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Prenatal smoking and the risk of early childhood caries: A prospective cohort study

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ABSTRACT

Introduction: Dental caries is a chronic complex disease of multifactorial etiology that affects a quarter of U.S. children. This study evaluated the association between prenatal smoking and offspring caries experience and used a negative control exposure analysis to assess if the association is causal.

Methods: Data from 1429 mother-offspring participants of the 1991/92 Avon Longitudinal Study of Parents and Children conducted in Bristol, England were analyzed. Prenatal smoking (yes v. no) and quantity smoked (none, < half pack, ≥half pack) were self-reported while offspring caries experience was determined by clinical oral examinations at 3 time points. Discrete time hazards regression estimated hazard odds of first occurrence of offspring caries, and substituted partner smoking for prenatal smoking in a negative control exposure analysis.

Results: Overall, 22% smoked during pregnancy while 36% of partners smoked. The adjusted hazard odds of first occurrence of caries experience in the offsprings of prenatal smokers compared to the offsprings of non-smokers was 1.42 (95% CI: 1.08, 1.86). Relative to non-smoking, smoking < half pack/day and ≥half pack/day during pregnancy were associated with higher adjusted hazard odds of offspring caries experience: 1.10 (95% CI: 0.79, 1.54) and 1.38 (0.98, 1.95) respectively. Partner smoking was associated with 33% (95% CI: 1.07, 1.65) higher adjusted hazard odds of first offspring caries experience occurrence.

Conclusions: Prenatal and partner smoking appear associated with greater offspring caries experience. The positive association with partner smoking suggests either a shared genetic predisposition or unmeasured common environmental factors with the mother as opposed to a direct biological effect of the intrauterine environment.

Implications

This is the first study to investigate if the relationship between prenatal smoking and offspring caries is causal by utilizing a negative control exposure method.

The negative impacts of prenatal smoking on offspring caries experience is not limited to factors going on in the intrauterine environment, the role of shared genetics with the partner is also likely at play.

1. Introduction

Dental caries is a chronic complex disease of multifactorial etiology (Chapple et al., 2017) that affects about a quarter of U.S. children (Dye et al., 2015). Widely accepted risk factors are a susceptible tooth, fermentable carbohydrates and caries bacteria. Given its multifactorial etiology and chronic complex nature, the etiology of dental caries comprises certain upstream risk factors —including prenatal exposures— that promote a favorable oral environment for caries susceptibility, development and progression. One such exposure is maternal smoking during pregnancy (prenatal smoking).

The United States is one of 10 countries comprising 2/3rds of all smokers worldwide (World Health Organization, 2013). While prenatal smoking rates continue to decline (Tong et al., 2013), a 2010 U.S. data from the World Health Organization suggests that 13.6% of women in

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obstetrics care smoke, with differences according to race/ethnicity and socio-economic position (Samet et al., 2010). More recent data based on the 2014 U.S. birth certificate records representing 95% of all births that year indicate that 8.4% of women smoked at any time during their pregnancy, with differences seen according to race/ethnicity and geographic location (Curtin and Matthews, 2016).

Maternal smoking during pregnancy alters fetal blood flow and protein metabolism (Zhou et al., 2014) and exposes the growing fetus to chemical toxins like nicotine through its direct metabolite (cotinine), known to cross the placenta and accumulate in fetal tissues (Maritz, 2008). Indeed, prenatal smoking is consistently reported to have negative effects on the health of the offspring. Among these are respiratory illnesses (Jurado et al., 2005; Metsala et al., 2008), cleft lip and palate (Chung et al., 2000), attention deficit hyperactivity disorders (Dong et al., 2018) as well as elevated systolic BP (Cabral et al., 2017).

Evidence linking prenatal smoking to offspring caries experience is sparse and methodologically inadequate (Williams et al., 2000; Claudia et al., 2016; Tanaka et al., 2015a, 2009b, 2015c; Majorana et al., 2014; Iida et al., 2007; Schroth et al., 2013). In a study of 1576 women, the association between prenatal smoking and offspring dental caries was derived from multivariable adjusted models where prenatal smoking was not the main exposure variable (Iida et al., 2007). Therefore, findings may have been biased by adjusting for variables that are not confounders. In another study, reliance only on mothers self-reported offspring decay (Claudia et al., 2016) is subject to recall bias especially for teeth missing for reasons (like trauma) other than dental decay and for sealants accidentally recalled as dental restorations. For other studies, the emphasis was on post-natal exposure of the child to environmental tobacco smoke (ETS) in the home (Williams et al., 2000; Tanaka et al., 2015; Hanioka et al., 2011) and thus does not capture exposures occurring prenatally. Among studies that specifically investigated prenatal smoking, smoking during pregnancy had to be recalled several years after the pregnancy (Claudia et al., 2016; Tanaka et al., 2015a, 2009b, 2015c; Majorana et al., 2014), and therefore also subject to under/mis-reporting and recall bias. Although a systematic review of cross-sectional studies of prenatal smoking and offspring caries was recently conducted, its findings were inconclusive and called for well-designed longitudinal studies (Kellesarian et al., 2017).

The aims of this study were two-fold: 1) to assess whether prenatal smoking and the quantity of cigarettes smoked during pregnancy were associated with offspring dental caries experience; 2) using a negative control exposure method to assess the potential causal nature of the prenatal smoking-offspring caries experience by substituting maternal smoking for partner smoking during pregnancy.

2. Methods

2.1. Data source and study population

The Avon Longitudinal Study of Parents and Children (ALSPAC), is a population based prospective cohort study aimed at investigating environmental, genetic and other factors on the health and development of children. Pregnant women living in three health districts in Bristol, England with an expected date of delivery between April 1991 and December 1992 were eligible. Of 14,541 pregnancies enrolled, 13,761 mothers with singleton live births participated in the study (Golding et al., 2001; Fraser et al., 2013). Of those recruited at baseline, 63% completed study questionnaires. Response rates were 89%, 75% and 69% at 2, 3, and 5 years respectively.

A random 10% sample of children born in the last 6 months (June–December 1992) of the study were invited to participate in a sub-study called the "children-in-focus" (CIF) study. The CIF sub-study allowed for an extensive examination (including oral health assessments) of the children in a way that could not be accomplished using questionnaires (Golding et al., 2001; Fraser et al., 2013). The CIF attended research clinics at approximate 6-month intervals during the first 5 years of life and at 31, 43 and 61 months of age underwent dental examinations conducted by dentists and health examiners (Golding et al., 2001; Kay et al., 2010). Training for the health examiners were done in six tutorial sessions totaling 16 h of training, accompanied by an hour-long session of mock examination and replication on 30 children. Reported kappa statistics for these health examiners was 0.63.

The current study was restricted to the CIF subsample because of available data on objectively assessed dental caries status and data on prenatal smoking collected contemporaneously during pregnancy. Informed consent at the time of data collected followed the recommendations of the ALSPAC Ethics and Law Committee. The current study was approved by the Institutional Review Board of Virginia Commonwealth University as exempt (#: HM20011742) and our reporting adhered to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

2.2. Exposure assessment and definition

2.2.1. Maternal smoking and quantity smoked during pregnancy

Smoking during pregnancy was reported on maternal-specific questionnaires mailed during the course of pregnancy. For this investigation, we defined prenatal smoking as binary (yes/no). The number of cigarettes smoked per day during pregnancy was pre-categorized into 0, 1–4, 5–9, 10–14, 15–19, 20–24, 25–29 and ≥30. To estimate the total number smoked, we assigned the mean of the grouped counts as the number smoked/day during pregnancy. For instance, a value of 2.5 was assigned to the 1–4 cigarettes group, a value of 7 to the 5–9 group etc. We subsequently categorized this into none, < half pack (< 10 cigarettes) and ≥half pack (≥10 cigarettes) for dose–response assessment.

2.3. Outcome assessment and definition

2.3.1. Dental caries in the offspring

Using the World Health Organization criteria (Kay et al., 2010; Organization, 2013), the number of decayed, missing and filled teeth (dmft) were assessed for caries experience at 31 mo., 43 mo. and 5 years old. Given the irreversible nature of cavitated carious lesions, we carried forward dmft values ≥ 1 among children with dmft > 0 at an earlier time period (for instance at 43 mo.) but missing or scored as zero at a later time period (for instance at 5 years old), only if missingness was not due to non-attendance of clinic visit. For this study, we analyzed caries experience as dmft ≥ 1 (yes vs. no) and as total dmft count. Given that caries experience is cumulative, we assigned total dmft count as the maximum of the recorded number of dmft at 31 mo., 43 mo., and 5 years old.

2.4. Covariates

Maternal-specific factors: were self-reported or abstracted from the medical records, (Fraser et al., 2013) and included maternal age at birth- modeled as continuous; education (≤O-level, A-level, and college degree); maternal race (white vs. non-white); breastfeeding duration (never, < 6 months, ≥6 months).

Child-specific factors: were based on maternal reports on mailed-in child-specific questionnaires or determined during clinical evaluation of the CIF sample (Golding et al., 2001; Boyd et al., 2013). They include: child gender (male, female); perinatal and childhood illness (chicken pox, measles, or rubella); frequency of daily tooth brushing (< 2 times daily vs. ≥2 times daily); fluoride supplement use (yes vs. no); dental visit within the past year (yes vs. no). Mothers of the CIF subsample kept a 3-day food diary for their children, which the parent ALSPAC study used to estimate total daily intake of sugars, carbohydrates, and several vitamins like C, D, E. Child dietary data is available at multiple time points and this study considered total sugar intake at 18, 43 and 61 months. The child-specific factors outlined above were

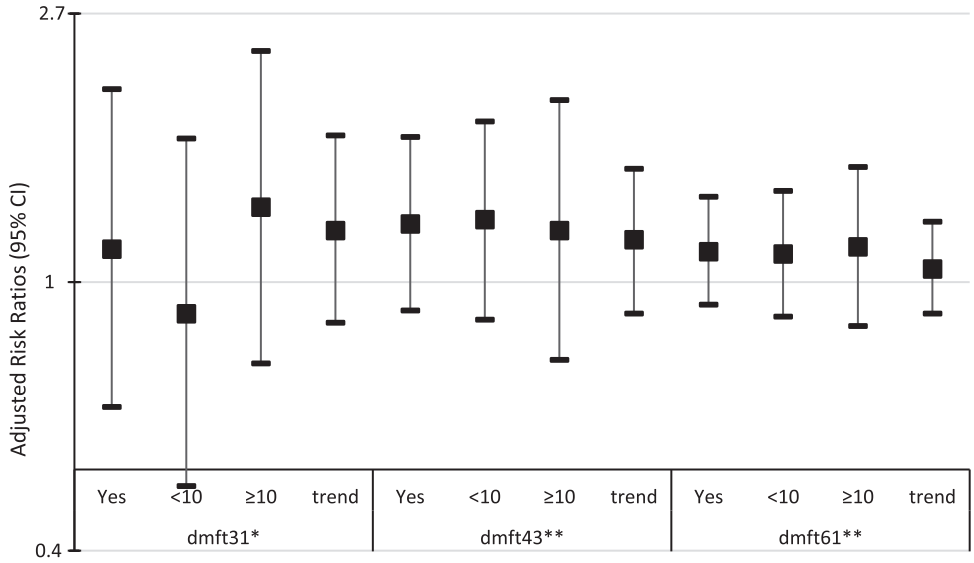

Fig. 1. Adjusted associations between prenatal smoking and quantity smoked with the 31, 43 and 61-month risk of and offspring caries experience: Avon Longitudinal Study of Parents and Children.

considered risk factors for caries experience during data analysis as opposed to confounders because none of them preceded the exposure of prenatal smoking.

The ALSPAC website contains details of all available data through a fully searchable data dictionary and variable search tool that can be accessed at: http://www.bristol.ac.uk/alspac/researchers/our-data/.

2.5. Statistical analysis

Data analysis was restricted to singleton births who were alive at age 1 year. Descriptive analysis began with an exploration of the distribution of selected covariates for the children-in-focus sample and children not selected for this subsample to assess if there were any meaningful differences between them. Means and SDs were reported for continuous variables while frequencies and relative frequencies were reported for categorical variables. Covariates included as confounders and outcome (offspring caries experience) risk factors were determined after analyzing a directed acyclic graph (Greenland et al., 1999; Akinkugbe et al., 2016) – Appendix B; Fig. 1. Regression analyses of the potential association between prenatal smoking and offspring caries experience were modeled in three ways: 1) we utilized log-binomial regression models to estimate the 31-month, 43-month and 5-year risks of objectively determined offspring dental caries experience (i.e. dmft $\geq$ 1) and the corresponding risk ratios (RR) and 95% confidence intervals (C.I); 2) we used a discrete time hazards regression (Richardson, 2010)) to estimate the hazard odds ratio (HOR) and 95% C.I. of first caries experience occurrence (see Appendix A for more detail); 3) we used a zero-inflated negative binomial (ZINB) regression (Preisser et al., 2012, 2016) to estimate the prenatal smoking association on total dmft count and evaluated the fit of the ZINB model using the Vuong's test (see Appendix A for more detail). We assessed likely dose–response association according to number of cigarettes smoked per day (none, < half pack, ≥half pack) during pregnancy with offspring caries experience for the methods of analyses previously described.

2.6. Assessment of effect measure modification

Given previously reported differences in tooth eruption times by gender, (Ntani et al., 2015; Bastos et al., 2007; Lukacs and Largaespada, 2006) and those suggesting that prenatal smoking promotes early tooth eruption (Ntani et al., 2015) and thus, a precursor for caries experience (Law and Seow, 2006; Caufield et al., 2012) we assessed likely effect measure modification (EMM) between prenatal smoking and offspring caries experience according to child gender. We accomplished this by including product interaction terms between prenatal smoking and child gender to assess if the joint effects on offspring decay are multiplicative. Statistically significant interaction was set apriori at $p < 0.1$ and we found no significant EMM between prenatal smoking and child gender hence, gender stratified results were not presented.

2.7. Sensitivity analysis

2.7.1. Negative control exposure analysis

Utilizing negative controls is an approach for drawing causal inference from studies of epidemiologic birth cohorts (Richmond et al., 2014). A negative control exposure is an exposure that does not involve the same causal mechanism as the exposure of interest but likely share similar social factors and sources of bias (Richmond et al., 2014; Smith, 2008) (see Appendix A for more detail).

For this study, we substituted self-reported partner smoking in the home during the 18th week of gestation for prenatal smoking to assess if any association is purely environmental and/or due to shared genetics (in which case the associations will be similar) or mostly due to intrauterine factors in which case, maternal smoking will show an independent association with offspring caries. If the effect of prenatal smoking on offspring caries is a direct biologic effect of intrauterine factors, then the association is expected to be much stronger for maternal than for paternal smoking.

2.8. Multiple imputation

Multiple imputation was performed for missing data using chained equations (White et al., 2011). We imputed the following variables with missing observations: the number of decayed, missing and filled teeth at 31, 43 and 61 months; mean sugar intake at 18, 43 and 61 months. We also imputed other covariates with missing observations, and the exposures (prenatal smoking and quantity smoked). Refer to Appendix C; Table 1 for the proportion of missing covariates that were imputed. A total of 50 datasets were imputed using 500 between imputation iterations. Trace plots (Appendix B; Fig. 3) assessed how the imputation algorithm performed, while kernel density plots (Appendix B; Fig. 4) assessed deviation of imputed values from observed. Multiple imputation was done using the PROC MI and MIANALYZE procedures in SAS

Table 1
Distribution of selected covariates between children selected and those not selected for the Children-in-focus (CIF) sub-study: Avon Longitudinal Study of Parents and Children.

	CIF sample (n = 1429)	Not in CIF sample (n = 13,449)
Maternal characteristics		
Prenatal Smoking	305 (22)	3300 (30)
missing	51	2562
Age at delivery, mean (IQR)	29 (26, 32)	28 (25, 31)
Age at delivery (yrs.)		
15–24	240 (17)	3098 (25)
25–35	1072 (75)	8588 (69)
36–44	116 (8)	851 (7)
Missing	1	912
Education		
O-level or less	819 (60)	7201 (65)
A-level	344 (25)	2443 (22)
College degree	199 (15)	1400 (13)
Missing	67	2405
Race		
White	1333 (98)	10,662 (97)
Non-white	31 (2)	292 (3)
Missing	64	2495
Child characteristics		
Gender		
Male	772 (54)	6828 (51)
Female	657 (46)	6621 (49)
Race		
White	1293 (96)	10,169 (95)
Non-white	47 (4)	562 (5)
Missing	89	2718

CIF – Children in Focus.

that assumes data are missing at random (MAR). The results from each imputed dataset were summarized using Rubin's rule (Rubin, 1987) into an overall estimate to account for both within and between imputation variances. All analyses were conducted in SAS v.9.4 (SAS Institute, Cary NC).

3. Results

Table 1 shows the distribution of selected covariates for the CIF sample and children not selected for the CIF sub-study. Mothers of the CIF sample were on average older, more likely to be aged between 25 and 35 years and to have advanced education as compared to mothers of children not selected for the CIF sample.

Overall, 22% percent of the mothers smoked during pregnancy, 14% smoked < half pack/day and 7.9% smoked ≥half pack/day during pregnancy. Three percent of the children had dmft ≥ 1 at 31 months, 16% and 31% at 43 months and 61 months respectively. The average time under study was 55 months for children of mothers who reported smoking during pregnancy and 57 months for children of mothers who did not smoke during pregnancy. Thirty-three percent of the children of non-smoking mothers developed caries at some point during follow-up with a mean dmft count of 0.33 as compared to 46% of children whose mothers smoked during pregnancy with a mean dmft count of 1.58 (Table 2).

Offspring caries experience risk in the prenatal smoking group was 4%, 21% and 38% at 31, 43 and 61 months respectively (Table 3). Further, prenatal smoking was associated with 41% increased risk of offspring caries (95% CI: 1.03, 1.91) at 43 months and a 30% (95% CI: 1.08, 1.58) increased risk at 61 months as compared to the risk in non-smoking mothers. Upon covariate adjustment, prenatal smoking retained its positive association with offspring caries experience, however, the magnitudes of the associations were smaller and less precisely

Table 2
Mean time under study, caries experience proportion and losses to follow-up according to prenatal smoking status and quantity smoked during pregnancy, ALSPAC study (n = 1429).

	Prenatal smoking		Quantity smoked/day	
	No	Yes	1–9	≥10
	1,114 (78%)	315 (22%)	202 (14%)	113 (8%)
Mean time under study (months)	56.7	55.0	54.7	55.9
Caries experience (% with dmft ≥ 1)	32.9%	45.7%	43.4%	49.8%
Mean dmft count	0.332	1.577	1.370	1.959
Losses to follow-up	33.2%	49.1%	46.8%	53.3%

Estimates presented in this table are averages from 50 rounds of multiple imputation, combined using the Rubins rule.
dmft-number of decayed, missing and filled teeth.

estimated (Fig. 1).

The adjusted hazard odds of first occurrence of offspring caries for prenatal smoking in contrast with no prenatal smoking was 1.42 (95% CI: 1.08, 1.86). Similarly, there appeared to be a dose–response increase in the hazard odds of caries experience according to the quantity of cigarettes smoked per day during pregnancy. Compared to children of non-smoking mothers, children whose mothers smoked < half pack/day were 10% more likely to experience caries while children of mothers who smoked ≥half pack/day were 38% (95% CI: 0.98, 1.95) more likely to experience caries (Table 4). Each additional half pack of cigarettes smoked per day increased the hazard odds of first offspring caries experience occurrence by 34% (95% CI: 1.05, 1.71). Findings from the ZINB model were consistent with increased caries experience according to prenatal smoking status as well as a dose–response association with quantity smoked (Appendix C; Table 2). Furthermore, the latent or logistic part (see Appendix A) of the ZINB model was consistent with an inverse association between prenatal smoking and offspring caries. In other words, prenatal smoking was associated with having fewer zeros (i.e. no caries experience) while the non-smoking group had more zeros. Results of complete case analysis (i.e. data analysis without imputation) were consistent in magnitude and direction as the analysis with imputed observations (Appendix D; Tables 1–3).

3.1. Negative control exposure sensitivity analysis

Partner smoking was associated with unadjusted and adjusted risk of offspring caries experience at 43 months of 1.39 (95% CI: 1.06, 1.82) and 1.24 (95% CI: 0.93, 1.65) respectively and 1.29 (95% CI: 1.07, 1.55) and 1.14 (95% CI: 0.95, 1.38) at 61 months respectively (Table 5).

The corresponding estimates for prenatal smoking were respectively, 1.41 (95% CI: 1.03, 1.91) and 1.24 (95% CI: 0.90, 1.71) at 43 months and 1.30 (95% CI: 1.08, 1.58) and 1.12 (95% CI: 0.92, 137) at 61 months. This was also the case for the hazard odds ratios, but the magnitude was slightly diminished for partner smoking when compared to maternal smoking (Table 4).

4. Discussion

In this prospective cohort study, both maternal- and partner-smoking during pregnancy were associated with slightly increased risk of dental caries developing in the offspring. Further, we found a positive dose–response association with the quantity of cigarettes smoked per day during pregnancy with respect to offspring caries experience.

Although we were unable to assess tooth eruption patterns in this study, Ntani and colleagues (Ntani et al., 2015) reported that children

Table 3
Risks and relative risks of the association between prenatal smoking and offspring caries experience: Avon Longitudinal Study of Parents and Children (N = 1429).

	Total N	31 months			43 months			61 months		
		N cases	Risk*	Unadjusted RR (95% CI)*	N cases	Risk*	Unadjusted RR (95% CI)***	N cases	Risk*	Unadjusted RR (95% CI)***
Prenatal smoking										
No	1114	31	0.028	Ref.	166	0.149	Ref.	320	0.287	Ref.
Yes	315	13	0.040	1.38 (0.61, 3.10)	66	0.209	1.41 (1.03, 1.91)	118	0.375	1.30 (1.08, 1.58)
Quantity smoked										
None	1114	32	0.028	Ref.	166	0.148	Ref.	320	0.287	Ref.
< 10	202	5	0.026	0.87 (0.26, 2.87)	41	0.203	1.36 (0.96, 1.94)	71	0.353	1.23 (0.97, 1.55)
≥10	113	7	0.065	2.21 (0.79, 6.19)	25	0.221	1.47 (0.93, 2.33)	47	0.415	1.44 (1.09, 1.91)
Trend estimate				1.80 (1.04, 3.10)			1.30 (1.02, 1.67)			1.20 (1.03, 1.40)

*unadjusted risks of decayed, missing and filled teeth (dmft) ≥1 at the respective time periods.
Trend estimate is for each additional 10 cigarettes smoked during pregnancy.
All estimates were averages from 50 rounds of multiple imputation combined using Rubin's rule and the variance a function of the within and between completed dataset variances.

Table 4
Unadjusted and adjusted rates of first occurrence of offspring caries experience over the study period: Avon Longitudinal Study of Parents and Children (n = 1429).

	Hazard OR (95% C.I.)*	Hazard OR (95% C.I.)**
Prenatal smoking		
No	Ref.	Ref.
yes	1.62 (1.27, 2.07)	1.42 (1.08, 1.86)
Quantity smoked		
None	Ref.	Ref.
1–9	1.10 (0.79, 1.53)	1.10 (0.79, 1.54)
≥10	1.64 (1.19, 2.27)	1.38 (0.98, 1.95)
Trend estimate	1.52 (1.21, 1.90)	1.34 (1.05, 1.71)
Partner smoking		
No	Ref.	Ref.
Yes	1.50 (1.22, 1.85)	1.33 (1.07, 1.65)

*Unadjusted.
**Adjusted.
Trend estimate is for each additional 10 cigarettes smoked per day.
Discrete time hazards regression.
All estimates were averages from 50 rounds of multiple imputation combine using Rubin's rule and the variance a function of the within and between completed dataset variances.
* Adjusted for breastfeeding status (never < 6, ≥6months); maternal age at birth; maternal education; maternal race; child gender; and sugar intake at 18 months.
** Adjusted for breastfeeding status (never < 6, ≥6months); maternal age at birth; maternal education; maternal race; child gender; history of childhood illness (chicken pox, measles, or rubella); brushing frequency at 38 or 54 months; dental visit at 38 or 54 months and sugar intake at 43 or 61 months. Partner smoking during the 18th week of gestation adjusts for the same variables as prenatal smoking as well as whether the partner is the child's biological father.

whose mothers smoked during pregnancy had more teeth erupted at ages 1 and 2 years compared to similarly aged children whose mothers did not smoke. This suggests that prematurely erupted teeth are likely more susceptible to *Mutan Streptococci* (caries bacteria) colonization (Law and Seow, 2006; Caufield et al., 2012) by way of exposure to frequent infant feedings and the corresponding oral environment longer than teeth that are not prematurely erupted and by extension, more opportunity for caries development. Other studies indicate that prenatal smoking (Jaddoe et al., 2008) is associated with low-birth weight and prematurity, conditions reported to increase the risk for developmental enamel defects (Caufield et al., 2012; Vello et al., 2010), that are highly susceptible to cariogenic bacteria (Plonka et al., 2013; Salanitri and Seow, 2013) in the presence of fermentable carbohydrates (Caufield et al., 2012).

The positive prenatal smoking association on offspring caries experience we observed at a younger age persisted to older ages and suggest that exposures in-utero may have detrimental oral health effects later in the life of the child. This is surprising given the expectation that caries when the child is older may be largely dependent on several factors including the child's oral hygiene habits as opposed to prenatal exposures. Nevertheless, the association in older children that we reported persisted even after adjusting for dental visit, sugar intake, fluoride supplement use and frequency of daily tooth brushing.

The magnitude of the estimates we reported for prenatal and partner smoking were dependent on the regression models we used. In our log-binomial regression estimating risk ratios and 95% C.I., the estimated risk ratios for partner smoking was of similar or of slightly higher magnitude than maternal smoking, while in the discrete time hazard regression, we found a higher magnitude for maternal smoking than for partner smoking. Nevertheless, our findings suggest that the association between prenatal smoking and offspring caries experience is not limited to events occurring in-utero. Indeed, the role of shared genetics with the partner and potential residual confounding by shared environmental factors are likely also at play.

4.1. Implications for clinical practice and public health

Cigarette smoking in women of reproductive age is becoming increasingly concentrated among the young, socioeconomically disadvantaged and those with lower educational attainment (Higgins et al., 2009; Kandel et al., 2009). This is especially concerning given the consequent adverse health risks to the mother and child if these women go on to have unplanned pregnancies. Health care providers, members of allied health professions, and community health workers must be involved as partners to improve a mother's knowledge and understanding of smoking's impacts on her pregnancy and child's oral health outcomes. A national consensus statement of the maternal and child oral health resource center (Workgroup, 2012) recommends that in addition to eliciting medical and dental histories, health professionals should review tobacco, alcohol, and recreational drug use patterns and provide patient centered resources and actions steps to mitigate these substance use behaviors. Recent data on tobacco use prevalence in a national sample of pregnant U.S. women suggest that cigarette use is not only problematic, use of non-cigarette tobacco products like e-cigarettes, and hookahs are also prevalent and should be included in routine clinical screening for tobacco use (Kurti et al., 2017). Indeed, more tobacco control and regulatory efforts to increase health care provider awareness and promote more consistent messaging on the prevalence and risks of cigarettes and other non-cigarette tobacco products use during pregnancy is important. These tobacco control and regulatory efforts should extend beyond pregnant to women of

Table 5
Negative control exposure analysis of the association between partner smoking and offspring caries experience: Avon Longitudinal Study of Parents and Children (=1429).

Partner smoking	Total N	Dmft31			Dmft43			Dmft61		
		N Cases	Unadjusted	Adjusted*	N Cases	Unadjusted	Adjusted**	N Cases	Unadjusted	Adjusted**
			RR (95% CI)			RR (95% CI)			RR (95% CI)	
No	911	24	Ref.	Ref.	129	Ref.	Ref.	253	Ref.	Ref.
Yes	517	20	1.46 (0.73, 2.93)	1.19 (0.71, 2.01)	102	1.39 (1.06, 1.82)	1.24 (0.93, 1.65)	185	1.29 (1.07, 1.55)	1.14 (0.95, 1.38)

All estimates were averages from 50 rounds of multiple imputation combined using Rubin's rule and the variance a function of the within and between completed dataset variances.
* Adjusted for breastfeeding status (never < 6, ≥6months); maternal age at birth; maternal education; maternal race; child gender; sugar intake at 18 months and whether partner is the biologic father.
** Adjusted for breastfeeding status (never < 6, ≥6months); maternal age at birth; maternal education; maternal race; child gender; history of childhood illness (chicken pox, measles, or rubella); brushing frequency at 38 or 54 months; dental visit at 38 or 54 months; sugar intake at 43 or 61 months and whether partner is the biologic father.

reproductive age.

4.2. Strengths and limitations

Data on prenatal smoking while collected during pregnancy was self-reported and may be subject to incomplete or under-reporting. Oral examination data was available only on a fraction of the children and the methodology used (i.e. dmft index) measured cavitated lesions. This is in contrast to contemporary methods like the international caries detection and assessment system (ICDAS) that records dental caries on a continuum that includes incipient lesions. In spite of this, the underlying biologic mechanism for the proposed association is undated and applicable even today. The non-diverse study population may limit statistical inference to other population subgroups but not necessarily the scientific inference of our findings (Rothman et al., 2013). While the prevalence of prenatal smoking (22%) in the ALSPAC cohort (Macdonald-Wallis et al., 2011) was higher than contemporary U.S. benchmarks of 9–14%, (Kurti et al., 2017; Berlin and Oncken, 2018) 25% of 5 year-olds in the ALSPAC study experienced caries, (Kay et al., 2010) as have similarly aged contemporary U.S. children (Dye et al., 2015). Our definition of smoking during pregnancy was time invariant and ignores the fact that smoking during pregnancy may be more harmful when used at certain points in pregnancy than others. Future studies should consider smoking during pregnancy and whether trimester of pregnancy smoking occurred is associated with differing offspring caries experience risk. Arbitrarily assigning the grouped average as the number of cigarettes smoked per day could have underestimated or overestimated the actual number smoked per day for those who smoked less or more than the average assigned respectively.

Study strengths include the longitudinal nature and the ability to minimize temporal ambiguity. Availability of contemporaneously collected prenatal smoking information is an added strength because this information is unbiased by parental knowledge of any conditions the child might develop. Furthermore, the availability of objectively assessed oral examination data at three time points represents another of this study's strengths. Lastly, the relatively large study sample and availability of covariate information on the mother and child allowed for a control of relevant confounding factors as well as outcome risk factors.

CRediT authorship contribution statement

Aderonke A. Akinkugbe: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Funding acquisition. **Tegwyn H. Brickhouse:** Conceptualization, Writing - review & editing, Funding acquisition. **Marcelle M. Nascimento:** Methodology, Writing - review & editing. **Gary D. Slade:** Formal analysis, Writing - review & editing.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2020.101201.

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