bahia, Brazil. The study was reported in accordance with the STROBE statement for cross-sectional studies. The protocol was approved by the Research Ethics Committee of the Santa Cruz State University (IRB approval number: 2,464,513) and followed the Declaration of Helsinki and the applicable Brazilian national regulations. All participants provided written informed consent, and fingerprint consent was obtained from non-literate participants.

2.2 Participants

Adults aged 18 to 65 years with signs and symptoms compatible with OSA, including habitual snoring, witnessed apneas, excessive daytime sleepiness, and unrefreshing sleep, were invited to participate. Exclusion criteria were diabetes mellitus, other endocrine disorders, severe heart disease, cancer within the preceding 12 months, alcohol intake of 30 g/day or more, previous pancreatic disease, use of hepatotoxic or pancreatotoxic drugs, autoimmune disease, prolonged systemic corticosteroid use, major psychiatric disorders, chronic lung disease with hypoxemia, previous bariatric surgery, and nonadherence to the study procedures. Sample size was estimated with Epi Info software. Eighty-six individuals were selected. Fourteen were excluded for not completing the requested examinations, and three were excluded because type 2 diabetes mellitus was diagnosed during the laboratory workup, leaving 72 participants for analysis (Fig. 1).

2.3 Clinical and anthropometric assessment

Age, sex, weight, height, and neck and waist circumferences were recorded. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and classified as normal, overweight, or obesity grades 1, 2, and 3 according to World Health Organization categories. The Mallampati classification was recorded, and daytime sleepiness was measured with the Epworth Sleepiness Scale.

2.4 Polysomnography

Participants underwent attended full-night polysomnography with electroencephalography, electro-oculography, electromyography, airflow, respiratory effort, electrocardiography, and pulse oximetry. Apnea was defined as a reduction in airflow of at least 90% lasting 10 seconds or longer, and hypopnea as a reduction of 30% to 90% lasting 10 seconds or longer accompanied by an oxygen desaturation of more than 3% or an arousal. The AHI was calculated as the number of apneas and hypopneas per hour of sleep and categorized as normal (below 5 events/h), mild (5 to below 15), moderate (15 to below 30), or severe (30 or above). Oxygen desaturation to 90% or below and the number of arousals were recorded as indices of hypoxemic burden and sleep fragmentation, and elevated arousal counts were dichotomized.

2.5 Abdominal ultrasonography

Abdominal ultrasonography was performed by the same physician in all participants using a convex transducer, after an overnight fast. Pancreatic steatosis was graded as absent (normal), mild (grade 1), moderate (grade 2), or severe (grade 3) according to pancreatic parenchymal echogenicity relative to the retroperitoneum and the liver. Participants with any grade of steatosis were classified as having NAFPD.

2.6 Laboratory assessment

Fasting venous blood was collected in a single laboratory for measurement of glucose, glycated hemoglobin, total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, uric acid, aspartate and alanine aminotransferases, gamma-glutamyltransferase, insulin, morning cortisol, and thyroid-stimulating hormone. Insulin resistance was estimated with the homeostasis model assessment (HOMA-IR), and BMI-specific thresholds of 4.65 for BMI above 28.9 kg/m² and 3.60 for BMI above 27.5 kg/m² were adopted to define an elevated value.

2.7 Statistical analysis

Continuous variables were described as mean and standard deviation or median, and categorical variables as absolute and relative frequencies. Normality was assessed with histograms, Q-Q plots, skewness, kurtosis, and the Kolmogorov-Smirnov test. Associations between categorical exposures and NAFPD were tested with the chi-square test, and the Fisher exact test was applied when expected counts were small. Prevalence ratios and odds ratios with 95% confidence intervals were estimated. For BMI and AHI categories, each stratum was compared with all remaining participants, and an AHI of 5 or higher was compared with a normal AHI. All tests were two-tailed with a significance level of $P < 0.05$. No multivariable adjustment or correction for multiple comparisons was performed. Analyses were conducted in R, version 4.6.2, and Epi Info.

3. Results

3.1 Characteristics of the cohort

The 72 analyzed participants comprised 35 men and 37 women, with a mean age of 44.1 years and a mean BMI of 31.4 kg/m² (Table 1). Mean waist circumference was 99.7 cm, consistent with a predominantly central adiposity phenotype, and mean Epworth score was 8.9.

Table 1
Baseline characteristics of the study population (n = 72).

Variable	Mean ± SD
Age (years)	44.13 ± 11.42
Weight (kg)	86.60 ± 17.28
Body mass index (kg/m²)	31.44 ± 5.40
Waist circumference (cm)	99.68 ± 14.52
Neck circumference (cm)	38.38 ± 4.07
Epworth Sleepiness Scale score	8.89 ± 4.54

3.2 Distribution of OSA severity and pancreatic steatosis

An AHI of 5 or higher was present in 58 participants (80.6%). Pancreatic steatosis was present in 42 participants (58.3%), and was mild in 12, moderate in 17, and severe in 13 (Table 2; Fig. 2).

Table 2
Distribution of OSA severity and ultrasonographic pancreatic steatosis grade (n = 72).

Category	OSA severity (AHI), n (%)	Pancreatic steatosis, n (%)
Normal / absent	14 (19.4)	30 (41.7)
Mild	22 (30.6)	12 (16.7)
Moderate	20 (27.8)	17 (23.6)
Severe	16 (22.2)	13 (18.1)

3.3 Apnea-hypopnea index and pancreatic steatosis

The AHI as a continuous variable was associated with NAFPD (P = 0.013), as was an AHI of 5 or higher (P = 0.014). The prevalence of NAFPD was 65.5% (38 of 58) in participants with an AHI of 5 or higher and 28.6% (4 of 14) in those with a normal AHI, corresponding to an OR of 4.75 (95% CI, 1.32 to 17.08). Stratified by severity, NAFPD prevalence was 54.5% (12 of 22) in mild, 70.0% (14 of 20) in moderate, and 75.0% (12 of 16) in severe OSA, but the confidence intervals of the stratum-specific odds ratios included unity (Table 3; Fig. 3).

Table 3
Prevalence of pancreatic steatosis and estimated risk according to OSA severity.

Exposure	NAFPD, n/N	Prevalence (%)	OR (95% CI)
AHI ≥ 5 vs normal AHI	38/58	65.5	4.750 (1.321 to 17.079)
Mild OSA vs others	12/22	54.5	0.800 (0.291 to 2.201)
Moderate OSA vs others	14/20	70.0	2.000 (0.665 to 6.013)
Severe OSA vs others	12/16	75.0	2.600 (0.747 to 9.052)
Normal AHI	4/14	28.6	Reference

3.4 Oxygen desaturation, arousals, and pancreatic steatosis

Oxygen desaturation to 90% or below was associated with NAFPD (P = 0.001). Elevated arousal counts were positively associated with moderate and severe grades of pancreatic steatosis.

3.5 Body mass index and pancreatic steatosis

The global association between BMI category and NAFPD did not reach statistical significance (P = 0.086). Participants with normal BMI had a lower likelihood of NAFPD, whereas the highest estimate was observed in obesity grade 1 (Table 4).

Table 4
Prevalence of pancreatic steatosis and estimated risk according to BMI category.

BMI category	Prevalence (%)	OR (95% CI)
Normal	14.3	0.098 (0.011 to 0.860)
Overweight	50.0	0.625 (0.221 to 1.767)
Obesity grade 1	75.0	3.286 (1.161 to 9.296)
Obesity grade 2	57.1	0.941 (0.289 to 3.064)
Obesity grade 3	66.7	1.450 (0.125 to 16.786)

3.6 Metabolic and hormonal correlates of OSA

HOMA-IR was not associated with any OSA category (all P between 0.316 and 0.552), and morning cortisol was not associated with OSA or pancreatic steatosis. Lipid abnormalities clustered in specific severity strata: low HDL cholesterol (P = 0.002) and elevated LDL cholesterol (P < 0.001) were associated with severe OSA, elevated VLDL cholesterol with mild (P = 0.020) and severe OSA (P = 0.045), and elevated triglycerides with mild OSA (P = 0.022). Total cholesterol showed no association with any stratum (Table 5).

Table 5
P values for the association between OSA severity and abnormal lipid parameters.

Parameter	AHI ≥ 5	Mild	Moderate	Severe	Normal AHI
Elevated total cholesterol	0.552	0.222	0.430	0.573	0.552
Low HDL cholesterol	0.290	0.188	0.408	0.002	0.290
Elevated LDL cholesterol	0.547	0.157	0.074	< 0.001	0.547
Elevated VLDL cholesterol	0.372	0.020	0.188	0.045	0.372
Elevated triglycerides	0.230	0.022	0.296	0.091	0.230

4. Discussion

This prospective study establishes a robust link between an adverse anthropometric phenotype, defined by elevated BMI, increased neck circumference, and central adiposity, and the presence of NAFPD in adults evaluated for suspected OSA. Rather than being an isolated observation, pancreatic steatosis was a predominant feature in this cohort, far exceeding the burden typically observed in the general population. These data expose a critical, yet often overlooked, metabolic vulnerability in patients presenting with sleep-disordered breathing, underscoring the urgent need to integrate routine pancreatic and metabolic risk stratification into the clinical management of suspected OSA.

In non-diabetic adults referred for suspected OSA, ultrasonographic pancreatic steatosis was common and tracked with polysomnographic severity and with nocturnal oxygen desaturation. The direction of the association agrees with a recent clinical cohort in which NAFPD was more prevalent in OSA than in controls and the apnea-hypopnea index retained an association after adjustment for adiposity and hypertension.[12] The present data extend that observation to a Brazilian population, to graded steatosis, and to a sample that excluded diabetes, although the estimates reported here were unadjusted and therefore cannot establish independence from obesity.

The association with desaturation is consistent with the liver literature, in which the time spent below a saturation threshold, rather than event frequency alone, has been related to steatohepatitis in patients with OSA.[13] Experimental and review evidence places hypoxia-inducible factor signaling at the center of hepatic lipid accumulation under low oxygen tension,[14,15] and the same pathway has been proposed for the pancreas.[10] According to that framework, intermittent hypoxemia stimulates carotid body chemoreceptors and sympathetic output, increases adipose tissue lipolysis and free fatty acid flux, and favors ectopic lipid storage in organs with high perfusion, including the pancreas (Fig. 4). A direct hypoxic effect on beta cells has also been suggested as a bridge between sleep apnea and diabetes.[11]

Arousals and sleep fragmentation represent a second, partly independent route to metabolic stress, because arousal-related sympathetic and hypothalamic-pituitary-adrenal activation occurs even in events without profound desaturation.[3] The positive relationship between elevated arousal counts and

higher steatosis grades supports the idea that the AHI captures only part of the exposure relevant to ectopic fat. Morning cortisol was unrelated to OSA or to pancreatic steatosis in this cohort, which does not exclude adrenal axis involvement, since a single morning sample is a coarse index of a pulsatile and sleep-dependent secretion.

The stratified analysis did not show a clean dose-response gradient. Prevalence was higher in moderate and severe strata, but stratum-specific estimates were imprecise, and the high prevalence in mild OSA probably reflects shared adiposity. This pattern fits the broader fatty pancreas literature, where obesity, visceral fat, and fatty liver are the dominant correlates,[16,17] and where visceral adipose tissue has been the strongest predictor of ectopic fat in the liver and pancreas, with sex-specific differences.[18] In our cohort the low likelihood of steatosis in participants with normal BMI points in the same direction, while the absence of a monotonic BMI gradient and the lack of a significant global BMI test suggest that body mass index is an imperfect proxy for the visceral depot that drives pancreatic fat.

The metabolic profile merits separate comment. Pancreatic fat has been related to impaired insulin secretion and beta-cell function in men and in individuals with impaired glucose regulation,[19,20] and OSA is an established correlate of dysglycemia.[21,22] The lack of association between HOMA-IR and OSA severity here may reflect the exclusion of diabetes, the sample size, and the fact that HOMA-IR mainly captures fasting hepatic insulin resistance rather than beta-cell function. The dyslipidemic pattern in severe OSA, with low HDL and high LDL, is compatible with the lipid disturbances attributed to intermittent hypoxia[3] and with the abnormal liver enzyme profile described in meta-analytic data on fatty liver in OSA.[23] Experimental work suggests that pancreatic steatosis precedes diabetes in obese rodents and is accompanied by an inflammatory milieu,[24,25] which provides a rationale for studying NAFPD as an early marker in OSA populations.

From a clinical standpoint, transabdominal ultrasonography is widely available, inexpensive, and already used for hepatic steatosis. Pancreatic steatosis is likely under-recognized in patients with sleep-disordered breathing, and a structured pancreatic assessment during abdominal ultrasonography in OSA clinics could generate prevalence data and identify patients for metabolic risk stratification, as previously proposed.[10] Whether treatment of OSA reduces pancreatic fat is unknown and testable in interventional cohorts.

The interpretation of these results is bounded by the cross-sectional design, which precludes causal inference and means that the temporal order of hypoxemia and fat deposition is unknown. Estimates were unadjusted for BMI, waist circumference, age, and sex, and no correction for multiple comparisons was applied. Pancreatic steatosis was graded by a single ultrasonographer without reliability testing, and transabdominal ultrasonography has limited sensitivity in obesity and cannot quantify fat content, unlike magnetic resonance imaging. The reference group with a normal AHI was small, and exclusion of diabetes may have attenuated associations with glycemic measures. The detailed estimates for desaturation and arousal indices were limited in the available source tables, and the single-center setting restricts generalizability.

5. Conclusions

In non-diabetic adults with suspected OSA, polysomnographic severity and nocturnal oxygen desaturation were associated with ultrasonographic pancreatic steatosis, whereas BMI showed an imprecise and non-monotonic relationship. These associations are hypothesis-generating. The next step is a multicenter prospective study with adjustment for visceral adiposity, quantitative pancreatic fat imaging by magnetic resonance, standardized hypoxemic burden and arousal metrics, and follow-up after continuous positive airway pressure therapy to determine whether treatment of OSA modifies pancreatic fat.

Declarations

Conflict of Interest:

None declared.

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Figures

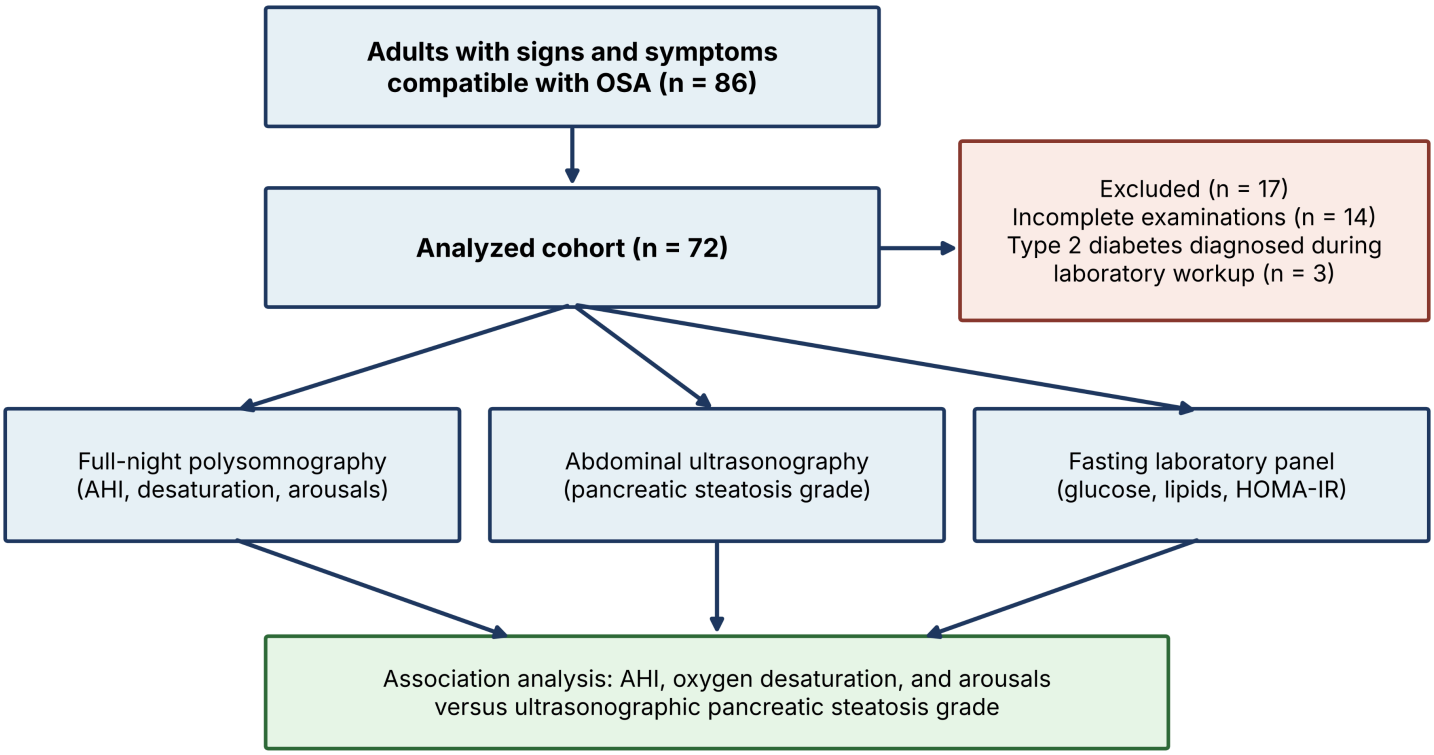


Figure 1

Flow of participants.

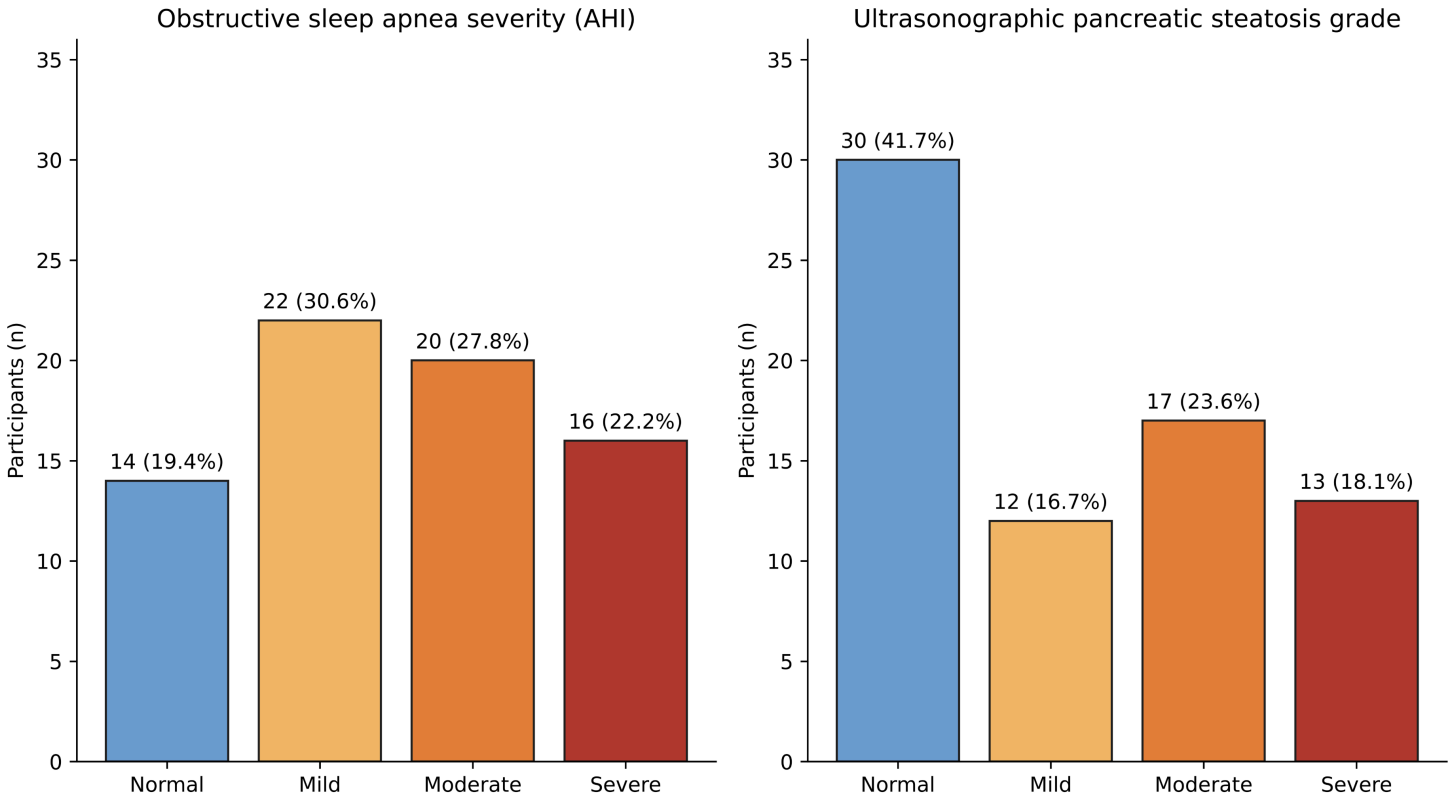


Figure 2

Distribution of obstructive sleep apnea severity (left) and ultrasonographic pancreatic steatosis grade (right) in 72 adults.

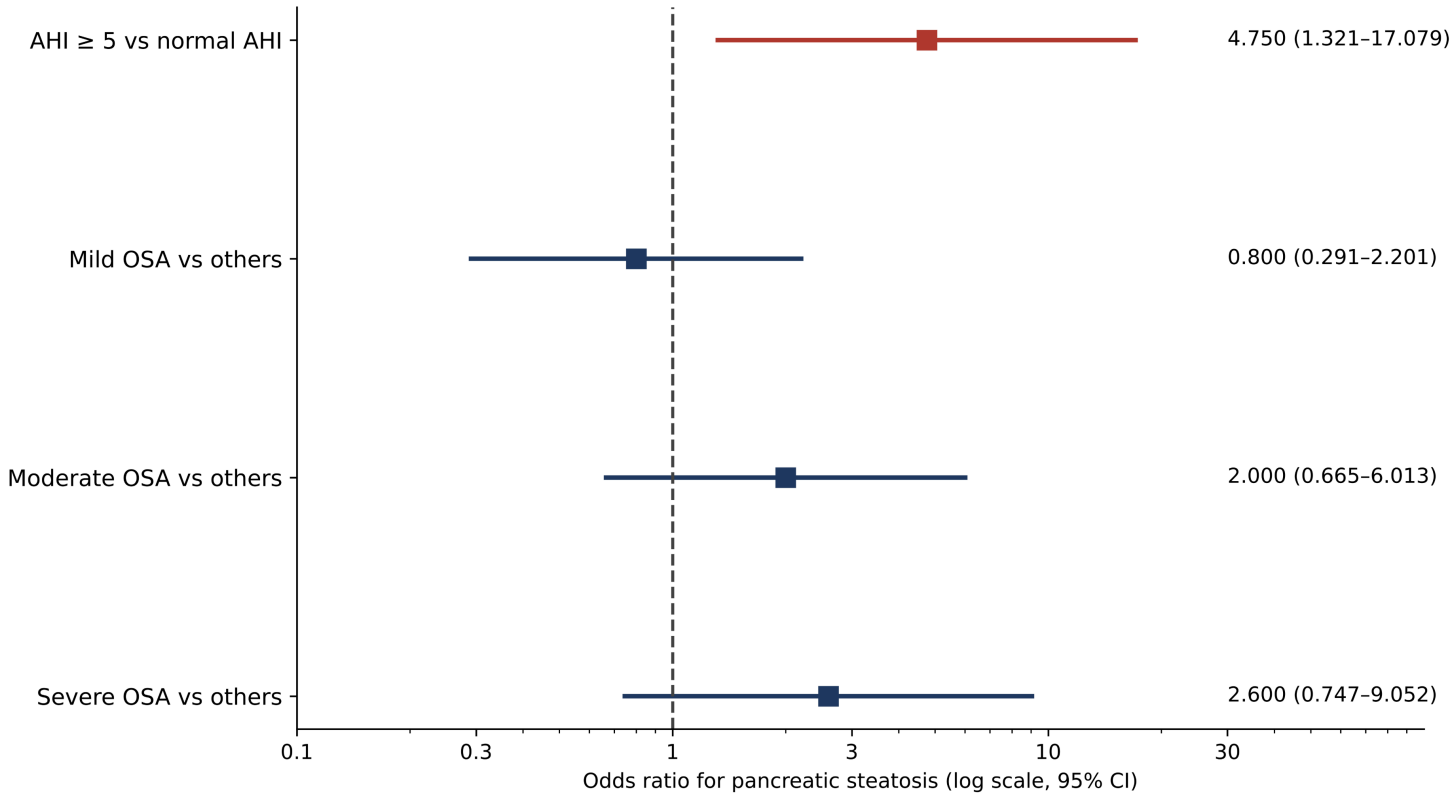
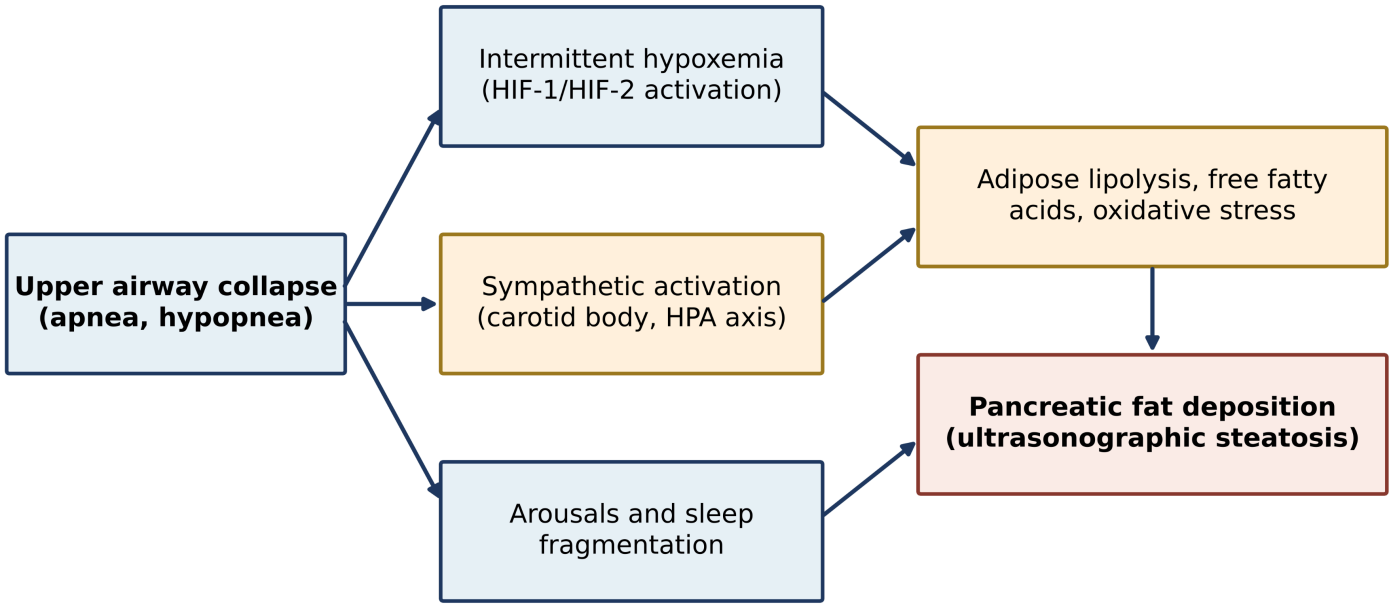


Figure 3

Odds ratios for pancreatic steatosis according to OSA severity. Squares indicate point estimates and horizontal lines indicate 95% confidence intervals; the dashed line marks an odds ratio of 1.



Hypothesized pathways; obesity and visceral adiposity act as shared upstream factors.

Figure 4

Conceptual model of hypothesized pathways linking obstructive sleep apnea to pancreatic fat deposition. The diagram is illustrative and was not tested in this study.