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A Model for the Analysis of Caries Occurrence in Primary Molar Tooth Surfaces

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Key Words
Generalised linear modelling · Multilevel modelling · Primary caries

Abstract
Recently methods of caries quantification in the primary dentition have moved away from summary 'whole mouth' measures at the individual level to methods based on generalised linear modelling (GLM) approaches or survival analysis approaches. However, GLM approaches based on logistic transformation fail to take into account the time-dependent process of tooth/surface survival to caries. There may also be practical difficulties associated with casting parametric survival-based approaches in a complex multilevel hierarchy and the selection of an optimal survival distribution, while non-parametric survival methods are not generally suitable for the assessment of supplementary information recorded on study participants. In the current investigation, a hybrid semi-parametric approach comprising elements of survival-based and GLM methodologies suitable for modelling of caries occurrence within fixed time periods is assessed, using an illustrative multilevel data set of caries occurrence in primary molars from a cohort study, with clustering of data assumed to occur at surface and tooth levels. Inferences of parameter significance were found to be consistent with previous parametric survival-based analyses of the same data set, with gender, socio-economic status, fluoridation status, tooth location, surface type and fluoridation status-surface type interaction significantly associated with caries occurrence. The appropriateness of the hierarchical structure facilitated by the hybrid approach was also confirmed. Hence the hybrid approach is proposed as a more appropriate alternative to primary caries modelling than non-parametric survival methods or other GLM-based models, and as a practical alternative to more rigorous survival-based methods unlikely to be fully accessible to most researchers.

The traditional method of quantifying the extent of caries is by summary 'whole mouth' measures recorded at the individual level, generally considering the total number of decayed, missing and filled primary teeth or surfaces (dmft or dmfs), or the counterpart measures for the permanent dentition (DMFT and DMFS). These measures are in widespread use in epidemiological surveys and have been used to compare treatments and subject groups defined by subject-level characteristics in terms of propensity to caries.

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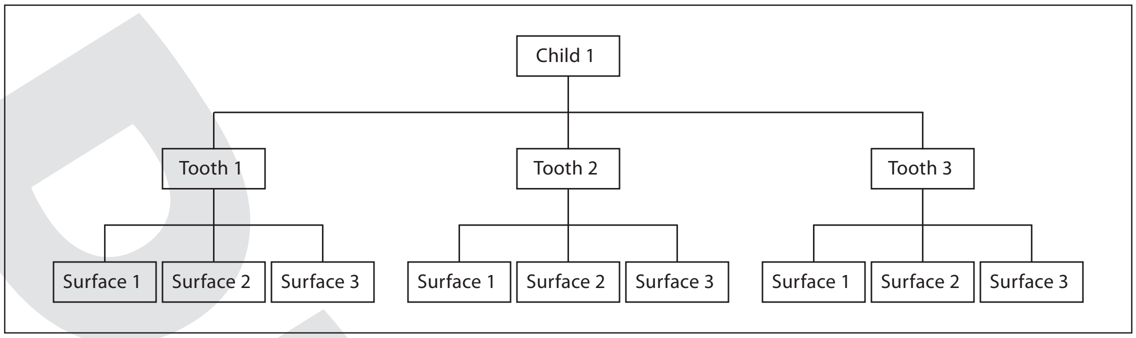

Fig. 1. Schematic of a possible three-level structure.

However, several authors have identified drawbacks to the use of these measures in the primary dentition [Kidd and Joyston-Bechal, 1997; Fejerskov and Kidd, 2008]. The key drawback identified is that while dmft or dmfs is usually treated as an absolute score, in reality it represents a fraction of the teeth or surfaces at risk to caries, the denominator of which is not constant due to concurrent exfoliation. Also, summary measures do not usually reflect information concerning the time that the tooth or tooth surface is at risk [Hujoel et al., 1994] and may mask differences in the caries susceptibilities of different tooth surfaces, for example clustering of data between surfaces associated with teeth belonging to a particular individual [Hannigan et al., 2001]. A schematic of one such possible hierarchy for the analysis of caries or other dental data is given in figure 1 in which surfaces, teeth and children are considered to be levels in a hierarchy. Hence many recent analyses of caries data have moved away from summary methods of quantification towards analyses based on either survival-based or generalised linear modelling (GLM) methodologies, usually at the surface or tooth levels. However, currently there appears to be no consensus as to the preferred method for the analysis of primary caries data.

Many authors have adopted an approach to the analysis of caries data based on survival analysis methodologies or related methods [Hannigan et al., 2001; Gilthorpe et al., 2002; Baelum et al., 2003; Leroy et al., 2005a, b; Stephenson et al., 2010a, b]. It has been noted [Mancl et al., 2002] that such survival-based approaches are potentially more efficient methods of analysis than traditional subject-level analyses, due to the capability to account for surface time at risk. However, the capability of most statistical software to analyse survival data with an underlying hierarchical structure is limited, often to a structure with two levels only. Furthermore, a rigorous treatment of interval censoring, as is found in many prospective cohort studies of dental data using survival-based methodologies, is unlikely to be a practical option to most researchers, and the selection of an optimal survival distribution from many available alternatives in parametric methods may also require knowledge of specialist techniques. Non-parametric survival methods are not appropriate for assessing the effect of prognostic variables on caries occurrence.

In the alternative GLM approach, a transformation is required to fit the relationship between a binary response, such as the presence or absence of caries on a given tooth or surface, and a set of covariates, into a linear regression framework. The preferred transformation in the analysis of caries data by this method has been the logit link, utilised in the analyses of Rodrigues and Sheiham [2000], Vanobbergen et al. [2001], Riley et al. [2004] and Burnside et al. [2007, 2008]. Vanobbergen et al. [2001] state that logistic regression models using longitudinal data are the preferred method of analysis for caries data. Although methods based on the GLM approach may also give rise to clustering issues, the capability of software to analyse hierarchical data structures is generally greater in models based on the GLM formulation than on the survival analysis formulation, and the wide applicability of the GLM formulation is likely to be more familiar than survival-based methods to medical and dental practitioners who are not specialist statisticians.

However, while many authors, such as Selwitz et al. [2007], report caries to be a time-dependent process, the traditional GLM-based approach using the logit link fails to take account of this time dependency. Hence the objective of this study was to assess, in terms of practicality and accuracy of inference, a proposed semi-parametric approach to the analysis of caries occurrence over a specific time period, such as those spanned by a prospective cohort study. This hybrid formulation combines the relative familiarity to researchers of the GLM method and its capability to account for complex hierarchical structures, with the capability of parametric survival-based methods to account for the time dependency of the caries process.

Subjects and Methods

Data Set

The data on which the current investigation is based arise from a cohort study undertaken by the Cardiff University School of Dentistry and previously analysed using parametric survival-based approaches [Stephenson et al., 2010a, b]. In this study children were recruited at age 5–7 years from the West Midlands and South Wales regions of Great Britain, and followed up for approximately 4.5 years until 2003. The study followed a cohort of children from randomly selected schools in two areas in both of the selected geographical regions. Ethical approval for the study was obtained from the ethical committees of the relevant Health Authorities. Positive consent was obtained from the children's parents or guardians at the start of the study. Parents were free to withdraw consent at any time during the study. Local Dental Committees, District Dental Advisory Committees and all dentists on Health Authority lists or working for the Community Dental Service were informed of the nature of the study. Although informing dentists of the study might have influenced their treatment patterns, they did not know whether any children they treated were participating in the study.

Children were examined on up to three occasions during the course of the study by trained examiners. The ages of the children at each examination were between approximately 5–7, 7–9 and 9–11 years. The examinations took place in the children's schools, with each child receiving one follow-up visit in the case of absence on the examination date. A total of 2,654 children were examined at baseline, with 2,408 seen at the final examination; thus about 9% of study participants were lost to follow-up.

Cohort study observations were recorded at surface level, with data collected according to British Association for the Study of Community Dentistry (BASCD) criteria for caries [Pitts et al., 1997]. The recording of any of the BASCD criteria codes 1–6 or R at each examination was considered to directly infer the presence of caries in a particular surface at that examination. Each observed tooth was also classified as being either primary or permanent, and observations of exfoliated teeth and teeth extracted due to caries were also noted. Recorded demographic data included gender, date of birth, socio-economic deprivation measured on the Townsend scale, and fluoridation status, which effectively may be represented by geographical area. The two regions selected for the study were selected primarily for their contrasting fluoridation levels: in South Wales, water is not fluoridated, whereas it is in the West Midlands at a level of 1 ppm. These regions also illustrate contrasting social backgrounds. While both are urban industrial regions, levels of socio-economic deprivation were significantly higher in the children sampled in the West Midlands area than from those sampled in the South Wales area, which has approximately median levels of socio-economic deprivation.

A sequence of up to three criteria codes was thus obtained for each tooth surface under investigation. Teeth surfaces with invalid code sequences, for example the code sequence carious – sound – carious, were identified and deleted from the data set before further processing.

Hierarchical Data Structures

In the current investigation, a model with surface-level responses was derived, assuming an underlying hierarchical structure comprising surface, tooth and child levels. A random intercepts formulation was utilised, following the practice of other recent hierarchical analyses of caries and other dental data [Gilthorpe et al., 2000a; Bower et al., 2007; Burnside et al., 2007, 2008].

Exploratory Variables

Factors and covariates tested for significance in the models were identical to those tested in previous analyses of the data set [Stephenson et al., 2010a, b] to allow for a comparison of modelling approaches. These corresponded to gender, fluoridation status and socio-economic status, obtained from demographic data recorded as part of the cohort study, and tooth and surface level factors defined from the structure of the data itself. These included the indicator variables First, Left and Upper, defined at tooth level to distinguish between 1st and 2nd primary molars, between teeth on opposite sides of the mouth, and between maxillary and mandibular teeth; and the single surface level indicator variable, Occlusal, used to distinguish between occlusal and non-occlusal surfaces. No distinction was made between non-occlusal surfaces, among which rates of caries occurrence were comparable. Age at each examination was also recorded and included in all models as the time variable, but did not form part of the prognostic index.

Statistical Model

All data were analysed using the multilevel modelling software MLwiN [Centre for Multilevel Modelling, 2008]. The approach in the current analysis, an extension of a methodology outlined by Collett [2003], is a semi-parametric method modelling the probability of the failure of primary molar teeth or surfaces to caries by fixed time points. The method is illustrated with the three-level model, but may be easily generalised to other hierarchical structures.

Let the time-dependent probability of the occurrence of caries on a particular primary molar surface i associated with tooth j belonging to child k by the age of the individual at the time of interest, t, be denoted by the failure function $F_{ijk}(t)$. A corresponding general survival function $S_{ijk}(t) = 1 - F_{ijk}(t)$ gives the probability of survival of the tooth surface to time t. The relationship between the baseline (i.e. no factors or covariates) survival function and a corresponding general function incorporating a prognostic index is given by $S_{ijk}(t,x) = S_{ijk}(t)^{\exp \mathrm{B}^{\mathrm{T}}\mathrm{x}}$ where $\mathrm{B}^{\mathrm{T}}\mathrm{x}$ is the matrix representation of the regression function, which may include random effects arising from a multilevel analysis. Interactions may also be included in the prognostic index. The complementary log-log transformation (CLL) of the failure function is given by the expression $\ln[-\ln(1 - F_{ijk}(t,x))] = \mathrm{CLL}F_{ijk}(t,x) = \mathrm{B}^{\mathrm{T}}\mathrm{x} + \ln(-\ln S_{ijk}(t))$. By putting $\beta_{0jk} = \ln(-\ln S_{ijk}(T))$, a GLM for the analysis using data extracted at time T is given by $\mathrm{CLL}F_{ijk}(T,x) = \beta_{0jk} + \mathrm{B}^{\mathrm{T}}\mathrm{x}$, giving a

Table 1. Statistical significance and odds ratios (ORs) in multivariate multilevel GLM for caries occurrence by the final examination of the cohort study (surface level)

Variable		p value	Estimate	Approximate OR	95% CI for OR[1]
Gender	male (reference)				
	female	0.001	–0.207	0.81	0.72–0.92
Townsend score[2]		<0.001	0.074	1.08	1.05–1.10
F status	fluoridated (reference)				
	non-fluoridated	<0.001	1.125	3.08	2.63–3.57
Tooth type	2nd molar (reference)				
	1st molar	0.841	0.005	1.01	0.96–1.06
Tooth location	lower (reference)				
	upper	<0.001	–0.138	0.87	0.83–0.91
Tooth location	right (reference)				
	left	0.677	0.010	1.01	0.96–1.06
Surface type	non-occlusal (reference)				
	occlusal	<0.001	0.616	1.85	1.77–1.93
Interactions	F status × occlusal	<0.001	0.363	1.44	1.33–1.55

[1] Calculated under the assumption of a three-level data hierarchy.
[2] 95% of Townsend scores are contained within an interval given by –3.92 and 3.92.

model for the occurrence of caries within specific periods of time. Using the illustrative data set in the current investigation, T was set to the end of each age range associated with each examination of the cohort study, approximately 8.4 years, 9.8 years and 11.8 years, plus an estimate of the age on eruption of primary molar teeth obtained from Ramirez et al. [1994].

Approximate odds ratios with associated 95% confidence intervals for each variable in the prognostic index were determined, using the property of the close correspondence between logistic transformation and CLL. Parameter significance was inferred from a confidence interval for the approximate odds ratio that did not include the value 1.00. Parameter estimates, from which the odds ratios were derived, were derived using the iterative generalised least squares procedure available in the MLwiN software.

Results

Table 1 summarises the statistical significance of all variables included in the surface-level GLM using the CLL to model the probability of caries occurrence by the time of the conclusion of the final series of examinations in the cohort study. It can be seen that gender, socio-economic status, fluoridation status, tooth location and surface type plus the interaction between fluoridation status and surface type are significantly associated with caries occurrence during this period, with higher rates of occurrence exhibited in boys, in children from poor socio-economic backgrounds, in those from non-fluoridated areas, in mandibular teeth and on occlusal surfaces. Additionally the interaction between fluoridation status and surface type is also found to be significant, with the interaction indicating that fluoride is less effective in preventing caries on occlusal surfaces.

Survival curves illustrating the effect of gender, socio-economic status, fluoridation status and surface type are illustrated in figures 2–4, in which the relative magnitude of the effects of surface type and fluoridation status, compared to the effect of other demographic and dental parameters, on survival of primary teeth surfaces to caries can be observed.

Discussion

The hybrid model described in the current analysis is related to both the survival analysis and GLM approaches which have been utilised in the analysis of caries data in recent years. The utilisation in the current analysis of the CLL, rather than the logit transformation, is more appropriate for a GLM modelling longitudinal analyses of cohort study data, in which the time dependency of the caries process is recognized.

Survival graphs generated from the application of the hybrid model (fig. 2–4) bear some resemblance to those derived from a traditional non-parametric Kaplan-Meier

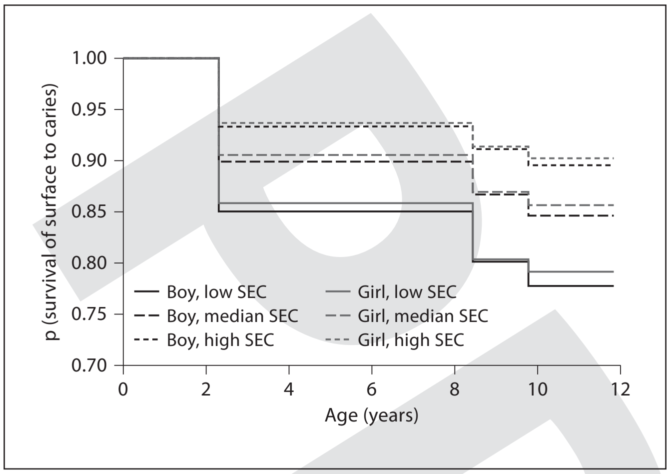

Fig. 2. Survival curve indicating the effect of gender and socio-economic class (SEC) on tooth surface survival to caries.

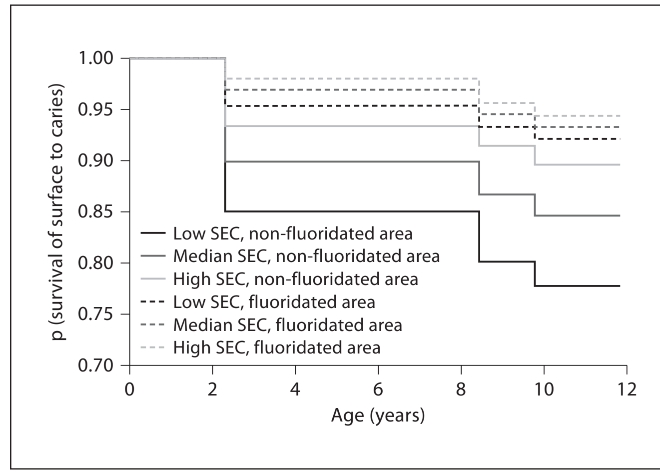

Fig. 3. Survival curve indicating the effect of fluoridation status and socio-economic class (SEC) on tooth surface survival to caries.

survival analysis, and hence would be recognized by researchers familiar with this method; yet the Kaplan-Meier method is generally unsuitable for an analysis of data in which the effect of several factors and covariates on survival times is to be assessed. Such effects may be addressed using the semi-parametric modelling approach proposed in the current study. Furthermore, most statistical software packages available for the current investigation have limited facility to account for an underlying data hierarchy in the derivation of Kaplan-Meier curves.

There are logical and clinical reasons for including children, teeth and surfaces as levels in the model structure. Many major recent analyses of childhood caries use responses at one or more of these levels [Hannigan et al., 2001; Levine et al., 2002; Tickle et al., 2002; Baelum et al., 2003; Hopcraft and Morgan, 2006; Burnside et al., 2007, 2008], and analyses of other types of dental data also consistently utilise response measures at these levels [Gilthorpe et al., 2000a, 2002]. The philosophy for the retention or otherwise of a particular level in the multilevel structure of the current investigation follows that stressed by Gilthorpe et al. [2000b], whereby if the residual variance associated with a particular level does not contribute substantially to the total model variance, then that level is redundant in the multilevel structure. Under these criteria, it can be shown that all levels in the model structures considered are associated with a sufficient proportion of model variance to justify their inclusion in the structures. Hence the method adopted for the analysis of

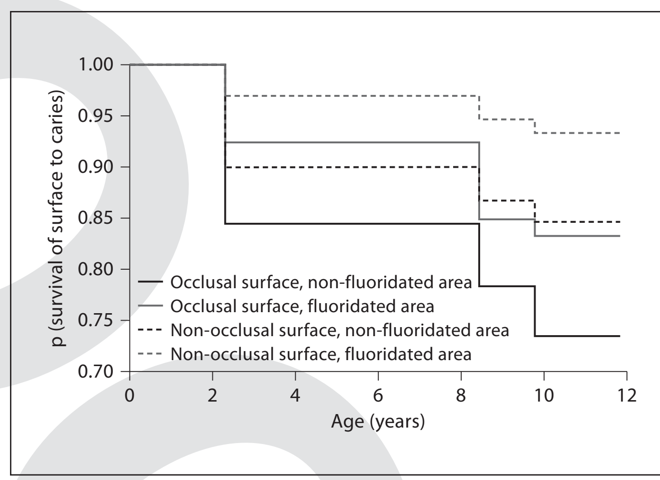

Fig. 4. Survival curve indicating the effect of fluoridation status and surface type class on tooth surface survival to caries.

the current data set appears advantageous over conventional parametric survival-based methods, in which the full hierarchical data structure would not be easily modelled, although for the illustrative data set, the parameter estimates and approximate odds ratios given in table 1 suggest that no changes in inferences of significance would be introduced as a result of amendments to the assumed underlying model hierarchy.

The inferences of significance of main effects and interactions determined using the current hybrid modelling approach may be compared with previous fully parametric survival-based analyses of the same data set [Stephenson et al., 2010a, b]. The findings summarized in table 1 using the current hybrid modelling approach of statistically significant associations between primary caries occurrence and fluoridation status, socio-economic status, gender, tooth type, tooth location and surface type, and the interaction between fluoridation status and surface type, are fully consistent with inferences of parameter significance using the previous fully parametric methods applied to the same data set. All inferences of parameter significance are clinically plausible. Fluoride is well recognised as playing a key role in the prevention and control of dental caries, by enhancing remineralisation through the presence of the fluoride ion in saliva [Kidd and Joyston-Bechal, 1997; Fejerskov, 2004]. A significant association between socio-economic status and primary caries occurrence have also been found in studies of caries data [Jones and Worthington, 1999; Rodrigues and Sheiham, 2000]. A study of caries in the permanent dentition [Hannigan et al., 2001] also noted a statistically significant interaction between fluoride and gender, assigned to girls brushing their teeth more frequently than boys. Burnside et al. [2007] noted that the lower arch has a higher probability of developing caries, due to the greater protective effect of saliva on the maxillary dentition, but other investigators have not found any asymmetry in caries occurrence between the left and right hand sides of the mouth [Burnside et al., 2008; Mejare and Stenlund, 2000]. It is also widely recognised that occlusal surfaces are subject to greater incidences of caries [Fejerskov and Kidd, 2008], and the differential effect of fluoride on occlusal and approximal surfaces has also been well established: an early instance of this finding is given by James et al. [1977]. In the current study the significance of the interaction between fluoridation status and surface indicates that fluoride is less effective in preventing caries on occlusal surfaces.

The consistency of inferences between the hybrid model and the fully parametric treatment suggests that the current hybrid model may be an acceptable alternative to parametric survival analysis in the analysis of cohort study data, avoiding the need for a rigorous treatment of data unlikely to be accessible to dental practitioners and non-specialist statisticians engaged in the analysis of dental data.

The proposed semi-parametric method appears to be conceptually more satisfactory than the logit model for the modelling of caries occurrence in cohort study data. The utilisation of the logistic transformation in a GLM of caries data, as previously identified to be preferred by many authors, is most meaningful under the circumstances that the primary molar tooth surfaces under investigation have reached a static state, i.e. the state of a given tooth surface should not be liable to change at any time after the analysis is completed. For this reason analyses of caries data based on logistic transformation are most often associated with retrospective data from case-control studies or clinical records. However, in the analysis of cohort study data, an outcome recording, say the state of a primary tooth surface (i.e. sound, or carious, filled or missing) at a particular examination may be considered as a response while the study remains in progress or while the tooth surfaces under consideration are still liable to change state. For some surfaces, a state will already have been reached from which no further changes of state are possible (for example surfaces associated with teeth extracted due to caries). In other cases post hoc changes of state are possible, as in the data of the illustrative data set in the current investigation, limiting the extent of the inferences that may be made from logistic regression analyses. Furthermore, logistic regression models cannot easily account for individuals lost to follow-up and are unable to consider the time for which a tooth surface has been in a carious state before being recorded as carious.

The cross-sectional nature of logistic regression models may lead to an analysis which fails to make use of the most updated information in all cases. For example, in the illustrative data set, if the occurrence of caries at the third examination of the cohort study is considered to be the response, inspection of the cohort data recorded at the previous examinations reveals that a certain number of primary molar tooth surfaces had become carious by the second examination. Thus a logistic regression analysis undertaken using this response would not utilise all the available information, as it can be definitively stated that a certain number of primary molar tooth surfaces became carious at an earlier stage than recorded. Conversely, if the incidence of caries at the first examination of the cohort study is considered to be the response, inspection of the cohort data recorded at the previous examinations reveals that a certain number of primary molar tooth surfaces remain sound by the second examination. Again, a logistic regression analysis undertaken using this response would not utilise this updated available information.

Many of the shortcomings of the logistic transformation are overcome with the replacement of this transformation by the CLL as in the proposed approach of the current investigation. While the output of each individual multilevel GLM using the CLL might be expected to be similar to that of a corresponding logistic regression model, in terms of inference of parameter significance or otherwise, utilisation of the CLL allows the interpretation of survival of primary molar teeth and surfaces as a time-dependent process and appropriately accounts for the issue of variation in ages of primary teeth or surfaces under consideration within a single examination. Information from primary molar teeth and surfaces of all children originally enrolled in the cohort study may be utilised, including those lost to follow-up. Although some information relating to the time of an event (e.g. the onset of caries in a primary molar tooth) is lost by the utilisation of the complementary log-log GLM, this effect is not as pronounced as in logistic regression modelling, as it concerns only transitions which occur prior to the point of analysis.

Some limitations of the proposed semi-parametric approach may be identified. Regardless of the transformation utilised, in the GLM approach for the modelling of caries in a particular tooth or surface, only surfaces in which evidence for the present or previous occurrence of caries by the examination of interest is actually observed are counted as positive observations. In the current investigation, some primary molar teeth will have been subject to caries between the second and third examinations, but subsequently exfoliate before the third examination. A small number of molars should also be similarly affected between the first and second examinations. The instance of caries in the surfaces of such teeth would go unrecorded in the cohort study observations. However, assuming that the rate of exfoliation is not significantly affected by caries, this should not result in an under-estimation of the occurrence of caries in the primary dentition, as tooth surfaces which were sound on exfoliation would also not be included in analyses undertaken at times after their exfoliation.

The semi-parametric model does not take into account the interval censoring inherent in the data. However, this cannot be rigorously addressed without specialist software; within the caries literature, treatment of interval censored data is almost universally restricted to consideration of the event at the mid-point of the interval [Hujoel et al., 1994; Beck et al., 1997; Baelum et al., 2003]. There is no particular justification for such assumptions, and it has been observed that this ad hoc approach can lead to biased and misleading results [Lindsey and Ryan, 1998] and that a midpoint approach to interval censored data may lead to invalid inferences [Leroy et al., 2005a]. Armitage et al. [2002] also observed that while the mid-point approach may be valid if the lengths of the interval are short compared with the total length of the study, otherwise a more stringent approach is necessary. This is the case in the illustrative data set and is likely to be the case in the majority of cohort studies of primary caries. It may be inferred that neither a rigorous treatment of interval censoring involving specialist software nor the approximate approach favoured by some of the authors above is appropriate in a model which aims to offer a rigorous but more accessible alternative to commonly used methods.

The illustrative data set considered data from primary molar tooth surfaces only. In the cohort study, the rate of primary caries occurrence in molars was about two orders of magnitude greater than the corresponding rate in incisors and canine teeth. Numerous epidemiological surveys and common clinical experience have repeatedly shown that molar teeth are the most vulnerable sites for dental caries [Kidd and Joyston-Bechal, 1997; Fejerskov and Kidd, 2008], and therefore the omission of incisors and canine teeth from analysis does not amount to a significant loss of information and may also take advantage of the homogeneity or near-homogeneity of the population in terms of caries type and tooth age upon eruption and exfoliation.

In conclusion, whilst ideally a fully parametric survival-based approach is probably to be preferred for the analysis of caries data, the practicalities of combining such an approach with an appropriate treatment of the data hierarchy, and selection of an optimum survival distribution, may be beyond the means of many researchers. The proposed hybrid semi-parametric modelling approach to the analysis of caries data within specific time periods allows for a more rigorous treatment of data than available non-parametric methods, accounts for both the natural underlying data hierarchy and the time-dependent nature of the caries process, and has been shown using an illustrative data set to lead to inferences of parameter significance which are consistent with those obtained from fully parametric survival modelling. The utilisation of the CLL rather than the logistic transformation removes the requirement of parametric survival modelling to specify a potentially restrictive functional form of the hazard function and is shown to be meaningful in an analysis in which the time dependence of the caries process is to be stressed. Hence the semi-parametric modelling approach to the analysis of caries data combines the predictive capability of parametric survival methods with the general familiarity of non-parametric survival methods and the more accessible hierarchical modelling facility of GLM methods.

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Disclosure Statement

The author has no conflicts of interest to declare.

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