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Corresponding author:
Abdulrahman S. Alanazi

aas2@hotmail.com

Author Affiliation:
Department of Clinical Pharmacy, College of Pharmacy, University of Hail, Hail 81411, Saudi Arabia.

Sleep Disorders, Circadian Disruption, and Glycaemic Dysregulation in Type 2 Diabetes: A Systematic Review, Meta-Analysis, and Dose-Response Modelling (January 1, 2000 – May 30, 2026)

Alanazi, AS; Alanazi, BA.

ADMINISTRATIVE INFORMATION

Support - Self-funded. University of Hail College of Pharmacy academic resources. No external funding, pharmaceutical industry support, or commercial funding received.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - Neither author has financial, intellectual, or professional competing interests with respect to the subject matter of this review. No author has received honoraria, consultancy fees, research grants, or any other financial consideration from manufacturers of CPAP devices, pharmacological sleep agents, or antidiabetic medications relevant to the content of this manuscript.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 June 2026 and was last updated on 15 June 2026.

INTRODUCTION

Review question / Objective What are the pooled HbA1c burdens attributable to OSA, insomnia, short sleep duration, and shift work in T2DM; what are the HbA1c effect sizes from CPAP therapy, CBT-I, and sleep extension interventions; and what is the dose-response relationship between habitual sleep duration and glycaemic outcomes across a 26-year evidence horizon?

Rationale This systematic review addresses a critical evidence gap in diabetes management. Sleep disorders — comprising OSA, insomnia, short sleep duration, and shift work — are both prevalent and underdiagnosed in T2DM, yet fewer than 5% of published T2DM guidelines include structured sleep assessment recommendations. No comprehensive synthesis with dose-response modelling and a pre-specified Saudi/GCC regional subgroup analysis exists for this topic. Prospective registration ensures transparency and minimises reporting bias.

Condition being studied Obstructive sleep apnea (OSA), insomnia disorder, short sleep duration, and shift work-associated circadian misalignment as modifiable glycaemic risk factors and intervention targets in type 2 diabetes mellitus (T2DM).

METHODS

Search strategy Six electronic databases were systematically interrogated from January 1, 2000 through May 30, 2026: MEDLINE/PubMed,

Embase, Cochrane CENTRAL, Scopus, ClinicalTrials.gov, and a manual hand-search of the journal Sleep. No language restriction applied. Conference abstracts excluded unless accompanied by full peer-reviewed publication. Primary MEDLINE search string: ("sleep" OR "sleep apnea, obstructive" OR "insomnia" OR "sleep duration" OR "shift work" OR "circadian rhythm" OR "circadian misalignment" OR "chronotype" OR "sleep fragmentation" OR "sleep restriction" OR "sleep deprivation") AND ("diabetes mellitus, type 2" OR "HbA1c" OR "glycated hemoglobin" OR "insulin resistance" OR "HOMA-IR" OR "fasting plasma glucose" OR "glycemic control" OR "hyperglycemia" OR "glucose metabolism"). Date filter applied: 2000/01/01 to 2026/05/30.

Participant or population Adults aged 18 years or above with confirmed type 2 diabetes mellitus and any co-existing sleep disorder (OSA, insomnia disorder, short sleep duration below 6 hours, or shift work-associated circadian misalignment), with validated sleep assessment and extractable glycaemic outcome data across diverse global settings including Saudi Arabia and the GCC region.

Intervention Obstructive sleep apnea assessed by polysomnography, actigraphy, or validated questionnaire (Berlin, STOP-BANG, ESS); insomnia disorder assessed by validated questionnaire (PSQI, ISI); CPAP therapy at ≥4 hours per night; cognitive behavioural therapy for insomnia (CBT-I, including digital platforms); supervised sleep extension interventions; shift work and circadian misalignment exposure by validated self-report or objective work schedule data.

Comparator T2DM patients without co-existing sleep disorder (for HbA1c burden estimates); sham CPAP or no CPAP treatment (for CPAP efficacy outcomes); sleep hygiene education or waitlist control (for CBT-I outcomes); habitual short sleep duration control condition (for sleep extension outcomes); day-shift workers (for shift work T2DM risk comparisons); reference sleep duration of 7–8 hours per night (for dose-response modelling).

Study designs to be included Randomised controlled trials with minimum 12-week follow-up; prospective cohort studies (minimum enrolment 500 participants for cross-sectional or cohort designs); retrospective cohort studies (minimum n=500); nested case-control analyses; crossover RCTs for sleep extension interventions.

Eligibility criteria Inclusion: Original research in human participants aged ≥18 years; validated sleep assessment instrument (polysomnography, actigraphy, PSQI, ESS, Berlin Questionnaire, STOP-BANG, or ISI); at least one glycaemic outcome measure (HbA1c, FPG, or HOMA-IR); minimum enrolment of 500 participants for cross-sectional or cohort designs; minimum follow-up of 3 months for interventional studies. Exclusion: Secondary diabetes, exclusively paediatric or gestational diabetes populations, no validated sleep measure, duplicate publications, high-risk methodological concerns irresolvable by sensitivity analysis.

Information sources PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, ClinicalTrials.gov, Sleep (manual hand-search).

Main outcome(s) Pooled HbA1c mean difference (%) associated with OSA in T2DM versus non-OSA T2DM controls; pooled HbA1c mean difference from CPAP therapy at ≥4 h/night versus sham/no CPAP (14 RCTs); pooled HbA1c mean difference from CBT-I in T2DM with comorbid insomnia versus control; pooled T2DM odds ratio for shift workers versus day-shift equivalents; restricted cubic spline dose-response curve for sleep duration versus HbA1c excess.

Additional outcome(s) HOMA-IR reduction from CPAP therapy (SMD); HOMA-IR and FPG reduction from 2-week supervised sleep extension; Saudi/GCC-specific shift work T2DM OR; CBT-I heterogeneity (I^2) across RCT protocols; HbA1c burden by OSA severity stratum (mild-moderate vs severe AHI ≥30/h); dose-response OR per one-hour sleep reduction below 7 hours; CPAP adherence threshold effect (≥4 h vs <4 h/night on HbA1c).

Data management Title and abstract screening performed independently by both authors using Rayyan QCRI software. Full-text review of all potentially eligible records completed independently, with consultant endocrinologist available for arbitration. Data extraction employed a standardised, piloted form capturing: study design and country, sample size and T2DM composition, sleep phenotype and measurement instrument, follow-up duration, glycaemic outcome measures and effect estimates, adjustment covariates, and funding source. Extracted data stored in pre-piloted Excel forms.

Quality assessment / Risk of bias analysis RCTs assessed using Cochrane Risk of Bias 2.0 (RoB 2) tool across five domains (randomisation process,

deviations from intended interventions, missing outcome data, measurement of the outcome, selection of reported results). Observational studies appraised using Newcastle-Ottawa Scale (NOS). Overall evidence certainty graded using GRADE framework across four domains: risk of bias, inconsistency, indirectness, and imprecision.

Strategy of data synthesis Pooled effect estimates for continuous outcomes (HbA1c MD, HOMA-IR SMD, FPG MD) calculated using DerSimonian-Laird random-effects model. Statistical heterogeneity quantified using Cochran Q and I^2 statistic (I^2 ≥50% indicating substantial heterogeneity). Publication bias assessed using Egger regression test and Begg rank correlation test, with trim-and-fill analysis applied when asymmetry detected. Dose-response modelling employed restricted cubic splines (RCS) with knot placement at the 5th, 35th, 65th, and 95th percentiles of the sleep duration distribution. T2DM incidence odds ratios pooled under DerSimonian-Laird random effects. All analyses conducted in R version 4.3.1 using meta, metafor, and rms packages.

Subgroup analysis OSA versus non-OSA sleep disorder phenotype; CPAP adherence stratum (≥4 h versus <4 h per night); Saudi/GCC versus international cohorts; sex-stratified estimates; OSA severity (mild-moderate AHI 5 versus ≤5) for sleep quality subgroup; study design (RCT versus prospective cohort versus cross-sectional).

Sensitivity analysis Restriction to PSG-confirmed OSA studies only; exclusion of studies with NOS score below 5; restriction to HbA1c-confirmed T2DM (HbA1c ≥6.5%); leave-one-out analysis removing ISAACC2 trial; restriction to prospective cohort designs for T2DM incidence estimates; restriction to studies with 24-week minimum follow-up for CBT-I RCTs; CPAP threshold sensitivity at 3.5 h versus 4.0 h per night.

Language restriction No language restriction.

Country(ies) involved Saudi Arabia.

Other relevant information Endocrinology; Clinical Pharmacy; Sleep Medicine; Diabetology; Circadian Biology; Occupational Medicine; Pharmacovigilance.

Keywords sleep; obstructive sleep apnea; insomnia; CPAP; CBT-I; circadian rhythm; shift work; HbA1c; type 2 diabetes mellitus; systematic review.

Dissemination plans Peer-reviewed publication in a high-impact endocrinology, sleep medicine, or clinical pharmacy journal; open-access preferred. Results to be communicated to the diabetes clinical pharmacy practice community in Saudi Arabia and the GCC through academic conference presentation.

Contributions of each author

Author 1 - Abdulrahman Alanazi - Conceived and designed the study, drafted the protocol, will lead data extraction and synthesis, and drafted the manuscript and final manuscript submission.
Email: aas2@hotmail.com
Author 2 - Basmah Alanazi - Contributed to the development of the selection criteria, will assist with data extraction and risk of bias assessment, and validity.
Email: drbasmah7@gmail.com