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Developmental defects of enamel in the primary dentition: protocol of an overview of systematic reviews

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ABSTRACT

Introduction Developmental defects of enamel (DDE) involve alterations in enamel formation. In the primary dentition, these defects can increase the risk of dental caries and lead to poor oral health outcomes. The epidemiology, associated factors and clinical consequences of DDE have been examined in several systematic reviews. However, the evidence remains fragmented. This overview of systematic reviews (OSR) will synthesise the available evidence on DDE in the primary dentition and identify gaps in the evidence.

Methods and analysis This protocol will provide an OSR of DDE in the primary dentition. The OSR will comply with the Preferred Reporting Items for Overviews of Reviews (PRIOR) reporting guidelines. Eligible publications will include systematic reviews, with or without a meta-analysis. Literature searches will be conducted in PubMed/MEDLINE, Scopus, Web of Science, Embase, the Cochrane Library and Google Scholar from inception to 28 August 2026. Two reviewers will independently screen records, assess study eligibility and extract data using EPPI-Reviewer. Extracted information from each review will include publication characteristics, participant details, diagnostic criteria for DDE, prevalence estimates, associated risk factors, clinical implications, preventive and therapeutic approaches and caries-related outcomes. Appraisal will use A MeaSurement Tool to Assess systematic Reviews V.2, Risk of Bias in Systematic Reviews or the Joanna Briggs Institute checklist according to the evidence domain. Findings will be synthesised within five domains, with de novo meta-analysis restricted to compatible intervention or association questions with adequate unique-study data and supplemented by an evidence gap map. The overlap between the reviews will be evaluated using citation matrices and the corrected covered area method.

Ethics and dissemination As this overview will only analyse and synthesise data from previously published systematic reviews and there will be no human participants or access to identifiable individual-level data, ethical approval is not required. The findings will be presented at relevant national and international scientific conferences and published in an international peer-reviewed journal.

PROSPERO registration number CRD420261321658.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Study selection, data extraction and appraisal will be undertaken independently by two reviewers.
⇒ Domain-specific eligibility, outcomes and appraisal will distinguish epidemiological, aetiological, clinical consequences, diagnostic and intervention evidence.
⇒ Citation matrices and prespecified procedures will identify overlap and prevent duplicate primary-study contributions to any de novo meta-analysis.
⇒ Differences in developmental defects of the enamel definitions, populations and outcome measures may limit comparability and quantitative synthesis.
⇒ English-language eligibility, reliance on existing reviews and limits on Google Scholar screening may restrict evidence coverage.

INTRODUCTION

Alterations during enamel formation can result in developmental defects of the enamel (DDE), which are qualitative or quantitative changes in the enamel and clinically present as demarcated or diffuse opacities or enamel hypoplasia.[1 2] These defects may arise from genetic, systemic, prenatal, perinatal or environmental insults that disrupt enamel matrix formation or mineralisation during critical stages of tooth development.[3 4] As primary tooth development commences in utero and continues throughout early infancy, it is particularly susceptible to DDE during this period.[5 6] DDE is associated with increased enamel porosity, plaque retention and post-eruptive enamel breakdown, thereby increasing the susceptibility to dental caries.[7 8]

Available evidence from systematic reviews (SRs) and meta-analyses (MAs) consistently supports an association between DDE and early childhood caries (ECC). Structural alterations in the defective enamel have been reported to increase plaque retention and reduce resistance to cariogenic challenges, thereby promoting the onset and progression of carious lesions in young children.[7 9] Among 123 evaluated risk indicators for ECC, Kirthiga *et al*[10] identified DDE as the most significant, a finding subsequently reinforced by the umbrella review by Thang Le *et al*[11]. DDE has also been linked to increased restorative treatment needs and poorer oral health

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outcomes in the primary dentition.[8] Beyond its association with ECC, several SRs have examined the epidemiology, aetiology and broader clinical implications of DDE in primary teeth.[5–8] Reported associated factors include prematurity, low birth weight, gestational diabetes mellitus, asthma, coeliac disease, genetic polymorphisms and prenatal or infancy-related exposures.[3–5 8 12–14] However, interpreting the evidence remains challenging owing to the heterogeneity in diagnostic criteria, study populations, outcome definitions and methods for assessing and classifying enamel defects.[1 7] In addition, many reviews have focused on isolated aetiological factors or specific outcomes, thereby limiting the comprehensive synthesis of the evidence base.[4 8 12]

Despite the growing body of evidence, a comprehensive overview integrating findings on DDE in the primary dentition and their correlation with ECC and related clinical outcomes is lacking. Consequently, the current evidence base remains difficult to interpret in terms of its consistency, methodological quality and certainty regarding the epidemiology, risk factors and clinical implications of DDE.[5–7] The aim of this overview will be to consolidate, critically appraise and interpret the available evidence on DDE affecting the primary dentition and to examine its relationship with ECC and other clinically important oral health outcomes.

RESEARCH QUESTION

The research question will be to systematically evaluate the existing evidence from SRs and MAs on the epidemiology, risk factors, diagnostic approaches, preventive and management strategies and clinical implications of DDE in the primary dentition.

However, the sub questions will be formulated separately for the evidence domains using appropriate frameworks based on the nature of the evidence being evaluated. Five domains will be addressed separately: epidemiology, aetiological and associated factors, diagnosis and assessment, preventive and therapeutic interventions and clinical consequences including associations with ECC.

1. *Epidemiology (PCO)*: What is the prevalence, incidence and distribution of DDE in the primary dentition?
2. *Aetiological and associated factors (PECO)*: What are the prenatal, perinatal, postnatal, genetic, systemic, environmental and nutritional factors associated with DDE in the primary dentition compared with the absence or alternative levels of these exposures?
3. *Diagnostic approaches (PIRT)*: What diagnostic criteria, classification indices and assessment methods are used to identify DDE in the primary dentition, and what is their reported diagnostic accuracy, wherever reported?
4. *Preventive and therapeutic interventions (PICO)*: What is the effectiveness of the various preventive and therapeutic interventions for DDE in the primary dentition compared with no intervention, usual care or alternative interventions?
5. *Clinical consequences (PECO)*: What are the clinical consequences associated with DDE in the primary dentition, including ECC and other oral health outcomes, compared with teeth/children without DDE, wherever applicable?

METHODOLOGY

The preparation and reporting of this protocol will follow the recommendations outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 (PRISMA-P 2015) statement.[15] The planned overview will follow contemporary methodological guidance for conducting overviews of SRs (OSRs). Reporting will comply with the Preferred Reporting Items for Overviews of Reviews (PRIOR)[16] statement. The registration of this protocol has been completed via PROSPERO (International Prospective Register of Systematic Reviews)—CRD420261321658.

Patient and public involvement

None.

Study design

This OSR will include SRs conducted with or without MAs, provided they use a systematic methodology, a transparent and reproducible search strategy and predefined eligibility criteria. Reviews synthesising evidence from observational research, interventional studies (randomised or non-randomised) or a combination of study designs will be eligible. Publications that do not meet the methodological criteria for an SR, including narrative reviews, scoping reviews, rapid reviews, conference abstracts, editorials, commentaries, expert opinions, case reports, case series and primary research articles, will be excluded.

Study dates and review status

Planned study start: 4 August 2026. Planned completion: 31 December. Current review stage: preliminary screening. Literature search dates: inception to 28 August 2026. Any changes from the registered protocol will be dated and documented with their rationale and timing.

Eligibility criteria

Participants/Population

This OSR will include SRs involving children with primary dentition. Reviews of healthy children and of children with medical, genetic, prenatal, perinatal or environmental conditions associated with DDE will be eligible. Reviews involving mixed or permanent dentitions will be eligible only when primary-dentition findings can be extracted separately. Reviews without separable primary-dentition findings will be excluded.

Exposure

DDE affecting the primary dentition will be the condition of interest for epidemiology and diagnosis, the outcome

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for aetiological questions and the exposure for clinical-consequence questions. Preventive and therapeutic interventions will be defined according to the relevant intervention question.

Comparator

Where applicable, comparator groups will include children without DDE, unexposed to the investigated risk factor or exposure or without the evaluated medical, environmental or behavioural condition. Reviews without a comparator group, such as prevalence reviews, will also be eligible for inclusion.

Eligible DDE will include qualitative defects such as demarcated and diffuse opacities and hypomineralisation, including hypomineralised second primary molars and quantitative defects such as enamel hypoplasia. Amelogenesis imperfecta and dental fluorosis will be eligible when primary-dentition findings are available, but will be synthesised separately from other DDE. The diagnostic index, case definition, severity threshold and unit of assessment will be extracted. Acquired enamel loss and carious demineralisation will not be classified as developmental defects. Posteruptive breakdown will be considered a consequence when attributed to a pre-existing developmental defect.

Search strategy

Evidence sources will be identified via comprehensive electronic searches of PubMed/MEDLINE, Scopus, Web of Science, Embase, the Cochrane Library and Google Scholar, with records indexed from database inception to 28 August 2026 considered for screening. In Google Scholar, up to the first 1000 accessible results per query will be screened in relevance order, or all accessible results if fewer are available. This is a pragmatic supplementary-search limit rather than a guarantee of exhaustive retrieval. Each query, date, settings, number screened and final rank reached will be recorded because relevance ranking and accessibility can change. The author GM will formulate the search strategy by integrating controlled indexing terms appropriate for each database with carefully selected free-text terms (online supplemental table 1). The completed strategy will be reviewed and approved by the subject experts MK, SMM, AS and VS. The search strategy will be independently peer-reviewed by the authors MK and SS in accordance with the Peer Review of Electronic Search Strategies (PRESS)[17] guidelines. Searches will not be limited by publication date, although only English-language reviews will be eligible for inclusion. To maximise the retrieval of relevant evidence, forward citation tracking will be conducted and additional records will be identified via manual searches. Before the formal screening process begins, the author GM will conduct pilot searches across all selected databases to evaluate the performance of the search strategy and refine the data extraction process to ensure consistent data collection throughout the OSR.

For each information source, the exact interface, database coverage, executed strategy, search date, limits and number retrieved will be reported. Search updates and the review stage will be distinguished from planned procedures. The abstract and methods will use the same verified search cut-off.

Study selection

The screening process will be conducted independently by the authors GM and SS in two sequential stages using EPPI-Reviewer software 6.[18] After removing duplicate records, titles and abstracts retrieved from the electronic searches will be assessed against the predefined eligibility criteria. Publications deemed relevant or potentially eligible will proceed to full-text assessment, which will also be conducted independently by GM and SS. Any discrepancies in study selection will initially be resolved via discussion. If consensus cannot be reached, SMM will adjudicate and make the final inclusion decision. Excluded full-text articles and the reasons for their exclusion will be documented and presented in the PRISMA flow diagram.

Data extraction

Information from eligible reviews will be extracted independently by GM and SS using a standardised data collection form that has been pilot-tested before use. The extracted information will include publication details, review objectives, characteristics and number of included studies, study settings, geographical location, participant characteristics and age group, diagnostic criteria and assessment methods for DDE, reported prevalence and distribution of DDE, investigated aetiological and risk factors, preventive and therapeutic interventions, comparator groups, outcomes related to DDE and dental caries, principal findings, measures of effect and heterogeneity, together with certainty of evidence and assessments of reporting bias, where available.

Data synthesis

The evidence reported in the included SRs and MAs will be synthesised using a structured narrative synthesis. The results will be grouped by type of developmental defect, population characteristics and assessed outcomes, including prevalence, aetiological factors, associations with dental caries and clinical consequences. An evidence map will be developed to visualise the distribution of available review evidence across exposures, populations and outcome domains. Evidence gap mapping will also be performed using the EPPI-Mapper tool[19] to visualise the distribution of evidence across DDE, population groups and outcome domains. This approach will facilitate the identification of research gaps, areas of redundant evidence and priorities for future research related to DDE in the primary dentition.

The extent to which primary studies are shared across the included SRs will be examined by constructing citation matrices and calculating the corrected covered area

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(CCA).[20] Where available, other reported indicators of overlap, including the ratio of observed to expected overlap, will also be recorded. The magnitude of overlap will be interpreted using predefined CCA thresholds and classified as slight (0–5%), moderate (>5–10%), high (>10–15%) or very high (>15%). This assessment will enable identification of redundant evidence across reviews and support an evidence synthesis that minimises the influence of duplicate primary studies.

Citation matrices will be constructed within domains and comparison–outcome groups where study membership can be established. Multiple reports of the same study will be linked using authors, setting, recruitment dates, sample characteristics and registration identifiers where reported. When reviews address the same question, their results will not be treated as independent confirmations. For the main review-level interpretation, one principal review will be selected as the priority using the following ordered criteria: relevance to the primary-dentition question, fewer serious methodological limitations, completeness of the relevant evidence and outcome reporting, and the most recent search date. Two reviewers will make and document these decisions independently, with disagreements resolved by SMM. Other reviews will contribute clearly identified complementary outcomes, populations or later evidence and will be used to investigate discrepancies. No review will be excluded solely because it overlaps with another review. Study or participant totals will not be summed across overlapping reviews.

For any de novo MA, a register of unique primary studies will be assembled across all reviews contributing to the eligible comparison. Eligibility will be applied consistently to the reported study characteristics. Duplicate reports, repeated estimates and overlapping cohorts will be identified before pooling. The most complete report or non-overlapping cohort data will be selected for the relevant outcome, while complementary reports may supply missing information without adding another study contribution. Multiarm studies, repeated time points and multiple outcomes will not contribute dependent estimates to the same pooled comparison. Where dependence or cohort overlap cannot be resolved from the reviews and their supplements, the affected data will not be pooled. CCA will describe the extent of overlap but will not itself remove duplicate study contributions.

Findings will be synthesised separately within the five predefined domains: epidemiology, aetiological and associated factors, diagnosis and assessment, preventive and therapeutic interventions, and clinical consequences. Within each domain, results will be grouped by defect subtype and definition, population, exposure or intervention, comparator, outcome and assessment time. Findings from different domains will not be combined into a common estimate. Existing meta-analytical estimates will be presented with their effect measures, 95% CIs and reported heterogeneity. Reanalysis will be considered only for a clearly defined question when sufficiently detailed primary-study data are available in the included reviews and their supplements.[21] Overlap alone will not be an indication for conducting a new MA.

De novo MA will be restricted to compatible intervention or association questions supported by at least two independent primary studies. It will require identifiable study populations, compatible outcome definitions and time points, effect estimates with SEs or CIs and outcome-relevant primary-study risk-of-bias information. Data reported in the included reviews will be used. A separate search for primary studies will not be undertaken. Each study will contribute once to a given comparison, outcome and time point. Randomised and non-randomised evidence, adjusted and unadjusted associations, and different effect measures will be analysed separately. For each study, the estimate that most closely matches the prespecified comparison, outcome, time point and relevant confounder adjustment will be selected without reference to statistical significance. The selected adjustment set and reasons will be documented.

Where these conditions are met, a random-effects inverse-variance model will be used because variation across study populations and methods is anticipated. Between-study variance will be estimated using restricted maximum likelihood. For three or more studies, CIs will use a modified Hartung-Knapp approach that does not reduce the conventional variance estimate. With two studies, a conventional random-effects CI will be reported and the limited estimation of heterogeneity will be acknowledged.[22] Ratio measures will be analysed on the logarithmic scale. ORs, risk ratios and HRs will not be combined as equivalent measures. Heterogeneity will be described using I^2, τ^2 and Cochran's Q rather than using a significance threshold to select the model. A sensitivity analysis excluding studies judged at high risk of bias will be undertaken when the reported assessments are comparable and at least two studies remain. New prevalence or diagnostic-accuracy MAs are not planned. Where the required information is unavailable or comparability is inadequate, the findings will remain in the structured narrative synthesis and the reason for not pooling will be reported.

Furthermore, heterogeneity across reviews will be explored qualitatively by examining differences in study designs, populations, diagnostic criteria and outcome measures. Publication bias assessments reported in the included reviews, such as funnel plot analyses, Egger's regression test or other methods used by review authors, will be extracted and narratively synthesised where available. Similarly, sensitivity analyses reported in the included reviews will be extracted and narratively synthesised to assess the robustness and consistency of the reported findings.

Discrepant findings will be examined using a comparison table covering search dates, eligibility criteria, shared and unique primary studies, populations, DDE definitions and diagnostic thresholds, outcome definitions and timing, study designs, confounder adjustment, analytical methods, review limitations and certainty. Effect estimates

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will retain their reported measures and 95% CIs. ORs, risk ratios, HRs, prevalence ratios and correlations will not be treated as interchangeable. Adjusted and unadjusted results and findings with different case definitions, denominators, comparators or follow-up periods will be presented separately. A significant finding in one review and a non-significant finding in another will not by itself establish contradictory effects. Direction, magnitude and precision will be considered without vote counting by p value or number of reviews. An imprecise estimate spanning the null will not be interpreted as proof of no association. Unexplained discrepancies will be reported as unresolved. Synthesis without meta-analysis will guide reporting of intervention-effect syntheses without MA, with relevant transparency principles applied to the remaining domains.[23]

Observational findings will be described as associations. Temporal ordering, residual confounding, selection bias, measurement error and reverse causation will be considered when interpreting proposed aetiological factors and clinical consequences. Cross-sectional findings will not establish temporal direction. Large associations, statistical significance, repeated reporting across overlapping reviews or high certainty ratings will not alone establish causality. Intervention effects will be considered separately in relation to study design and risk of bias.

Methodological quality and certainty of evidence

The methodological rigour and risk of bias of the included SRs will be assessed independently by GM and SS using tools appropriate to the evidence domain. A MeaSurement Tool to Assess systematic Reviews (AMSTAR) 2[24] will be used for reviews of preventive and therapeutic healthcare interventions within its intended scope. Risk of Bias in Systematic Reviews (ROBIS)[25] will be used for reviews of aetiological and associated factors, diagnosis and clinical consequences. Reviews of prevalence and incidence will be appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Systematic Reviews and Research Syntheses.[26] Reviews covering several domains will be appraised for the relevant components using the appropriate tools. Disagreements will be resolved through discussion or adjudication by SMM. AMSTAR 2 will be interpreted using its critical domains rather than a summed score. ROBIS domain and overall judgements and JBI item-level judgements will be reported separately. Review-level appraisal will not substitute for primary-study risk of bias or outcome-specific certainty. Information on publication bias and other reporting-bias assessments will be extracted where available.

Reported Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessments will be extracted with the population, comparison, outcome, assessment time, contributing studies and reasons for each judgement. Certainty will be considered for each outcome-specific body of evidence rather than assigned to an entire review or domain. Assessments will not be transferred to a different primary-dentition subgroup or evidence body without examining their applicability. Overlapping reviews' ratings will not be averaged and repeated inclusion of the same studies will not increase certainty.

The prespecified outcomes for certainty assessment are associations between each investigated exposure and DDE, associations between DDE and ECC or other caries outcomes, posteruptive enamel breakdown, restorative treatment needs and other reported oral health consequences, and the benefits and harms of preventive or therapeutic interventions for those outcomes. Diagnostic sensitivity and specificity will be assessed where reviews provide accuracy evidence. Epidemiological estimates and descriptions of diagnostic indices will be handled separately as specified below. Distinct exposures, interventions, defect subtypes, study designs and assessment times will not be merged into a single certainty judgement. Caries outcomes, enamel breakdown and restorative treatment needs will take priority over other clinical outcomes. Selection will not depend on statistical significance or effect size.

De novo GRADE assessment will be undertaken only when the reviews and supplements provide the outcome-specific contributing studies and designs, study and participant numbers, effect estimates and precision, primary-study risk-of-bias information and sufficient information to judge inconsistency, indirectness, imprecision and publication bias. This requirement applies to a newly pooled body of unique studies as well as to an eligible finding without a reported assessment. GM and SS will assess independently using GRADEpro GDT, with disagreements resolved by SMM. Each judgement will be documented. If the required information is unavailable, certainty will be recorded as not assessed with the reason, rather than automatically classified as very low.

Under the conventional GRADE approach,[27] randomised intervention evidence will start at high certainty and non-randomised intervention or association evidence will start at low certainty. Separate study-design bodies will be assessed separately. Risk of bias, inconsistency, indirectness, imprecision and publication bias will be considered. Rating up will be considered where a large association, a dose–response gradient or plausible residual confounding acting against the observed association can be substantiated. Imprecision will be judged from CIs and their implications for the clinical question. The null value and any established clinically important thresholds will be considered, with the absence of a defensible threshold stated explicitly. A GRADE rating for an observational association will not itself establish causation.

Diagnostic-accuracy evidence will use GRADE guidance for tests.[28] Appropriate cross-sectional or cohort accuracy studies with a valid reference standard may start at high certainty, with subsequent judgements for risk of bias, indirectness, inconsistency, imprecision and publication bias. Sensitivity and specificity at different diagnostic thresholds will remain distinct. Accuracy will not be equated with improved clinical outcomes. Reviews describing diagnostic indices or examiner agreement will be summarised without a new GRADE rating. For prevalence and incidence, any reported certainty

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assessments will be extracted with the adaptation used. No de novo prevalence or incidence GRADE adaptation is prespecified. These findings will instead be described using precision, sampling, representativeness, case definitions and reported primary-study limitations.

Where reviews overlap, de novo certainty assessment will refer to one identifiable evidence body for the specific outcome. If primary-study data are reanalysed, GRADE will apply to the deduplicated body actually contributing to that analysis. Otherwise, it will apply to the principal review's relevant evidence body. Differences between reported ratings will be investigated against their contributing studies and stated reasons. Eligible assessments will be reported as high, moderate, low or very low and evidence profiles will distinguish review-reported from newly assessed ratings.

Outcomes

Outcomes will be defined within the five domains. Epidemiology will include DDE prevalence, incidence and distribution by defect subtype and severity. Child-level, tooth-level and surface-level estimates will be distinguished and reported with their denominators, CIs and observation periods where available. Aetiological and associated-factor outcomes will concern the occurrence of DDE in relation to each specified exposure, with the reported effect measure and adjustment set. Diagnostic outcomes will distinguish descriptions of indices from sensitivity and specificity against a reference standard and reliability measures such as kappa or intraclass correlation coefficients. Preventive and therapeutic outcomes will include the reported benefits and harms of interventions for DDE or its consequences. Clinical consequences will include ECC, caries severity using the reported index, posteruptive enamel breakdown, restorative treatment needs and other reported oral health outcomes. Binary, continuous and time-to-event outcomes will retain their reported measures and 95% CIs. Outcome definitions, units of analysis, instruments and assessment times will be recorded. Caries occurrence or severity, enamel breakdown and restorative treatment needs will take priority over other clinical outcomes. Findings at different times will remain separate and no outcome or time point will be selected because it yields a more favourable result.

Ethics and dissemination

As this OSR will analyse evidence derived solely from previously published SRs and MAs, without accessing individual participant data or involving human participants, approval from an institutional ethics committee will not be required. The OSR will be published in a peer-reviewed scientific journal.

DISCUSSION

The OSR will provide a comprehensive compilation of evidence on DDE in the primary dentition. To our knowledge, no previous OSR has synthesised evidence from SRs and MAs on the epidemiology, determinants, diagnostic approaches, clinical consequences, preventive and management strategies and caries-related outcomes of DDE in the primary dentition. This OSR will provide a broad understanding of the current evidence base and identify areas of consistency, uncertainty and evidence gaps.

Despite the extensive scope of this overview, several methodological challenges are anticipated owing to variability in the available evidence base and in the characteristics of existing SRs. Variability across the included reviews is expected, given the inconsistencies in diagnostic criteria, participant characteristics, outcome definitions and approaches to identifying and classifying DDE.[1 7] Such heterogeneity may limit direct comparisons across reviews and affect the consistency of the reported findings. Overlap of primary studies across SRs may lead to duplication of evidence and overestimation of the findings. Potential duplication of primary studies across the included reviews will be systematically evaluated by constructing citation matrices and calculating the CCA. The conclusions drawn from this OSR will inevitably reflect the methodological rigour, risk of bias and completeness of reporting in the included SRs, which may influence the overall certainty of the synthesised evidence. As this OSR will rely exclusively on published SRs, recently completed primary studies that have not yet been incorporated in an eligible review are unlikely to be included. Moreover, restricting eligibility to English-language reviews may introduce language bias. To maximise the retrieval of relevant evidence, electronic database searches will be complemented by backward and forward citation tracking and manual searches of reference lists. Where feasible, the literature search will be rerun before the OSR is completed to identify any newly published eligible SRs.

Other anticipated challenges relate to the completeness of the search, comparability of findings and limitations of evidence appraisal. Google Scholar's relevance ranking changes over time, and its accessible results and prespecified screening limit may affect the reproducibility and completeness of the search. Furthermore, differences in DDE definitions, diagnostic thresholds, units of analysis and outcome timing may limit direct comparisons and the feasibility of pooling results. Although the CCA quantifies overlap among SRs, it does not eliminate statistical dependence between reviews. Incomplete reporting may also prevent identification of all duplicate studies or cohorts. Decisions regarding the selection of principal reviews and eligibility for reanalysis will therefore be documented transparently. Methodological appraisal and certainty assessment present additional challenges. AMSTAR 2 is designed primarily for SRs of healthcare interventions, whereas ROBIS and JBI tools assess methodological quality or risk of bias rather than certainty in an outcome-specific body of evidence. GRADE assessments may be infeasible when sufficient primary-study information is unavailable. Prevalence and descriptive diagnostic evidence will not undergo new certainty assessments unless an appropriate adaptation is specified. Finally,

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any de novo MA will be restricted to data available in the included reviews and will not constitute an independent update of the primary-study literature

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Contributors Conception, Guarantor: MSM conceived the idea for the overview of reviews. Methodology: GM, SS and VS designed the methodology, including the eligibility criteria and the planned approach for literature searching, study selection, quality appraisal and evidence synthesis. Search strategy: GM, SS and MK developed the literature search strategy. Protocol registration: GM registered the protocol with PROSPERO. Writing—original draft: GM drafted the manuscript. Writing—review and editing: AS, VD, HR, VS, MSM and MK critically reviewed and revised the manuscript for important intellectual content. Final approval: All authors reviewed and approved the final version of the manuscript for submission and agree to be accountable for all aspects of the work.

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Author note The corresponding author attests that all listed authors meet the ICMJE authorship criteria and that no authors meeting these criteria have been omitted.

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