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Caries Risk Prediction models in medical healthcare setting

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Abstract

Introduction—Despite development of new technologies for caries control, tooth decay in primary teeth remains a major global health problem. Caries risk assessment models for toddlers and preschoolers are rare. Among them, almost all models use dental factors (e.g. past caries experience) to predict future caries risk, with limited clinical/community applicability owing to relatively uncommon dental visits compared to frequent medical visits during first year of life.

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Disclosure of potential conflict of interest

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Objectives—To construct and evaluate risk prediction models using information easily accessible to medical practitioners to forecast caries at 2- and 3-years of age.

Methods—Data was obtained from Growing Up in Singapore Towards healthy Outcomes (GUSTO) mother-offspring cohort. Caries was diagnosed using modified ICDAS criteria. Risk prediction models were constructed using multivariable logistic regression coupled with Receiver Operating Characteristic (ROC) analyses. Imputation was performed using Multiple Imputation by Chained Equations to assess effect of missing data.

Results—Caries rates at ages 2-years (n=535) and 3-years (n=721) were 17.8% and 42.9%, respectively. Risk prediction models predicting overall caries risk at 2 and 3 years demonstrated AUC (95%CI) of 0.81 (0.75-0.87) and 0.79 (0.74-0.84), respectively, while those predicting moderate-extensive lesions showed 0.91 (0.85-0.97) and 0.79 (0.73-0.85), respectively. Post-imputation results showed reduced AUC of 0.75 (0.74-0.81) and 0.71 (0.67-0.75) at Year 2 and 3, respectively for overall caries risk; while AUC was 0.84 (0.76-0.92) and 0.75 (0.70-0.80), respectively for moderate-extensive caries. Addition of anterior caries significantly increased AUC in all Year-3 models with/without imputation (all $P < 0.05$). Significant predictors/protectors were identified including ethnicity, prenatal tobacco smoke exposure, history of allergies before 12 months, history of chronic maternal illness, maternal brushing frequency, childbearing age, etc.

Conclusion—Integrating oral-general healthcare using medical CRA models may be promising in screening caries susceptible infants/toddlers, especially when medical professionals are trained to “lift the lip” to identify anterior caries lesions.

Keywords

medical community; longitudinal study; risk prediction; preschoolers; early childhood caries

Introduction

Despite rapid development of new approaches for caries prevention and control, the global burden of untreated caries in primary teeth (early childhood caries) has remained relatively unchanged for three decades (Peres et al. 2019), with caries in deciduous teeth ranking fifth amongst the top thirty conditions exhibiting highest incidence rates (Vos et al. 2017). Families of children with early childhood caries (ECC) may experience significant financial burden (Righolt et al. 2018), compromised oral health-related quality of life (Chaffee et al. 2017), increased susceptibility to caries in permanent teeth (Isaksson et al. 2013), lower self-esteem (Filstrup et al. 2003) and even lethal infection/sepsis (Casamassimo et al. 2009). A skewed distribution of disease burden has been reported with 16-25% of children bearing 75-80% of the overall lesions (Gao et al. 2009; Kaste et al. 1996). Thus, to lessen the widening gap of oral health disparities, accurate and applicable early caries risk assessment (CRA) may be critical, especially for infants/toddlers. However, conventional CRA models use “past caries experience” and/or “dental factors” as predictors, which require a separate dental examination/visit, reportedly low in the first year with <2% infants visiting dentists, in contrast to >82% medical utilization (Chi et al. 2013). While the integration of oral and general healthcare has been advocated (Donoff et al. 2014) and proven to be effective (Stearns et al. 2012), dentistry remains as an isolated profession in the healthcare system

(Sheiham et al. 2015). With a steep increase in global incidence rates of ECC per capita (from 0.10 to 0.70) in 1- to 4-years old children (Kassebaum et al. 2017), a “medical” CRA instead of a “dental” CRA model may be more effective for early and timely identification of caries-susceptible individuals (Watt et al. 2019). Hence, this study was purposed to build “medical CRA models”, using information available to medical professionals, through a longitudinal mother-offspring cohort study to predict caries formation at 2 and 3 years of age.

Materials and Methods

Study design and data collection

Ethical approval was obtained from Centralized Institutional Review Board (CIRB) of SingHealth (reference 2009/280/D) and Domain Specific Review Board (DSRB) of Singapore National Healthcare Group (reference D/09/021). Only Singapore citizens or permanent residents of Chinese, Malay and Indian ethnicity with homogenous ethnic background and who intend to reside in Singapore for the next 5 years were approached (Soh et al. 2014) to be a part of the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort. The primary objective of the GUSTO cohort was to investigate the role of prenatal and post-natal influences (fetal, developmental and epigenetic factors) during early development, affecting the pathways to disease. A total of 1247 healthy pregnant women, aged 18 years and above, were recruited as part of the GUSTO mother-offspring cohort during their first trimester (<14 weeks' gestation) at two major public maternity hospitals in Singapore. Mothers and their offspring (n=1176) were followed up postnatally at periodic intervals during childhood (Figure 1). Mothers receiving chemotherapy, psychotropic drugs or with Type I diabetes mellitus were excluded from the study.

Interviewer-administered questionnaires were used to collect data on a) *demographic/socioeconomic characteristics* (e.g. ethnicity, mother's and father's educational status, maternal child bearing age, mother's occupational status, monthly household income, parity status), b) *maternal general health-related factors* (history of any chronic illness, active/passive prenatal tobacco smoke exposure) at 26-week gestation visit, and c) *child's general health during infancy* such as history of any medical condition within 3-6 months, history of allergies before 12 months (runny nose within 9-12 months /itchy rashes within 6-12 months) history of allergies before first tooth eruption (runny nose/itchy rashes), intake of medications (oral medicines within 6-12 months /nebulizers within 9-12 months /antibiotics within 9-12 months /medications for runny nose within 0-12 months), history of infections (ear infections/vomiting/diarrhoea prior to first tooth eruption). Separate oral health questionnaires were used at 24-month dental visit to obtain data for a) *mother's oral health behaviors* (brushing frequency, regular dental check-ups, knowledge of cause of tooth decay, sharing of feeding/drinking utensils with child), and b) *child's oral health data* - duration of pacifier use (in months), duration of breastfeeding (in months), age of introduction of solid food (in months), number of teeth present at first year, age for first tooth eruption (in months), night-time bottle feeding and previous dental visit during the first 24 months. Collectively, the biopsychosocial data, obtained till 1 and 2 years of age, was used to build prediction models for caries risk at 2 and 3 years of age, respectively.

Oral examination

Dental examinations in children were carried out at 2- and 3-year clinic visit by trained calibrated dentists, with a single examiner at the 2-year visit and three examiners at the 3-year visit. Children were refrained from eating, drinking, and tooth-brushing for at least 1 hour prior to any oral-related clinical procedures. Examinations were conducted using knee-to-knee position and teeth were assessed by visual inspection, using plane surface mouth mirrors, and aided by tactile inspection, when deemed necessary. Autoclavable blunt WHO probes were used to avoid damaging sound enamel surfaces. Caries detection was performed by modified International Caries Detection and Assessment System (ICDAS II) diagnostic criteria (Ismail et al. 2007), without recording ICDAS code 1 due to logistical constraints. No additional detection methods or radiographs were used.

Data analysis

Data analysis was performed using SPSS statistical software (Version 25, IBM SPSS Statistics, Armonk, N.Y., USA) and STATA (Version 12.1). The continuous variables are presented as mean $\pm$ S.D., while the categorical variables are presented as N (%). Inter- and intra-examiner reliability was assessed during the training phase and quantified using Intraclass Correlation Coefficient (ICC) scores. The binary outcome variable, caries-affected (dmfs>0) and caries-free (dmfs=0), was used to build CRA models: (i) Model I for 2-year-old and (ii) Model II for 3-year-old children. Thereafter, these models were sub-categorized based on the type of lesions detected: (i) Model A (ICDAS codes 2-6): all caries lesions including non-cavitated, cavitated lesions in enamel and dentin; (ii) Model B (ICDAS codes 3-6): moderate-extensive caries lesions excluding code 2 lesions. Thus, the medical CRA models reported in the current study are: Model I-A and II-A predicting “overall caries lesions” at 2 and 3 years respectively; Model I-B and II-B predicting risk of “moderate-extensive caries” at 2 and 3 years respectively. Multivariable logistic regression was employed to develop risk prediction models excluding all the factors that were not feasible/or difficult to obtain by medical professionals. Factors with a p-value $\leq$ 0.05 in the bivariate logistic regression were selected as the core variables for the multivariable model, along with factors which were closely associated with etiological factors, of clinical relevance and/or increased the maximum variance in the outcome explained by the models. Pseudo R^2 was used to estimate the amount of variation in the outcome that could be explained by the model. Receiver Operating Characteristic (ROC) analysis was used to evaluate predictive accuracy of the models, using area under the curve (AUC). Sensitivity and specificity values were obtained from the AUC, followed by estimation of the accuracy of the model. To overcome the constraint of biased/overestimated results that may arise as a result of missing data, Multiple Imputation by Chained Equation (MICE) was used to impute the missing covariates for all the models (Model I-Ai, Model I-Bi, Model II-Ai, Model II-Bi), as a sensitivity test. Details of the MICE technique have been presented in the Appendix. To simulate a possible scenario where the medical professionals were trained to identify caries lesions in anterior teeth using quick screening tools such as “lift the lip” (Kaste et al. 1996), anterior caries lesions at Year 2 were added to the medical models (Model II-A-a, II-Ai-a, II-B-a and II-Bi-a) and the model performance was evaluated. The data and analysis reported for this longitudinal study follows the STROBE guidelines.

Results

The potential risk determinants for all caries and moderate-extensive caries lesions have been presented in Table 1 and Appendix Table 1, respectively. A total of 535 and 721 participants were examined at the 2- and 3-year clinic visits, respectively. The ECC prevalence rates at 2- and 3-years were 17.8% (95/535) and 42.9% (309/721), respectively. Moderate-extensive caries were observed in 3.9% (21/535) and 20.6% (149/721) at 2- and 3-years, respectively. A single investigator performed clinical examinations at the 2-year visit, with intra-examiner reliability of 0.95 (for ICDAS code 2) and 1.00 (for ICDAS codes 3-6). Furthermore, three examiners performed oral examinations at the 3-year visit, with mean inter- and intra-examiner reliability scores of 0.84 and 0.80, respectively (for ICDAS code 2) and 0.85 and 0.90, respectively (for ICDAS codes 3-6).

The multivariable medical CRA models for 2-year-old toddlers, Models I-A and I-B, demonstrated an AUC (95%CI) of 0.81 (0.75-0.87) and 0.91 (0.85-0.97), and an accuracy of 74% and 87%, respectively, while explaining 33%-35% of the variance in the outcome (Table 2). Models II-A and II-B demonstrated an AUC (95%CI) of 0.79 (0.74-0.84) and 0.79 (0.73-0.85) and an accuracy of 71% and 72%, respectively, with the models explaining 20%-24% of the variance in the outcome (Table 3).

Significant risk predictors in Model I-A (all lesions) were “history of allergies before first tooth eruption” (OR 2.58, 95%CI 1.44-6.14, $P=0.01$), “intake of medications during the first year” (OR 2.98, 95%CI 1.44-6.14, $P=0.003$) and “history of infections before first tooth eruption” (OR 3.11, 95%CI 1.44-6.74, $P=0.004$); while protective factors were “monthly household income (2000-3999 SGD)” (OR 0.26, 95%CI 0.08-0.79, $P=0.01$) and “history of maternal illness” (OR 0.16, 95%CI 0.07-0.38, $P<0.001$). Significant risk predictors in Model I-B (moderate-extensive lesions) include “higher maternal childbearing age” (OR 1.26, 95%CI 1.00-1.48, $P=0.04$), “prenatal tobacco smoke exposure” (OR 6.79, 95%CI 1.40-32.90, $P=0.01$) and “history of allergies before 12 months” (OR 9.18, 95%CI 1.34-62.73, $P=0.02$) detailed in Appendix Table 2.

Significant risk predictors in Model II-A were “Chinese ethnicity” (OR 2.67, 95%CI 1.00-7.10, $P=0.04$), “mother’s occupation (non-professional)” (OR 2.50, 95%CI 1.30-4.83, $P=0.006$), “prenatal tobacco smoke exposure” (OR 2.57, 95%CI 1.33-4.99, $P=0.005$), “higher mother’s brushing frequency (2 times/day)” (OR 2.79, 95%CI 1.16-6.70, $P=0.02$), “higher mother’s brushing frequency (3 times/day)” (OR 3.58, 95%CI 1.12-11.42, $P=0.03$), “higher frequency of in between meal sweet snacks (2 times/day)” (OR 3.21, 95%CI 1.50-6.95, $P=0.003$), “greater number of teeth present at 1-year” (OR 1.16, 95%CI 1.00-1.34, $P=0.04$) and “delayed tooth eruption” (OR 1.19, 95%CI 1.02-1.40, $P=0.03$); while “mother’s education (secondary school)” (OR 0.33, 95%CI 0.12-0.91, $P=0.03$), “history of chronic maternal illness” (OR 0.34, 95%CI 0.19-0.62, $P<0.001$), “parental reported cause for tooth decay (sugar and bacteria)” (OR 0.50, 95%CI 0.25-0.99, $P=0.04$) and “increased use of pacifier” (OR 0.96, 95%CI 0.93-0.99, $P=0.02$) were protective risk factors. Significant risk predictors in Model II-B were “Malay ethnicity” (OR 6.16, 95%CI 1.60-23.76, $P=0.008$), “Chinese ethnicity” (OR 5.09, 95%CI 1.38-18.69, $P=0.01$), “higher mother’s brushing frequency (2 times/day)” (OR 3.74, 95%CI 1.09-12.79, $P=0.03$), “higher

frequency of in between meal sweet snacks (2 times/day)” (OR 3.60, 95%CI 1.42-9.14, $P=0.007$) and “child with pre-existing medical conditions” (OR 2.24, 95%CI 1.08-4.67, $P=0.03$) along with protective factors such as “history of maternal illness” (OR 0.48, 95%CI 0.24-0.94, $P=0.03$) and “increased use of pacifier” (OR 0.94, 95%CI 0.90-0.98, $P=0.003$) detailed in Appendix Table 3.

After accounting for the missing data, multivariable medical CRA models for 2-year-old toddlers, Models I-Ai and I-Bi, demonstrated an AUC (95%CI) of 0.75 (0.70-0.81) and 0.84 (0.76-0.92) (Table 4) whereas the post imputation performance of Models II-Ai and II-Bi, for caries risk prediction at 3 years, demonstrated an AUC (95%CI) of 0.71 (0.67-0.75) and 0.75 (0.70-0.80) (Table 4).

On simulation of a hypothetical scenario where medical professionals were trained to “lift the lip” to identify caries lesions on anterior teeth at 2-years, significant improvement was demonstrated in the performance of both non-imputed (Model II-A-a: AUC 0.86, 95%CI 0.81-0.90, $P<0.05$; Model II-B-a: AUC 0.86, 95%CI 0.81-0.91, $P<0.05$) and imputed models (Model II-Ai-a: AUC 0.80, 95%CI 0.76-0.84, $P<0.05$; Model II-Bi-a: AUC 0.83, 95%CI 0.78-0.88, $P<0.05$) (Tables 3 and 4).

Discussion

This study aims to explore the potential of medical-based CRA models for early screening of susceptible young children in a medical healthcare setting for timely dental referral and effective preventive initiatives, such as fluoride varnish application with motivational interviewing in combination with anticipatory guidelines (Jamieson et al. 2018; Marinho et al. 2013).

Studies have shown greater utilization of medical services in the early years of life compared to dental utilization rates (Chi et al. 2013). Furthermore, physician-delivered preventive oral health services have been shown to reduce 32% treatment cost of caries-related hospital episodes in children up to 3 years (Stearns et al. 2012). While recent studies have advocated performing individual risk assessment by medical health care providers (AAPD 2019; Fontana et al. 2019; Ramos-Gomez et al. 2007), the predictive potential of these models has not been well established yet.

The medical models developed in the present study performed better in predicting caries risk at 2 years (AUC=0.91) than the models predicting caries risk at 3 years (AUC=0.79), reflecting the temporal impact of predictors on the predictive accuracy of the models and the increasing variability of behavioral/psychosocial influence at the later stage of life. The current medical models (AUC 0.91 for Year 2 and 0.79 for Year 3) in Singaporean children appeared to be comparable to a recent US-based medical model developed for 4-year old children (AUC 0.73) (Fontana 2019). As such, previous CRA models requiring a separate dental examination, have been shown to predict new cavitated lesions at 3 years with an AUC=0.75 (Fontana et al. 2011). When the applicability of the medical model (Model II-B) was tested to predict 1-year increase in moderate-extensive lesions, the AUC=0.80 (0.74-0.86) was comparable to the previously reported model relying on past caries

experience (AUC=0.75) (Fontana et al. 2011) (Appendix Table 4). Although the current study models explained 20-35% of the variation in the outcome, ongoing studies including genetic factors and oral microbiome information, may further improve the model performance at the expense of feasibility/utility.

Additionally, a few important associations, not necessarily causal but potentially reversed causal, were identified. Prenatal tobacco smoke exposure was shown to be a risk factor for ECC development at both 2 and 3 years, possibly due to speculated prenatal exposure of developing tooth to harmful chemical toxins (Tanaka et al. 2009) and increased growth of cariogenic bacteria in mothers after nicotine use (Lindemeyer et al. 1981) via vertical transmission from mothers to children (Chaffee et al. 2014). Similar to the findings from a nation-wide preschooler study (Gao et al. 2010), higher caries rates in Malay children and a biphasic caries risk of socioeconomic indicators (e.g. monthly household income in the present study), with higher caries rates in low and high-income groups, compared to intermediate group, was observed. The higher caries rates in Malays, compared to Indians, may possibly be due to lower monthly household income levels (74.5% vs 50.4%) and higher prenatal tobacco smoke exposure (67.1% vs 25.5%). History of allergies (e.g. eczema) before 12 months collected via a questionnaire, was shown to be an ECC risk factor, confirming the previous findings (Kalhan et al. 2017), possibly due to a 2-fold higher risk of hypomineralization reported in children with infantile eczema (Silva et al. 2019). A common pathogenic pathway via an underlying ectodermal structural defect may be plausible.

Although unconventional and counterintuitive, higher maternal brushing frequency was shown to be a risk factor for ECC development in children. This may possibly be due to fear-driven behavioral change (e.g. brushing habit) and/or a “reverse causality” (Un Lam et al. 2017), suggesting maternal brushing habits might have been changed after/due to the caries/outcome or potential/perceived risk of outcome which took place before our clinical examination. Our previous study showed brushing frequency of child’s teeth to be associated with reduced plaque accumulation (OR=0.62), but increased caries risk at 2 years (OR=1.88) using a bivariate probit model (Un Lam et al. 2017). Additionally, our current data shows increased frequency of brushing in mothers (2 times/day) to be associated with increased brushing frequency (2 times/day) in children ($P<0.001$).

Furthermore, the study findings show prolonged use of pacifier to exert a protective effect. While pacifiers have been reported to increase ECC risk in preschoolers (Vazquez-Nava et al. 2008), contrasting evidence exists reporting no association (Huntington et al. 2002) or lower ECC risk associated with pacifier usage (Menghini et al. 2008). Addition of sweeteners (Hallett and O’Rourke 2002) and/or ineffective oral sugar clearance leading to reduced plaque pH (Ollila et al. 1997), may potentially affect the association, necessitating future studies to explore the mechanistic explanation.

The findings also show a pre-existing maternal health condition to be a protective factor for ECC development. A previous nation-wide study has also reported lower ECC rates in 3-6-year-old children of mothers with health conditions (Gao et al. 2010). It is speculated that the health conditions of mother or child may heighten the health consciousness and modify

certain health behaviors (Un Lam et al. 2017), possibly explaining the protective effect. On the other hand, presence of child infections prior to first tooth eruption, was shown to be a risk factor, along with increased medication use in the first year. Studies have shown increased use of prescription medications to modify the cariogenic oral flora and increase caries susceptibility (Jurasic et al. 2019).

One of the most common problems encountered with a longitudinal study design is the missing data. Amongst the commonly employed methods to handle missing data, such as complete case analyses (ignoring the missing data), missing-indicator method, single imputation and multiple imputation, the latter has been demonstrated to be better in handling the missing data (van der Heijden et al. 2006). As a part of sensitivity test to assess the potential bias and influence of the missing data on the performance of risk prediction models (Hughes et al. 2019), Multiple Imputation by Chained Equations (MICE) was performed. The imputed models, demonstrated comparatively lower AUC compared to original models (AUC: Model I-A=0.75 vs 0.81; Model I-B=0.84 vs 0.91; Model II-A=0.71 vs 0.79; Model II-B=0.75 vs 0.79) (Table 4), reiterating the need for cautious interpretation of model performance in longitudinal studies with substantial missing data. Furthermore, internal validation of the models was carried out in the present study to verify the “reproducibility” of the model (Appendix Table 5).

Identification of caries in anterior teeth by medical professionals using dental health screening guides such as “lift the lip” have been reported, showing high inter- and intra-examiner reliability ($\kappa > 0.85$) (Kaste et al. 1996). Our simulated scenario showed that, incorporating information related to upper anteriors, the performance of medical models significantly increased with AUC > 80% in all non-imputed and imputed models (Tables 3 and 4). Therefore, training pediatricians or their assistants to assess anterior teeth of infants/toddlers, coupled with the algorithms or software derived from aforementioned CRA models, might further enhance the performance of medical models in screening caries susceptible children, in line with the global need to integrate oral and general healthcare (Watt et al. 2019).

The study had some limitations. Firstly, the cohort may not be representative of the entire population, warranting cautious extrapolation of study findings, although the participant characteristics and disease burden (20.7% cavitated lesions at 3 years) were comparable to the previous nation-wide study using a randomized sample (27% cavitated lesions at 3-4 years). Secondly, substantial missing data across multiple time-points (ranging between 1.1%-19.4% and 0.8%-25.8% for Year 2 and 3 outcomes, respectively) was observed and handled as mentioned above. The strengths of the study include its longitudinal cohort design. The oversampling of Malay and Indian mothers in the GUSTO cohort provided a diverse multi-ethnic sample.

In conclusion, risk prediction models utilizing easily attainable data for medical professionals may be clinically promising in early identification of caries-susceptible infants/toddlers, especially after training medical colleagues to identify caries lesions in anterior teeth. This may echo the need in integrating oral health services into the mainstream healthcare system, thus possibly reducing global oral health disparities in children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Schematic representation of the study design

Abbreviations: M= months

N* indicates the number of GUSTO participants who received oral examination at the age of 2 years and 3 years.

Table 1
Potential determinants for all caries lesions

Potential Risk Predictors (categorical variables)	All lesions [N (%)] (ICDAS codes 2-6)			
	Year 2		Year 3	
	Caries-affected (dmfs>0)	Caries-free (dmfs=0)	Caries-affected (dmfs>0)	Caries-free (dmfs=0)
Ethnicity	<i>p=0.12</i>		<i>p=0.02</i>	
Chinese	55 (18.8%)	238 (81.2%)	176 (43.1%)	232 (56.9%)
Malay	31 (20.1%)	123 (79.9%)	94 (48.7%)	99 (51.3%)
Indian	9 (10.2%)	79 (89.8%)	39 (32.5%)	81 (67.5%)
Mother's education	<i>p=0.49</i>		<i>p=0.15</i>	
Primary and below	4 (16.7%)	20 (83.3%)	13 (46.4%)	15 (53.6%)
Secondary	41 (20.6%)	158 (79.4%)	124 (47.5%)	137 (52.5%)
Polytechnic	20 (14.2%)	121 (85.8%)	77 (43.0%)	102 (57.0%)
Bachelor's degree and above	28 (17.0%)	137 (83.0%)	93 (37.7%)	154 (62.3%)
Father's education	<i>p=0.64</i>		<i>p=0.07</i>	
Primary and below	5 (22.7%)	17 (77.3%)	19 (63.3%)	11 (36.7%)
Secondary	15 (16.9%)	74 (83.1%)	44 (41.9%)	61 (58.1%)
Polytechnic	32 (20.0%)	128 (80.0%)	94 (48.2%)	101 (51.8%)
Bachelor's degree and above	29 (18.1%)	131 (81.9%)	82 (40.0%)	123 (60.0%)
Mother's occupation	<i>p=0.03</i>		<i>p=0.005</i>	
Unemployed	21 (12.7%)	145 (87.3%)	75 (35.7%)	135 (64.3%)
Non-professional	40 (23.5%)	130 (76.5%)	114 (50.9%)	110 (49.1%)
Professional	32 (17.5%)	151 (82.5%)	111 (41.0%)	160 (59.0%)
Monthly household income	<i>p=0.7</i>		<i>p=0.15</i>	
0-1999 SGD	16 (20.0%)	64 (80.0%)	57 (52.8%)	51 (47.2%)
2000-3999 SGD	25 (15.7%)	134 (84.3%)	86 (42.8%)	115 (57.2%)
4000-5999 SGD	26 (19.1%)	110 (80.9%)	74 (43.8%)	95 (56.2%)
>6000 SGD	25 (20.8%)	95 (79.2%)	76 (39.2%)	118 (60.8%)
Prenatal tobacco smoke exposure	<i>p=0.35</i>		<i>p=0.03</i>	
Yes	39 (19.9%)	157 (80.1%)	124 (47.5%)	137 (52.5%)
No	50 (16.6%)	251 (83.4%)	166 (39.2%)	257 (60.8%)
History of chronic maternal illness	<i>p=0.001</i>		<i>p=0.004</i>	
Yes	22 (10.9%)	180 (89.1%)	113 (36.7%)	195 (63.3%)
No	59 (22.2%)	207 (77.8%)	189 (47.6%)	208 (52.4%)
In-between meal sweet snacks frequency	<i>p=0.27</i>		<i>p=0.008</i>	

Potential Risk Predictors (categorical variables)	All lesions [N (%)] (ICDAS codes 2-6)			
	Year 2		Year 3	
	Caries-affected (dmfs>0)	Caries-free (dmfs=0)	Caries-affected (dmfs>0)	Caries-free (dmfs=0)
Twice or more per day	38 (19.2%)	160 (80.8%)	123 (51.0%)	118 (49.0%)
Once per day	36 (17.9%)	165 (82.1%)	100 (42.2%)	137 (57.8%)
None	9 (11.3%)	71 (88.7%)	36 (33.6%)	71 (66.4%)
<i>Parental reported cause for tooth decay</i>	<i>p=0.51</i>		<i>p=0.08</i>	
Sugar and bacteria	44 (15.4%)	241 (84.6%)	141 (41.0%)	203 (59.0%)
Sugar or bacteria	2 (13.3%)	13 (86.7%)	8 (50.0%)	8 (50.0%)
Ineffective toothbrushing	13 (21.0%)	49 (79.0%)	35 (41.2%)	50 (58.8%)
Tooth worms/ heatiness	24 (20.5%)	93 (79.5%)	74 (53.2%)	65 (46.8%)
<i>Night-time bottle feeding[¶]</i>	<i>p=0.69</i>		<i>p=0.07</i>	
Yes	20 (14.5%)	118 (85.5%)	202 (46.2%)	235 (53.8%)
No	23 (16.20%)	119 (83.8%)	96 (39.2%)	149 (60.8%)
<i>Sharing feeding/ drinking utensils</i>	<i>p=0.16</i>		<i>p=0.18</i>	
Frequently	12 (11.5%)	92 (88.5%)	47 (39.2%)	73 (60.8%)
Seldom	43 (20.1%)	171 (79.9%)	123 (48.2%)	132 (51.8%)
Never	28 (17.3%)	134 (82.7%)	89 (42.0%)	123 (58.0%)
<i>History of allergies before 12 months (runny nose: 9-12 months; itchy rashes: 6-12 months)</i>	<i>p=0.04</i>		<i>p=0.44</i>	
Yes	12 (28.6%)	30 (71.4%)	29 (47.5%)	32 (52.5%)
No	65 (16.2%)	337 (83.8%)	254 (42.5%)	344 (57.5%)
<i>History of allergies before first tooth eruption (runny nose, itchy rashes)</i>	<i>p=0.009</i>		<i>p=0.37</i>	
Yes	40 (23.4%)	131 (76.6%)	111 (45.1%)	135 (54.9%)
No	43 (13.9%)	266 (86.1%)	198 (41.7%)	277 (58.3%)
<i>Intake of medications (oral medicines: 6-12 months; nebulizers: 9-12 months; antibiotics: 9-12 months; medications for runny nose: 0-12 months)</i>	<i>p=0.006</i>		<i>p=0.10</i>	
Yes	32 (26.2%)	90 (73.8%)	85 (47.8%)	93 (52.2%)
No	47 (14.9%)	268 (85.1%)	197 (40.6%)	288 (59.4%)

Potential Risk Predictors (categorical variables)	All lesions [N (%)] (ICDAS codes 2-6)							
	Year 2				Year 3			
	Caries-affected (dmfs>0)		Caries-free (dmfs=0)		Caries-affected (dmfs>0)		Caries-free (dmfs=0)	
History of infection (ear infection/ vomiting/diarrhoea) before first tooth eruption	p=0.12				p=0.09			
Yes	28 (21.7%)		101 (78.3%)		94 (48.0%)		102 (52.0%)	
No	55 (15.7%)		296 (84.3%)		215 (41.0%)		309 (59.0%)	
Mother's brushing frequency	p=0.33				p=0.003			
3 times/day	13 (22.4%)		45 (77.6%)		39 (51.3%)		37 (48.7%)	
2 times/day	62 (17.4%)		295 (82.6%)		201 (45.9%)		237 (54.1%)	
1 times/day	8 (12.3%)		57 (87.7%)		19 (26.0%)		54 (74.0%)	
Child has pre-existing medical condition	p=0.89				p=0.05			
Yes	17 (18.1%)		77 (81.9%)		68 (50.4%)		67 (49.6%)	
No	71 (17.5%)		334 (82.5%)		215 (41.0%)		310 (59.0%)	
Maternal regular dental check-up	p=0.78				p=0.27			
Yes	34 (16.7%)		169 (83.25%)		106 (41.6%)		149 (58.4%)	
No	49 (17.7%)		228 (82.31%)		153 (46.1%)		179 (53.9%)	
Presence of dry mouth at 18 months	p=0.77				p=0.53			
Yes	3 (20.0%)		12 (80.0%)		6 (35.3%)		11 (64.7%)	
No	75 (17.1%)		363 (82.9%)		276 (42.9%)		368 (57.1%)	
Previous dental visit	p=0.03				p=0.12			
Yes	4 (44.4%)		5 (55.56%)		11 (61.1%)		7 (38.9%)	
No	79 (16.8%)		392 (83.2%)		296 (42.7%)		397 (57.3%)	
	ECC at Year 2				ECC at Year 3			
Potential Risk Predictors (continuous variables)	All lesions (ICDAS codes 2-6)		Moderate-extensive lesions (ICDAS codes 3-6)		All lesions (ICDAS codes 2-6)		Moderate-extensive lesions (ICDAS codes 3-6)	
	Mean (S.D.)		Mean (S.D.)		Mean (S.D.)		Mean (S.D.)	
	dmfs>0	dmfs=0	dmfs>0	dmfs=0	dmfs>0	dmfs=0	dmfs>0	dmfs=0
Maternal childbearing age (in years)	31.78 (5.40)	30.88 (5.18)	33.27 (5.16)	30.95 (5.21)	30.92 (5.39)	31.13 (5.09)	31.45 (5.26)	30.91 (5.21)
Parity status	1.17 (1.31)	0.86 (0.97)	1.06 (1.12)	0.91 (1.04)	1.05 (1.19)	0.80 (0.89)	1.23 (1.35)	0.82 (0.91)
Child's BMI at 12 months	16.66 (1.45)	16.31 (1.44)	16.42 (1.47)	16.36 (1.45)	16.49 (1.41)	16.27 (1.48)	16.46 (1.42)	16.34 (1.46)
Child's age for first tooth eruption (in months)	8.34 (2.42)	8.65 (2.64)	8.07 (2.94)	8.62 (2.60)	8.49 (2.50)	8.70 (2.70)	8.47 (2.57)	8.64 (2.62)
Number of teeth at 12 months	5.91 (2.21)	5.46 (2.55)	6.47 (2.18)	5.50 (2.51)	5.75 (2.44)	5.37 (2.54)	5.69 (2.50)	5.49 (2.50)

Potential Risk Predictors (categorical variables)	All lesions [N (%)] (ICDAS codes 2-6)							
	Year 2				Year 3			
	Caries-affected (dmfs>0)		Caries-free (dmfs=0)		Caries-affected (dmfs>0)		Caries-free (dmfs=0)	
<i>Age of introduction of solid food</i>	5.60 (1.10)	5.55 (1.21)	5.42 (1.24)	5.57 (1.19)	5.59 (1.16)	5.54 (1.21)	5.62 (1.21)	5.54 (1.19)
<i>Duration of pacifier use (in months) ¶</i>	4.73 (5.51)	5.17 (5.68)	3.00 (5.08)	5.18 (5.66)	7.18 (9.78)	9.66 (10.55)	5.99 (9.30)	9.31 (10.44)
<i>Duration of breastfeeding (in months) ¶</i>	4.69 (4.86)	4.22 (4.53)	6.60 (5.62)	4.23 (4.53)	6.09 (7.69)	5.07 (6.60)	7.34 (8.43)	4.98 (6.60)

¶ up to 12 months for ECC at 2 years outcome and up to 24 months for ECC at 3 years outcome

Table 2
Evaluation of medical CRA models predicting caries risk at 2 years

<i>Model I-A: All lesions (ICDAS codes 2-6)</i>						
Adjusted *N	AUC (95%CI)	Cut-off	Sensitivity	Specificity	Accuracy [§]	Pseudo R ²
276	0.81 (0.75-0.87)	0.213	78	73	74	0.33
<i>Model I-B: Moderate-extensive lesions (ICDAS codes 3-6)</i>						
Adjusted **N	AUC (95%CI)	Cut-off	Sensitivity	Specificity	Accuracy [§]	Pseudo R ²
299	0.91 (0.85-0.97)	0.067	83	87	87	0.35

* **Risk predictors (17) in Model I-A:** *Prenatal factors*- Ethnicity, maternal childbearing age, maternal occupation, parity status, history of chronic maternal illness, monthly household income, prenatal tobacco smoke exposure; *Peri-natal factor*: mode of delivery; *Post-natal factors*: History of allergies before 12 months (runny nose: 9-12 months; itchy rashes: 6-12 months), history of allergy before first tooth eruption (runny nose, itchy rashes), intake of medications (oral medicines: 6-12 months; nebulizers: 9-12 months; antibiotics: 9-12 months; medications for runny nose: 0-12 months), BMI (12 months), history of infection (ear infection/vomiting/diarrhoea) before first tooth eruption, number of teeth present (12 months), duration of breastfeeding (in months), child's age for first tooth eruption (in months), age of introduction of solid food (in months)

** **Model I-B:** Having the same predictors as those of Model I-A, but without monthly household income and mode of delivery (owing to high standard error)

[§] Accuracy calculated as [(sensitivity x prevalence of outcome) + (specificity x non-prevalence of outcome)/100].

Table 3
Evaluation of medical CRA models predicting caries risk at 3 years

	Adjusted N	AUC (95%CI)	Cut-off	Sensitivity	Specificity	Accuracy [§]	Pseudo R ²
<i>Model II-A: All lesions (ICDAS codes 2-6)</i>							
Model II-A *	312	0.79 (0.74-0.84)	0.44	71	71	71	0.24
Model II-A-a **	251	0.86 (0.81-0.90)	0.44	77	76	76	0.33
<i>Model II-B: Moderate-extensive lesions (ICDAS codes 3-6)</i>							
Model II-B *	312	0.79 (0.73-0.85)	0.25	72	72	72	0.20
Model II-B-a **	251	0.86 (0.81-0.91)	0.26	78	78	78	0.31

* Risk predictors (22) in Model II-A/B: **Prenatal factors:** Ethnicity, household income, maternal educational levels, maternal occupation, father educational levels, parity status, history of chronic maternal illness, prenatal tobacco smoke exposure; **Post-natal factors:** Parental belief for cause of tooth decay (24 months), mother's brushing frequency (24 months), child's pre-existing medical condition (6 months), frequency of in between meal sweet snacks (24 months), duration of pacifier use (in months), duration of breastfeeding (in months), maternal regular dental check-up (24 months), child's brushing frequency (24 months), number of teeth (12 months), sharing feeding/drinking utensils, night-time bottle feeding (24 months), child's age for first tooth eruption (in months), dry mouth (18 months), previous dental visit (24 months).

[§] Accuracy calculated as [(sensitivity x prevalence of outcome) + (specificity x non-prevalence of outcome)/100].

** Model II-A-a/B-a: Upon addition of "year-2 anterior caries lesions" as a covariate into Model II-A/B, significant improvement was demonstrated in the model performance (both P<0.05).

Table 4
Performance of medical-CRA models post-imputation

MODELS	Adjusted N	AUC (95%CI)	Cut-off	Sensitivity	Specificity	Pseudo R ²
<i>Medical CRA models predicting caries risk at 2 years</i>						
Model I-Ai *	535	0.75 (0.70-0.81)	0.17	69	67	0.12
Model I-Bi #	535	0.84 (0.76-0.92)	0.03	80	72	0.17
<i>Medical CRA models predicting caries risk at 3 years</i>						
Model II-Ai **	721	0.71 (0.67-0.75)	0.41	69	63	0.10
Model II-Ai-a ***	480	0.80 (0.76-0.84)	0.14	69	69	0.22
Model II-Bi **	721	0.75 (0.70-0.80)	0.40	70	62	0.13
Model II-Bi-a ***	480	0.83 (0.78-0.88)	0.20	75	75	0.27

* **Model I-Ai: Prenatal factors-** Ethnicity, maternal childbearing age, maternal occupation, parity status, history of chronic maternal illness, monthly household income, prenatal tobacco smoke exposure; **Peri-natal factor:** mode of delivery; **Post-natal factors:** History of allergies between 6-12 months (runny nose: 9-12 months; itchy rashes: 6-12 months), history of allergy before first tooth eruption (runny nose, itchy rashes), intake of medications (oral medicines: 6-12 months; nebulizers: 9-12 months; antibiotics: 9-12 months; medications for runny nose: 0-12 months), BMI (12 months), history of infection (ear infection/vomiting/diarrhoea) before first tooth eruption, number of teeth present (12 months), duration of breastfeeding (in months), child's age for first tooth eruption (in months), age of introduction of solid food (in months)

Model I-Bi: Inclusion of risk predictors similar to Model I-A, except monthly household income and mode of delivery (excluded owing to high standard error)

** **Model II-Ai/Bi: Prenatal factors:** Ethnicity, household income, maternal educational levels, maternal occupation, father educational levels, parity status, history of chronic maternal illness, prenatal tobacco smoke exposure; **Post-natal factors:** Parental belief for cause of tooth decay (24 months), mother's brushing frequency (24 months), child's pre-existing medical condition (6 months), frequency of in between meal sweet snacks (24 months), duration of pacifier use (in months), duration of breastfeeding (in months), maternal regular dental check-up (24 months), child's brushing frequency (24 months), number of teeth (12 months), sharing feeding/drinking utensils, night-time bottle feeding (24 months), child's age for first tooth eruption (in months), dry mouth (18 months), previous dental visit (24 months).

*** **Model II-Ai-a/Bi-a:** Upon addition of "year-2 anterior caries lesions" as a covariate into Model II-Ai/Bi, significant improvement was demonstrated in the model performance (both P<0.05).