Review Article

Vitamin D Dosage and Extra-Skeletal Outcomes in Adults: A Systematic Review Protocol

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Background: Vitamin D supplementation is widely prescribed for conditions beyond skeletal health, yet the optimal dosage for extra-skeletal outcomes such as cardiovascular events, cancer, respiratory illness, and autoimmune disease remains contested. Conflicting results from large-scale randomised controlled trials (RCTs), including VITAL and D-Health, have left clinicians without clear dose-response guidance. We describe a protocol for a systematic review that will evaluate the comparative effectiveness of different vitamin D dosages on critical clinical outcomes in adults.

Methods: This review was prospectively registered with PROSPERO (CRD420251011893) and the Clinical Trials Registry of India (CTRI/2025/09/094241), and approved by a seventeen-member institutional ethics committee (ECARP/2025/109). We will search Embase, Ovid MEDLINE, CINAHL, Cochrane CENTRAL, Scopus, Web of Science, ClinicalTrials.gov, and CTRI for RCTs comparing different vitamin D dosages in adults aged 18 years or older. Two reviewers will independently screen records, extract data, and assess risk of bias using the Cochrane RoB 2.0 tool. Random-effects meta-analyses will pool binary outcomes as risk ratios and continuous outcomes as mean differences with 95% confidence intervals. Heterogeneity will be quantified using I^2, τ^2, and prediction intervals. Certainty of evidence will be graded using the GRADE framework.

Conclusions: This protocol establishes a transparent, pre-registered plan for synthesising trial evidence on vitamin D dose-response relationships across extra-skeletal outcomes. The completed review aims to inform supplementation guidelines and identify persisting evidence gaps for future trials.

 doi.org/10.32388/DVWQWJ

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Introduction

Rationale

Vitamin D is a secosteroid hormone central to calcium-phosphate homeostasis and skeletal integrity. Over the past two decades, observational data have linked low circulating 25-hydroxyvitamin D [25(OH)D] concentrations to an expanding list of non-skeletal disorders, including cardiovascular disease, several cancers, type 2 diabetes, respiratory infections, autoimmune conditions, and all-cause mortality [1][2]. These associations prompted a wave of interventional research: the VITamin D and OmegA-3 TriaL (VITAL), enrolling 25,871 participants, reported a modest reduction in cancer mortality with 2000 IU/day cholecalciferol but no effect on major cardiovascular events [1]. The D-Health trial (n = 21,315) observed a borderline reduction in cancer mortality with monthly bolus dosing [3]. A pooled analysis of 25 RCTs suggested that daily or weekly supplementation, rather than large intermittent boluses, confers benefit against acute respiratory tract infections in individuals with baseline 25(OH)D below 25 nmol/L [4]. Vitamin D has also shown analgesic properties in preclinical pain models, though translational evidence remains inconsistent [5].

Despite this extensive trial portfolio, a central question persists: does the clinical benefit of vitamin D vary by dose, and if so, what constitutes the optimal regimen? Existing systematic reviews have typically pooled studies irrespective of dose, or focused on a single disease domain, making dose-response comparisons across outcomes difficult [2][6]. The Endocrine Society and the Institute of Medicine guidelines diverge on recommended intake, reflecting persistent uncertainty [7]. No published systematic review has simultaneously evaluated dose-dependent effects of vitamin D across cardiovascular, oncological, respiratory, autoimmune, and pain-related outcomes from RCTs, despite calls for such synthesis [1].

We therefore designed a systematic review to address three linked objectives: (i) to determine the comparative effectiveness of different vitamin D dosages on primary clinical outcomes including all-cause mortality, cardiovascular events, and cancer outcomes in adults; (ii) to characterise the dose-response relationship across these extra-skeletal endpoints; and (iii) to catalogue the adverse effect profile of vitamin D supplementation at varying doses. This protocol was developed and is reported in

accordance with the PRISMA-P 2015 statement [8] and was prospectively registered before screening commenced.

Protocol

Study design and registration

This is a protocol for a systematic review with planned meta-analysis. The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 30 July 2025 (registration number: CRD420251011893) and with the Clinical Trials Registry of India (CTRI) on 4 September 2025 (registration number: CTRI/2025/09/094241) [9][10]. Institutional ethics committee approval was granted by the seventeen-member Ethics Committee for Academic Research Projects (ECARP) at Topiwala National Medical College and BYL Nair Charitable Hospital, Mumbai, on 20 August 2025 (approval number: ECARP/2025/109). This protocol is reported following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement [8]. A completed PRISMA-P checklist is appended.

Amendments

The ethics committee required two substantive amendments before approval: (i) the principal investigator was changed from Dr. Shakeeb Dhorajiwala (contractual assistant professor) to Dr. Pramod D. Shankpal (permanent faculty), and (ii) a defined sample size estimation plan was incorporated. One co-investigator (Dr. Shubham Kangulwar) was removed from the team. All amendments are documented in the ethics committee correspondence, available as supplementary material. Any future protocol amendments will be dated, described, and reported in the PROSPERO record and the final review publication.

Eligibility criteria

Studies will be selected using the Population, Intervention, Comparator, Outcomes, Timeframe, and Study design (PICOTS) framework (Table 1).

Element	Inclusion criteria	Exclusion criteria
Population	Adults aged ≥18 years, regardless of sex, ethnicity, or baseline health status	Paediatric populations (<18 years)
Intervention	Vitamin D supplementation (cholecalciferol [D3], ergocalciferol [D2], or calcifediol) at any dose and frequency	Co-interventions where the independent effect of vitamin D cannot be isolated
Comparator	Placebo, standard of care, or a different dose/frequency/form of vitamin D	No comparator group
Outcomes (primary)	All-cause mortality; cardiovascular events (MI, stroke, heart failure, MACE); cancer outcomes (tumour-specific biomarkers, OS, PFS, tumour regression); inflammatory biomarker change; respiratory outcomes (severe asthma exacerbations, pneumonia, need for mechanical ventilation in COVID-19)	
Outcomes (secondary)	Cognitive function; wellbeing; infection risk; tuberculosis cure rate; CD4 count in HIV/TB co-infection; adverse events (nephrolithiasis, hypercalcaemia, hypercalciuria, serious adverse events)	
Timeframe	Published from 1 January 2020 through 31 December 2024 (with eligible studies published in 2025 also considered)	
Study design	Randomised controlled trials (parallel-group, crossover, cluster-randomised)	Observational studies, case reports, case series, non-randomised trials, reviews, editorials, unpublished trial reports, full text unavailable

Table 1. Eligibility criteria defined by PICOTS framework

Only studies published in English will be included. Studies with insufficient outcome data for quantitative synthesis will be excluded.

Information sources

We will search the following electronic databases from inception (or earliest available date) to the search date: Embase (via Embase.com), Ovid MEDLINE (via OvidSP), CINAHL Ultimate (via EBSCOhost), the Cochrane Central Register of Controlled Trials (CENTRAL via the Cochrane Library), Scopus (Elsevier), and Web of Science (Clarivate). Clinical trial registries (ClinicalTrials.gov and CTRI.nic.in) will be searched for completed but unpublished trials. We will screen ProQuest Dissertations & Theses Global for unpublished dissertations and medRxiv and bioRxiv for relevant preprints. Reference lists of included studies and pertinent systematic reviews will be hand-searched. We will contact corresponding authors of identified trials to inquire about unpublished or ongoing studies. Full texts will be obtained through institutional subscriptions, interlibrary loan, or direct author contact. Studies for which full text cannot be obtained after these efforts will be listed with the reason for exclusion.

Search strategy

The search strategy was developed collaboratively by a pharmacologist (SSD) and an endocrinologist (SR), refined through iterative pilot searches, and structured around three concept blocks combined with Boolean AND: (i) vitamin D and its analogues, (ii) dosage and administration terms, and (iii) an RCT methodological filter. Controlled vocabulary (MeSH, Emtree, CINAHL headings) was supplemented with free-text synonyms in title, abstract, and keyword fields. No date or language restrictions were applied at the search stage. The full electronic search strategies for all six databases are provided in the supplementary file (Table 2 presents the Embase strategy as an exemplar). The search was developed following Cochrane guidance on searching for studies [11].

Line	Search terms
#1	'vitamin d'/exp OR 'cholecalciferol'/exp OR 'ergocalciferol'/exp OR '25 hydroxyvitamin d'/exp OR 'vitamin d':ti, ab OR 'cholecalciferol':ti, ab OR 'ergocalciferol':ti, ab OR 'calcidiol':ti, ab OR 'calcitriol':ti, ab
#2	'drug dose'/exp OR 'drug dose comparison'/exp OR 'dose response'/exp OR 'drug administration'/exp OR 'dose':ti, ab OR 'dosage':ti, ab OR 'regimen':ti, ab OR 'high dose':ti, ab OR 'low dose':ti, ab OR 'loading dose':ti, ab OR 'bolus':ti, ab OR 'daily':ti, ab OR 'weekly':ti, ab OR 'monthly':ti, ab OR 'intermittent':ti, ab OR 'supplementation':ti, ab OR 'intake':ti, ab
#3	'randomized controlled trial'/exp OR 'clinical trial'/exp OR 'controlled clinical trial'/exp OR 'random*':ti, ab OR 'placebo':ti, ab OR 'blind*':ti, ab OR 'control group':ti, ab
#4	#1 AND #2 AND #3

Table 2. Search strategy for Embase (exemplar)

Note: Complete search strategies for Ovid MEDLINE, CINAHL, Cochrane CENTRAL, Scopus, and Web of Science are provided in the supplementary file.

Study records

Data management

Search results from all databases will be exported to a reference manager (EndNote or Zotero) for deduplication. Deduplicated records will be imported into Covidence (Veritas Health Innovation, Melbourne, Australia) for screening. Extracted data will be managed in Microsoft Excel for Microsoft 365 (Version 2508, Build 16.0.19127.20192, 64-bit).

Selection process

Two reviewers (SSD and SR) will independently screen titles and abstracts against the eligibility criteria using standardised forms in Covidence. Before formal screening, we will pilot the process on 10 randomly selected records and calculate inter-rater reliability using Cohen's kappa; a threshold of $\kappa \geq 0.80$ will be required before proceeding to full screening. Full texts of potentially eligible records will be retrieved and assessed independently by the same two reviewers. Disagreements at any stage will be resolved by

discussion; if consensus cannot be reached, a third reviewer (PDS) will arbitrate and that decision will be final. We will report the number of records screened, excluded at each stage with reasons, and inter-rater agreement coefficients. The study selection process will be documented in a PRISMA flow diagram (Figure 1).

Data collection process

A standardised, piloted data extraction form will be used. Two reviewers will extract data independently and in duplicate. Discrepancies will be resolved by consensus or referral to the third reviewer. For trials with missing outcome data, we will contact corresponding authors (up to two email attempts over two weeks). If data remain unavailable, we will conduct sensitivity analyses excluding trials with greater than 20% missing data and assess whether missingness is related to effect size.

Data items

The following information will be extracted from each included study:

- Study characteristics: first author, year, country, setting, study design (parallel-group, crossover), randomisation method, blinding status, sample size, study duration.
- Participant characteristics: age (mean, SD, range), sex distribution, ethnicity/race, baseline 25(OH)D concentration (mean, SD), comorbidities.
- Intervention details: type of vitamin D (D3, D2, calcifediol), dose (IU or µg), frequency, duration, route, co-interventions (e.g. calcium).
- Comparator details: type, dose, frequency, duration, route.
- Outcome data: effect estimates for all pre-specified primary and secondary outcomes (mean differences, risk ratios, hazard ratios with 95% CIs), number of events and participants per group, timepoints of assessment.
- Funding source, conflict of interest declarations, and trial registration status.

Outcomes and prioritisation

Primary outcomes: (i) all-cause mortality; (ii) cardiovascular events, defined as myocardial infarction, stroke, heart failure, or major adverse cardiovascular events (MACE); (iii) cancer outcomes, including change in tumour-specific biomarker levels from baseline (e.g. IL-2, IL-6, IFN-γ), overall survival, progression-free survival, and tumour regression time; (iv) change in inflammatory biomarker levels

from baseline; and (v) respiratory outcomes, comprising severe asthma exacerbations requiring systemic corticosteroids, asthma symptom control, lung function, radiologically confirmed pneumonia risk, and need for invasive mechanical ventilation in COVID-19 patients.

Secondary outcomes: (i) cognitive function (e.g. executive function), functional outcomes, and wellbeing; (ii) risk of infection (any, bacterial vaginosis), tuberculosis cure rate, sputum smear/culture positivity in tuberculosis, CD4 cell count in HIV/TB co-infection; and (iii) adverse events including nephrolithiasis, hypercalcaemia, hypercalciuria, vomiting (in COVID-19), and serious adverse events.

Primary outcomes were selected based on their clinical significance and the weight of existing evidence suggesting a plausible vitamin D effect. Intention-to-treat analyses will be prioritised. Secondary outcomes will be analysed if sufficient data are available.

Risk of bias in individual studies

Two reviewers (PB and SaR) will independently assess risk of bias in each included RCT for each primary outcome using the Cochrane Risk of Bias 2.0 tool (RoB 2.0) [12]. Five domains will be evaluated: (i) randomisation process, (ii) deviations from intended interventions, (iii) missing outcome data, (iv) measurement of the outcome, and (v) selection of the reported result. Each domain will be rated as 'low risk', 'some concerns', or 'high risk'. An overall risk of bias judgement will be derived per the RoB 2.0 algorithm: low risk if all domains are low; high risk if one or more domains are high risk or three or more domains raise some concerns; and some concerns for all other cases. Disagreements between reviewers will be resolved by a senior reviewer (SSD), whose decision will be final. Risk of bias results will be presented graphically using traffic-light plots generated with the robvis package in R. We will conduct sensitivity analyses excluding trials judged as high risk of bias.

Data synthesis

Criteria for quantitative synthesis

Meta-analysis will be performed when at least three studies report comparable interventions, populations, and outcomes. If studies are too heterogeneous for meaningful pooling (based on clinical and methodological assessment), we will present results in structured tables with a narrative synthesis following Synthesis Without Meta-analysis (SWiM) reporting guidelines.

Summary measures and models

For binary outcomes (all-cause mortality, cardiovascular events, infection risk), we will calculate risk ratios (RR) with 95% confidence intervals using random-effects models fitted via restricted maximum likelihood (REML) estimation. For continuous outcomes (serum 25(OH)D levels, biomarker changes, cognitive scores), we will calculate mean differences (MD) when outcomes are measured on the same scale, or standardised mean differences (SMD) when different scales are used, each with 95% CIs. Heterogeneity will be assessed using the Cochran Q test (significance threshold $P < 0.10$), I^2 statistic (interpreted as low [0-40%], moderate [30-60%], substantial [50-90%], or considerable [75-100%] per the Cochrane Handbook), τ^2, and 95% prediction intervals to inform clinical applicability. If I^2 exceeds 50% and τ^2 indicates substantial between-study variance, we will explore sources through pre-specified subgroup analyses.

Subgroup and sensitivity analyses

Pre-specified subgroup analyses for primary outcomes will be conducted if 10 or more studies are available per subgroup:

1. Baseline vitamin D status: deficient (<25 nmol/L) vs. insufficient (25-50 nmol/L) vs. sufficient (>50 nmol/L). Rationale: treatment effects may be greater in deficient individuals.
2. Dosage category: low dose (≤1000 IU/day) vs. moderate (1001-4000IU/day) vs. high (>4000 IU/day). Rationale: dose-response evaluation.
3. Disease type: cardiovascular vs. cancer vs. respiratory vs. autoimmune. Rationale: extra-skeletal effects may vary by pathophysiology.
4. Dosing regimen: daily vs. weekly vs. monthly/bolus. Rationale: frequency may influence efficacy.

Subgroup differences will be tested using the chi-squared test for interaction ($P < 0.10$ considered significant). All subgroup analyses are pre-specified and confirmatory; any additional exploratory subgroups will be clearly labelled as such.

Sensitivity analyses will include: (i) excluding trials at high risk of bias; (ii) excluding trials with greater than 20% missing outcome data; (iii) restricting to trials using daily (vs. intermittent) dosing; and (iv) using fixed-effect models to assess robustness of random-effects estimates.

Narrative synthesis

Where quantitative synthesis is not appropriate, we will present results in evidence tables organised by outcome, dose, and population. We will describe effect direction, magnitude, and consistency across studies using the vote-counting method based on direction of effect, following SWiM guidance.

Meta-biases

Publication bias will be assessed for each meta-analysis that includes 10 or more studies by visual inspection of funnel plots and by Egger's regression test (significance threshold $P < 0.10$). We will also assess selective reporting within studies by comparing outcomes reported in trial registrations and protocols against published results. All analyses will be conducted using Cochrane Review Manager (RevMan, version 5.4 or later) and R (version 4.3 or later) with the *meta*, *metafor*, and *dmetar* packages.

Confidence in cumulative evidence

Two reviewers (SSD and PDS) will independently assess the certainty of evidence for each primary outcome using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework. Five domains will be evaluated: (i) risk of bias (downgraded if >25% of pooled weight derives from high-risk trials), (ii) inconsistency (downgraded if $I^2 > 50\%$ with unexplained heterogeneity), (iii) indirectness (downgraded if populations or interventions differ materially from the review question), (iv) imprecision (downgraded if the 95% CI crosses a clinically meaningful threshold or the optimal information size is not met), and (v) publication bias (downgraded if Egger's test $P < 0.10$ or funnel plot asymmetry is evident). Evidence certainty will be rated as high, moderate, low, or very low. Results will be presented in Summary of Findings (SoF) tables with absolute effect estimates expressed per 1000 patients. GRADE assessments will be performed using GRADEpro GDT software (McMaster University, Hamilton, Canada).

Timeline

The estimated duration of the review is 6 to 18 months from the date of ethics committee approval (20August 2025).

Strengths and limitations of this protocol

This protocol has several strengths. It is the first, to our knowledge, to attempt a dose-response synthesis of vitamin D across multiple extra-skeletal outcome domains simultaneously, using a comprehensive search of six bibliographic databases, two trial registries, grey literature sources, and preprint servers. Prospective registration in both PROSPERO and a national clinical trials registry, together with institutional ethics approval and independent grant funding, reinforce methodological accountability. The planned use of GRADE-based Summary of Findings tables will translate statistical results into clinically interpretable absolute effect estimates.

We acknowledge several limitations at the protocol stage. Restricting inclusion to English-language publications may exclude relevant trial data from non-English-speaking populations. Our focus on RCTs, while necessary to evaluate causality, means that important observational evidence on long-term supplementation or rare adverse events falls outside this review's scope. The broad range of clinical outcomes may yield considerable heterogeneity, potentially limiting the precision of pooled estimates. Finally, the five-year publication window (2020–2024, with extension into 2025) was chosen to capture the most recent trial landscape but will necessarily exclude landmark earlier trials; their findings will, however, be contextualised in the Discussion.

Ethics and dissemination

Institutional ethics committee approval was granted by a seventeen-member full-board meeting of the Ethics Committee for Academic Research Projects (ECARP), Topiwala National Medical College and BYL Nair Charitable Hospital, Mumbai (approval number: ECARP/2025/109; date: 20 August 2025). As this systematic review will analyse published aggregate data from previously approved trials, individual participant consent is not required.

The completed systematic review will be submitted for publication in a peer-reviewed open-access journal. Findings will be disseminated through presentations at relevant scientific conferences, shared with the research community via ResearchGate and institutional repositories, and summarised in plain language for public audiences through social media platforms (LinkedIn, YouTube) and blog posts. The PROSPERO and CTRI registrations will be updated to reflect the final review findings and publication details.

UN Sustainable Development Goal alignment

This research contributes to United Nations Sustainable Development Goal 3 (Good Health and Well-being), specifically Target 3.4, which calls for the reduction of premature mortality from non-communicable diseases through prevention and treatment. By synthesising randomised trial evidence on vitamin D dosing for cardiovascular disease, cancer, and respiratory conditions, our findings may inform supplementation policies aimed at reducing the burden of these leading causes of death worldwide. A secondary contribution aligns with SDG 3, Target 3.8, which promotes universal health coverage and access to quality essential medicines. Clarifying the optimal dose of an inexpensive, widely available supplement such as vitamin D supports efforts to integrate evidence-based nutritional interventions into primary healthcare, particularly in low- and middle-income settings where vitamin D deficiency is prevalent.

PRISMA-P 2015 Checklist

Section/topic	Item	Checklist item	Addressed in section	Status
Title: Identification	1a	Identify report as protocol of a systematic review	Title; Study design and registration	✓
Title: Update	1b	If protocol is for an update, identify as such	Not applicable (this is not an update)	✓
Registration	2	If registered, provide registry name and number	Study design and registration (PROSPERO, CTRI)	✓
Authors: Contact	3a	Name, affiliation, email of all authors; mailing address of corresponding author	Author block	✓
Authors: Contributions	3b	Describe contributions; identify guarantor	Author contributions (CRediT table)	✓
Amendments	4	Describe protocol amendments or state plan	Amendments section	✓
Support: Sources	5a	Indicate sources of support	Grant information	✓
Support: Sponsor	5b	Provide name of funder/sponsor	Grant information	✓
Support: Role	5c	Describe role of funder/sponsor	Grant information	✓
Rationale	6	Describe rationale in context of existing knowledge	Introduction: Rationale	✓
Objectives	7	Explicit statement of questions (PICO)	Introduction: Rationale (final paragraph); Eligibility criteria (PICOTS table)	✓
Eligibility criteria	8	Study and report characteristics for eligibility	Eligibility criteria (Table 1)	✓
Information sources	9	All intended information sources with dates	Information sources	✓

Section/topic	Item	Checklist item	Addressed in section	Status
Search strategy	10	Draft search strategy for ≥1 database	Search strategy; Table 2 (Embase); Supplementary file	✓
Data management	11a	Mechanism for managing records/data	Data management	✓
Selection process	11b	Process for selecting studies	Selection process	✓
Data collection	11c	Method of extracting data	Data collection process	✓
Data items	12	List and define all variables	Data items	✓
Outcomes	13	List, define, and prioritise outcomes	Outcomes and prioritisation	✓
Risk of bias	14	Methods for assessing risk of bias	Risk of bias in individual studies	✓
Synthesis: Criteria	15a	Criteria for quantitative synthesis	Criteria for quantitative synthesis	✓
Synthesis: Methods	15b	Summary measures, handling, combining data	Summary measures and models	✓
Synthesis: Additional	15c	Additional analyses (sensitivity, subgroup)	Subgroup and sensitivity analyses	✓
Synthesis: Narrative	15d	Summary if quantitative synthesis not appropriate	Narrative synthesis	✓
Meta-biases	16	Assessment of meta-biases	Meta-biases	✓
Confidence	17	Strength of body of evidence (e.g. GRADE)	Confidence in cumulative evidence	✓

Statements and Declarations

Grant information

This work is funded by a research grant from the Research Society of Topiwala National Medical College and BYL Nair Charitable Hospital, Mumbai, India (grant approved 8 December 2025). The funding body had no role in protocol design, will have no role in data collection, analysis, interpretation, or manuscript preparation, and all decisions will rest with the research team.

Potential Competing Interests

No competing interests were disclosed.

Data Availability

No data are associated with this article.

Software Availability

Data synthesis will be conducted using Cochrane Review Manager (RevMan, version 5.4 or later; The Cochrane Collaboration, London, UK) and R (version 4.3.0 or later; R Foundation for Statistical Computing, Vienna, Austria) with the *meta* (version 7.0-0), *metafor* (version 4.4-0), and *robvis* packages. GRADE assessments will be performed using GRADEpro GDT (McMaster University, Hamilton, Canada). Microsoft Excel for Microsoft 365 (Version 2508) will be used for data management. Covidence (Veritas Health Innovation, Melbourne, Australia) will be used for screening. All software versions will be documented in the final review.

Author Contributions

Author	CRediT contributions
Shakeeb S. Dhorajiwala (SSD)	Conceptualisation, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Project administration
Pramod D. Shankpal (PDS)	Supervision, Validation, Writing – review & editing, Project administration
Sarang Dhage (SD)	Conceptualisation, Writing – review & editing, Investigation
Pawan Bhaote (PB)	Investigation, Methodology, Writing – review & editing
Shobhit Raj (SR)	Investigation, Data curation, Writing – review & editing
Sanjay Rathod (SaR)	Investigation, Validation, Writing – review & editing

All authors meet the ICMJE criteria for authorship, approved the final version, and agree to be accountable for all aspects of the work.

Use of Generative AI

The large language model Microsoft Copilot was used for language editing with prompts limited to formal tone adjustment. All AI-generated suggestions were critically reviewed and verified by authors against primary sources. Deep research functions were not employed to preserve the originality of the systematic review methodology. The final manuscript was further refined using Claude (Anthropic, Opus 4.6) for structural formatting per F1000Research guidelines; all content decisions were made by the authors.

Additional Information

- **PROSPERO registration:** CRD420251011893
- **CTRI registration:** CTRI/2025/09/094241
- **Ethics approval:** ECARP/2025/109

Acknowledgements

The authors thank the members of the institutional ethics committee for their constructive critique of the protocol. We acknowledge Dr. Prajwal Kadam (NIHR Academic Clinical Fellow in Cardiology) for methodological guidance, and the scientific committees of BMJ Open and MAHE Research for their valuable feedback during protocol development.

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Supplementary data: available at https://doi.org/10.32388/DVWQWJ

Declarations

Funding: This work is funded by a research grant from the Research Society of Topiwala National Medical College and BYL Nair Charitable Hospital, Mumbai, India (grant approved 8 December 2025). The funding body had no role in protocol design, will have no role in data collection, analysis, interpretation, or manuscript preparation, and all decisions will rest with the research team.

Potential competing interests: No potential competing interests to declare.