DOI: 10.1111/ipd.12042

Dental caries prevalence in children and adolescents with cystic fibrosis: a qualitative systematic review and recommendations for future research

DONALD L. CHI

Department of Oral Health Sciences, University of Washington, Seattle, WA, USA

International Journal of Paediatric Dentistry 2013; 23: 376–386

Background. Children and adolescents with cystic fibrosis (CF) are believed to be at low risk for dental caries, but this paradigm has not been critically evaluated.

Aims. To conduct a qualitative systematic review of the international literature on dental caries prevalence in children and adolescents with CF and make recommendations on future CF-related oral health research priorities.

Design. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was used to identify relevant studies published between 1960 and 2013.

Results. The search resulted in 696 studies. Fifteen publications were included in the qualitative systematic review. Ten studies concluded that children with CF had significantly lower caries prevalence than control children, three studies reported that children with CF had higher caries prevalence, and two studies found no difference by CF status. Of the seven studies including age-based subgroup analyses, only one study supported the current paradigm. All studies had limitations that may bias study results.

Conclusions. While children with CF may be a lower risk for dental caries, adolescents with CF may not be at lower caries than those without CF. Additional research is needed to evaluate a potentially flawed paradigm regarding caries risk in children and adolescents with CF.

Introduction

Cystic fibrosis (CF) is the most common terminal genetic disorder among Caucasians. Over 70,000 individuals worldwide have CF[1]. Each year, more than 1000 individuals are diagnosed with CF[2]. The prevalence of CF is highest among Northern Europeans, with nearly 1 in 2500 newborns being affected[3]. CF disproportionately affects Southern Europeans, Ashkenazi Jews, and African Americans[4].

Cystic fibrosis is linked to multiple mutations of a single gene [cystic fibrosis transmembrane regulator (CFTR)] on chromosome 7 that affects regulation of cellular chloride channels. CF is a disease that leads to the overproduction and accumulation of mucus in the lungs, which can result in airway obstruction and life-threatening bacterial infections. Most patients with CF take systemic antibiotics to treat CF-related respiratory infections. Additional systemic manifestations of CF include pancreatic insufficiency (with subsequent deterioration of exocrine function), liver disease, and infertility[4]. Historically, individuals with CF died in their early 20s from CF-related complications. Newer pharmaceutical treatment advances have improved the prognosis of patients with CF, with median survival reaching 40 years[5]. Over 50% of individuals in the US Cystic Fibrosis Foundation Patient Registry are under age 18 years[1].

Children and adolescents with CF are thought to be at increased risk for dental caries because of four factors related to CF: (1) a 20-fold increase in intraoral *Streptococcus mutans* levels; (2) gastroesophageal reflux disease (GERD); (3) high calorie diets to maintain weight; and (4) enamel defects[6–8]. Despite these risk factors, however, most studies report that individuals with CF are at low risk for dental caries[9–15]. A potential explanation for

*Correspondence to:
Donald L. Chi, DDS, PhD, Department of Oral Health Sciences, University of Washington, Box 357475, Seattle, WA 98195, USA. Email: dchi@uw.edu

INTERNATIONAL JOURNAL OF PAEDIATRIC DENTISTRY

the apparent discrepancy between caries risk factors and clinical findings is that children and adolescents with CF may engage in more meticulous oral hygiene behaviours to avoid oral infections that can spread to the lungs. This hypothesis has not been formally tested. Another more commonly accepted explanation is that patients with CF are on chronic antibiotics, which are thought to protect against dental caries. Sickle cell anaemia is an example of another condition in which chronic use of antibiotics is thought to be protective. The proposed mechanism is that antibiotics reduce intraoral levels of *S. mutans* and outweigh the other risk factors. Accordingly, the clinical paradigm taught in two widely used paediatric dentistry textbooks is that children and adolescents with CF are at low risk for caries[16,17]. Another popular paediatric dentistry textbook used worldwide does not mention CF[18], which suggests that dental caries is not a significant clinical problem for children and adolescents with CF.

The belief that antibiotics lower intraoral levels of *S. mutans* and caries risk is likely to be true for children, but may not be the case for adolescents with CF. First, the antibiotics used to treat adolescents with CF have changed significantly over time. Older studies were conducted when beta-lactam penicillins were used to treat *Staphylococcus aureus*, a gram-positive species and the main pathogen in children with CF[19]. Penicillins target *S. mutans* and may thereby protect younger children with CF against dental caries. At age 11, a respiratory microbiologic shift, however, results in *Pseudomonas aeruginosa* (a gram-negative bacterium) becoming the predominant chronic lung pathogen. In response to this problem, newer antibiotics were developed, including inhaled tobramycin, an aminoglycoside that targets *P. aeruginosa* and the main antibiotic prescribed to adolescents with CF[5,20,21]. Because tobramycin does not affect *S. mutans*, adolescents with CF may lose protection against caries. In fact, inhalation forces this anti-gram-negative antibiotic into the mouth, which may exert ecologic pressure in favour of gram-positive flora such as *S. mutans*, thereby increasing caries risk in adolescents with CF.

The current paradigm regarding dental caries risk in children and adolescents with CF does not account for recent advances in CF-related antibiotic therapies and has not been critically evaluated based on published studies. Dental caries prevention is critical in patients with CF because these medically vulnerable individuals are susceptible to infection, which influences quality of life and survival. Furthermore, it is essential to have a clear understanding of dental caries risk in children and adolescents with CF that can be accurately reflected in clinical guidelines and applied in practice settings. The primary goal of this study is to conduct a qualitative systematic review of the literature on dental caries prevalence in children and adolescents with CF. This review will serve as an important starting point for the recommendation of clinical research priorities in paediatric dentistry regarding dental caries risk in children and adolescents with CF.

Materials and methods

Eligibility criteria

This qualitative systematic review focused on human clinical trials, evaluation studies, and systematic reviews related to dental caries prevalence in children and adolescents with CF under age 18 years. The review included studies published in English in calendar years 1960–2013. Editorials, reviews, commentaries, nonhuman studies, and studies focusing only on participants older than age 18 years were excluded. The study did not involve human subjects and did not require institutional review board approval.

Protocol registration and information sources

A protocol for this study was not registered. Three online databases – Medline, Web of Science, and Embase – were used to identify relevant references and citations using a combination of the following search terms: 'cystic fibrosis', 'dental caries', 'caries', 'tooth decay', and 'oral health'. The last search date was 13 February 2013.

Search Strategy, Data Collection, and Reporting of Data

The search strategy was based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[22] (Fig. 1). The PubMed Advanced Search Builder (i.e., Medline) was accessed on 13 February 2012. The terms 'cystic fibrosis' AND 'dental caries' OR 'caries' OR 'tooth decay' OR 'oral health' were entered into the search fields. Identical methods were used to search for relevant publications in Web of Science and Embase. PICO (Patient/Population, Intervention, Comparison group, and Outcome) criteria were used to screen studies by title and abstract. In addition, the reference section of each study was hand searched to identify additional publications not found in the databases. The following data were abstracted for studies meeting inclusion criteria: year of study, country of study, study participant ages, sample size, control group characteristics, dental caries prevalence estimates, statistical methods, and study conclusions. This study was not a quantitative systematic review (e.g., meta-analysis), and findings were not pooled into a single effect size estimates. Rather, the goal of qualitative systematic reviews is to summarize the literature using *a priori* methods, identify trends and potential sources of bias, and design future studies that minimize bias.

Assessment of bias

The risk of bias was assessed at the study level (control group selection and statistical analyses) and outcome level (validity of measure, number of examiners, and reliability) using seven criteria adapted from the PRISMA statement[22]: (1) control group included; (2) rationale provided for the control group; (3) statistical approach justified; (4) validated dental caries measure adopted (e.g., dmfs, dmft, deft, DMFS, DMFT); (5) multiple trained and calibrated dental examiners; (6) dental examiner(s) blinded; and (7) intra- and/or inter-rater reliability assessed. The studies meeting all seven criteria were classified as being at low risk of bias. The studies meeting four or six criteria were classified as medium risk of bias. Remaining studies were classified as being at high risk of bias.

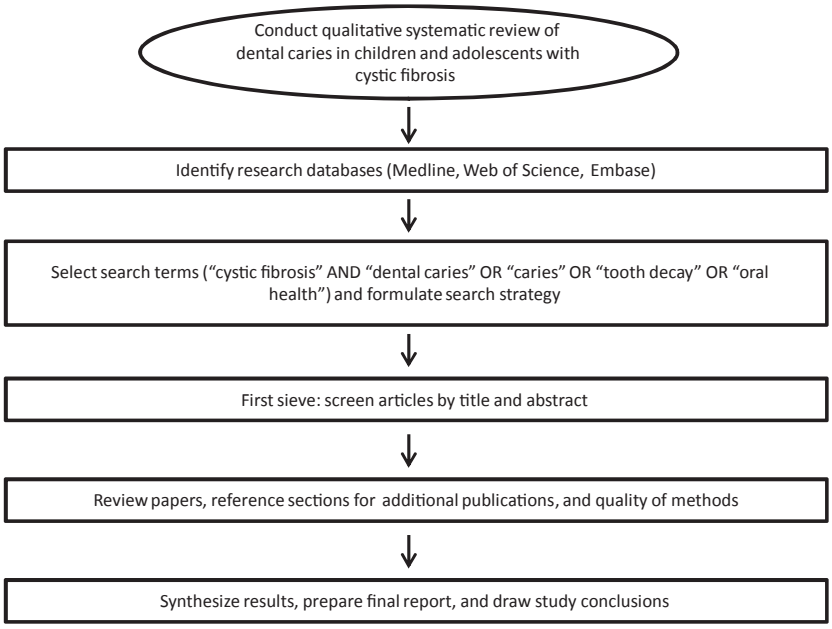

Fig. 1. Flow chart indicating search strategy for qualitative systematic review on dental caries prevalence in children and adolescents with cystic fibrosis.

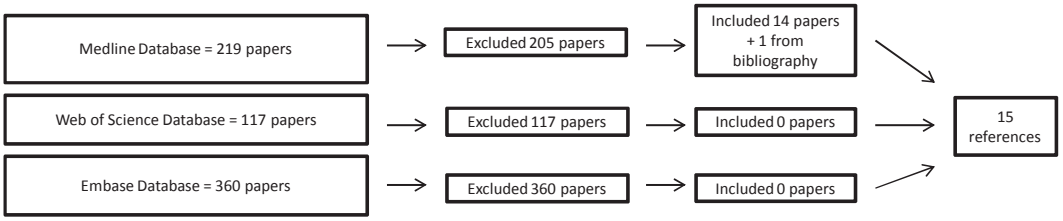

Fig. 2. Flow chart indicating number of references identified and included in qualitative systematic review on dental caries prevalence in children and adolescents with cystic fibrosis.

Results

Study selection

The search resulted in 696 publications from Medline, Web of Science, and Embase databases. Based on information provided in the study title and abstract, 681 publications were excluded from the review (Fig. 2). Fifteen publications[9–15,23–30] met the eligibility criteria and were included in the qualitative systematic review.

Study characteristics

Data were abstracted from each publication (Table 1). Most studies were published before calendar year 2000 and based on CF populations in Europe. The earliest study was published in 1967[30], and the latest study was published in 2009[15]. There were only two US studies (published in 1976 and 1980)[9,10]. Five studies included children and study participants older than age 18 years[10,23,25–27]. CF sample sizes ranged from 22[29] to 164[14]. Four of the studies had healthy controls[15,25–27]; four studies had a control group matched on selected demographic characteristics (e.g., age, gender, race, social class)[10,13,14,23]; three studies had a control group consisting of children with disabilities or chronic respiratory conditions[24,28,29]; three studies had a sibling control group[9,11,12]; and one study had no control group[30]. Ten studies used bivariate statistical methods to compare caries prevalence rates[10–15,24–27]; two studies used multiple variable regression models[28,29]; two studies did not use statistical tests[23,30]; and one study did not provide enough information to evaluate the statistical methods used[9].

Study results

Of the fifteen studies, 10 concluded that children with CF had significantly lower caries prevalence than children in the control group[9–15,26,27,30], three studies reported that children with CF had higher caries prevalence[23,28,29], and two studies found no significant difference in caries prevalence for children with and without CF[24,25].

Seven studies examined dental caries prevalence by age- or dentition-based subgroups[9–13,23,24]. One study reported that younger children with CF ages 2–12 years had higher caries prevalence than controls, whereas children with CF ages 13–24 had lower prevalence than controls[23]. A second study found no significant difference in caries prevalence across all age groups[24]. Of the remaining five studies[9–13], all of which concluded that children with CF had lower caries prevalence, only one study reported consistently lower caries prevalence rates for younger and older children with CF compared to controls[10], whereas the other four studies reported mixed findings[9,11–13].

Assessment of bias

Twelve studies were classified as being at high risk of bias and three as medium risk (Table 2). No studies were at low risk of bias. While most studies had a control group, no studies provided a rationale for why a particular control group was selected. Five studies adopted nonparametric statistical methods, and two studies used multiple variable regression methods. The remaining eight studies adopted parametric statistical methods without demonstrating whether statistical modelling assumptions were met. All 15 studies

Table 1. Data abstracted from studies included in qualitative systematic review of dental caries prevalence in children and adolescents with cystic fibrosis (*N* = 15 studies).

References	Country	Patient age (years)	Sample size	Description of control group	Dental caries prevalence estimates, standard deviation or standard error of the mean, and *P*-Value from statistical tests		Statistical methods	Study conclusions
					CF Group	Control Group		
Swallow *et al.*[30]	UK	2–15	CF: 63	No control group	dmft range: 0–20 DMFT range: 0–8	n/a	None	'The number of children examined was too small to draw any firm conclusions as to whether their caries experience was high, average, or low compared with other children. …There is, however, a tendency for the caries experience of the children with CF to be lower than that of the physically handicapped children'.
Jagels and Sweeney[9]	USA	5–14	CF: 63 Controls: 56	Non-CF siblings	Mean deft, ages 4–6 ($P < 0.01$) CF ($n = 6$): 1.0 ± 0.7 Mean DMFT, ages 4–6 CF ($n = 6$): 0.7 ± 0.7 Mean deft, ages 7–9 ($P < 0.01$) CF ($n = 22$): 1.7 ± 0.4 Mean DMFT, ages 7–9 CF ($n = 22$): 0.8 ± 0.3 Mean deft, ages 10–11 CF ($n = 21$): 2.6 ± 0.6 Mean DMFT, ages 10–11 ($P < 0.01$) CF (n=21): 2.5 ± 0.3 Mean deft, ages 12–14 CF ($n = 14$): 0.2 ± 0.1 Mean DMFT, ages 12–14 CF ($n = 14$): 3.5 ± 0.9	Control ($n = 12$): 4.8 ± 0.7 Control ($n = 12$): 0.4 ± 0.1 Control ($n = 11$): 3.2 ± 1.1 Control ($n = 11$): 2.3 ± 0.5 Control ($n = 19$): 2.4 ± 0.6 Control ($n = 19$): 4.3 ± 0.7 Control ($n = 14$): 0.9 ± 0.4 Control ($n = 14$): 7.4 ± 1.2	Unable to determine	'Caries was significantly decreased' in CF patients
Primosch[10]	USA	3–24	CF: 86 Controls: 86	Sex-, race-, chronologic age-, and fluoride status-matched patients at University dental school clinic	Mean defs, primary dentition ($P < 0.005$) CF: 2.1 ± 0.7 Mean defs, mixed dentition ($P < 0.005$) CF: 3.0 ± 0.9 Mean defs, primary and mixed dentition ($P < 0.001$) CF: 2.6 ± 0.9 Mean DMFS, mixed dentition ($P < 0.005$) CF: 2.6 ± 0.5 Mean DMFS, permanent dentition ($P < 0.005$) CF: 11.5 ± 1.3 Mean DMFS, mixed and permanent dentition ($P < 0.001$) CF: 7.9 ± 1.0	Control: 6.8 ± 1.3 Control: 9.8 ± 1.6 Control: 8.5 ± 1.1 Control: 5.1 ± 0.7 Control: 15.9 ± 1.4 Control: 11.5 ± 1.1	Student's *t*-test	There is 'a significantly reduced dental caries experience in' CF patients

(Continued)

Table 1 (Contd.)

References	Country	Patient age (years)	Sample size	Description of control group	Dental caries prevalence estimates, standard deviation or standard error of the mean, and *P*-Value from statistical tests		Statistical methods	Study conclusions
					CF Group	Control Group		
Kinirons [11]; Kinirons [12]	Northern Ireland	0–17	CF: 118 Controls: 85	Non-CF siblings	Mean dmf, ages 1–5 ($P < 0.05$) CF ($n = 42$): 0.5 ± 0.2 Mean DMF, ages 6–10 ($P > 0.05$) CF ($n = 35$): 1.5 ± 0.2 Mean DMF, ages 11–15 ($P < 0.05$) CF ($n = 39$): 3.1 ± 0.5	Control ($n = 30$): 1.8 ± 0.5 Control ($n = 26$): 2.0 ± 0.3 Control ($n = 29$): 5.4 ± 0.7	*t*-test	'The caries experience of the CF children was relatively low'
Storhaug[28]	Norway	1–6	CF: 27 Controls: 433	Preschool-aged children with disabilities (including CF)	Unadjusted dmft CF: 6.9 Adjusted dmft CF: 8.6	Control: 6.3 Control: not reported	Multiple class analysis	'CF children had more caries than other chronically ill preschool children'
Storhaug and Holst[29]	Norway	7–16	CF: 22 Controls: 415	School-aged children with disabilities (including CF)	Unadjusted DMFT CF: 6.1 Adjusted DMFT CF: 6.5	Control: 5.9 Control: 5.9	Multiple class analysis	Highest DMFT 'was found in children with juvenile rheumatoid arthritis, epilepsy, and cystic fibrosis'.
Kinirons[13]	Northern Ireland	3–17	CF: 131 Controls: 131	Age-, sex-, and social class-matched controls recruited from schools	Mean dmft, ages 3–9 ($P < 0.001$) CF: 0.6 ± 2.0 Mean dmfs, ages 3–9 ($P < 0.001$) CF: 2.2 ± 3.1 Mean DMFT, ages 7–17 ($P = 0.05$) CF: 3.7 ± 3.2 Mean DMFS, ages 7–17 ($P = 0.08$) CF: 5.3 ± 5.7	Control: 3.1 ± 2.7 Control: 4.3 ± 3.9 Control: 4.7 ± 4.1 Control: 7.3 ± 7.7	Wilcoxon signed rank test of matched pairs	Patients with CF 'had significantly less caries in the primary dentition than their controls. There was also a lower experience of caries in the permanent dentition…'
Kinirons[14]	Northern Ireland	4–18	CF: 164 Controls: 164	Age-, sex-, and social class-matched controls recruited from schools	Mean DMFT ($P < 0.01$) CF: 3.5 ± 2.5	Control: 4.8 ± 3.4	Kruskal–Wallis ANOVA	CF children had 'lower dental caries experience'
Aps *et al.*[25]	Belgium	CF homozygotes (A): 8–19 CF heterozygotes (B): 7–19 Controls (C): 8–19	A: 20 B: 20 C: 20	Healthy patients without 'cardiovascular, endocrine, haematological, infectious, or genito-urinary diseases ' recruited from a University outpatient dental clinic	Mean DMFT A: 1.3 ± 2.0 B: 2.2 ± 2.9 A↔B↔C ($P = 0.646$) A↔B ($P > 0.10$) A↔C ($P > 0.10$) B↔C ($P > 0.10$) A↔B and C ($P = 0.588$) Mean DMFS A: 1.9 ± 3.5 B: 4.8 ± 8.5 A↔B↔C ($P = 0.627$) A↔B ($P > 0.10$) A↔C ($P > 0.10$) B↔C ($P > 0.10$) A↔B and C ($P = 0.397$)	C: 1.3 ± 2.2 C: 30.0 ± 4.7 *(sic)*	Kruskal–Wallis and Mann–Whitney *U* tests	CF homozygotes 'did not have significantly more dental decay' than CF heterozygotes or controls

(Continued)

Table 1 (Contd.)

References	Country	Patient age (years)	Sample size	Description of control group	Dental caries prevalence estimates, standard deviation or standard error of the mean, and *P*-Value from statistical tests		Statistical methods	Study conclusions
					CF Group	Control Group		
Aps *et al.*[26]; Aps *et al.*[27]	Belgium	CF homozygotes (A): 16.2 ± 8.1 CF heterozygotes (B): 29.5 ± 15.9 Controls (C): 19.9 ± 11.5	A: 42 B: 48 C: 62	Healthy patients without 'cardiovascular, genitourinary, endocrine, haematological, or infectious diseases' recruited from a University outpatient dental clinic	Mean DMFT A: 4.1 ± 5.4 B: 9.9 ± 8.1 A↔B↔C (P = 0.001) A↔B (P = 0.011) A↔C (P < 0.001) B↔C (P = 0.06) Mean DMFS A: 9.4 ± 16.2 B: 34.9 ± 36.2 A↔B↔C (P < 0.001) A↔B (P = 0.004) A↔C (P < 0.001) B↔C (P = 0.06)	C: 6.8 ± 6.1 C: 20.0 ± 23.1	Kruskal–Wallis and Mann–Whitney U tests	Patients homozygous for CF have a significantly lower caries experience than control subjects
Narang *et al.*[24]	UK	2–16	CF: 74 Controls: 106	Children with other chronic respiratory disorders	Mean dmfs, age <6 (P = 0.46) CF: 0.2 ± 0.4 Mean dmfs, ages 6–9 (P = 0.61) CF: 0.9 ± 2.5 Mean DMFS, ages 6–9 (P = 0.83) CF: 0.006 ± 0.2 Mean dmfs, age >9 (P = 0.13) CF: 0.3 ± 0.7 Mean DMFS, age >9 (P = 0.82) CF: 0.9 ± 2.1	Control: 0.4 ± 0.3 Control: 1.4 ± 2.5 Control: 0.008 ± 0.3 Control: 1.2 ± 0.1 Control: 1.0 ± 1.0	Student *t*-test	'Nonsignificant trends towards lower caries prevalence in both dentitions…in the patients with CF'
Dabrowska *et al.*[23]	Poland	2–24	CF: 23 ages 2.5–5: 4 ages 6–12: 9 ages 13–24: 10 Controls: 23	Age- and gender-matched controls from University specialist dental clinic	Mean dmft, ages 2.5–5 CF: 3.3 Mean DMFT+dmft, ages 6–12 CF: 6.0 Mean DMFT, ages 13–24 CF: 10.9	Control: 2.8 Control: 2.5 Control: 12.8	None	'Higher caries incidence rate within the age ranges of 6-12 and 13-24 years in CF patients'
Ferrazzano *et al.*[15]	Italy	7–12	CF: 54 Controls: 101	Healthy (ASA I or II) children randomly selected from 10 public schools	Mean dmft (P < 0.0001) CF: 0.4 ± 0.9 Mean DMFT (P < 0.01) CF: 1.5 ± 2.2	Control: 3.0 ± 3.3 Control: 3.7 ± 3.9	One-way ANOVA	'CF patients showed a mean DMFT and dmft significantly lower than control subjects'

Table 2. Summary measures used to assess study bias.

References	Included a control group	Provided rationale for control group	Justified statistical approach	Adopted validated dental caries measure	Number of dental caries examiners	Examiner(s) blinded	Assessment of intra- or inter-rater reliability	Risk of bias
Swallow *et al.*[30]	No	Not applicable	No	Yes	Unknown	Unknown	Unknown	High
Jagels and Sweeney[9]	Yes	No	No	Yes	1	Unknown	Unknown	High
Primosch[10]	Yes	No	No	Yes	1	Unknown	Yes	High
Kinirons[11]	Yes	No	No	Yes	1	Unknown	Yes	High
Kinirons[12]	Yes	No	No	Yes	1	Unknown	Yes	High
Storhaug[28]	Yes	No	Yes	Yes	1	Unknown	No	High
Storhaug and Holst[29]	Yes	No	Yes	Yes	Unknown	Unknown	Unknown	High
Kinirons[13]	Yes	No	Yes	Yes	1	Unknown	Unknown	High
Kinirons [14]	Yes	No	Yes	Yes	1	Unknown	Unknown	High
Aps *et al.*[25]	Yes	No	Yes	Yes	1	Unknown	Yes	Medium
Aps *et al.*[26]	Yes	No	Yes	Yes	1	Unknown	Yes	Medium
Aps *et al.*[27]	Yes	No	Yes	Yes	1	Unknown	Yes	Medium
Narang *et al.*[24]	Yes	No	No	Yes	1	Unknown	Unknown	High
Dabrowska *et al.*[23]	Yes	No	No	Yes	1	Unknown	Unknown	High
Ferrazzano *et al.*[15]	Yes	No	No	Yes	2	Unknown	Unknown	High

adopted standard dental caries measures (e.g., dmft, dmfs, defs, DMFT, DMFS). Most studies had only one examiner and did not provide sufficient information on intra- or inter-rater reliability.

Discussion

The goal of this qualitative systematic review was to critically evaluate the literature on dental caries prevalence for children and adolescents with cystic fibrosis (CF). Of the fifteen studies included in the review, 10 studies concluded that children and adolescents with CF have a lower caries prevalence than controls[9–15,26,27,30], three concluded the opposite[23,28,29], and two found no CF-based differences in caries prevalence[24,25]. Of the seven studies that included age-based subgroup analyses[9–13,23,24], six studies reported findings that are inconsistent with the well-accepted paradigm that children and adolescents with CF have lower caries rates than controls[9,11–13,23,24]. Most importantly, all fifteen studies included in the systematic review contained critical limitations that increase the likelihood of biased study results. Collectively, these findings challenge the established paradigm in paediatric dentistry that both children and adolescents with CF are at low risk for dental caries. Future research should address four main limitations associated with existing studies on dental caries in children and adolescents with CF.

The first limitation is the lack of clarity regarding control group selection. First, a decision must be made to determine attributes of the control group. This decision is driven by the research question. If an investigator is interested in testing the hypothesis that children and adolescents with CF are at lower risk for dental caries than those without CF, then a non-CF control group is necessary. On the other hand, an investigator may be interested in constructing a caries risk model specifically for children and adolescents with CF, in which case a non-CF control group is not required. Control group selection is a key factor that has the potential to introduce bias into a study. Intervention scientists encounter similar challenges regarding control groups when designing randomized trials. In the current review, some studies adopted healthy controls, others matched on demographic variables such as gender or age, and still other studies adopted control groups consisting of siblings or individuals with chronic respiratory conditions or

disabilities. None of the studies provided an explanation for control group selection. In future studies, it is important for investigators to assess the need for a control group as well as explain why a particular control group was chosen and why other options were rejected. These decisions are dictated entirely by the research question of interest.

The second limitation is the absence of statistical power calculations. No studies in the review were based on power calculations, a limitation that introduces the possibility that none of the studies were adequately powered to detect statistically significant differences in caries prevalence. CF is a relatively rare disease, and patients with CF are not likely to aggregate in small geographical areas. Future studies should recruit subjects based on power calculations. There may need to recruit subjects with CF from multiple study sites to increase sample sizes and ensure adequate statistical power.

The third limitation is the possibility of bias associated with having a single dental examiner assessing outcomes. If a study has only one examiner, there must be a protocol to ensure that the examiner is trained and calibrated by a gold standard examiner and that a random sample of subjects is re-examined to allow for an assessment of intra-rater reliability. In addition, to the extent possible, the examiner should be blinded to the patient's CF status, an important potential source of bias that was not addressed in any of the fifteen studies. Studies with multiple dental examiners must implement similar training and calibration protocols and incorporate multiple examinations of a random subset of subjects that would allow for assessments of both intra- and inter-rater reliability.

The fourth limitation is the cross-sectional design adopted by all existing studies on caries in children and adolescents with CF. Historically, patients with CF had shorter life expectancies, which made longitudinal studies difficult. The median life expectancy of patients with CF is 40 years and continues to increase[5], which underscores the importance of understanding dental caries risk as children with CF get older. Adolescence is an important period in terms of caries risk for patients with CF because of the changes in the antibiotics used to treat respiratory infections. In addition, caries risk tends to increase during adolescence because of changes in oral health behaviours such as decreased frequency of toothbrushing and poor diet. Longitudinal studies that comprehensively assess the social, behavioural, biological, medical, and intraoral factors related to dental caries in children with CF as they enter adolescence would help to identify the subgroups of individuals with CF at increased risk for caries. These data could then be used to develop targeted interventions and policies that help to improve the oral health of the highest risk children and adolescents with CF.

This is the first published systematic review of the dental literature on dental caries prevalence in children and adolescents with CF. A strength was that *a priori* criteria were used to systematically identify relevant studies from the literature. In addition, the PRISMA statement was used to report findings from the review. The study, however, has two main limitations. The first is that only one reviewer was involved in assessing study bias, which itself has the potential to introduce bias. The adoption of PRISMA criteria, however, helped to minimize this. The second limitation is that an attempt was made to identify all published studies, but there is the possibility that relevant publications were omitted. To address this limitation, the main databases containing dental science literature were used and the search criteria were standardized.

Conclusion

The current paradigm in paediatric dentistry is based on the notion that children and adolescents with CF are at low risk for dental caries because they use chronic antibiotics that protect against cariogenic bacteria. Findings from the qualitative systematic review, however, indicate otherwise. While children with CF may be a lower risk for dental caries, adolescents with CF may not be at lower caries than those without CF. All of the studies included in the review contained critical limitations. Thus, the current paradigm may be flawed and requires careful re-evaluation.

Additional research is needed on caries risk in children and adolescents with CF to ensure optimal oral health for this group of medically vulnerable patients.

Why this paper is important to paediatric dentists

- It provides an up-to-date qualitative systematic review on caries prevalence in children and adolescents with cystic fibrosis (CF).
- It challenges a commonly accepted paradigm in paediatric dentistry that children and adolescents with CF are at low risk for dental caries – a paradigm based on biased and statistically underpowered studies.
- It outlines future research priorities in paediatric dentistry that address the oral health of paediatric patients with CF.

Acknowledgements

This paper won the 2013 International Association of Pediatric Dentistry Bengt Magnusson Memorial Prize in Child Dental Health. The author would like to thank the US National Institute of Dental and Craniofacial Research (NIDCR) Grant Number K08DE020856 for supporting this study.

Conflict of interest

The author has no conflicts of interest.

References

1 Cystic Fibrosis Foundation Website. About Cystic Fibrosis. Accessed on February 18, 2013. Available at: http://www.cff.org/AboutCF/.
2 Grosse SD, Boyle CA, Botkin JR *et al*. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Recomm Rep* 2004; **53**: 1–36.
3 Tsui LC, Buchwald M. Biochemical and molecular genetics of cystic fibrosis. *Adv Hum Genet* 1991; **20**: 153–266, 311-2.
4 Collins FS. Cystic fibrosis: molecular biology and therapeutic implications. *Science* 1992; **256**: 774–779.
5 Strausbaugh SD, Davis PB. Cystic fibrosis: a review of epidemiology and pathobiology. *Clin Chest Med* 2007; **28**: 279–288.
6 Arquitt CK, Boyd C, Wright JT. Cystic fibrosis transmembrane regulator gene (CFTR) is associated with abnormal enamel formation. *J Dent Res* 2002; **81**: 492–496.
7 Smyth RL, Walters S. Oral calorie supplements for cystic fibrosis. *Cochrane Database Syst Rev* 2012; **10**: CD000406.
8 Catalán MA, Scott-Anne K, Klein MI, Koo H, Bowen WH, Melvin JE. Elevated incidence of dental caries in a mouse model of cystic fibrosis. *PLoS ONE* 2011; **6**: e16549.
9 Jagels AE, Sweeney EA. Oral health of patients with cystic fibrosis and their siblings. *J Dent Res* 1976; **55**: 991–996.
10 Primosch RE. Tetracycline discoloration, enamel defects, and dental caries in patients with cystic fibrosis. *Oral Surg Oral Med Oral Pathol* 1980; **50**: 301–308.
11 Kinirons MJ. Increased salivary buffering in association with a low caries experience in children suffering from cystic fibrosis. *J Dent Res* 1983; **62**: 815–817.
12 Kinirons MJ. Dental health of children with cystic fibrosis: an interim report. *J Paediatr Dent* 1985; **1**: 3–7.
13 Kinirons MJ. Dental health of patients suffering from cystic fibrosis in Northern Ireland. *Community Dent Health* 1989; **6**: 113–120.
14 Kinirons MJ. The effect of antibiotic therapy on the oral health of cystic fibrosis children. *Int J Paediatr Dent* 1992; **2**: 139–143.
15 Ferrazzano GF, Orlando S, Sangianantoni G, Cantile T, Ingenito A. Dental and periodontal health status in children affected by cystic fibrosis in a southern Italian region. *Eur J Paediatr Dent* 2009; **10**: 65–68.
16 Cameron A, Widmer R. Handbook of Pediatric Dentistry, 3rd edn. London: Mosby-Wolfe, 2008.
17 McDonald RE, Avery DR, Dean JA. Dentistry for the Child and Adolescent. Maryland Heights, MO: Mosby Elsevier, 2011.
18 Pinkham J, Casamassimo P, Fields HW, McTigue DJ, Nowak A. Pediatric Dentistry: Infancy Through Adolescence, 4th edn. St. Louis, MO: Mosby Elsevier. 2005.
19 Phair JP, Tan JS, Watanakunakorn C, Schwab L, Sanders LW. Carbenicillin treatment of Pseudomonas pulmonary infection. Use in children with cystic fibrosis. *Am J Dis Child* 1970; **120**: 22–25.
20 van Westreenen M, Tiddens HA. New antimicrobial strategies in cystic fibrosis. *Paediatr Drugs* 2010; **12**: 343–352.
21 Bals R, Hubert D, Tümmler B. Antibiotic treatment of CF lung disease: from bench to bedside. *J Cyst Fibros* 2011; **10**: S146–S151.
22 Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8**: 336–341.
23 Dabrowska E, Błahuszewska K, Minarowska A, Kaczmarski M, Niedźwiecka-Andrzejewicz I, Stokowska W. Assessment of dental status and oral hygiene in the study population of cystic fibrosis patients in the Podlasie province. *Adv Med Sci* 2006; **51**: 100–103.

24 Narang A, Maguire A, Nunn JH, Bush A. Oral health and related factors in cystic fibrosis and other chronic respiratory disorders. *Arch Dis Child* 2003; **88**: 702–707.
25 Aps JK, Van Maele GO, Claeys G, Martens LC. Mutans streptococci, lactobacilli and caries experience in cystic fibrosis homozygotes, heterozygotes and healthy controls. *Caries Res* 2001; **35**: 407–411.
26 Aps JK, Van Maele GO, Martens LC. Caries experience and oral cleanliness in cystic fibrosis homozygotes and heterozygotes. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002a; **93**: 560–563.
27 Aps JK, Van Maele GO, Martens LC. Oral hygiene habits and oral health in cystic fibrosis. *Eur J Paediatr Dent* 2002b; **3**: 181–187.
28 Storhaug K. Caries experience in disabled pre-school children. *Acta Odontol Scand* 1985; **43**: 241–248.
29 Storhaug K, Holst D. Caries experience of disabled school-age children. *Community Dent Oral Epidemiol* 1987; **15**: 144–149.
30 Swallow JN, De Haller J, Young WF. Side-effects to antibiotics in cystic fibrosis: dental changes in relation to antibiotic administration. *Arch Dis Child* 1967; **42**: 311–318.