Early childhood caries is defined as the presence of one or more decayed, missed or filled surface in any primary tooth of a child under six years of age. It is a common condition that affects more than 560 million children worldwide, causing difficulties to eat, sleep and attaining school due to loss of tooth substance and pain. A systematic review has reported more than 100 unique biological, genetic, social and behavioural risk factors for early childhood caries in a complex interplay. Perinatal factors may also play a role, and studies have examined possible associations between early childhood caries and preterm birth, low birth weight, childhood body mass index and the metabolic syndrome, all with conflicting results. Preterm birth occurs before 37 completed weeks of gestation and the global incidence is 11%.

A systematic review and meta-analysis published in 2019 has addressed the association between preterm birth and low birth weight and early childhood caries. The authors concluded that children born preterm had a similar caries experience to those born full term, but the certainty of evidence was very low due to methodological shortcomings. Although children with preterm birth and children with low birthweight were analysed separately,
the preterm group included extremely preterm and very preterm children that commonly exhibit intrauterine growth restriction and elevated morbidity rates. One strategy to overcome this overlap is to focus on investigations that have selectively been performed on moderate to late preterm children. The aim of this study was to systematically examine and pool the available literature on moderate to late preterm birth and caries in the primary dentition. The focused question was ‘Is there a relationship between moderate to late preterm birth and the development of early childhood caries?’

1.1 METHODS

This systematic review was conducted according to a predefined plan and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. The PECO was Population—Infants, toddlers and preschool children, 2-6 years of age; Exposure—Moderate to late preterm birth (between 32 and 37 gestational weeks); Comparison—Full term birth (37-41 gestational weeks); and Outcome—Prevalence of early childhood caries in the primary dentition up to six years of age. The authors included prospective studies (birth cohorts), cross-sectional studies, case-control designs and register-based studies. Articles reporting convenience samples, case series and case reports were excluded. We also excluded studies that mixed preterm and low birth weight definitions, as well as studies including any co-morbidity and children with syndromes. Studies exclusively addressing extremely preterm (<28 gestational weeks) or very preterm children (<32 gestational weeks) were not included in this review. The study protocol was not preregistered in a publicly assessable database.

1.2 Search methods for identification of studies

The following electronic databases were searched from 1 January 2000 to 28 February 2020: PubMed, Scopus and the Cochrane Oral Health Group’s Trials Register. The search words used were ((pre-school child) AND (preterm birth OR premature birth OR full term birth OR term birth OR risk factors) AND (dental caries OR early childhood caries OR tooth decay)). Only studies published in English were eligible for inclusion. Clinical trials.gov was used to identify registered ongoing studies by combining the phrase ‘preterm birth’ with ‘caries’. The reference lists of all identified studies, including one systematic review, were hand-searched for additional studies.

1.3 Selection of studies

The titles and abstracts of potentially eligible studies were independently assessed by two authors (ST, KB). If there was any doubt, the full-text papers were ordered and evaluated by the same authors. Any disagreement was resolved by discussions with a third author (JD). A flow chart of the study selection is shown in Figure 1. The excluded studies, and the main reason for their exclusion, are listed in Table S1.

Key notes

- Early childhood caries is a common non-communicable disease with biological, genetic, social and behavioural risk factors, but the association to perinatal factors is controversial.
- This systematic review and meta-analysis shows that children born moderate to late preterm may have a significantly higher prevalence of early childhood caries than those born full term.
- The gestational age should be noted in the paediatric dental records as risk factor for caries development.

1.4 Data extraction and management

Two examiners (ST, KB) read the full papers and extracted the data independently. We tabulated the following data: first author, year of publication, country of origin, study design, study size, follow-up period, caries scoring level and clinical examination procedures. The outcome measure was prevalence of caries (decayed, missed and filled primary teeth, score > 0; International Caries Detection and Assessment System, score > 0), expressed as percent. When several follow-up time points were available, we selected the examination closest to six years. In studies where data were unclear or missing, we contacted the corresponding author by e-mail for clarifications.

1.5 Assessment of risk of bias in included studies

Each study was independently examined for the risk of bias by two authors (ST, KB), and any disagreement was discussed within the whole author group. We used the Newcastle-Ottawa Scale (NOS) to assess the quality of the included studies. Since none of the included studies could secure the absence of outcome before the exposure (birth), we deleted this item under the selection domain, giving a maximum score of eight stars. An overall assessment of the risk of bias was made for each included study: ≥7 stars = low risk of bias, 6 stars = moderate risk of bias and ≤ 5 stars = high risk of bias.

1.6 Data synthesis

The authors conducted a narrative synthesis of the included studies and calculated the odds ratio using basic two-by-two tables. We applied unadjusted dichotomous data, namely caries versus caries-free, to calculate the odds ratio with 95% confidence intervals for each separate study. The caries prevalence according to gestational age was then pooled in a random-effects model using the Review Manager 5.3 tool (The Nordic Cochrane Centre, Copenhagen, Denmark). The clinical heterogeneity was assessed by examining the characteristics of the studies, the similarity between the types
Table 1. Characteristics of the included studies

| Study Location   | Study Design       | Number of Participants | Caries Detection Level | Clinical Examiners |
|------------------|--------------------|------------------------|------------------------|--------------------|
| Asia             | Prospective        | 128                    | Dentin                 | 1                  |
| Europe           | Cross-sectional    | 117,175                | Dentin                 |                   |
| South America    | Case-control       | 128                    | Dentin                 |                   |

FIGURE 1  Flow chart for search, screening and exclusion of literature

2  | RESULTS

2.1  | Characteristics of the included studies

The authors included 14 studies covering 210,691 children in this review, and the main characteristics are shown in Table 1. Three studies were based on prospective birth cohorts, and two used population registers. Seven were cross-sectional trials, and two employed a case-control design. The number of participating children per study ranged from 128 to 117,175 with a median value of 1,019. Most studies were from Asia (n = 7), followed by Europe (n = 5) and South America (n = 2). Most studies were published from 2014 to 2020 (n = 11), and only three were published 2011-2014. The threshold for caries detection was based on dentin (cavitated) level in eight studies, but four studies also scored non-cavitated early enamel lesions. Two studies failed to report the caries scoring system. In general, bitewing radiographs were not used but in two studies, radiographs were captured based on individual indications. The number of clinical examiners ranged from one...
to 44, and the majority of the included studies reported data on examiner calibration and reliability tests. Most studies reported caries status at 3-5 years (range 2-6 years).

2.2 | Quality assessment

Five of the included studies had a low risk of bias, three displayed a moderate risk, and six had a high risk of bias (Table 2). All studies except one scored at least one star in each of the three domains of ‘selection’, ‘comparability’ and ‘outcome’. The main weaknesses were lack of representativeness, small sample sizes with even smaller number of preterm events, and outcome assessments.

2.3 | Early childhood caries

The prevalence of early childhood caries ranged from 6.0% to 91.7% (median 48.8%) in the preterm group and from 6.2% to 91.9% (median 20.5%) in the full term group. The crude univariate odds ratio (OR) for the separate studies is shown in Table S2. There was a considerable inconsistency between the studies. The prevalence of ECC was significantly higher in moderate to late preterm children ($P < .05$) in seven studies,12,15,16,19,22,23,25 five reported no significant differences between preterm and full term children14,17,18,20,24 while one study found significantly more caries among the full term children.13 When the studies were pooled in a meta-analysis (Figure 2), the overall OR was 1.48 (1.16-1.89; $P < .001$) showing a clear trend of an elevated prevalence of early childhood caries in preterm children. The heterogeneity was high with an $I^2$ value of 89% ($\text{Tau}^2 = 0.13$).

3 | DISCUSSION

The main finding of this review was the increased prevalence of early childhood caries in moderate to late preterm children. However, the certainty of this finding was low. In general, results from meta-analyses that are based on observational studies are more hazardous than results from randomised controlled trials. We combined results from prospective birth cohorts, cross-sectional studies, case-control studies and register-based studies in our analyses although different methods of background data collection and caries detection were used. Despite this, it was interesting to find that conflicting results were reported within each of the abovementioned study categories. Furthermore, we calculated unadjusted univariate associations between gestational age and caries, which was an oversimplification.
Both preterm birth and early childhood caries have common co-
variables affecting the prevalence, such as socio-economic factors,
parental education and smoking.9 In addition, early childhood caries
have a complex aetiology, that is affected by a number of behav-
ioral, dietary and nursing factors, in addition to biology and ge-
netics.1 Some of the included studies used a blend of confounding
factors to adjust the multivariate analyses concerning caries back-
ground variables, but we decided to only extract the crude data in
order to be able to pool the outcome. However, we would welcome
an attempt to create a consensus-based ‘core outcome set’ to be col-
lected and presented in future prospective trials. Such consensus
among researchers would facilitate the compilation and increase the
certainty of evidence in future systematic reviews.

There are several possible direct and indirect explanations for
a relationship between preterm birth and early childhood caries.
Preterm birth is strongly associated with enamel defects,26,27 and
such hypomineralizations are predisposing for caries develop-
ment.28 Preterm birth and immature immunity are also linked to an
early oral colonisation of Streptococcus mutans and other acid-toler-
ating strains with cariogenic properties.29,30 Early-in-life treatment
with antibiotics can affect the composition of the developing micro-
biota with a disturbed abundance of commensal genera.31 Preterm
children may also have a greater likelihood of frequent day and night
feeding to secure a desired weight gain and this is a major risk factor
for dental health.5 Taken together, we argue that the finding of this
review suggests that the gestational age is a factor that should be
registered in the paediatric dental records.

The authors found high heterogeneity between the included
studies, reflecting variations in population size, study group charac-
teristics, methods for caries detection, duration and follow-up. The
included studies were of mixed quality, and it was notable that the
majority were cross-sectional studies designed to map a variety of
general and local risk factors for early childhood caries. A common
shortcoming was that such background factors were often collected
through self-reported questionnaires or parental interviews, which
may introduce both selection and reporting bias. The registry-based
studies profited from their large sizes, but suffered from weak re-
liability in the outcome assessment. Only three studies had a true
birth cohort design, in which the data were collected prospectively
from pregnancy along with the children’s growth and development.

### Table 2: Risk of bias according to the Newcastle-Ottawa Scale

| Study                                | Selection | Comparability | Outcome/Exposure | Total Score |
|--------------------------------------|-----------|---------------|------------------|-------------|
| Boustedt, 2020                       | ⋆ ⋆ ⋆ ⋆   | NA            | ⋆ ⋆ ⋆ ⋆          | 6           |
| Nirunsittirat, 2016                  | ⋆ ⋆ ⋆ ⋆   | NA            | ⋆ ⋆ ⋆ ⋆          | 6           |
| Wigen, 2011                          | ⋆ ⋆ ⋆ ⋆   | NA            | ⋆ ⋆ ⋆ ⋆          | 8           |
| Campus, 2009                         | ⋆ ⋆ ⋆ ⋆   | NA            | ⋆ ⋆ ⋆ ⋆          | 8           |
| dos Santos Junior, 2014              | ⋆ ⋆ − − ⋆ | NA            | ⋆ − ⋆ ⋆          | 4           |
| Hisano, 2018                         | ⋆ − − ⋆   | NA            | ⋆ − ⋆ ⋆          | 4           |
| Saraiva, 2007                        | ⋆ ⋆ ⋆ ⋆   | NA            | ⋆ ⋆ ⋆ ⋆          | 8           |
| Sun, 2017                            | ⋆ − − ⋆   | NA            | ⋆ − ⋆ ⋆          | 4           |
| Tanaka, 2014                         | ⋆ − − ⋆   | NA            | ⋆ − ⋆ ⋆          | 4           |
| Schuler, 2018                        | ⋆ ⋆ − − ⋆ | ⋆ ⋆ ⋆ ⋆      | ⋆ ⋆ ⋆ ⋆          | 7           |
| Sridevi, 2018                        | ⋆ − − − ⋆ | − − − ⋆      | ⋆ ⋆ ⋆ ⋆          | 4           |
| Soares, 2020                         | ⋆ ⋆ ⋆ ⋆   | NA            | − ⋆ ⋆ ⋆          | 7           |
| Yokomichi, 2015                      | ⋆ ⋆ ⋆ ⋆   | ⋆ − − − ⋆   | ⋆ ⋆ ⋆ ⋆          | 6           |

Note: Criteria for prospective, cross-sectional and registry-based studies: (1) Representativeness of the exposed cohort; (2) Selection of the non-exposed cohort; (3) Ascertainment of exposure; (4) Demonstration that outcome of interest was not present at start of study; (5) Comparability of cohorts on the basis of the design or analysis; (6) Assessment of outcome; (7) Was follow-up long enough for outcomes to occur; (8) Adequacy of follow-up of cohorts.

Criteria for case-control studies: (1) Is the case definition adequate?; (2) Representativeness of the cases; (3) Selection of controls; (4) Definition of controls; (5) Comparability of cases and controls on the basis of the design or analysis; (6) Ascertainment of exposure; (7) Same method of ascertainment for cases and controls; (8) Non-response rate.
This study design is the most desirable when it comes to collecting reliable good-quality evidence. Thus, we encourage future evaluations of prospective birth cohorts in various populations across the globe.

A concern was that two papers failed to report the methodology for caries detection and eight studies scored the prevalence of caries on the cavity level, including missed and filled teeth. Therefore, the true prevalence of caries was underestimated because initial, non-cavitated carious lesions makes up the majority of all children aged 3-6 years, particularly in industrialised countries.32 The rare use of bitewing radiographs was a further driver of false-negative caries scores and this, together with the low frequency of events, might jeopardise the statistical power.

Another potential limitation of this review was that we may have unintentionally included a minor proportion of children with very preterm birth, or very low birth weight, simply because of the lack of detailed information in the reports. Thus, the possible influence of co-morbidity on the present results cannot be ruled out. Our result was somewhat divergent from a previous systematic review,9 which can be explained by differences in the inclusion criteria. We included fewer and more recent studies, and excluded studies that exclusively or apparently addressed extremely and very preterm children, as well as those that mixed preterm children with those with low birth weight. We limited our search to publications from the last two decades due to the global decline in caries and the shift towards a more effective caries-preventive management and care.2

4 | CONCLUSION

Within the limitations of this systematic review, we found a significantly higher prevalence of early childhood caries in children born moderate to late preterm than in children born full term. However, the certainty of this relationship was low due to inconsistency and heterogeneity across the included studies. This finding indicates that gestational age should be included as a risk factor in the paediatric dental record.

CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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