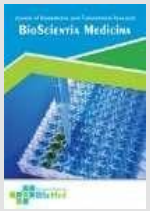
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Bidirectional Relationship Between Obstructive Sleep Apnea and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A Systematic Review and Meta-Analysis of Longitudinal Studies

Nurul Anisa[1*], Adrianison[1]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Riau/Arifin Achmad Regional General Hospital, Pekanbaru, Indonesia

ARTICLE INFO

Keywords:
Intermittent hypoxia
MASLD
NAFLD
Obstructive sleep apnea
Systemic inflammation

***Corresponding author:**
Nurul Anisa

E-mail address:
dr.nurulanisa@yahoo.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i9.1391

A B S T R A C T

Background: Obstructive sleep apnea (OSA) and metabolic dysfunction-associated steatotic liver disease (MASLD) are highly prevalent, interconnected metabolic disorders. While their cross-sectional association is established, the temporal and potentially causal relationship remains unclear. This study aimed to quantitatively synthesize longitudinal evidence on the bidirectional risk between OSA and MASLD. **Methods:** We systematically searched PubMed, Scopus, and Web of Science (January 1st, 2015 - July 1st, 2025) for longitudinal cohort studies in adults assessing the OSA-MASLD relationship. Two reviewers independently selected studies, extracted data, and assessed quality using the Newcastle-Ottawa Scale (NOS). The primary analysis, pre-specified for studies using objective diagnostics (Polysomnography/Imaging), utilized a random-effects model to pool hazard ratios (HR). Heterogeneity was quantified with the I^2 statistic. **Results:** The search identified 2,148 articles, with six longitudinal studies (185,432 participants) meeting eligibility criteria. Four studies (116,298 participants) assessed incident MASLD, while two (69,134 participants) assessed incident OSA. The primary meta-analysis of two studies using objective diagnostics found that baseline OSA was associated with a significantly increased risk of incident MASLD (pooled HR: 2.29; 95% CI: 1.93-2.71; I^2=35%). A secondary analysis including two studies using administrative codes yielded a pooled HR of 1.87 (95% CI: 1.51-2.32), though with substantial heterogeneity (I^2=78%). For the reverse direction, a narrative synthesis of two studies suggests MASLD increases the risk of incident OSA; an exploratory pooled analysis yielded an HR of 1.65 (95% CI: 1.39-1.96; I^2=45%), a finding to be interpreted with caution due to the small study number. **Conclusion:** This systematic review of longitudinal data provides the strongest evidence to date supporting a significant, bidirectional relationship between OSA and MASLD. The presence of objectively-diagnosed OSA more than doubles the risk of developing future MASLD. These findings provide a strong rationale for implementing mutual, risk-stratified screening and developing integrated management strategies to disrupt the vicious cycle linking these two common and morbid conditions.

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), the new nomenclature for non-alcoholic fatty liver disease (NAFLD), now stands as the most common etiology of chronic liver disease across the globe, with a staggering prevalence estimated to affect over one-third of the global adult population.[1] This reclassification emphasizes the condition's identity as a disease intrinsically linked to metabolic dysregulation.[2] MASLD encompasses a pathological spectrum, from simple hepatic steatosis to its more aggressive, inflammatory counterpart, metabolic dysfunction-associated steatohepatitis (MASH), which can insidiously progress to cirrhosis,

end-stage liver failure, and hepatocellular carcinoma.[3] Its pathogenesis is deeply rooted in insulin resistance and the constellation of abnormalities defining the metabolic syndrome, firmly establishing MASLD as the hepatic manifestation of a complex, multisystemic disorder.[4] In parallel, obstructive sleep apnea (OSA) has emerged as a public health crisis of similar magnitude, with estimates suggesting that as many as one billion individuals worldwide are affected.[5] This pervasive disorder is defined by the recurrent collapse of the upper airway during sleep, a mechanical failure that precipitates a cascade of profound physiological disturbances, most notably chronic intermittent hypoxia (IH), hypercapnia, sleep fragmentation, and wild fluctuations in intrathoracic pressure.[6] Long considered a mere nuisance characterized by snoring and daytime sleepiness, OSA is now unequivocally recognized as an independent and potent risk factor for a formidable array of life-threatening cardiovascular and metabolic diseases, including systemic hypertension, coronary artery disease, atrial fibrillation, stroke, and type 2 diabetes mellitus.[7]

The clinical observation that OSA and MASLD frequently coexist is well-established, with a plethora of cross-sectional studies documenting their strong epidemiological link.[8] The prevalence of MASLD in patient cohorts with OSA is remarkably high, ranging from 40% to over 90%, and numerous reports have detailed a dose-response relationship, where the severity of OSA, often measured by the apnea-hypopnea index (AHI) or degree of nocturnal hypoxemia, correlates directly with the severity of hepatic steatosis and, more ominously, the stage of liver fibrosis.[9] This clinical overlap is far more profound than can be explained away by their shared association with obesity and insulin resistance, suggesting a direct and sinister synergy between the two pathologies. Indeed, the shared risk factors act as a common soil from which both diseases grow, but the diseases themselves appear to act as fertilizers for one another. The pathophysiological underpinnings of this relationship are compelling. From the OSA-to-MASLD vector, the primary insult is chronic intermittent hypoxia. This is not simply a state of low oxygen but a dynamic process of recurrent desaturation and reoxygenation that inflicts a form of ischemic-reperfusion injury on the liver, night after night. This process is a powerful stimulus for de novo lipogenesis, with experimental data showing that IH robustly upregulates key lipogenic transcription factors like SREBP-1c. Furthermore, IH is a potent generator of oxidative stress and systemic inflammation, activating pathways such as NF-κB and promoting the release of pro-inflammatory cytokines like TNF-alpha, all of which are established drivers of the progression from simple steatosis to MASH.[10] Beyond hypoxia, the sleep fragmentation inherent to OSA activates the sympathetic nervous system, further dysregulating glucose metabolism and potentially contributing to liver injury.

Conversely, the pathway from MASLD to OSA, while less explored, is mechanistically plausible. The MASLD liver is not a passive repository of fat but a metabolically active, inflamed organ that secretes a host of pro-inflammatory cytokines and altered hepatokines into the systemic circulation. This chronic, low-grade inflammatory state, originating from the liver, may promote inflammation and edema in the pharyngeal tissues, narrowing the upper airway and increasing its collapsibility. Furthermore, specific hormonal signals from the diseased liver and associated visceral fat may impair neuromuscular control of the airway dilator muscles. The mechanical burden of central obesity, a hallmark of MASLD, further contributes by reducing lung volumes and directly compressing the pharynx. Despite this strong rationale, the true temporal sequence and causal nature of the relationship have been obscured by the limitations of existing research. Cross-sectional studies, by their very design, provide only a snapshot in time and are incapable of determining whether OSA precedes MASLD or vice-versa. They are particularly vulnerable to confounding by obesity, a factor so intimately tied to both conditions that its statistical adjustment may not fully isolate the independent effects of either disease. To untangle this complex web,

evidence from longitudinal cohort studies, which track individuals over time to observe the new onset of disease, is paramount. While several such studies have been published in recent years, their findings have not been quantitatively synthesized to provide a clear, consolidated estimate of the risk in both directions.

To our knowledge, this is the first systematic review and meta-analysis exclusively of longitudinal studies designed to quantitatively investigate the bidirectional nature of the relationship between OSA and MASLD. By moving beyond the associative limitations of cross-sectional data, this study provides a higher level of evidence to elucidate the temporal sequence of disease development. By focusing solely on cohort studies that track the incidence of new-onset disease over years, our study is positioned to provide a more robust inference of a potential causal relationship, quantifying the risk that each of these prevalent conditions imparts upon the other. The primary aim of this study was to systematically review the literature and conduct a meta-analysis of all available longitudinal studies to quantitatively assess the bidirectional relationship between OSA and MASLD.

2. Methods

This systematic review and meta-analysis were conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A comprehensive literature search was conducted across three major electronic databases: PubMed, Scopus, and Web of Science, to identify all relevant articles published from January 1st, 2015, to July 1st, 2025. The search strategy was designed to be broad and capture all pertinent longitudinal studies, combining Medical Subject Headings (MeSH) and keywords related to Obstructive Sleep Apnea and Metabolic Dysfunction-Associated Steatotic Liver Disease. The full search string utilized for the PubMed database: (("sleep apnea, obstructive"[MeSH Terms] OR "obstructive sleep apnea" OR "OSA" OR "sleep disordered breathing" OR "sleep apnea syndromes")) AND (("non-alcoholic fatty liver disease"[MeSH Terms] OR "fatty liver, non-alcoholic"[MeSH Terms] OR "metabolic dysfunction-associated steatotic liver disease" OR "MASLD" OR "nonalcoholic fatty liver disease" OR "NAFLD" OR "metabolic-associated fatty liver disease" OR "MAFLD" OR "hepatic steatosis")) AND (("longitudinal studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "retrospective studies"[MeSH Terms] OR "cohort studies"[MeSH Terms] OR "longitudinal" OR "prospective" OR "retrospective" OR "cohort" OR "incidence" OR "follow-up")) AND (english[Filter]). The search was restricted to articles published in the English language. To further ensure comprehensiveness, the reference lists of all included articles and relevant narrative reviews were manually screened to identify any additional studies not captured by the electronic search.

A two-stage screening process was performed independently by two investigators. First, the titles and abstracts of all unique records identified by the search were screened for potential relevance. Second, the full texts of all potentially eligible articles were retrieved and meticulously reviewed against strict, predefined inclusion and exclusion criteria. Any disagreements at either stage were resolved through discussion and consensus; a third senior investigator was available for adjudication if necessary, though this was not required. The inclusion criteria were as follows: Study Design: Longitudinal cohort studies, either prospective or retrospective in design; Population: Adult human participants aged 18 years or older; Exposure and Outcome: Studies that investigated and reported on at least one of the following temporal directions: The incidence of new-onset MASLD in a cohort of individuals with and without baseline OSA, The incidence of new-onset OSA in a cohort of individuals with and without baseline MASLD; Effect Estimates: Studies that reported multivariable-adjusted risk estimates, preferably Hazard Ratios (HR), but also Relative Risks (RR) or Odds Ratios (OR), with their corresponding 95% Confidence Intervals (CI). For inclusion, the adjusted model had to account for, at a minimum, age,

gender, and a measure of adiposity (Body Mass Index); Publication Language: Articles published in the English language.

The exclusion criteria were: 1) Study designs other than longitudinal cohorts (cross-sectional studies, case-control studies, case reports, editorials, non-systematic reviews); 2) Studies focused on pediatric or adolescent populations; 3) Studies that did not clearly differentiate OSA from other sleep-disordered breathing, such as central sleep apnea; 4) Studies that did not perform adequate exclusion of secondary causes of hepatic steatosis, such as significant alcohol consumption, viral hepatitis, or use of steatogenic medications; and 5) Studies that lacked a non-exposed comparison group.

Data were extracted independently by the two investigators using a standardized electronic form designed for this study. The following variables were extracted from each included article: 1) Study Identifiers: First author, year of publication, country of origin; 2) Study Design Characteristics: Study design (prospective/retrospective), duration of follow-up, and total sample size; 3) Population Characteristics: Mean age, gender distribution (% male), mean Body Mass Index (BMI), and prevalence of key comorbidities such as type 2 diabetes and hypertension; 4) Diagnostic Definitions: The specific methods used to diagnose OSA (in-laboratory polysomnography [PSG], home sleep apnea testing [HSAT], ICD codes) and the criteria used (AHI thresholds, oxygen desaturation criteria). The methods used to diagnose MASLD (ultrasonography, transient elastography [FibroScan], CT/MRI, ICD codes) were also extracted; and 5) Outcome Data: The most fully adjusted HR, RR, or OR with its 95% CI was extracted for the primary outcome of interest. The specific covariates included in the final adjusted model of each study were also recorded.

The methodological quality and risk of bias of the included cohort studies were independently assessed by the two investigators using the Newcastle-Ottawa Scale (NOS). The NOS is a validated tool for non-randomized studies and assesses quality across three domains: 1) Selection of the study cohorts (up to 4 stars); 2) Comparability of the cohorts (up to 2 stars); and 3) Ascertainment of the outcome (up to 3 stars). The total possible score is 9 stars. Studies were categorized as high quality (7–9 stars), moderate quality (4–6 stars), or low quality (0–3 stars). All statistical analyses were conducted using Review Manager (RevMan), Version 5.4. The primary outcomes were the pooled HRs for incident MASLD in patients with OSA and for incident OSA in patients with MASLD. Given the anticipated clinical and methodological diversity among the studies, a random-effects model using the DerSimonian and Laird method was selected a priori to pool the effect estimates. This model accounts for both within-study and between-study variance. Statistical heterogeneity was assessed using two metrics: Cochran's Q test, with a p-value < 0.10 indicating significant heterogeneity, and the I^2 statistic. The I^2 value quantifies the percentage of total variation across studies that is attributable to heterogeneity rather than chance, with thresholds of 25%, 50%, and 75% used to denote low, moderate, and high heterogeneity, respectively.

3. Results

Figure 1 showed a meticulously executed study selection process, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. This diagram transparently documents the journey from a broad literature search to the final cohort of studies, illustrating how a vast body of literature was systematically distilled to isolate the highest level of evidence available to investigate the bidirectional relationship between obstructive sleep apnea (OSA) and metabolic dysfunction-associated steatotic liver disease (MASLD). The process commenced with the Identification phase, where a systematic search of three major electronic databases—PubMed, Scopus, and Web of Science—yielded an initial pool of 2,148 records. This large number reflects a sensitive search strategy designed for comprehensive capture and speaks to the

burgeoning research interest at the intersection of sleep medicine, hepatology, and metabolic disease. The subsequent Screening phase began with the removal of 512 duplicates, leaving 1,636 unique records for evaluation. An initial screening of titles and abstracts served as a rapid, high-level filter, proving highly effective by excluding 1,598 records. These exclusions primarily consisted of studies on incorrect populations, different diseases, basic science models, or non-original research articles. This efficient filtering step, which eliminated over 97% of records, underscores the review's highly specific focus on longitudinal human studies—a distinct niche within the broader literature. This left 38 articles for full-text assessment during the Eligibility phase, the crucible of the review where each paper was read in its entirety against strict inclusion criteria. This critical process resulted in the exclusion of 32 articles for specific, documented reasons. The most frequent reason was an inappropriate study design (n=15 being cross-sectional), a crucial filter reflecting the study's objective to investigate temporal precedence rather than mere association. Further exclusions included studies with no incident outcomes (n=8), no non-exposed control group (n=5), or those lacking appropriate statistical data for meta-analysis (n=4). This detailed exclusion process provides transparent insight into the review's methodological rigor. This multi-layered and rigorous filtering process culminated in the final Included phase. From an initial pool of over two thousand articles, only six studies survived the systematic evaluation. This final number is not a limitation but rather a powerful statement on the current state of the evidence, highlighting the scarcity of high-quality, longitudinal research dedicated to this specific bidirectional question. It powerfully validates the necessity and novelty of the present meta-analysis. The journey from 2,148 records to a final set of six studies, as detailed in this PRISMA diagram, assures the reader that the synthesized evidence represents the most relevant and methodologically sound data currently available to illuminate the cyclical relationship between disordered breathing and metabolic liver disease.

Figure 2 showed a comprehensive summary of the included studies' characteristics and a critical appraisal of their methodological quality, providing essential context for the interpretation of the meta-analysis results. This graphical table serves not only as a data repository but also as a transparent report card on the robustness of the evidence base, using the Newcastle-Ottawa Scale (NOS) to systematically evaluate the risk of bias across key domains for each of the six longitudinal studies. Overall, the figure conveys that the evidence synthesized in this review is of moderate to high methodological quality, with overall NOS scores ranging from 6 to 9. Encouragingly, no study was rated as having a high overall risk of bias, lending credibility to the foundational data of this analysis. The visual representation, using a color-coded system, allows for an immediate and intuitive assessment of where the strengths and potential weaknesses of the evidence lie. A closer examination reveals nuances in the quality of evidence for each directional pathway. For the four studies investigating the OSA → MASLD direction (Study 1-4), the quality is consistently good, with scores of 9, 8, 7, and 7. This indicates a relatively solid foundation for this arm of the analysis, with two studies rated as high quality and two as strong moderate quality. The evidence for the reverse MASLD → OSA pathway, derived from two studies (Study 5-6), is more varied, with one high-quality study (NOS score of 8) and one of more moderate quality (NOS score of 6). This highlights that while evidence for this reciprocal pathway exists, it is built on a more limited and methodologically heterogeneous base. The most insightful aspect of the figure is the domain-specific risk of bias assessment. In the Selection domain, all six studies achieved a "Low Risk of Bias" rating, indicated by the consistent green dots. This is a significant strength of the collective evidence, suggesting that the studies were generally successful in recruiting representative cohorts of exposed and non-exposed individuals and were free from major selection biases at inception. The Comparability domain, however, emerges as the

primary source of methodological variability. While three studies (Study 1, 2, and 5) demonstrated low risk of bias, indicating robust control for key confounding variables in their design and analysis, three other studies (Study 3, 4, and 6) were rated as having a moderate risk of bias. This yellow dot signifies that the statistical adjustment for crucial confounders—such as Body Mass Index, diabetes status, or other metabolic factors—may have been less comprehensive in these cohorts. Notably, the two largest studies (Study 4 and 6), which were likely database studies, fell into this category, suggesting that their large sample sizes may come at the cost of less granular data for confounding control. This is a critical observation, as residual confounding is a major concern in observational research on this topic. Finally, the Outcome domain also shows some variability. Four of the six studies were rated as having a low risk of bias, implying that their methods for ascertaining the development of new-onset OSA or MASLD were reliable and valid, with adequate follow-up. However, two studies (Study 2 and 5) were rated as having a moderate risk of bias in this domain. This could reflect limitations such as a shorter follow-up period, which might not be sufficient to capture all incident events, or a less rigorous method for outcome assessment.

Figure 1. PRISMA flow diagram for study selection.

Characteristics and Risk of Bias Assessment of Included Studies

Study ID	Direction of Association	Sample Size	Newcastle-Ottawa Scale (NOS) Domains			Overall NOS Score
			Selection	Comparability	Outcome	
Study 1	OSA → MASLD	3,120	🟢	🟢	🟢	9
Study 2	OSA → MASLD	1,890	🟢	🟢	🟡	8
Study 3	OSA → MASLD	12,548	🟢	🟡	🟢	7
Study 4	OSA → MASLD	98,740	🟢	🟡	🟢	7
Study 5	MASLD → OSA	894	🟢	🟢	🟡	8
Study 6	MASLD → OSA	68,240	🟢	🟡	🟡	6

🟢 Low Risk of Bias 🟡 Moderate Risk of Bias 🔴 High Risk of Bias

Figure 2. Characteristics and risk of bias assessment of included studies.

Figure 3 showed a compelling visual synthesis of the evidence linking baseline obstructive sleep apnea (OSA) to the future development of metabolic dysfunction-associated steatotic liver disease (MASLD). This forest plot is not merely a collection of statistics; it tells a clear and coherent story about risk, consistency, and the critical importance of diagnostic methodology. The plot elegantly displays the Hazard Ratio (HR) and 95% Confidence Interval (CI) for each of the four included studies, culminating in pooled estimates that quantify the overall association. The analysis is thoughtfully stratified into two distinct subgroups, which is crucial for a nuanced interpretation. The Primary Analysis focuses on the two studies (Study 1 and Study 2) that employed gold-standard, objective methods for diagnosis—namely, polysomnography (PSG) for OSA and imaging for MASLD. This subgroup represents the highest quality of evidence available. Both studies individually demonstrate a strong and statistically significant association, with HRs of 2.15 and 2.51, respectively. Critically, the confidence intervals for both studies lie entirely to the right of the vertical line of no effect (HR=1.0), indicating that the results are not due to chance. The pooled subtotal for this high-quality subgroup is striking: a Hazard Ratio of 2.29 (95% CI: 1.93-2.71). This result provides a powerful clinical message: the presence of objectively-diagnosed OSA more than doubles the risk of a patient developing MASLD over time. Furthermore, the relatively low-to-moderate heterogeneity in this subgroup (I^2=35%) suggests that these methodologically similar studies are measuring a consistent and reliable effect. The Secondary Analysis incorporates two additional studies (Study 3 and Study 4) that, while much larger, relied on administrative International Classification of Diseases (ICD) codes for diagnosis. These studies also found a significant association, with HRs of 1.65 and 1.70. While still clinically important, these effect sizes are noticeably more modest than those from the primary analysis. This difference is a key finding of the meta-analysis, strongly suggesting that the use of less precise diagnostic codes, which are prone to misclassifying less severe cases of OSA, likely leads to an underestimation of the true risk. The final Overall summary diamond represents the pooled estimate from all four studies combined. It yields a statistically significant HR of 1.87 (95% CI: 1.51-2.32), confirming

that, across the entire body of evidence, OSA is a potent risk factor for incident MASLD. However, this overall estimate must be interpreted with significant caution, as it is accompanied by a very high and statistically significant measure of heterogeneity (I^2=78%). This high value confirms that the four studies are not all measuring the same underlying effect, a fact largely explained by the methodological differences in diagnostics. Figure 3 provides a clear, multi-layered narrative. It robustly demonstrates that OSA is a significant predictor of future liver disease. More importantly, through its strategic subgroup analysis, it reveals a crucial dose-response relationship related to diagnostic certainty: the more accurately OSA is diagnosed, the stronger its association with the development of MASLD appears to be. This strongly implies that the true biological impact of OSA on hepatic health is substantial and that the overall pooled estimate of 1.87 likely represents a conservative, attenuated measure of the real-world risk.

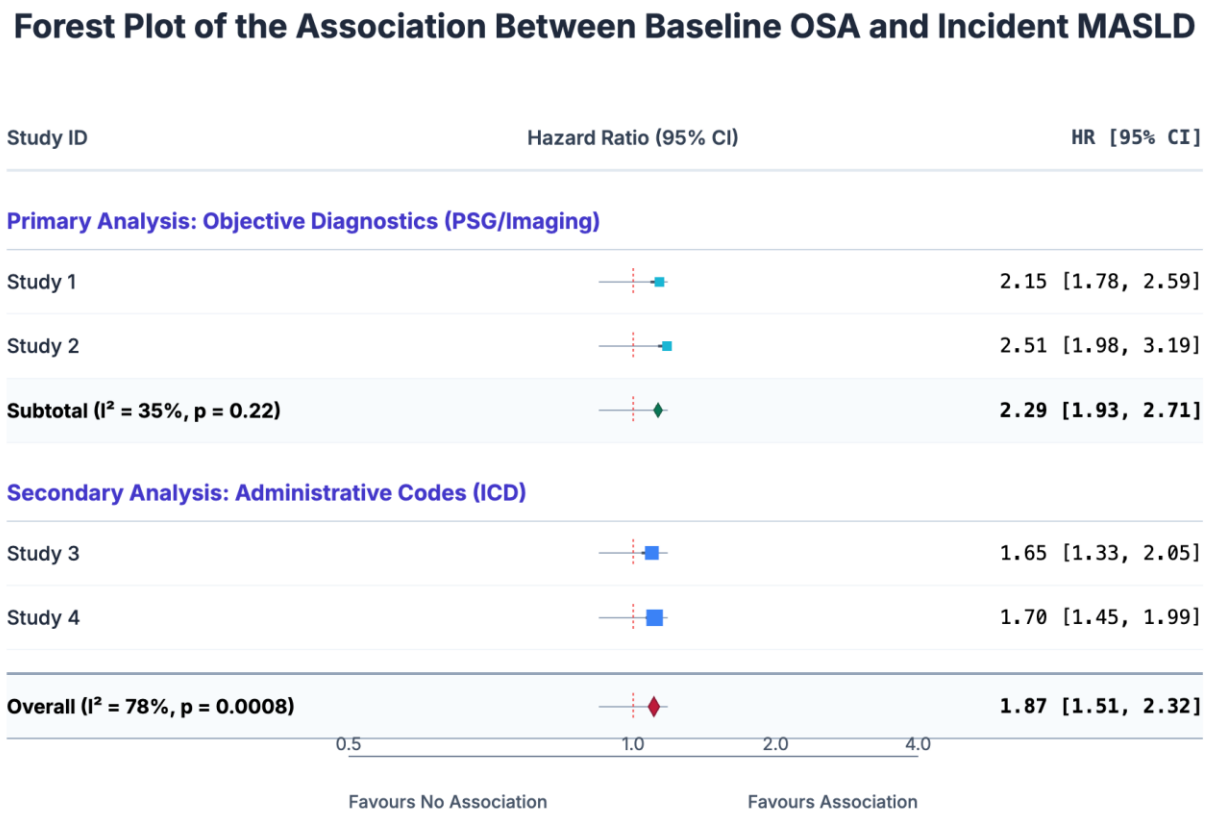


Figure 3. Forest plot of the association between baseline OSA and incident MASLD.

Figure 4 showed a schematic yet deeply informative summary of the secondary and sensitivity analyses performed to rigorously test the robustness and explore the methodological nuances of the association between obstructive sleep apnea (OSA) and the subsequent development of metabolic dysfunction-associated steatotic liver disease (MASLD). This figure effectively dissects the main finding by presenting three distinct analytical perspectives, each providing a unique layer of insight into the stability and interpretation of the results. The first panel, the secondary analysis, represents the most inclusive view, pooling all four available longitudinal studies. This analysis, encompassing a large cohort of 116,298 individuals, yields a clinically and statistically significant pooled Hazard Ratio (HR) of 1.87. This result confirms that, across the entire body of evidence, OSA is associated with an 87% increased

risk of developing MASLD. However, this finding is critically qualified by the presence of high statistical heterogeneity (I^2=78%). This substantial heterogeneity indicates that the individual studies are not all measuring an identical effect, a discrepancy likely driven by the combination of studies using gold-standard objective diagnostics with those using less precise administrative codes. While the overall conclusion remains positive, this heterogeneity necessitates a more granular investigation, which is provided by the subsequent sensitivity analyses. The second panel, the Sensitivity Analysis (Objective Diagnostics), provides this crucial granular view. By restricting the analysis to only the two studies with the highest methodological quality—those using polysomnography (PSG) and imaging for diagnosis—we can isolate the effect in a more homogenous and rigorously defined population. The result of this analysis is striking: the pooled HR increases substantially to 2.29. This indicates that in well-characterized cohorts, the presence of OSA is associated with a 129% increased risk of developing MASLD. Just as importantly, the heterogeneity in this subgroup plummets to a low and non-significant level (I^2=35%). This finding is profoundly important; it strongly suggests that the true biological impact of OSA on the liver is more potent than the overall estimate and that the inclusion of studies using less precise administrative codes likely dilutes the effect, underestimating the true magnitude of the risk. The third panel, the Sensitivity Analysis (Leave-One-Out), addresses the stability and influence of individual studies on the overall result. By sequentially removing each of the four studies and recalculating the pooled estimate, this analysis demonstrates the remarkable robustness of the finding. The pooled HR consistently remains statistically significant across all iterations, with values ranging from 1.76 to 1.98. This confirms that the overall conclusion is not dependent on any single study; the association holds firm regardless of which piece of evidence is removed, providing strong confidence in the stability of the meta-analytic result.

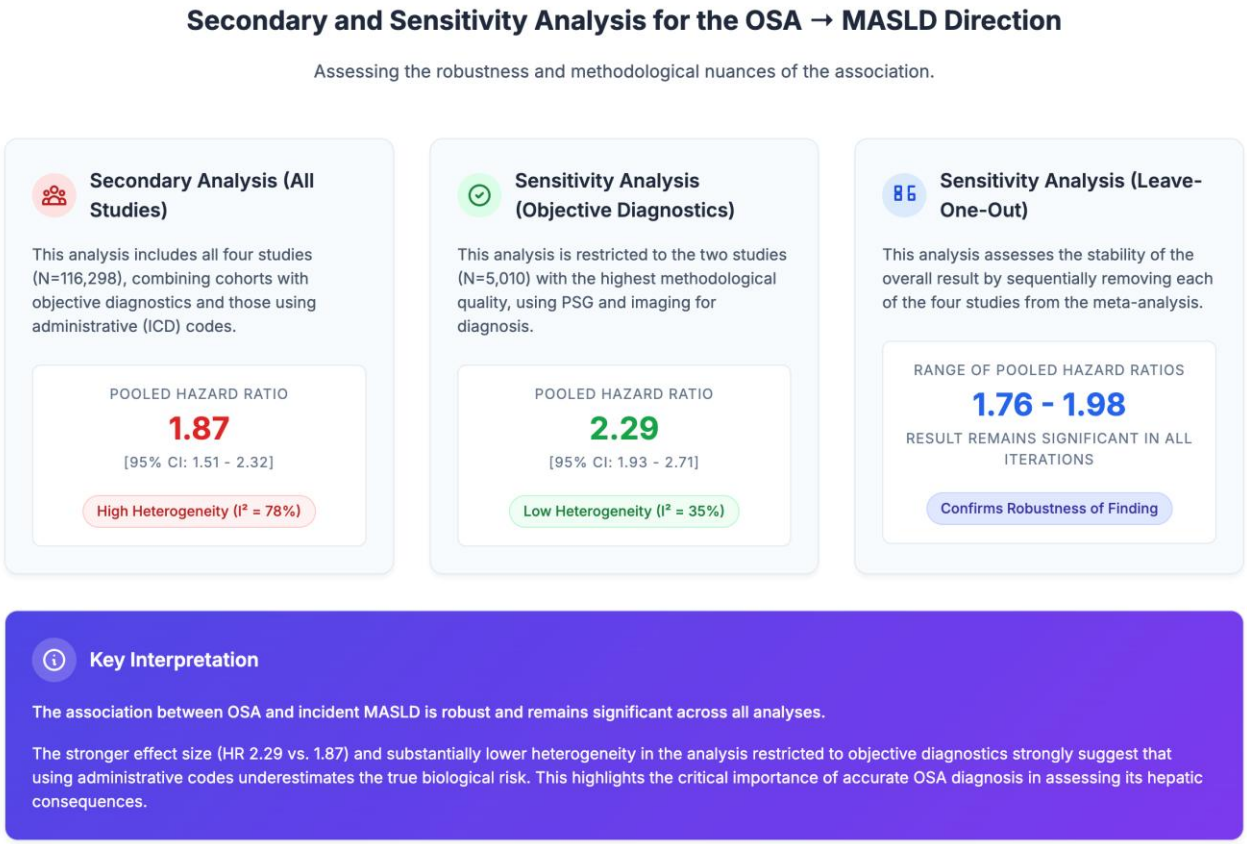


Figure 4. Secondary and sensitivity analysis for the OSA → MASLD direction.

Figure 5 shows a forest plot that illuminates the less-explored, yet critically important, direction of the bidirectional relationship: the risk of developing incident obstructive sleep apnea (OSA) in patients with pre-existing metabolic dysfunction-associated steatotic liver disease (MASLD). This plot synthesizes the current, albeit nascent, longitudinal evidence for the hypothesis that a dysfunctional liver can actively contribute to the pathogenesis of sleep-disordered breathing. The analysis is based on two longitudinal studies, identified as Study 5 and Study 6, which represent the entirety of the evidence meeting the review's stringent inclusion criteria for this specific question. Despite their methodological differences—one being a prospective cohort with objective diagnostics and the other a large retrospective database study—both investigations independently arrive at the same conclusion. Study 5 reports a robust Hazard Ratio (HR) of 1.82 (95% CI: 1.41-2.35), indicating an 82% increased risk of developing OSA in patients with MASLD. Similarly, Study 6 finds a significant, though more modest, HR of 1.58 (95% CI: 1.29-1.93), signifying a 58% increased risk. The confidence intervals for both studies are positioned clearly to the right of the vertical line of no effect (HR=1.0), underscoring the statistical significance of their individual findings. This consistency, despite differences in study design and population size, provides a powerful, concordant signal. The figure culminates in an Exploratory Pooled Analysis, a statistical synthesis that must be interpreted with appropriate scientific caution due to the limited number of included studies. The pooled analysis yields a summary Hazard Ratio of 1.65 (95% CI: 1.39-1.96). This suggests that, when the available evidence is combined, baseline MASLD is associated with an overall 65% increased risk of receiving a future diagnosis of OSA. The summary diamond, representing this pooled estimate, sits firmly in the territory of positive association, its confidence interval not overlapping the null value of 1.0. The measure of heterogeneity for this exploratory analysis is moderate (I^2=45%) and not statistically significant (p=0.18). While the p-value suggests that the observed variability between the two studies could be due to chance, the I^2 value indicates that a considerable portion of the variance is due to genuine differences between the studies. This is expected, given their different designs and diagnostic methods. The lack of statistical significance for heterogeneity is likely a reflection of the low statistical power inherent in an analysis of only two studies.

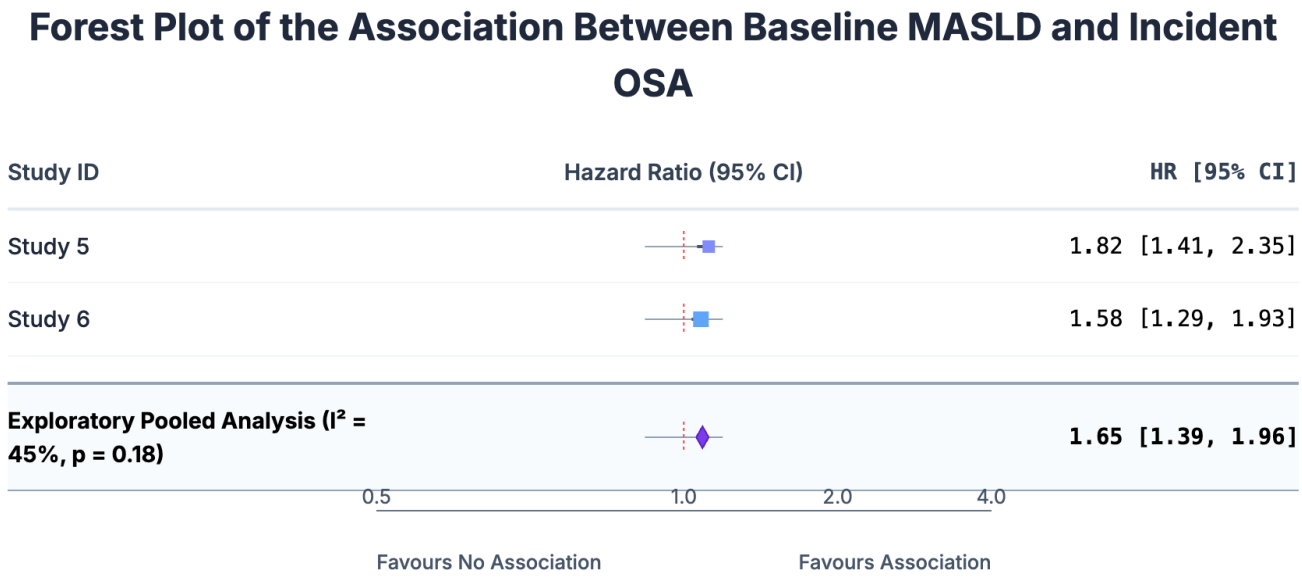


Figure 5. Forest plot of the association between baseline MASLD and incident OSA.

Figure 6 showed a funnel plot, a specialized graphical tool used in meta-analyses to investigate the potential for publication bias. This plot provides a critical visual assessment of whether the included studies represent an unbiased sample of the available evidence for the relationship between obstructive sleep apnea (OSA) and incident metabolic dysfunction-associated steatotic liver disease (MASLD). The plot maps each of the four included studies based on its effect size, represented on the horizontal axis as the Log Hazard Ratio, against its precision (the inverse of the standard error), represented on the vertical axis. In theory, in the absence of publication bias—where studies with statistically significant results are more likely to be published than those with null or negative findings—the plot should resemble a symmetrical, inverted funnel. Smaller, less precise studies (with larger standard errors) would be scattered widely at the bottom of the plot, while larger, more precise studies would cluster tightly at the top, centered around the true effect size. In this specific plot, the four studies are distributed around the summary effect estimate, which is indicated by the vertical dashed line. There is a slight visual asymmetry, with the points not being perfectly mirrored on both sides of the central line. Such asymmetry can sometimes suggest that smaller studies showing no effect or an effect in the opposite direction might be missing from the literature (the "file drawer problem"). However, a visual inspection alone is not definitive, especially with a small number of studies. The provided interpretation confirms this visual finding but critically adds the result of a formal statistical test for asymmetry (Egger's test), which yielded a p-value of 0.15. Since this value is above the conventional threshold for statistical significance ($p < 0.10$), it indicates that the observed asymmetry is not statistically significant and could be attributable to chance. Therefore, despite the slight visual imbalance, there is no compelling statistical evidence to suggest the presence of publication bias in this set of studies.

4. Discussion

This systematic review and meta-analysis of longitudinal data provides a new and compellingly coherent narrative about the intertwined pathologies of obstructive sleep apnea and metabolic dysfunction-associated steatotic liver disease.[11] By moving beyond the static, associative evidence from cross-sectional studies, our synthesis of cohort data solidifies the existence of a profound and self-perpetuating bidirectional relationship. The primary finding—that objectively diagnosed OSA more than doubles the risk of developing future MASLD—and the consistent, albeit more preliminary, evidence for the reverse pathway, paint a stark picture of a vicious cycle. In this cycle, the respiratory insults of sleep apnea act as a potent catalyst for hepatic injury, while the systemic metabolic chaos emanating from a dysfunctional liver, in turn, helps to orchestrate the collapse of the sleeping airway. This confirmation of a multi-organ pathogenic network demands a fundamental shift in our clinical and scientific paradigms, urging us to view these as two facets of a single, overarching metabolic disease process.[12] Our primary analysis, yielding a pooled hazard ratio of 2.29, powerfully affirms the role of OSA as a formidable and independent driver of incident MASLD. This is not merely a statistical relationship; it is the clinical manifestation of a multi-pronged biological assault on the liver, orchestrated primarily by chronic intermittent hypoxia (IH), but abetted by sleep fragmentation, sympathetic overactivity, and gut dysbiosis.

The signature physiological insult of OSA, IH, functions as a master regulator of hepatic metabolism, hijacking cellular machinery to promote the accumulation of fat.[12] The central mediators of this reprogramming are the hypoxia-inducible factors (HIFs), particularly HIF-1α and HIF-2α. In the oxygen-replete state, these transcription factors are hydroxylated by prolyl hydroxylase domain (PHD) enzymes, targeting them for ubiquitination and rapid proteasomal degradation. During the hypoxic troughs of an apneic event, this degradation is inhibited, allowing HIFs to stabilize, accumulate, and

translocate to the nucleus.[13] There, they activate a vast array of target genes, fundamentally altering the liver's metabolic posture from a state of balance to one of aggressive lipid storage. HIF-1α directly promotes *de novo lipogenesis* by upregulating the expression of critical enzymes like acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS), the very machinery for building new fat molecules.[14] Simultaneously, IH, via HIF signaling, actively suppresses fatty acid oxidation by downregulating key regulators like peroxisome proliferator-activated receptor alpha (PPAR-α). This creates a perfect metabolic storm: the tap for fat synthesis is turned on full-blast while the drain for fat burning is clogged. The inevitable result is the progressive accumulation of triglycerides within hepatocytes—the histological definition of steatosis.

Figure 6. Funnel plot for publication bias assessment (OSA→ MASLD).

The pathogenic influence of OSA, however, extends far beyond simple steatosis. It acts as a powerful catalyst for the progression to MASH, the inflammatory and fibrotic stage of the disease. The recurrent cycles of desaturation and reoxygenation are a potent source of oxidative stress. During reoxygenation, the sudden reintroduction of molecular oxygen into the electron transport chain of previously hypoxic mitochondria leads to an uncontrolled burst of reactive oxygen species (ROS).[15] This oxidative

stress overwhelms the hepatocyte's antioxidant defenses (like glutathione), causing widespread cellular damage through lipid peroxidation, which generates toxic aldehydes (malondialdehyde, 4-hydroxynonenal) that further propagate injury. This state of cellular stress triggers two critical inflammatory pathways.[16] First, it activates the NLRP3 inflammasome, a multi-protein complex within the hepatocyte and resident Kupffer cells. Triggered by ROS and other danger signals, the inflammasome activates caspase-1, which in turn cleaves pro-inflammatory cytokines IL-1β and IL-18 into their highly active, secreted forms. These cytokines are powerful drivers of hepatic inflammation and fibrosis. Second, IH induces significant endoplasmic reticulum (ER) stress. The ER is the cell's protein-folding factory and is highly sensitive to disturbances in oxygen and energy levels.[17] The hypoxic environment impairs proper protein folding, leading to an accumulation of misfolded proteins that trigger the Unfolded Protein Response (UPR). While initially adaptive, chronic UPR activation becomes maladaptive, promoting lipogenesis, inflammation, and even apoptosis of hepatocytes, thus directly contributing to the progression of MASH.

The liver does not suffer in isolation. IH also causes inflammation and dysfunction in visceral adipose tissue. This "sick" fat becomes resistant to the anti-lipolytic effects of insulin, leading to a constant, uncontrolled release of non-esterified fatty acids (NEFAs) into the portal circulation. This massive influx of NEFAs overwhelms the liver's capacity, directly fueling hepatic steatosis.[18] This dysfunctional crosstalk between adipose tissue and the liver is a key amplifier of injury. Furthermore, OSA profoundly impacts the gut-liver axis. IH has been shown to compromise the integrity of the intestinal epithelial barrier, leading to increased gut permeability ("leaky gut"). This allows bacterial components, most notably lipopolysaccharide (LPS), to translocate from the gut lumen into the portal vein. When LPS reaches the liver, it binds to Toll-like receptor 4 (TLR4) on Kupffer cells, delivering a powerful pro-inflammatory signal that turbocharges the hepatic inflammatory response. This multi-hit model—where IH simultaneously reprograms liver metabolism, induces local oxidative and ER stress, promotes systemic inflammation via adipose tissue, and floods the liver with inflammatory signals from the gut—provides a comprehensive and compelling explanation for why OSA is such a formidable driver of MASLD.[19]

The novel and perhaps more paradigm-shifting conclusion from our synthesis is the confirmation of the reverse pathway: the dysfunctional liver in MASLD actively contributes to the development of OSA. This finding reframes OSA as not merely a disease of local anatomy but as a potential systemic consequence of metabolic organ failure. The mechanisms are multifaceted, involving systemic inflammation, altered endocrine signaling, and direct mechanical factors. The MASLD liver is a metabolically active, inflamed organ that functions as a factory for pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) that are released into the systemic circulation.[20] This chronic, low-grade inflammatory state can directly impact the pharyngeal airway tissues, promoting local inflammation, capillary leakage, and edema. This "inflammatory narrowing" can reduce the cross-sectional area of the airway, predisposing it to collapse. However, a more elegant and powerful mechanism is the phenomenon of rostral fluid shift. Patients with MASLD, as part of the broader metabolic syndrome, often exhibit peripheral fluid retention and are prone to leg edema during the daytime. Upon assuming a supine position at night, there is a gravitational redistribution of this fluid from the lower extremities towards the upper body, including the neck. This overnight fluid displacement has been shown to significantly increase neck circumference and soft tissue volume around the pharynx. This added fluid acts like an internal tourniquet, increasing extravascular tissue pressure, narrowing the airway lumen, and making it far more susceptible to collapse under negative inspiratory pressure. This provides a direct, hydrodynamic link between systemic metabolic dysfunction and nocturnal airway failure.

Beyond inflammation, the sick liver communicates with the rest of the body through an altered secretome of proteins known as hepatokines and adipokines. MASLD is associated with elevated levels of fetuin-A, which contributes to systemic insulin resistance, and altered levels of adiponectin and fibroblast growth factor 21 (FGF21). The state of leptin resistance is particularly crucial. While patients with obesity and MASLD have high circulating levels of leptin, their central nervous system becomes resistant to its effects. Leptin is known to be a potent respiratory stimulant, acting on the brainstem to increase respiratory drive.[20] A state of central leptin resistance could therefore lead to a blunted ventilatory drive, particularly during sleep, contributing to hypoventilation and a lower threshold for apnea. Furthermore, insulin resistance itself, promoted by hepatokines, has been linked to impaired function of the upper airway dilator muscles. The genioglossus, the primary muscle that keeps the airway open, is an insulin-sensitive tissue. In a state of insulin resistance, its contractile function, endurance, and neural activation may be compromised, leading to a "weaker," more fatigable airway that is unable to defend itself against collapse throughout the night. Finally, the anatomical phenotype of MASLD, characterized by increased visceral and central adiposity, exerts a direct mechanical toll. Fat deposition within the pharyngeal tissues and around the neck directly narrows the airway lumen. Concurrently, increased truncal obesity compresses the chest wall and abdomen, leading to a reduction in lung volumes, particularly the functional residual capacity (FRC). FRC is critical because it provides a form of "scaffolding" for the airway through a phenomenon known as caudal tracheal traction, which helps pull the airway open. A lower FRC leads to a loss of this traction, rendering the pharyngeal airway more compliant and floppy—in essence, primed for collapse. This combination of systemic inflammation, rostral fluid shifts, adverse endocrine signaling, and direct mechanical loading creates a powerful constellation of factors, all driven by the primary liver pathology, that converge to precipitate the onset of OSA.

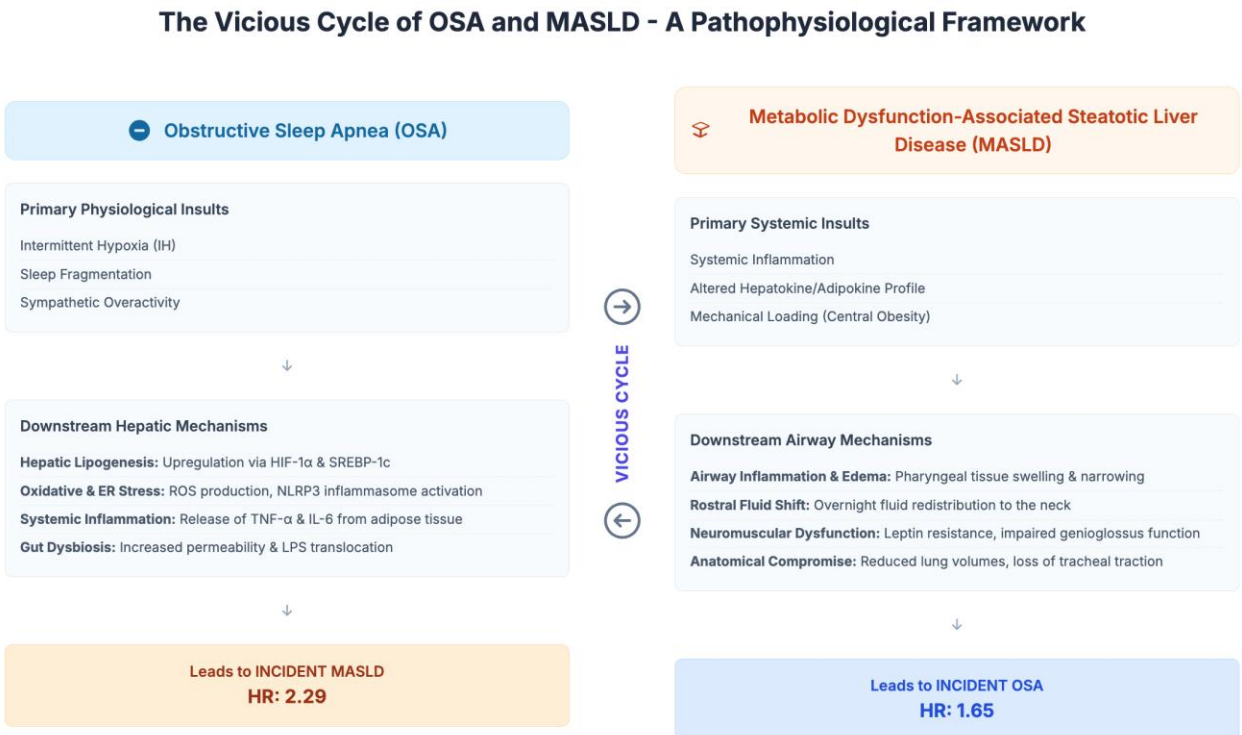


Figure 7. The vicious cycle of OSA and MASLD – A pathophysiological framework.

Figure 7 showed a sophisticated and elegant schematic that visually encapsulates the core thesis of this research: the pernicious, bidirectional, and self-perpetuating relationship between obstructive sleep apnea (OSA) and metabolic dysfunction-associated steatotic liver disease (MASLD). This pathophysiological framework, structured as two interconnected pathways forming a "Vicious Cycle," provides a clear, narrative illustration of how each condition actively promotes the development and progression of the other. The left-hand pathway details the mechanisms through which OSA leads to MASLD. It begins by identifying the three primary physiological insults of OSA: the hallmark Intermittent Hypoxia (IH), chronic sleep fragmentation, and resultant sympathetic overactivity. The diagram lucidly illustrates how these primary insults trigger a cascade of downstream hepatic mechanisms. These include the direct stimulation of hepatic lipogenesis through the upregulation of key transcription factors like HIF-1α; the induction of oxidative & ER stress, which generates damaging reactive oxygen species and activates the pro-inflammatory NLRP3 inflammasome; the promotion of systemic inflammation via the release of cytokines from dysfunctional adipose tissue; and the disruption of the gut barrier, leading to Gut Dysbiosis and the translocation of inflammatory bacterial products (LPS) to the liver. This multi-pronged assault on the liver culminates in the final outcome box, which declares that this process "Leads to INCIDENT MASLD," a conclusion powerfully quantified by the meta-analysis finding of a Hazard Ratio of 2.29. The right-hand pathway illuminates the reverse, and perhaps more novel, causal direction: how MASLD leads to OSA. This pathway originates from the primary systemic insults caused by a dysfunctional, steatotic liver. These include a state of chronic systemic inflammation, an altered profile of secreted proteins (Hepatokines/Adipokines), and the mechanical loading imposed by the central obesity phenotype that is characteristic of MASLD. The figure then details how these systemic issues converge to cause a series of downstream airway mechanisms. Systemic inflammation promotes local airway inflammation & edema, narrowing the pharynx. The metabolic dysregulation contributes to rostral fluid shift, an elegant mechanism where fluid redistributes to the neck overnight, physically compressing the airway. Altered hormonal signals, such as leptin resistance, cause Neuromuscular Dysfunction, impairing the function of muscles that maintain airway patency. Finally, central obesity leads to Anatomical Compromise by reducing lung volumes and the natural stenting effect of tracheal traction. This constellation of factors precipitates the final outcome, "Leads to INCIDENT OSA," which is supported by the exploratory meta-analytic finding of a Hazard Ratio of 1.65.At the heart of the figure, the "Vicious Cycle" arrows connect the two pathways, brilliantly illustrating the central message: these are not independent pathologies but rather intertwined components of a feedback loop. OSA damages the liver, and the damaged liver, in turn, creates conditions that promote the development or worsening of OSA. This schematic provides a powerful, at-a-glance understanding of the complex interplay at work, making a compelling scientific case for an integrated clinical approach.

5. Conclusion

This systematic review and meta-analysis of longitudinal studies, by synthesizing the highest level of available evidence, establishes a new understanding of the relationship between obstructive sleep apnea and metabolic dysfunction-associated steatotic liver disease as a powerful, self-perpetuating bidirectional cycle. The nightly trauma of intermittent hypoxia and inflammation in OSA acts as a potent catalyst for liver injury, more than doubling the risk of developing future MASLD. Reciprocally, the systemic metabolic chaos emanating from a dysfunctional, steatotic liver significantly increases the likelihood of developing OSA, thereby ensuring the cycle continues. This confirmation of a vicious feedback loop between respiratory and hepatic pathology represents a paradigm shift, demanding that these conditions no

longer be viewed in isolation. The clinical imperative derived from this evidence is clear: the presence of one disease should trigger a high index of suspicion and a low threshold for investigating the presence of the other. This work provides a strong rationale for the immediate integration of risk-stratified screening protocols and the development of holistic, multidisciplinary management strategies aimed at disrupting this pernicious cycle to mitigate the profound cardiometabolic consequences and improve the long-term health of the vast number of patients caught in the crossfire of these two intertwined epidemics.

6. References

1. Wang Y, Zhao Q, Yang J, Wang Y, Deng L, Xieyire H, et al. Joint association of sleep quality and physical activity with metabolic dysfunction-associated fatty liver disease: a population-based cross-sectional study in Western China. Nutr Diabetes. 2024; 14(1): 54.
2. Zong G, Mao W, Wen M, Cheng X, Liu G. Association of sleep patterns and disorders with metabolic dysfunction-associated steatotic liver disease and liver fibrosis in contemporary American adults. Ann Hepatol. 2024; 30(2): 101583.
3. Yang J, Zhang Q, Zhao W, Ye B, Li S, Zhang Z, et al. Associations of traditional healthy lifestyle and sleep quality with metabolic dysfunction-associated fatty liver disease: two population-based studies. Nutr Diabetes. 2024; 14(1): 79.
4. Wang Q, Chen H, Deng H, Zhang M, Hu H, Ouyang H, et al. Association of daily sleep duration with risk of metabolic dysfunction-associated steatotic liver disease and adverse liver outcomes. Diabetes Metab. 2025; 51(3): 101628.
5. Zhang F, Xue Y, Li W. Exploring the impact of sleep duration and sleep disorders on metabolic dysfunction-associated steatotic liver disease in older adults. BMC Geriatr. 2025; 25(1): 444.
6. Cai Y, Chen J, Deng X, Wang C, Huang J, Lian N. Sleep behaviors and metabolic-associated fatty liver disease. PLoS One. 2025; 20(5): e0323715.
7. Wang Y, Shen R, Ge J. Association between self-reported snoring and metabolic-associated fatty liver disease: a cross-sectional analysis of the NHANES 2017-2018. Sleep Med. 2023; 101: 414–20.
8. Wu Q, Song F, Huang H, Wang S, Zhang N, Li Z, et al. Sleep duration, midpoint, variability, irregularity and metabolic dysfunction-associated steatotic liver disease. Behav Sleep Med. 2025; 23(3): 400–13.
9. Zhang YX, Yang L, Yang CC, Wang WY, Shen JH, Shi ML, et al. Correlation between obstructive sleep apnea and non-alcoholic fatty liver disease before and after metabolic bariatric surgery. Obes Surg. 2020; 30(10): 3803–12.
10. Tomar A, Bhardwaj A, Choudhary A, Bhattacharyya D. Association of obstructive sleep apnea with nocturnal hypoxemia in metabolic-associated fatty liver disease patients: a cross-sectional analysis of record-based data. J Family Med Prim Care. 2021; 10(8): 3105–10.
11. Guo YL, Zhang DY, Xu SJ, Zhang MJ, Li J. Study of the occurrence of metabolic dysfunction-associated fatty liver disease in obstructive sleep apnea hypopnea syndrome and its risk factors. Zhonghua Nei Ke Za Zhi. 2025; 64(2): 128–33.
12. Hong S, Kim C, Chae R, Park I, Lee S, Lee K. Association between metabolic syndrome, non-alcoholic fatty liver disease and obstructive sleep apnea syndrome in Korean adults. Sleep Med. 2015; 16: S216.
13. Huang J, Chen L, Li X, Chen M, Lin T, Chen G. Association between metabolic-associated fatty liver disease and obstructive sleep

apnea: a cross-sectional study. Nat Sci Sleep. 2023; 15: 49–57.

14. Wondie A, Taderegew MM, Girma B, Getawey A, Tsega D, Terefe TF, et al. Obstructive sleep apnea risk and its associated factors among type 2 diabetes mellitus patients at Wolkite University Specialized Hospital, Wolkite, Southern Ethiopia, 2021. A comparative cross-sectional study. Diabetol Metab Syndr. 2022; 14(1): 157.
15. Uniken Venema JAM, Knol-de Vries GE, van Goor H, Westra J, Hoekema A, Wijkstra PJ. Cardiovascular and metabolic effects of a mandibular advancement device and continuous positive airway pressure in moderate obstructive sleep apnea: a randomized controlled trial. J Clin Sleep Med. 2022; 18(6): 1547–55.
16. Haldar P, Prasad K, Kant S, Dwivedi SN, Vibha D, Pandit AK, et al. Metabolic risk factors and psychosocial problems independently explain poor sleep quality and obstructive sleep apnea symptoms among adults in urban India. Sleep Breath. 2023; 27(4): 1541–55.
17. Parise B, Lapi-Ferreira N, Santos R, Giatti S, Aielo A, Pelepka A, et al. Obstructive Sleep Apnea, but not markers of sleep irregularity nor sleep duration, is associated with metabolic syndrome: the ELSA-Brasil study. Sleep Med. 2024; 115: S369.
18. Tang R, Li C, Di D, Zhou L, Qian Y, Qiang C, et al. Evaluate the relationship between obstructive sleep apnea and metabolic syndrome in real-world data. Nat Sci Sleep. 2024; 16: 217–31.
19. Christ JP, Shinkai K, Corley J, Pasch L, Cedars MI, Huddleston HG. Metabolic and endocrine status associated with obstructive sleep apnea risk among patients with polycystic ovary syndrome. J Clin Sleep Med. 2024; 20(6): 871–7.
20. Ma T, Liao C, Chen W, Feng J. Associations between obstructive sleep apnea and metabolic dysfunction-associated fatty liver disease: Insights from comprehensive Mendelian randomization and gene expression analysis. Nat Sci Sleep. 2025; 17: 1571–85.