

Protocol

Association between digestive function and sleep outcomes: a systematic review protocol

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ABSTRACT

Background: Digestive disturbances and sleep disorders frequently coexist and are increasingly recognized to share interconnected circadian, metabolic, inflammatory, and neuroendocrine pathways. The gut–sleep axis has emerged as a framework describing bidirectional interactions between gastrointestinal physiology, gut microbiota, and sleep regulation. Ayurveda presents a parallel systems-based perspective through the concepts of Agni (digestive capacity) and Nidra (sleep), emphasizing that impaired digestion and accumulation of Ama may contribute to disturbed sleep and systemic imbalance. This systematic review aims to synthesize available evidence evaluating the relationship between digestive function and sleep outcomes and to explore the underlying physiological and mechanistic pathways linking these processes.

Methods: Human clinical and observational studies will form the primary evidence base, while experimental and animal studies investigating digestive–sleep mechanisms will be considered separately to support mechanistic interpretation and will not be included in quantitative synthesis. Literature searches will be conducted across MEDLINE, Embase, CENTRAL, Scopus, Web of Science, the AYUSH Research Portal, and Google Scholar, with citation tracking and screening of Ayurvedic postgraduate and doctoral dissertations, for studies published up to October 2025. Methodological quality will be independently assessed by two reviewers using the RoB-2 and ROBINS-I tools. Findings will primarily be synthesized narratively, with meta-analysis undertaken only if methodological and outcome homogeneity permit; heterogeneity will be assessed using the I^2 statistic and certainty of evidence evaluated using the GRADE approach.

Conclusions: This review is expected to provide an integrative understanding of digestive–sleep interactions and inform future research and evidence-based clinical strategies.

Trial registration: PROSPERO CRD420251178526.

Keywords: Ayurveda, Circadian rhythm, Digestive function, Gut-sleep axis, Sleep, Systematic review

INTRODUCTION

Sleep and digestion are fundamental processes essential for survival and systemic homeostasis. Disturbances in sleep or digestive function are highly prevalent in modern populations contributing to metabolic disorders, neurocognitive impairment, chronic inflammation, and reduced quality of life.¹ Insomnia and poor sleep quality are commonly reported in individuals with

gastrointestinal disturbances such as functional dyspepsia, irritable bowel syndrome, metabolic syndrome etc. indicating a clinically relevant underexplored bidirectional relationship.²

Biomedical research increasingly conceptualizes this interaction as the gut–sleep axis, wherein inflammatory mediators, gut microbiota, and circadian regulation collectively influence sleep architecture and sleep–wake

rhythms.³⁻⁵ Studies showed that alterations in gut microbiota composition and intestinal permeability can disrupt sleep quality and circadian alignment.⁶ Conversely, sleep deprivation and circadian misalignment adversely affect digestive efficiency reinforcing a self-perpetuating pathological cycle.^{7,8}

Long before the emergence of these biomedical frameworks, Ayurveda described digestion and sleep as interdependent pillars of health. Classical Ayurvedic literature recognizes Agni and Nidra as essential determinants of physiological stability, emphasizing that impairment of digestive capacity leads to systemic dysfunction, including disturbed sleep.⁹ Impaired Agni results in formation of Ama, described as incompletely processed metabolic by-products that obstruct physiological pathways and disturb Dosha equilibrium.¹⁰ Nidra is conceptualized as a naturally restorative process governed by Dosha balance, particularly Kapha and Vata, and is profoundly influenced by digestive and metabolic status.¹¹ Thus, Ayurveda presents a unified, process-oriented understanding of digestion and sleep rather than treating them as isolated functions.

Despite conceptual convergence between Ayurvedic principles and modern gut-sleep physiology, existing scientific literature remains fragmented. Current systematic reviews predominantly examine isolated domains without synthesizing digestive sleep interactions within a comprehensive systems-based framework.¹² Furthermore, Ayurvedic concepts such as Agni, Ama, and Nidra are largely absent from contemporary evidence perspective, limiting integrative interpretation and translational potential.

Given the heterogeneity of study designs, outcomes, and conceptual frameworks, a systematic review is necessary to systematically identify, evaluate, and integrate evidence examining the bidirectional relationship between digestion and sleep. A predefined and prospectively registered systematic review protocol provides a transparent methodological framework, reducing the risk of selective outcome reporting, post hoc analytical decisions, and reporting bias. Adherence to PRISMA-P guidelines and registration in PROSPERO ensures methodological accountability, facilitates reproducibility, and minimizes unnecessary duplication of research efforts.

METHODS

This review will evaluate studies examining associations between digestive function and sleep outcomes across biomedical and Ayurvedic frameworks. Intervention studies, where available, will be synthesized separately from observational evidence.

Studies in which gut regulating interventions are combined with other non Ayurvedic or standard interventions will be categorized as combination

interventions and analyzed separately to assess their contributory role. Where outcomes related specifically to digestive or sleep regulation attributable to the gut-focused component are reported independently, priority will be given to those findings. In cases where such differentiation is not possible, the overall effect of the combined intervention will be considered.

For experimental and observational studies evaluating gut microbiota, metabolic pathways, inflammatory markers, or circadian mechanisms in relation to sleep, exposures will be analyzed descriptively to map mechanistic associations rather than to infer direct therapeutic effects.

Inclusion criteria

The review will include studies that meet all of the following criteria:

Population

Studies involving participants experiencing digestive disturbances, altered digestive physiology, or sleep-related outcomes will be included. Healthy populations will only be included where digestive-sleep interactions are explicitly evaluated.

Study designs

Randomized controlled trials, non-randomized studies, cohort, case-control, cross-sectional and mechanistic studies will be included. Review articles will be screened for citation harvesting only and will not be included in synthesis.

Exposure or focus

Studies evaluating digestive or metabolic functions including Agni, Ama, gut microbiota, digestion, metabolism, inflammation, or circadian rhythm in relation to sleep parameters such as sleep quality, duration, latency, architecture, or circadian alignment.

Models

Human studies will constitute the primary evidence base. Experimental and animal studies will be included only to support mechanistic interpretation and will be synthesized narratively.

Language and time frame

Studies published in English or Sanskrit with verified translations. All studies published up to October 2025 will be considered.

Exclusion criteria

Studies will be excluded if they are editorials, commentaries, letters to the editor, conference abstracts

lacking complete data or reports with insufficient methodological detail. Research that does not examine a direct relationship between digestive function and sleep outcomes will not be considered. Studies focusing exclusively on psychological or neurological disorders without relevance to digestive or sleep physiology will be excluded, as well as publications reporting non-specific wellness outcomes that lack clearly defined sleep-related endpoints.

Outcome measures

The primary outcomes of this review will focus on sleep-related parameters reflecting sleep regulation and overall sleep status. These outcomes will include changes or differences in sleep quality, sleep duration, sleep latency, sleep efficiency, sleep architecture, and circadian rhythm alignment, as assessed using subjective or objective methods reported within the included studies. Where available, validated and standardized measures of sleep assessment will be prioritized to improve comparability across studies.

Secondary outcomes will include indicators of digestive, metabolic, and gut-related function that may influence or reflect digestive–sleep interactions. These outcomes may include gastrointestinal symptoms, bowel regularity, digestive efficiency, gut microbiota characteristics, and metabolic or inflammatory markers associated with digestive physiology. In studies adopting an Ayurvedic framework, clinically or operationally defined indicators corresponding to Agni status will also be extracted where explicitly described. In addition, symptoms conceptually corresponding to Ama, such as digestive discomfort, heaviness, lethargy, and mental fatigue, will be considered when reported.

Where sufficient information is available, the review will additionally explore associations between digestive function and sleep outcomes and examine proposed mechanistic pathways underlying digestive–sleep interactions. Findings will be synthesized with consideration of conceptual convergence and divergence across biomedical and Ayurvedic perspectives, while accounting for variations in study design and outcome assessment.

Search methods for study identification

A comprehensive literature search will be conducted to identify studies examining the relationship between digestive function and sleep outcomes.

Electronic searches will be performed across MEDLINE (via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Scopus, and Web of Science. In addition, domain-specific databases relevant to traditional and integrative medicine, including the AYUSH Research Portal, will be searched.

To maximize retrieval of relevant evidence and reduce publication bias, supplementary searches will include Google Scholar, screening of reference lists of included studies, and forward and backward citation tracking. Grey literature sources, including Ayurvedic postgraduate (PG) and Doctor of Philosophy (PhD) dissertations available through institutional repositories and publicly accessible databases, will also be screened where relevant.

Search strategies will be developed using controlled vocabulary and free-text terms and adapted according to database-specific indexing and search requirements. Searches will be rerun prior to final synthesis to identify newly published studies. Where registered studies are identified without corresponding published results, attempts will be made to contact study authors to obtain additional information. A preliminary search strategy for MEDLINE (via PubMed) was developed to ensure transparency and reproducibility of study identification. The complete search strategy is presented in (Table 1) and will be adapted for other databases as required.

Table 1: Preliminary electronic search strategy for MEDLINE (via PubMed).

Search ID	Search strategy
1	((digestion) OR ("gastrointestinal function") OR ("gut health") OR ("gut microbiota") OR (microbiome) OR ("digestive physiology") OR (metabolism) OR (inflammation))
2	((sleep) OR ("sleep quality") OR (insomnia) OR ("sleep architecture") OR ("sleep duration") OR ("sleep latency") OR ("circadian rhythm") OR ("sleep-wake cycle"))
3	((Ayurveda) OR (Agni) OR (Ama) OR (Nidra))
4	((#1) AND (#2))
5	((#4) OR ((#4) AND (#3)))
6	Apply filters: Publication period (January 2000-October 2025)
7	Restrict language to English and Sanskrit (verified translation)
8	Final search set: ((#5) AND (#6) AND (#7))

The search strategy will be adapted according to database-specific indexing systems and syntax requirements while maintaining conceptual consistency across databases. Searches will be rerun prior to final synthesis to identify newly published studies. Where relevant registered studies are identified without published findings, attempts will be made to contact study authors to obtain additional information.

Selection of studies

All records identified through electronic database searches and additional sources will be collated, and duplicate entries will be removed prior to screening. At

least two reviewers will independently screen the titles and abstracts of all retrieved records to determine their potential eligibility according to the predefined inclusion and exclusion criteria.

Studies will be classified as included, excluded, or uncertain at the title and abstract screening stage. Full-text articles will be retrieved for all studies categorized as included or uncertain, and the same reviewers will independently assess the full texts for final eligibility using a standardized selection form.

Any disagreements between reviewers at either stage of screening will be resolved through discussion, and if consensus cannot be achieved, a third reviewer will be consulted to make the final decision. Inter-reviewer agreement during study selection will be assessed using Cohen's kappa coefficient to evaluate consistency between reviewers. The overall study selection process will be documented and reported using a PRISMA flow diagram, detailing the number of records identified, screened, assessed for eligibility, excluded, and included in the review.

Data extraction form

A standardized data extraction form will be developed for this review to ensure consistent and comprehensive collection of relevant data from all included studies. The form will be designed in accordance with the review objectives and eligibility criteria. Prior to full data extraction, the form will be pilot tested on a subset of included studies and refined as necessary to improve clarity and uniformity.

The data extraction form will record bibliographic details (author and year of publication), study characteristics (study design, setting, and sample size), and population characteristics (age, gender, and health status). Information related to digestive or gut-related exposures, mechanisms, or conceptual frameworks including descriptions of *Agni*, *Ama*, gut microbiota parameters, metabolic or inflammatory markers, and circadian rhythm variables will be documented where applicable.

Sleep-related data to be extracted will include the type of sleep disturbance assessed, sleep outcome measures (such as sleep quality, duration, latency, architecture, or circadian alignment), assessment tools used, and duration of follow-up where relevant. Key findings describing associations between digestive function and sleep outcomes will also be recorded.

Data extraction

Data extraction will be carried out independently by two reviewers using the predefined data extraction form. Each reviewer will extract data from all included studies, and the extracted information will be cross-checked for accuracy and completeness.

Any discrepancies identified during data extraction will be resolved through discussion between the reviewers. If consensus cannot be achieved, a third reviewer will be consulted. Where required data are missing or insufficiently reported, attempts will be made to contact the corresponding authors to obtain additional information.

The extracted data will be used for narrative synthesis and where appropriate, quantitative analysis in accordance with the planned data synthesis strategy.

Missing data

If relevant data are missing, unclear, or insufficiently reported in the included studies, attempts will be made to contact the corresponding authors via email to obtain the required information. A reasonable time period will be allowed for response before proceeding with analysis.

If missing data cannot be retrieved, the available information will be analyzed as reported, and the extent of missing data will be documented. No imputation of missing data will be performed. The potential impact of missing data on the findings of the review will be considered and discussed narratively in the final manuscript.

Data synthesis and assessing heterogeneity

Narrative synthesis will serve as the primary analytical approach. Quantitative synthesis will be undertaken only where at least three studies demonstrate sufficient clinical and methodological homogeneity. Where sufficient quantitative data with comparable outcome measures are available from at least three studies, a meta-analysis will be considered. In such cases, effect sizes will be calculated using standardized mean differences or odds ratios with corresponding 95% confidence intervals, as appropriate. A random effects model will be employed to account for expected clinical and methodological heterogeneity.

Statistical heterogeneity among studies included in quantitative synthesis will be assessed using the I^2 statistic. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sources of heterogeneity will be explored through subgroup analyses based on study design, population characteristics, and type of exposure or intervention where feasible. If heterogeneity is substantial and cannot be adequately explained, meta-analysis will not be performed, and findings will be reported narratively.

Subgroup analysis

If sufficient data are available, subgroup analyses will be performed to explore potential sources of heterogeneity. Subgroups may be defined based on study design (clinical, observational, experimental), population

characteristics (human or animal studies), and the primary focus of outcomes (digestive-related versus sleep-related parameters). Subgroup analyses will be conducted only where adequate and comparable data are available; otherwise, findings will be synthesized narratively.

Risk of bias in individual studies

Risk of bias in the included studies will be assessed independently by two reviewers. Any disagreements in the assessment will be resolved through discussion, and if consensus cannot be reached, a third reviewer will be consulted.

Randomized controlled trials will be evaluated using the Cochrane Risk of Bias tool–2 (RoB-2), which assesses bias across domains including the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each domain will be judged as low risk, some concerns, or high risk of bias.

Nonrandomized studies of interventions and observational studies will be assessed using the ROBINS-I tool, which evaluates bias due to confounding, selection of participants, classification of interventions or exposures, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results.

For experimental and mechanistic studies, risk of bias will be assessed using design-appropriate criteria focusing on methodological clarity, outcome measurement, and reporting transparency. Only studies included in the final evidence synthesis will undergo formal risk of bias assessment using design-appropriate tools.

The results of risk of bias assessment will be presented in tabular and graphical formats and will be considered during data synthesis and interpretation of findings.

Assessment of publication bias

Publication bias will be assessed if sufficient studies are available for quantitative synthesis. Funnel plots and Egger's test will be used when at least ten studies are included. If formal assessment is not feasible, potential publication bias will be considered narratively during interpretation of the findings.

Assessment of strength of evidence

The strength of evidence will be assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach. GRADE evaluates the quality of evidence based on predefined domains. Risk of bias will be assessed by considering the methodological quality and potential biases of the included studies. Inconsistency will be evaluated by

examining variability in results across studies. Indirectness will be assessed by analyzing the applicability of the evidence to the review question. Imprecision will be determined by evaluating the precision of effect estimates based on confidence intervals and sample sizes.

Data analysis

Descriptive analysis

Descriptive analysis will be conducted to summarize the characteristics of the included studies. Extracted data will be presented in terms of frequencies, percentages, and thematic patterns, as appropriate. Study characteristics such as study design, population, type of exposure or intervention, and outcome measures related to digestion and sleep will be described.

The descriptive synthesis will be used to map patterns, trends, and conceptual overlaps between Ayurvedic and contemporary biomedical perspectives on the digestion–sleep relationship. Findings will be organized to highlight consistencies, divergences, and evidence gaps across different study types and outcome domains.

Statistical analysis

To analyze primary outcomes related to sleep, such as sleep latency, sleep duration, sleep quality scores, and circadian rhythm parameters, we will calculate the mean difference or standardized mean difference for continuous variables where applicable. For dichotomous sleep related outcomes, such as the presence or absence of insomnia or poor sleep quality, odds ratios or relative risks will be estimated.

For digestive and metabolic outcomes, including bowel regularity, digestive efficiency, inflammatory markers, and gut microbiota related measures, continuous outcomes will be analyzed using mean difference or standardized mean difference, depending on measurement scales used across studies. Associations between digestive parameters and sleep outcomes will be synthesized quantitatively where comparable data are available.

The choice between fixed effects or random-effects models will be guided by the level of heterogeneity, which will be assessed using the I^2 statistic. Where substantial heterogeneity is identified, a random effects model will be preferred. If adequate data permit, subgroup analyses may be conducted based on study design or outcome type to explore sources of heterogeneity. When quantitative synthesis is not feasible, findings will be reported narratively.

Ethical considerations

Ethical approval is not required for this study as it is a systematic review based on previously published data. No

individual patient data will be collected or analyzed. Confidentiality of any unpublished information obtained from study authors will be maintained. The review will be conducted in accordance with established ethical standards for systematic reviews.

Expected contribution

This review is expected to identify evidence patterns, mechanistic pathways, conceptual overlap and research gaps relevant to digestion–sleep interactions.

DISCUSSION

Disturbances in digestion and sleep frequently coexist and exert bidirectional effects on metabolic, neuroendocrine, and inflammatory pathways. Epidemiological and clinical studies have demonstrated that poor sleep quality and insomnia are commonly observed in individuals with gastrointestinal disorders, including functional dyspepsia, irritable bowel syndrome, and metabolic conditions, highlighting a clinically relevant digestion–sleep interface.¹³ These associations have contributed to the emergence of the gut–sleep axis as a conceptual framework within contemporary biomedical research.

Existing evidence indicates a potential bidirectional interaction between digestive physiology and sleep regulation; however, findings remain fragmented across disciplines and study designs. Ayurvedic literature proposes a conceptual relationship between digestive status and sleep regulation that may provide an additional interpretative framework for understanding digestive–sleep interactions.

Despite conceptual convergence between Ayurvedic principles and modern gut–sleep physiology, existing scientific literature remains fragmented. Current systematic reviews largely examine isolated domains such as sleep and metabolism, gut microbiota and circadian rhythm, or sleep and inflammation, without synthesizing digestion sleep interactions within a unified framework. Moreover, Ayurvedic constructs such as Agni, Ama, and Nidra remain underrepresented in evidence syntheses, limiting integrative interpretation and translational relevance. Also, this protocol seeks to address these gaps by proposing a structured synthesis of evidence across clinical, observational, experimental, and conceptual studies from both Ayurvedic and biomedical domains. By employing predefined eligibility criteria, standardized risk of bias assessment, and transparent data synthesis methods, the review aims to integrate mechanistic insights with clinically relevant associations while accommodating methodological heterogeneity.¹⁴

An integrative synthesis of digestion sleep interactions may inform future research by identifying convergent mechanisms, evidence gaps, and methodological limitations. Such insights may support the design of hypothesis driven clinical trials and contribute to the

development of evidence based integrative strategies for managing sleep disturbances associated with digestive dysfunction.

Implications, limitations, and dissemination

This systematic review aims to synthesize available evidence on the interrelationship between digestion and sleep to support an integrative understanding of the gut–sleep axis. By collating findings from Ayurvedic and contemporary biomedical studies, the review may help clarify mechanistic associations and inform future research directions in sleep and digestive health.

A key anticipated limitation is the limited availability of high quality clinical studies from traditional medicine systems, including Ayurveda, in major bibliographic databases, as well as the potential non publication of relevant academic research. Methodological heterogeneity across studies may further limit quantitative synthesis.

The findings of this review will be disseminated through publication in a peer-reviewed journal and shared in electronic and print formats. The certainty of evidence will be assessed using the GRADE approach to summarize the current state of evidence and guide future research.

Additional limitations may include publication bias, language restrictions, conceptual translation of Ayurvedic constructs and heterogeneity across measurement approaches.

CONCLUSION

This systematic review protocol establishes a structured, PRISMA-P-informed framework for synthesizing biomedical and Ayurvedic evidence on the relationship between digestive function and sleep outcomes. By applying design-specific risk-of-bias assessment, predefined eligibility criteria, and a transparent narrative synthesis strategy, this review is expected to clarify convergent mechanisms linking digestive and sleep disturbances, identify existing evidence gaps, and inform future hypothesis-driven and integrative clinical research.

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