

The Effects of Chrononutrition on Circadian Rhythm and Gut Microbiota Diversity in Type 2 Diabetes Mellitus: A Systematic Review Protocol

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025110030

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 November 2025 and was last updated on 11 November 2025.

INTRODUCTION

Review question / Objective This systematic review seeks to address the following research questions:

1. What are the effects of chrononutrition (i.e., meal timing, meal frequency, breakfast skipping, night eating, time-restricted eating, and timing of largest meal) on circadian rhythm in adults with type 2 diabetes mellitus?
2. What are the effects of chrononutrition (i.e., meal timing, meal frequency, breakfast skipping, night eating, time-restricted eating, and timing of largest meal) on gut microbiota diversity in adults with type 2 diabetes mellitus?

Rationale Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and persistent hyperglycemia. Individuals with T2DM have been shown to experience disrupted circadian rhythms and altered gut microbiota diversity, making this

population ideal for investigating chrononutrition effects on these parameters.

Condition being studied Chrononutrition and its effects on circadian rhythm and gut microbial diversity in the type 2 diabetes mellitus (T2DM) population.

METHODS

Search strategy Systematic searches will be conducted using the following electronic databases: PubMed, Web of Science, EMBASE, and Cochrane, from database inception to end of August 2025. Searches will be limited to English-language publications. The search strategy will be conducted using both free-text keywords and medical subject headings (MeSH) related to chrononutrition, circadian rhythms, gut microbiota, and type 2 diabetes, combined with Boolean operators (AND, OR, NOT). The keywords are follows: (“Chrononutrition” OR

“chrono-nutrition” OR “meal timing” OR “meal frequency” OR “breakfast skipping” OR “night eating” OR “time-restricted eating” OR “intermittent fasting” OR “evening eating” OR “food timing” OR “eating patterns” OR “feeding schedule” OR “temporal eating”) AND (“circadian rhythm” OR “circadian clock” OR “biological clock” OR “clock genes” OR “PER1” OR “PER2” OR “PER3” OR “BMAL1” OR “CRY” OR “ARNTL” OR “melatonin” OR “cortisol”) OR (“gastrointestinal microbiome” OR “gut microbiota” OR “gut microbiome” OR “intestinal microbiota” OR “microbiota composition” OR “microbial diversity”)) AND (“Diabetes Mellitus, Type 2” OR “Diabetes Mellitus” OR “T2DM” OR “T2D” OR “Non-insulin dependent diabetes”) NOT (“Type 1 diabetes” OR “T1DM” OR “T1D” OR “insulin dependent diabetes” OR “prediabetes” OR “impaired glucose tolerance” OR “impaired fasting glucose” OR “gestational diabetes” OR “GDM” OR “maturity onset diabetes of the young” OR “MODY” OR “diabetes insipidus”).

Secondary search strategies will include manual screening of reference lists from all included articles and contacting experts in the field to identify additional articles that may not be accessible through electronic databases.

Participant or population

Inclusion

Adults aged 18 years and above diagnosed with Type 2 diabetes mellitus (T2DM) with or without antidiabetic treatment, as well as rodent models of diabetes with no restrictions on species, gender, or age. Studies that include healthy participants or rodents as control groups will be considered for inclusion.

Exclusion

1. Individuals diagnosed with any form of diabetes other than T2DM, including prediabetes, type 1 diabetes mellitus (T1DM), maturity-onset diabetes of the young (MODY), gestational diabetes mellitus (GDM), and diabetes insipidus.
2. Patients with underlying comorbidities such as active cancers, renal failure, liver failure, thyroid disorders, sleep disorders, and mental disorders that may interfere with dietary interventions.
3. Hospitalized patients.
4. Animals other than rodents.

Intervention Inclusion: Studies that investigated any one of the chrononutrition-based interventions/exposures (i.e., meal timing, meal frequency, breakfast skipping, night eating, time-restricted eating, and timing of largest meal) with no restrictions on diet type (high-carbohydrate meals, high-fat meals, protein distribution) or

intervention duration.

Exclusions: Studies focusing solely on diet composition without sufficient information on chrononutrition, as well as those investigating chrononutrition in non-diabetic populations, will be excluded.

Comparator Inclusion: Placebos, standard dietary advice, usual care or other control conditions, including different chrononutrition interventions/exposures against each other, with no restrictions on intervention duration. Observational studies without formal comparators will also be included. Exclusion: Studies where the comparator includes dietary supplements or pharmacological interventions/exposures will be excluded.

Study designs to be included Inclusion: Randomized Controlled trials (RCTs), observational studies (case control studies, cohort studies, and cross-sectional), and animal experimental studies. Exclusion: Quasi-experimental studies, case reports, case series, reviews and meta-analyses, in vitro studies, editorials, commentaries, conference abstracts, grey publications, and studies with unavailable full text.

Eligibility criteria This systematic review will examine chrononutrition interventions in T2DM patients globally, with no restrictions on geographical location or cultural background.

Information sources Systematic searches will be conducted using the following electronic databases: PubMed, Web of Science, EMBASE, and Cochrane, from database inception to end of August 2025. Searches will be limited to English-language publications. Secondary search strategies will include manual screening of reference lists from all included articles and contacting experts in the field to identify additional articles that may not be accessible through electronic databases.

Main outcome(s) 1. Alteration in circadian rhythm biomarkers, including molecular markers (i.e., clock genes PER 1/2/3, BMAL1, CRY, ARNTL) and hormonal markers (i.e., melatonin, cortisol). 2. Changes in gut microbiota composition/diversity (i.e., taxonomic composition, alpha diversity, beta diversity, richness, and evenness).

Measures of effect:

Continuous data: Standardized mean difference (SMD) will be calculated with a confidence interval (CI) set to 95%.

Dichotomous data: Relative risk (RR) and Odds ratios (OR) will be calculated with a CI set to 95%

and proportions for categorical/compositional data where appropriate.

Additional outcome(s) 1. Changes in circadian physiological markers (i.e., core body temperature, heart rate variability).

2. Changes in glycemic control parameters (i.e., fasting blood glucose, postprandial blood glucose, insulin resistance, insulin sensitivity, HbA1c levels)

Measures of effect:

Continuous data: Standardized mean difference (SMD) will be calculated with a confidence interval (CI) set to 95%.

Dichotomous data: Relative risk (RR) and Odds ratios (OR) will be calculated with a CI set to 95% and proportions for categorical/compositional data where appropriate.

Data management

Screening

Studies that are retrieved through systematic searches will be exported to the Rayyan systematic software for selection, and duplicate records will be removed before screening. Two independent reviewers will screen the titles and abstracts based on predefined inclusion and exclusion criteria, followed by independent full-text assessment of potentially eligible studies. Any disagreement will be resolved by consensus, and if disagreement persists, a third reviewer will provide conflict resolution. In case of missing information, we will contact the corresponding author via email to request missing data. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram will be constructed to show the study selection process.

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Quality assessment / Risk of bias analysis Two reviewers will independently assess the quality of selected items using the appropriate tool

according to the study design:

1. Randomized controlled trials: Cochrane's revised risk of bias tool (RoB 2).

2. Cohort and case-control studies: Newcastle-Ottawa Scale (NOS)

3. Cross-sectional studies: Modified Newcastle-Ottawa scale or Joanna Briggs Institute Critical Appraisal Checklist

4. Animal studies: SYRCLE's risk of bias tool

Any disagreements between reviewers will be resolved through discussion and consensus, with a third reviewer consulted for a final decision if consensus cannot be reached.

Strategy of data synthesis Data will be synthesized and presented as a narrative synthesis, including study design, population characteristics, exposures, comparators (if applicable), outcomes, and results. Covariates will be reported for studies conducting adjusted analyses.

If feasible, a meta-analysis will be performed using Review Manager (RevMan) software for studies that report sufficiently homogeneous outcomes using comparable methods. Odds ratios and relative risks will be calculated with 95% confidence intervals for dichotomous data, while the standardized mean difference will be calculated with 95% confidence intervals for continuous data.

Statistical heterogeneity will be assessed using Higgins' I^2 statistic. Fixed-effects and random-effects models will be employed, where appropriate based on heterogeneity level.

Publication bias will be assessed using funnel plots if 10 or more studies are included in the meta-analysis.

Quality assessment results will be summarized in tables to show trends across studies.

Subgroup analysis Planned subgroup analyses include:

1. Individuals diagnosed with T2DM with and without antidiabetic treatment.

2. Type of chrononutrition intervention.

Sensitivity analysis Sensitivity analyses will be conducted by systematically excluding studies to assess variability across studies.

Language restriction The search will be restricted to English language publications.

Country(ies) involved Malaysia.

Keywords Chronobiology; Chrononutrition; circadian rhythm; gut microbiota; microbial diversity; type 2 diabetes; systematic review.

Dissemination plans The completed systematic review will be published in a peer-reviewed open-access journal and presented at relevant scientific conferences.

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