6 母子のライフサイクルを見据えた健康状況の把握

妊娠期からの児童虐待防止対策は、「健やか親子２１（第２次）」の重点課題である。特定妊婦や要支援家庭への妊娠期からの支援には保健・福祉・医療等関係機関の連携が求められている。産前・産後サポート事業、産後ケア事業や利用者支援事業（母子保健型）による子育て世代包括支援センターの整備などの事業[22]が始まっている。しかしこうした妊娠期からの支援事業の評価は十分ではない。愛知県では、妊娠届出書の項目を統一し、ハイリスク妊婦を早期に把握し支援につなげる試みが実施されている。モデル地域の自治体において実施した調査において、妊娠届出時から３～４か月児健診までに転出したケースが10％を超えて存在することが明らかとなった（表４）。対象地域の住民全体の転出者の割合[3]*が平均3.6％であることから、その比率は相当に高い。かつ妊娠届出時のスクリーニング点数からリスクの高いグループは22.2％と高い頻度で転居を認めていた[23]。妊娠期からの支援においては、市町村間の即時性のある情報共有が不可欠と言える。

表４ 妊娠届出書によるスクリーニング点数と転出ケースの状況

スクリーニング点数	３～４か月健診					対象外（流産等）	計
	受診	未受診	対象外（転出）				
			転出（妊娠中に）	転出（出産後に）	転出計（再掲）		
３点未満	178	1	13	5	18	8	205
	86.8%	0.5%	6.3%	2.4%	8.8%	3.9%	100.0%
３点以上	35		8	2	10		45
	77.8%		17.8%	4.4%	22.2%		100.0%
計	213	1	21	7	28	8	250
	85.2%	0.4%	8.4%	2.8%	11.2%	3.2%	100.0%

対象：モデル自治体５市において平成25年８月～９月に妊娠届出書を受理したケースのうち、各市連続50件ずつ計250件。

乳幼児健診は、地域の健康状況を把握する重要な機会であるが、妊婦健診や医療機関で実施される産婦健診や新生児期の健診、１か月児健診にも同様の意義を見出すことが可能である。沖縄県ではすでに妊婦健診と乳幼児健診の個別データを連結[24]し、妊婦の生活習慣や健康状況が児の体格に与える影響などが分析されている[25]。今後、乳幼児健診と同様に把握率の高い学校健診とのデータ結合やさらに思春期の健康課題を妊婦健診と連携させるなど、それぞれの健診情報を共有化することで母子のライフサイクルを見据えた地域の健康状況の把握が可能となる（図５）。すべての子どもが健やかに育つ社会を構築するためには、「健やか親子２１（第２次）」のみならず、少子化対策や貧困対策なども含めた地方自治体の事業を経年的に評価する情報の利活用が必要と考えられる。

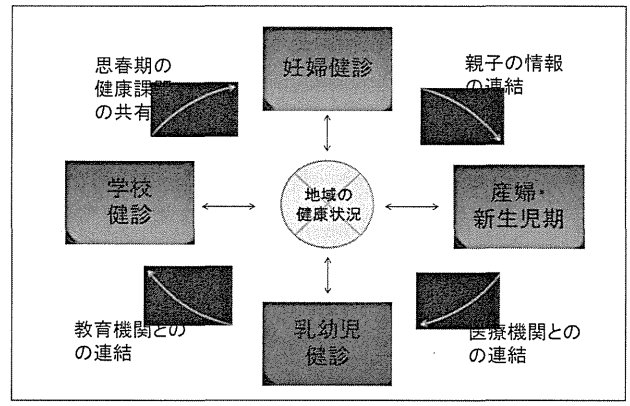

図５ 母子のライフサイクルを見据えた健康状況の把握

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１＊ 市町村：「健やか親子２１（第２次）」の指標名は「市区町村」であるが、本稿では「市町村」で表記する。

２＊ 検診：特定の病気に対する早期発見・早期治療を目的とする「検診」と、健康診査の略である「健診」とを区別して記述する。

３＊ 市町村別の「転出者数」を「人口総数」で除したもの、出典：社会・人口統計体系の市区町村データ（総務省統計局：統計でみる市区町村の姿 2014, http://www.e-stat.go.jp/SG1/estat/List.do?bid=000001053740&cycode=0）

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RESEARCH ARTICLE

Macrosomic Neonates Carry Increased Risk of Dental Caries in Early Childhood: Findings from a Cohort Study, the Okinawa Child Health Study, Japan

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Abstract

Background

Although many studies have discussed health risks in neonates with a low birth weight, few studies have focused on the risks in neonates with a high birth weight. The objective of this study was to determine whether differences in the incidence of dental caries in early childhood are associated with birth weight status.

Methods

A total of 117,175 children born in Okinawa Prefecture, Japan from 1997 to 2007 were included in this study. Medical professionals collected information about birth records, growth and development, parental child-rearing practices and dental health at 3 months, 18 months and 3 years of age. The risk of dental caries among neonates with macrosomia (birth weight $\geq$4000 g) was compared with that among neonates with normal weight (2500–3999 g). Sensitivity analyses included 'large for gestational age' (LGA, birth weight above the 90th percentile for gestational age), which was relative to 'appropriate for gestational age' (birth weight between 10th and 90th percentiles). Relative risks and relative risk increases were estimated by multivariate Poisson regression.

Results

At 3 years of age, the relative risk increases for dental caries after adjusting for confounding factors were 19% [95% confidence interval (CI), 11%–28%, P < 0.001] for macrosomic neonates and 12% (95% CI, 9%–16%, P < 0.001) for LGA neonates.

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Competing Interests: The authors have declared that no competing interests exist.

Conclusion

Macrosomia and LGA were associated with an increased risk of dental caries in early childhood. Particular attention should be paid to abnormally large neonates.

Introduction

Difficulties experienced during pregnancy and childbirth form the subject of on-going clinical and basic research worldwide. Children born to obese mothers exhibit increased rates of childhood obesity and subsequent paediatric lifestyle-related diseases;[1, 2] furthermore, a controlled maternal weight at birth reduces the risk of adulthood obesity.[3–6] Although numerous available studies have evaluated low birth weight as a risk factor for growth retardation, metabolic syndrome,[7] early puberty and attention-deficit hyperactive disorder (ADHD),[8] few have report the risks associated with macrosomia. Moreover, macrosomic infants are not carefully monitored.

The potential risk factors and preventive factors associated with paediatric dental caries include hypoplastic enamel,[9] early dental eruption, dental hygiene (brushing the teeth by parents, fluoridated water [10]), excess consumption of sweets,[11] prolonged breastfeeding, [12] prolonged nursing with a bottle,[13] irregular consumption of meals and snacks,[14] insufficient dietary calcium in both the mother and child, low parental socioeconomic status, [15] parental smoking[16, 17] and support for child rearing.[18] Although all of these environmental and genetic factors are potentially causative or preventative candidates in terms of caries, the neonatal size has not been considered in these studies, despite its potential impact on the child's dental health.

Although considerable research has been undertaken to determine whether caries are associated with obesity, previous reports have been unable to end the controversy because of confounding factors.[19] In particular, the association between obesity in toddlerhood and caries in primary teeth remains inconclusive.[20] Similarly, whether a low birth weight is a protective or risk factor for dental caries remains controversial.[21, 22] Moreover, there are no published data on the incidence of dental caries among neonates with high birth weights. Only one cohort study in the United Kingdom reported a small linear relationship between the caries incidence and birth weights ranging from low to high (odds ratio = 1.08 per 100 g of birth weight); however, this relationship was not significant.[23] In the previous study, the number of enrolled children was limited to 985, and the applied linear regression analysis did not investigate the possible J-shaped caries risk from low to high birth weights. Therefore, we aimed to determine whether a high birth weight was associated with the incidence of dental caries in primary teeth in a large population, simultaneously considering many risk factors associated with caries.

Methods

Ethics statement

The Ethics Review Committee of the Faculty of Medicine of the University of Yamanashi approved the study protocol in accordance with the ethical guidelines and regulations of the Declaration of Helsinki. The Japanese guidelines permit the use of data from medical examinations without consent if the data are anonymous; therefore, informed consent was not required for the current investigation.

Study design and participants

The Okinawa Child Study is a cohort study based on the free health examinations provided to children by administrative authorities.[24] More than 82% of the approximately 16,000 children born annually in Okinawa participate in these health examinations at 3 months, 18 months and 3 years of age.[25] The present study was conducted using data from participants born between 2 April 1997 and 1 April 2007 (i.e. Japanese school years from 1997 to 2006). In this study, data from children who lacked birth records, medical records or oral health records were excluded.

Measurements

Data regarding birth records, family composition, parental child-rearing practices, dietary habits and dental examinations were collected from the child health examinations. We analysed data for the following variables: sex, birth weight, gestational age, parity, siblings, children's dental hygiene, children's history of dental fluoridation, use of a bottle for nursing, consumption of cow's milk and snacks, parental age, parental occupation, parental smoking habits and people involved in child-rearing. Qualified public health nurses and paediatricians performed all examinations for determining parental child-rearing practices, anthropometrics, growth and development. Qualified dentists evaluated the children's oral health and diagnosed dental caries. Each child underwent this dental examination conducted by an on-site dentist. During the paediatric health examinations, the public health nurses interviewed mothers regarding their child-rearing practices. Macrosomia, normal birth weight and low birth weight were defined as birth weights of $\geq$4000 g,[26–29] 2500–3999 g and $<$2500 g, respectively, in accordance with the standards of the World Health Organization.[30] The definitions of 'large for gestational age' (LGA), 'appropriate for gestational age' (AGA) and 'small for gestational age' (SGA) were weights above the 90th percentile, between the 10th and 90th percentiles and below the 10th percentile for gestational age, respectively.[31, 32] Herein, birth weight reference categories used to compare the risk of caries were normal birth weight and AGA.

Statistical analysis

The risks of having caries at 3 years of age among neonates with macrosomia and low birth weights were compared with the risks in other neonates. Multivariate Poisson regressions were used to estimate the relative risks (RR) with respect to the controlled confounding factors, as odds ratios tend to misrepresent the risks of exposure for high prevalence or incidence.[33, 34] RRs were determined for the following explanatory variables: sex, birth weight, mother's age, gestational age, birth order, the number of teeth at 18 months, parents' employment status, use of a bottle for nursing at 18 months, dental fluoridation, siblings, parental smoking, brushing the teeth by parents at 18 months and 3 years of age, drinking cow's milk at 18 months and 3 years of age, eating irregular meals and snacks at 18 months and 3 years of age and watching TV or videos. Although some literature suggests breastfeeding as a risk factor of dental caries,[35] as a cultural norm, Japanese paediatricians and domestic public health nurses encourage mothers to begin ablactating at 5–6 months and to finish by the time their child is 18 months age.[36] Therefore, breastfeeding and ablactating were not considered confounding factors for dental caries at 3 years of age. Regarding the use of pacifiers, the Japanese Society of Pediatric Dentistry and Japanese mothers are aware of the risks of interrupted normal bite resulting from pacifier use.[37] As a result, the proportion of pacifier use is low; therefore, we did not consider it to be a confounding factor in Japan. Relative risk increases (RRI) were calculated as RR − 1. Furthermore, we calculated the adjusted least square estimates of the number of decayed or filled teeth to assess the marginal means over a population that had been adjusted

according to other explanatory variables in a multivariable regression. Descriptive statistical analyses and estimations of RRs were performed using SAS statistical software (version 9.3, SAS Institute, Cary, NC, USA). Descriptive statistics are reported as means and standard deviations (SDs), and point estimates are reported with 95% confidence intervals (CI). All reported P values are 2-sided, and a P-value <0.05 was considered statistically significant.

Sensitivity analysis

The United States Preventive Service Task Force and American Academy of Pediatrics recommend that fluoride varnish treatment should begin with primary tooth eruption.[38, 39] Accordingly, we believed that previous clinical fluoridation of primary teeth might have modified the risks, and therefore previous use of fluoride varnish was included in the first sensitivity analysis; this was restricted to the school years of 2006 and 2007, when detailed records of previous clinical fluoride varnish treatment were preserved. The second sensitivity analysis included LGA, AGA and SGA instead of macrosomia, normal birth weight and low birth weight, respectively; LGA, AGA and SGA were applied to the subjects who were evaluated according to the standards for Japanese children in the guidelines of Japan Obstetrics and Gynaecology.[32] In the third sensitivity analysis, the included children were restricted to those born through labour at term (i.e. gestational age of 37–41 weeks); accordingly, children born through pre- and post-term deliveries were excluded to minimize the result of exposure on the outcome, as gestational age may be associated with an earlier or later eruption of teeth susceptible to caries. Fourth, multivariate analyses of the association between macrosomia and dental caries were performed in the school years 1997–1999, 2000–2002 and 2003–2006 to explore how secular changes in diet contributed to the results. In all sensitivity analyses, multivariate Poisson regressions to adjust for confounding factors were conducted in the same manner used for the main analysis.

Results

Among the 117,651 participants who underwent the health examination and for whom demographic data were available, we excluded 476 children who were toothless at 3 years of age, leaving a final sample size of 117,175. Table 1 shows the following mean demographic values among the population with 60,167 (51.4%) male subjects: birth weight, 3014 g (SD, 434); gestational age, 38.0 weeks (SD, 5.6); age of the mother at the 3-month examination, 29.7 years (SD, 5.6); birth order, 1.9 (SD, 1.0) and number of teeth at 18 months of age, 14.5 (SD, 2.7). Dental

Table 1. Background characteristics of children and their mothers in Okinawa, Japan.

Characteristics	Mean (SD) or number (%)
Number of children	117,175
Number of male children	60,167 (51.4)
Birth weight, g	3014 (434)
Gestational age, weeks	38.0 (5.6)
Age of mother when child is 3 months, years	29.7 (5.6)
Order of birth	1.9 (1.0)
Number of teeth at 18 months	14.5 (2.7)
Number of children with caries at 3 years	53,924 (46.0)
Number of neonates born with macrosomia[1]	1266 (1.1)

[1]Macrosomia was identified as a birth weight ≥4000 g

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caries were present in 53,924 children (46.0%) at 3 years of age, and 1266 children (1.1%) were born with macrosomia.

On univariate analysis, the risk of having caries at 3 years of age was significantly higher among children with macrosomia relative to those with normal birth weights (RRI, 23%, CI, 18–29, $P < 0.001$). Other univariate analyses yielded the following RRIs: 19% (CI, 17–21, $P < 0.001$) for a maternal age <25 years, 7% (CI, 0.01–14, $P = 0.0496$) for post-term delivery, 21% (CI, 19–22, $P < 0.001$) for non-firstborn babies, 14% (CI, 12–16, $P < 0.001$) for ≥14 teeth at 18 months of age, 22% (CI, 19–25, $P < 0.001$) for unemployed parents, 21% (CI, 19–23, $P < 0.001$) for maternal or paternal smoking, −5% (CI, −6–−3, $P < 0.001$) for no siblings at 3 years of age, 27% (CI, 23–31, $P < 0.001$) for no support for child rearing, 40% (CI, 38–42, $P < 0.001$) for occasional brushing the teeth by parents at 3 years of age, −19% (CI, −20–−18, $P < 0.001$) for drinking cow's milk and 32% (CI, 30–34, $P < 0.001$) for irregular consumption of meals and snacks at 18 months of age (Table 2).

The following RRIs were obtained through the main multivariate regression: 19% (CI, 11–28, $P < 0.001$) for macrosomic babies, 17% (CI, 14–20, $P < 0.001$) for a maternal age <25 years, 7% (CI, −3–18, $P = 0.21$) for post-term delivery, 26% (CI, 24–29, $P < 0.001$) for non-firstborn babies, 11% (CI, 6–16, $P < 0.001$) for unemployed parents, 15% (CI, 13–17, $P < 0.001$) for maternal or paternal smoking, 17% (CI, 13–22, $P < 0.001$) for no support for child rearing, 22% (CI, 19–25, $P < 0.001$) for occasional brushing the teeth by parents at 3 years of age, −12% (CI, −14–−10, $P < 0.001$) for drinking cow's milk and 16% (CI, 13–18, $P < 0.001$) for irregular consumption of meals and snacks at 18 months of age (Table 2).

The first sensitivity analysis, which was adjusted for previous clinical fluoride varnish treatment, estimated the RRIs for macrosomic birth weight and the effect of fluoridation on the incidence of caries at 3 years of age to be 4% (CI, −17–30, $P = 0.72$) and 4% (CI, −2–9, $P = 0.16$), respectively. In the second sensitivity analysis, the estimated RRIs for LGA and SGA were 12% (CI, 9–16, $P < 0.001$) and −1% (CI, −4–2, $P = 0.49$), respectively. In the third sensitivity analysis, which was restricted to children born via labour at term, the RRI of a macrosomic birth weight for caries at 3 years of age was 19% (CI, 11–28, $P < 0.001$). In the fourth sensitivity analysis, the estimated RRIs for macrosomia were 20% (CI, 6–36, $P < 0.01$) during 1997–1999, 17% (CI, 4–32, $P < 0.01$) during 2000–2002 and 16% (CI, 3–30, $P = 0.01$) during 2003–2007.

Discussion

Main findings

Among macrosomic children, the RRI of caries at 3 years of age was 19%, representing a significant increase relative to children with normal birth weights. Four sensitivity analyses, which considered the clinical use of fluoride varnish, LGA, labour at term and secular trends, yielded approximately the same RRIs for children with high birth weights.

Possible reasons for these associations

Although the mechanism underlying the formation of caries after exposure to intrauterine over-nutrition is not understood, relatively high concentrations of glucose and amino acids in utero may increase the postnatal appetite or insulin secretion. Evidence indicates that overweight pregnant women have high concentrations of inflammatory cytokines and increased insulin resistance,[40] and subsequently compensatory hyperinsulinaemia and foetal adiposity occur in utero.[41, 42] Hoegsberg et al. observed that macrosomic neonates of nondiabetic mothers are more likely to exhibit hyperinsulinaemia than normal size neonates.[43] Moreover, in foetal rhesus monkeys, external insulin injection resulted in the delivery of macrosomic

Table 2. Relative risk increases (RRIs) of developing caries among 3-year-old children in Okinawa, Japan by univariate and multivariate Poisson regressions. Relative risk increase equals relative risk minus 1.

Risk factors		No. of children	Proportion of having caries at 3 years (%)	Univariate analyses			Multivariate analysis			Adjusted no. of decayed and filled teeth at 3 years[4]
				Crude RRI (%)	95% CI[3]	P value	Adjusted RRI (%)	95% CI[3]	P value	
Sex	Girls	57,008	44.7	Ref	—	—	Ref	—	—	2.79
	Boys	60,167	47.2	6	4–7	<0.001	3	2–5	<0.001	2.84
Birth weight (g)	2500–3999	104,442	46.1	Ref	—	—	Ref	—	—	2.65
	≥4000	1266	56.9	23	18–29	<0.001	19	11–28	<0.001	3.30
	<2500	11,467	44.1	−4	−6–−2	<0.001	−5	−8–−1	0.005	2.50
Age of mother (years)	25–34	74,344	43.9	Ref	—	—	Ref	—	—	2.64
	<25	20,091	52.1	18	17–21	<0.001	17	14–20	<0.001	3.08
	≥35	22,740	47.5	8	7–10	<0.001	2	0.1–5	0.04	2.72
Gestational age	Labour at term	106,409	45.8	Ref	—	—	Ref	—	—	2.76
	Pre-term delivery	9801	47.7	4	2–6	<0.001	3	−1–7	0.10	2.89
	Post-term delivery	965	48.9	7	0.01–14	0.0496	7	−3–18	0.21	2.80
Order of birth	first	50,354	41.1	Ref	—	—	Ref	—	—	2.53
	other	66,801	49.7	21	19–22	<0.001	26	24–29	<0.001	3.10
No. of teeth at 18 months	0–13	19,042	38.9	Ref	—	—	Ref	—	—	2.59
	14–20	56,059	44.3	14	12–16	<0.001	13	11–16	<0.001	3.04
Both parents are jobless at 3 years	No	111,984	45.6	Ref	—	—	Ref	—	—	2.58
	Yes	5191	55.6	22	19–25	<0.001	11	6–16	<0.001	3.05
Bottle use at 18 months	No	40,407	42.3	Ref	—	—	Ref	—	—	2.76
	Yes	34,668	44.3	5	3–7	<0.001	4	2–6	<0.001	2.87
Experience of dental fluoridation at 3 years[1]	Yes	8023	35.8	Ref	—	—	—	—	—	—
	No	8195	37.5	2	−2–7	0.07	—	—	—	—
Maternal or paternal smoking at 3 years	No	51,352	40.9	Ref	—	—	Ref	—	—	2.64
	Yes	51,298	49.5	21	19–23	<0.001	15	13–17	<0.001	2.99
Sibling <6 years at 3 years[2]	No	54,062	47.2	Ref	—	—	—	—	—	2.85
	Yes	63,113	45	−5	−6–−3	<0.001	—	—	—	2.78
Someone who supports child rearing at 3 years	Yes	6564	36.7	Ref	—	—	Ref	—	—	2.63
	No	110,529	46.6	27	23–31	<0.001	17	13–22	<0.001	3.00
Brushing the teeth by parents at 18 months	Daily	41,668	38.4	Ref	—	—	Ref	—	—	2.60
	Sometimes/ never	33,589	49.3	29	26–31	<0.001	18	16–20	<0.001	3.03

(*Continued*)

Table 2. (*Continued*)

Risk factors		No. of children	Proportion of having caries at 3 years (%)	Univariate analyses			Multivariate analysis			Adjusted no. of decayed and filled teeth at 3 years[4]
				Crude RRI (%)	95% CI[3]	P value	Adjusted RRI (%)	95% CI[3]	P value	
Brushing the teeth by parents at 3 years	Daily	101,153	43.6	Ref	—	—	Ref	—	—	2.42
	Sometimes/ never	13,867	61	40	38–42	<0.001	22	19–25	<0.001	3.21
Drinking cow's milk at 18 months	No	68,864	49.9	Ref	—	—	Ref	—	—	3.04
	Yes	48,311	40.5	−19	−20–−18	<0.001	−12	−14–−10	<0.001	2.59
Drinking cow's milk at 3 years	No	41,593	49.3	Ref	—	—	Ref	—	—	2.85
	Yes	75,582	44.2	−10	−12–−9	<0.001	−5	−6–−3	<0.001	2.78
Irregular meals and snacks at 18 months	No	54,088	39.8	Ref	—	—	Ref	—	—	2.55
	Yes	20,487	52.4	32	30–34	<0.001	16	13–18	<0.001	3.08
Irregular meals and snacks at 3 years	No	73,838	41.6	Ref	—	—	Ref	—	—	2.58
	Yes	39,345	54	30	28–31	<0.001	16	14–19	<0.001	3.05
TV or video watching every day at 3 years[1]	No	1964	43.2	Ref	—	—	—	—	—	—
	Yes	2355	44.8	4	−3–11	0.30	—	—	—	—

[1]These variables were eliminated from the multivariate analysis because many values were missing.

[2]This variable was eliminated from the multivariate analysis to avoid multicollinearity.

[3]Confidence interval

[4]Least square estimates in a multivariate regression calculated adjusted number of decayed and filled teeth at 3 years of age.

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neonates with hyperinsulinaemia.[44] Dörner et al. suggested that perinatal hyperinsulinaemia alters the function of hypothalamic ventromedial nuclei, which play a determining role in satiety, appetite and insulin secretion from pancreatic β-cells.[45] Studies in rats have revealed foetal β-cell hyperplasia in the offspring of moderately diabetic mothers.[46, 47] The 'Developmental over-nutrition hypothesis', which was recently submitted based on animal model studies, proposes that maternal nutritional and hormonal conditions during pregnancy programme the appetite and energy expenditure of the offspring, as well as the hormonal, neuronal and autocrine mechanisms that contribute to the offspring's energy balance.[48] Thereafter, the primary teeth of LGA children may be more frequently exposed to cariogenic food and drink than the teeth of AGA children. Furthermore, the finding that LGA neonates remain classified as overweight until the age of 83 months[49, 50] might reflect the hypothetical programming in utero and subsequent voracious appetite.

Comparison with other studies

Regarding the positive effect of macrosomia on dental caries, we have calculated the following: if the previous report from the UK regarding a small positive association between birth weight and the risk of caries (odds ratio (OR) = 1.08 per 100 g of birth weight)[23] could be directly applied to 4000 g (lower limit of macrosomia) with a reference of, for instance, 3000 g, the OR may be calculated as 2.16 [i.e. 1.08 to the 10^{th} power, where 10 equals (4000−3000)/100]; the

calculated OR is mathematically equivalent to a RR of 1.41 and RRI of 41%, given that the risk of caries was 46% among children born at a weight of 3000 g. Therefore, our estimated RRI = 19% was not overly large, and we consider our result to be consistent with the previous study. Regarding the negative RRI of −5% for a low birth weight, our results were similarly consistent with the above-described report from the UK. In addition, Saraiva et al. suggested that SGA, foetal growth restriction and pre-term birth should be associated with a lower incidence of dental caries among Caucasian, African-American and Mexican-American children aged 2–5.9 years.[51] Our results regarding low birth weight and SGA provided evidence from a Japanese population to support the findings of Saraiva et al. A programmed lower appetite, as discussed above, might explain these observations related to the lower incidence of caries in children with low birth weights.

Sensitivity analyses

In the first sensitivity analysis, which was restricted to data from 2 school years and included the clinical use of fluoride varnish, the RRI adjusted for previous fluoride varnish use was 4% (CI, −17–30, P = 0.72), with a lower result in the main multivariate analysis. Taking the large CI and non-significance into account, we considered that these data related to fluoride varnish use were unreliable for estimating the effect of macrosomia. In other words, in an era when almost all commercial fluoridated dental toothpastes contain fluoride and dental clinics and individual dentists routinely apply fluoride rinses, gels or varnishes to the primary teeth during paid clinical examinations, we do not consider previous fluoride varnish use to be an important confounding factor in the present study. The paradoxical effect of previous clinical fluoride varnish use, which has an RRI of 4% (CI, −2–9, P = 0.16), may represent the uselessness of this information in the present-day survey.

In the second sensitivity analysis, in which our exposure variable of interest was changed from rare macrosomia (birth weight ≥4000 g) to LGA, the RRI of LGA for caries development (12%) was similar to that of macrosomia (19%); in addition, the relatively lower RRI associated with LGA can be reasonably explained by the fact that LGA is, by definition, more frequent than macrosomia. It should be emphasized that the third sensitivity analysis, which excluded children born via pre- and post-term delivery and was therefore restricted to those born through labour at term, yielded the same RRI of 19%. Because the timing of tooth eruption and the number of susceptible teeth among term neonates are considered to be approximately the same, this sensitivity analysis confirmed our report regarding the effect of macrosomia on dental caries in early childhood. Moreover, the fourth sensitivity analysis confirmed the RRI of macrosomia in recent years as 16–20%.

Strengths and limitations

To the best of our knowledge, this is the first report to raise an alarm over the risk of a high birth weight with respect to dental caries of the primary teeth. A study in the UK suggested a weak linear relationship between incidental caries and birth weights ranging from low to high, [23] but that previous study could not clarify the risk of macrosomia by its linear regression analysis. In this study, we used birth weights as a categorical variable to examine whether both high and low birth weights are risk factors for dental caries (J-shaped risk); however, the results were not similar to those of the previous study. Second, our large amount of data obtained from the free health service provided to resident children by the administrative authorities retained sufficient statistical power to determine the risks of a high birth weight, whereas the data set in the previous study in the UK also lacked statistical power. Third, the sensitivity analyses confirmed the postulated risk of macrosomia. Furthermore, the measurements were valid

because all of the health professionals were qualified to evaluate caries, anthropometrics and interviews addressing parental child-rearing practices and several socioeconomic statuses.

One limitation of this study was the lack of available information about parental dental hygiene and typical socioeconomic status. Parental self-dental care may have directly affected the incidence of caries in their children. However, because parental lifestyles and dental hygiene are reflected by the socioeconomic status, this potential confounding bias might have been reduced by adjusting for information regarding the parental employment status, smoking habits, siblings, child-rearing support provided by others, parental support for brushing their children's teeth and irregular consumption of meals and snacks. Another limitation in interpreting the results would be that the dental caries were neither validated by other dentists nor validated for different periods of time. Owing to the nature of administrative massive health examinations, the number of on-site dentists is limited. Because there is no published data describing the likelihood of dental caries diagnosis at health examination centres compared to that at dental clinics, the influence of lack of validation on the number of diagnosed caries in this report is unknown. However, even if a misclassification of children with and without caries existed, dentists were unlikely to diagnose caries in view of child birth weights; therefore, we believe that the bias because of this influence in the reported RRIs would be minimal. The other potential limitation of this study is its regional restriction to Okinawa; therefore, the results may not be applicable to other regions of Japan. Moreover, during the study period, approximately 25% of children in Okinawa did not undergo health examinations or were excluded from the study because of insufficient information. It is possible that these missing children had poor access to health examinations and were born to families with low socioeconomic statuses. As a result, the frequencies of high birth weight and caries in that population might have exceeded those of the children studied, and accordingly the missing data might have biased the RRIs of our results.

Implications and conclusions

To the best of our knowledge, we are the first to report that macrosomia significantly increases the risk of dental caries. Our focus on the influence of high birth weight on this paediatric lifestyle-related disease represents a new perspective in perinatal research. The mechanism of the relationship between macrosomia and dental caries remains under debate, and further laboratory and clinical studies are warranted. We recommend that children with macrosomia should receive close attention from medical professionals during development.

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Author Contributions

Conceived and designed the experiments: ZY. Performed the experiments: HY TT KS TA. Analyzed the data: HY. Contributed reagents/materials/analysis tools: TT KS. Wrote the paper: HY ZY KS.

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RESEARCH ARTICLE

Association between Maternal Smoking during Pregnancy and Low Birthweight: Effects by Maternal Age

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Abstract

Background

Maternal smoking during pregnancy has been consistently related to low birthweight. However, older mothers, who are already at risk of giving birth to low birthweight infants, might be even more susceptible to the effects of maternal smoking. Therefore, this study aimed to examine the modified association between maternal smoking and low birthweight by maternal age.

Methods

Data were obtained from a questionnaire survey of all mothers of children born between 2004 and 2010 in Okinawa, Japan who underwent medical check-ups at age 3 months. Variables assessed were maternal smoking during pregnancy, maternal age, gestational age, parity, birth year, and complications during pregnancy. Stratified analyses were performed using a logistic regression model.

Results

In total, 92641 participants provided complete information on all variables. Over the 7 years studied, the proportion of mothers smoking during pregnancy decreased from 10.6% to 5.0%, while the prevalence of low birthweight did not change remarkably (around 10%). Maternal smoking was significantly associated with low birthweight in all age groups. The strength of the association increased with maternal age, both in crude and adjusted models.

Conclusions

Consistent with previous studies conducted in Western countries, this study demonstrates that maternal age has a modifying effect on the association between maternal smoking and

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birthweight. This finding suggests that specific education and health care programs for older smoking mothers are important to improve their foetal growth.

Introduction

Maternal smoking during pregnancy has long been proposed to be one of the most critical preventable factors that can affect the intrauterine environment. [1,2] Studies carried out in different ethnic groups have consistently revealed that maternal smoking is associated with reduced birthweight and elevated prevalence of low birthweight. [3–5] Moreover, maternal age has also been associated with birthweight. A U-shaped relationship between maternal age and birthweight has been identified; both younger and older mothers are more likely to give birth to low birthweight infants. [6,7] Additionally, a series of physiological changes may occur in older mothers that can make their foetuses more vulnerable to unfavourable environments. [8,9] Therefore, it is plausible that older mothers, who are already at risk of giving birth to low birthweight infants, are more susceptible to the effect of maternal smoking. Identifying these high-risk groups contributes to designing targeted intervention programs. However, regarding the effect of maternal smoking on birthweight, only a few studies have discussed the susceptibility of mothers at different ages. [10, 11, 12] These studies were all carried out in Western countries in children before or around the 1990s. The Japanese population is quite different regarding culture, lifestyle habits, prevalence of smoking, and body mass index (BMI) compared to Western populations. Additionally, there might be some secular changes across different time periods. In addition, parity is another notable factor because of its close relationship to birthweight and maternal age. [13] However, no related previous reports referred to the possible effect of parity. Therefore, in this study, we aimed to examine the association between maternal smoking during pregnancy and birthweight in different age groups by parity in a large sample of a Japanese women conducted between 2004 and 2010.

Methods

Study population

The study population was from the Okinawa Child Study, which is a cohort study based on free medical check-ups for children. [14] According to Japanese law, free medical check-ups are provided for the maintenance of children's health. [15] The mothers were obligated to take their children for regular medical check-ups and bring along the Mother and Child Health Handbook, which recorded the health examinations during pregnancy and at delivery. [16] A questionnaire survey was given to all mothers during the medical check-ups. This study covered more than 82% of infants born in Okinawa during the study period. This study included mothers with singleton pregnancies and their infants born between 2004 and 2010 in Okinawa, Japan.

Measurements

Maternal and birth characteristics were obtained from related birth records and the questionnaire survey given to the mothers when the infants were 3 months of age. During the survey, the mothers were allowed to refer to their Mother and Child Health Handbooks for related information. Maternal smoking was determined by the question: "Did you smoke during pregnancy?" The answer was "Yes" or "No". Birthweight was classified into two categories: Low

birthweight (<2500 g) and not low birthweight (≥2500 g). Other information investigated included: maternal age at delivery (age accurate to year was categorised into 6 groups (≤19y, 20–24 y, 25–29 y, 30–34 y, 35–39 y, and ≥40 y) for stratified analysis), complications during pregnancy (including anaemia, pregnancy-induced hypertension [or preeclampsia], gestational diabetes, etc.), parity (categorical: 1st, 2nd, and 3rd, or more), birth year (accurate to year), and gestational age (accurate to week).

Ethics statement

The study was approved by the ethical review board of the University of Yamanashi, School of Medicine and was conducted in accordance with the Guidelines Concerning Epidemiological Research (Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare, Japan). We did not obtain informed consent because the Japanese guidelines permit the use of medical examination data without consent if the data are anonymous. In this study, participants' information was anonymised prior to analysis.

Statistical methods

The association between maternal smoking during pregnancy and birthweight was examined using a logistic regression model (for prevalence of low birthweight) and a multiple linear regression model (for birthweight). The association was examined based on stratification by birth year, maternal age alone, and then by maternal age and parity. Potential confounders included in the models stratified by maternal age were gestational age (continuous), parity (categorical: 1st, 2nd, 3rd, or more), birth year (categorical: 2004, 2005, 2006, 2007, 2008, 2009, and 2010), and complications during pregnancy (binominal: yes or no). When stratified by both maternal age and parity, the same potential confounders except for parity were included in the models. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Overall, 104415 mothers responded to the questionnaire survey. In total, 92641 (89%) of them completed information on all the characteristics studied and were included in the analysis. Descriptive results of maternal and birth characteristics are shown in Table 1. Mothers had a mean maternal age of approximately 30 years. From 2004 to 2010, the proportion mothers of smoking during pregnancy decreased from 10.6% to 5.0%, while the prevalence of low birthweight (<2500 g) remained stable at a level of approximately 10%. We first examined the association between maternal smoking during pregnancy and low birthweight by birth years (Table 2). The results indicated that in all birth year groups, infants whose mothers smoked during pregnancy were more likely to be of low birthweight compared to infants with non-smoking mothers. The association was stronger in children born between 2008 and 2010 than in children born before 2008.

We subsequently examined the association based on stratification by maternal age and parity, and the results are displayed in Table 3. Teenage mothers had the highest prevalence of smoking during pregnancy, and the prevalence decreased as the mother's age increased. Additionally, the prevalence of maternal smoking during pregnancy increased with parity. Conversely, the prevalence of low birthweight also differed across maternal age groups. Both younger mothers and older mothers tended to have low birthweight babies. Examination of the associations demonstrated maternal smoking during pregnancy was associated with increased risk of low birthweight in all age groups. The strength of the association increased with maternal age, both in crude and adjusted models (adjusted for gestational age, whether born via caesarean section, parity, birth year, complications during pregnancy). The trends did not change

Table 1. Characteristics of participants by birth year.

	Birth year						
	2004	2005	2006	2007	2008	2009	2010
Number of participants	13308	13014	13433	13721	13628	13530	12007
Maternal characteristics							
Maternal age, years, mean (SD)	29.7 (5.5)	29.8 (5.4)	30.0 (5.5)	30.2 (5.5)	30.2 (5.7)	30.5 (5.7)	30.6 (5.8)
Complications during pregnancy, yes, n (%)	3359 (25.2)	3169 (24.4)	3402 (25.3)	3664 (26.7)	3588 (26.3)	3778 (27.9)	3243 (27.0)
Smoking during pregnancy, yes, n (%)	1409 (10.6)	1200 (9.2)	1127 (7.8)	1072 (7.8)	947 (7.0)	879 (6.5)	601 (5.0)
Birth characteristics							
Birthweight, g, mean (SD)	3003 (434)	3003 (427)	3000 (427)	2996 (431)	3001 (418)	2991 (418)	2994 (410)
Low birthweight, n (%)	1362 (10.2)	1277 (9.8)	1361 (10.1)	1429 (10.4)	1317 (9.7)	1384 (10.2)	1179 (9.8)
Gestational age, weeks, mean (SD)	38.4 (4.4)	38.4 (4.2)	38.3 (4.8)	38.3 (4.3)	38.4 (4.0)	38.2 (4.6)	38.0 (5.4)
Parity							
1st, n (%)	5716 (43.0)	5463 (42.0)	5669 (42.2)	5569 (42.2)	5533 (40.6)	5536 (40.9)	4911 (40.9)
2nd, n (%)	4495 (33.8)	4352 (33.4)	4676 (34.1)	4676 (34.1)	4484 (32.9)	4392 (32.5)	3854 (32.1)
3rd or more, n (%)	3097 (23.3)	3199 (24.6)	3476 (25.3)	3476 (25.3)	3611 (26.5)	3602 (26.6)	3242 (27.0)

SD, standard deviation

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when models were further stratified by parity. The adjusted difference in birthweight between children with non-smoking and smoking mothers increased from 76 g to 160 g with maternal age, and this difference increased with parity.

Discussion

The study covered 92641 mothers and their infants born between 2004 and 2010 in Okinawa, Japan. A decrease in prevalence of smoking but not in low birthweight was observed during the investigation period. In each period, maternal smoking during pregnancy was associated with increased risk of low birthweight. Because the effect of maternal smoking during pregnancy on birthweight was largest in the most recent period, the prevention of maternal smoking during pregnancy might be a higher priority than previously. Additionally, the strength of the association increased with increasing maternal age.

This study confirmed the association between maternal smoking during pregnancy and risk of low birthweight in mothers from all age groups in a large Japanese population. This result is consistent with many previous studies. [3, 4, 5, 17] The proportion of low birthweight infants born to teenage mothers was higher than that in mothers aged 20–29 years, but the odds ratio of infants being low birthweight in smoking mothers were similar for both age groups. These

Table 2. Association between maternal smoking during pregnancy and low birthweight by birth year.

Birth year	Maternal smoking during pregnancy		p for trend	No maternal smoking during pregnancy		p for trend	OR for low birthweight
	N (%)	Low birthweight (%)		N (%)	Low birthweight (%)		
			<0.0001			1	
2004–2005	2609 (9.9)	14.0		23713 (90.1)	9.6		1.53 (1.36–1.73)
2006–2007	2199 (8.1)	14.5		24955 (91.9)	9.9		1.54 (1.36–1.75)
2008–2010	2427 (6.2)	16.3		36738 (93.8)	9.5		1.86 (1.66–2.08)

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Table 3. Association between maternal smoking during pregnancy and low birthweight by maternal age by parity.

Maternal age (years)	No maternal smoking during pregnancy				Maternal smoking during pregnancy				OR for low birthweight	Adjusted OR for low birthweight	Adjusted difference in birthweight (g) Mean (95% CI)
	N	Proportion (%)	Birthweight (g) Mean (SD)	Low birthweight (%)	N	Proportion (%)	Birthweight (g) Mean (SD)	Low birthweight (%)			
All children											
≤19	1331	78.9	2955 (406)	11.5	356	21.1	2900 (451)	16.0	1.47 (1.06–2.04)	1.56 (1.15–2.10)[a]	76 (33–120)[a]
20–24	11243	87.0	2984 (404)	9.8	1677	13.0	2917 (400)	13.2	1.40 (1.20–1.64)	1.49 (1.29–1.72)[a]	76 (57–95)[a]
25–29	24099	91.6	3007 (406)	9.0	2211	8.4	2909 (403)	13.3	1.56 (1.37–1.77)	1.65 (1.46–1.87)[a]	108 (91–125)[a]
30–34	28695	94.0	3015 (422)	9.2	1847	6.1	2900 (441)	14.5	1.66 (1.45–1.91)	1.72 (1.51–1.96)[a]	123 (104–142)[a]
35–39	16537	94.7	3016 (445)	10.5	934	5.4	2833 (478)	21.1	2.28 (1.93–2.68)	2.35 (2.00–2.77)[a]	189 (160–217)[a]
≥40	3242	94.7	2997 (480)	12.3	181	5.3	2832 (532)	22.1	2.02 (1.40–2.91)	2.18 (1.53–3.12)[a]	160 (94–228)[a]
1st child											
≤24	8649	87.7	2973 (398)	10.3	1211	12.3	2919 (419)	13.9	1.41 (1.18–1.68)	1.48 (1.26–1.74)[b]	69 (47–90)[b]
25–29	11729	93.8	2982 (398)	9.8	773	6.2	2900 (390)	12.7	1.34 (1.08–1.67)	1.50 (1.22–1.83)[b]	99 (72–126)[b]
30–34	10019	94.9	2974 (423)	10.6	544	5.2	2910 (435)	14.2	1.39 (1.08–1.78)	1.44 (1.13–1.84)[b]	70 (35–105)[b]
≥35	5194	94.9	2951 (452)	13.6	278	5.1	2808 (451)	21.9	1.78 (1.33–2.40)	1.92 (1.43–2.59)[b]	141 (88–194)[b]
2nd child											
≤24	3373	84.3	3000 (410)	8.9	628	15.7	2934 (386)	12.4	1.45 (1.11–1.89)	1.75 (1.37–2.23)[b]	81 (48–113)[b]
25–29	8149	91.6	3023 (407)	8.1	748	8.4	2924 (418)	11.6	1.50 (1.18–1.90)	1.50 (1.20–1.88)[b]	95 (66–123)[b]
30–34	10604	95.1	3022 (420)	8.8	550	4.9	2901 (432)	14.2	1.71 (1.34–2.20)	1.75 (1.37–2.23)[b]	129 (95–163)[b]
≥35	6372	95.7	3014 (439)	10.1	285	4.3	2850 (464)	19.7	2.17 (1.60–2.94)	2.32 (1.72–3.13)[b]	176 (126–227)[b]
3rd child or more											
≤24	811	78.4	2990 (455)	11.8	223	21.6	2833 (424)	16.1	1.43 (0.95–2.17)	1.24 (0.82–1.88)[b]	143 (77–207)[b]
25–29	4221	86.0	3042 (423)	8.5	690	14.1	2903 (401)	15.8	2.02 (1.61–2.55)	2.07 (1.65–2.59)[b]	137 (104–170)[b]
30–34	8072	91.5	3055 (419)	8.0	753	8.5	2893 (453)	14.9	2.00 (1.61–2.48)	1.95 (1.58–2.41)[b]	156 (126–186)[b]
≥35	8213	93.7	3052 (455)	9.6	552	6.3	2836 (515)	21.7	2.63 (2.12–3.26)	2.56 (2.07–3.17)[b]	208 (171–246)[b]

[a] Adjusted for gestational age, parity, birth year, complications during pregnancy.

[b] Adjusted for gestational age, birth year, complications during pregnancy.

OR, odds ratio

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