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High Parity Is an Independent Risk Factor for Tooth Loss in Women: A Community-Based Takahata Study in Japan

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Risk factors for tooth loss have been widely examined previously. However, no previous study has comprehensively investigated the risk factors, including lifestyle-related specific factors (parity, oral health habits, and socioeconomic status), for fewer than 20 teeth among women in the general population in Japan. This cross-sectional study explored the association of these risk factors, especially parity, with having fewer than 20 teeth among Japanese women. A self-reported questionnaire including items on lifestyle-related risk factors (parity, oral health, diet [e.g., alcohol and sucrose consumption]) and socioeconomic status was sent by post to female residents (age ≥ 40 years) of Takahata town, Yamagata Prefecture, in 2005. Multivariate logistic regression analysis including 3,854 eligible participants was performed to investigate the association between various factors (including parity) and having fewer than 20 teeth. The results indicated that, compared with nulliparous women, women with two, three, and four completed pregnancies had 2.485-, 2.844-, and 4.305-fold increased risk of having fewer than 20 teeth, respectively. Our study is the largest-scale study of the general female population in Japan and the first study to comprehensively investigate risk factors (parity, oral health status, and socioeconomic status) for fewer than 20 teeth. We thus found that higher parity, especially, two or more, was independent risk factors for having less than 20 teeth among Japanese women. In conclusion, the present study emphasizes the importance of good oral health habits in women, especially, during pregnancy and in the postpartum period, to maintain 20 or more teeth.

Keywords: cross-sectional study; multivariate logistic regression analysis; number of teeth; oral health; parity
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Introduction

Tooth loss is a serious oral health concern that causes mastication dysfunction (Steele et al. 1997; Tatematsu et al. 2004). Recently, several studies that evaluated the associations between tooth loss and systemic disease have reported positive correlations between tooth loss and various diseases, such as cancer, respiratory diseases, and cardiovascular diseases (Aida et al. 2011; Michaud et al. 2016, 2017; Maisonneuve et al. 2017; Koka and Gupta 2018). Therefore, prevention of tooth loss is very important not only for the maintenance of functional mastication but also

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for the benefit of the individual's general health.

Many epidemiological studies have determined the risk factors for tooth loss. Poor oral health status due to dental caries and periodontitis and poor oral health habits such as infrequent brushing and lack of routine dental check-ups are the reported risk factors for tooth loss (Chambrone and Chambrone 2011; Kim et al. 2016; Laguzzi et al. 2016; Lee et al. 2017; Ishikawa et al. 2019b). Moreover, excessive sugar and alcohol consumption, smoking, low socioeconomic status (SES), and the presence of systemic diseases such as diabetes mellitus have also been reported as risk factors for tooth loss (Yanagisawa et al. 2009; Ueno et al. 2012; Patel et al. 2013; Ehrenthal et al. 2016; Kim et al. 2016; Kim et al. 2017; Moradi et al. 2017; Wagner et al. 2017; Fernandez de Grado et al. 2018).

The phrase "A tooth for every child," which implies that a mother loses one tooth every time she gives birth to a child, is commonly used in many countries. Higher parities are thought to be risk factors for tooth loss (Christensen et al. 1998; Ueno et al. 2013; Oziegbe and Schepartz 2019). Clinically, it is well known that periodontal disease, which is one of the most common diseases resulting in tooth loss, worsens during pregnancy (Taani et al. 2003; Russell et al. 2010; Gil et al. 2019). However, there is a paucity of epidemiological investigations regarding the association between the tooth number and parity, and to the best of our knowledge, only nine epidemiological studies have determined this association (Stalp and Zuhrt 1979; Wysokińska-Miszczuk 1987; Rundgren and Osterberg 1987; Christensen et al. 1998; Scheutz et al. 2002; Russell et al. 2008; Ueno et al. 2013; Han et al. 2017; Oziegbe and Schepartz 2019). In six of these nine studies, increased parity was associated with a decreased number of teeth (Rundgren and Osterberg 1987; Christensen et al. 1998; Russell et al. 2008; Ueno et al. 2013; Han et al. 2017; Oziegbe and Schepartz 2019). However, the remaining three studies found no association between parity and tooth loss (Stalp and Zuhrt 1979; Wysokińska-Miszczuk 1987; Scheutz et al. 2002). Whether or not an association exists between parity and fewer number of teeth remains to verified scientifically. In Japan, only one study has determined the association between tooth loss and parity (Ueno et al. 2013). This Japanese study included 649 women (age range, 40-59 years) and reported that there was a significant decline in the number of teeth with increased parity. However, the study did not survey parity in detail or investigate whether high parity was a risk factor for tooth loss. Furthermore, their assessment did not consider tooth number, whether or not it was fewer than 20 (Ueno et al. 2013).

In Japan, the Ministry of Health, Labor, and Welfare has carried out a campaign, since more than 30 years, to promote the preservation of 20 or more natural teeth among individuals aged ≥ 80 years, and the importance of maintaining more than 20 teeth has been emphasized (Ueno et al. 2012; Ishikawa et al. 2019b). Consequently, there has been an increase in the number of people with 20 or more natural teeth at the age of 80 years (https://www.mhlw.go.jp/toukei/list/62-28.html). The evidence emphasizing the importance of having 20 or more natural teeth for an individual's general health has accumulated, as compared to that emphasizing that an individual should simply have several teeth regardless of the total number (Aida et al. 2012; Yamamoto et al. 2012a, b). Hence, there is a need to examine the association between having fewer than 20 teeth and overall health.

Therefore, a cross-sectional study was conducted with 3,854 community-dwelling Japanese women, with a broad age range. This is the second study to determine the association between parity and the number of teeth in Japan. However, this is the largest study of the general female population in Japan and the first to comprehensively determine the association between parity and having fewer than 20 teeth.

Materials and Methods

Study design and participants

This study was conducted as part of an ongoing molecular epidemiological study utilizing the regional characteristics of participants in the 21st Century Center of Excellence (COE) Program in Japan. In the present study, community-based baseline surveillance data on various lifestyle-associated factors were obtained using a self-reported questionnaire, as previously reported (Ishikawa et al. 2019a, b).

The survey population in this study comprised community-dwelling Japanese women aged ≥ 40 years residing in Takahata town, Yamagata Prefecture, Japan (the total population of women ≥ 40 years of age in 2004 was 8,298). In 2005, the self-reported questionnaire was sent by post to every resident of Takahata town, and 5,696 responses were received. Among these responses, 1,842 were excluded because of missing or incomplete data, leaving a total of 3,854 valid responses for inclusion in the data analysis.

Our institution—Faculty of Medicine, Yamagata University—has been performing physical check-up for the residents of Takahata town in an epidemiological study, since 2000. We have since built a good relationship with the residents and the local government of Takahata town. We had received a grant from the Regional Characteristics of the 21st Century COE to perform the Molecular Epidemiological Study in Yamagata Prefecture, including Takahata town (the Yamagata cohort study), in 2004. Using this grant, we started to collect extensive and detailed information on the health status of Takahata town residents in 2005. Therefore, in this study, we used the data of Takahata town residents collected in 2005.

Ethical approval

This study was approved by the ethics committee of Yamagata University. Informed consent was obtained from all participants before the study initiation. All procedures involving human participants were carried out in accor-

dance with the 1964 Helsinki Declaration and its later amendments and also in accordance with the ethical standards of the institutional research committee.

Measurements

The self-reported questionnaire used in the present study included items on lifestyle, medical history, oral health status and habits, SES, and dietary intake (e.g., alcohol, sucrose); the details are described elsewhere (Ishikawa et al. 2019a, b). The questionnaire included the following lifestyle question with regard to the number of completed pregnancies: "How many times have you given birth?" Concerning oral health, the questionnaire included items on the number of remaining teeth, daily brushing habits, and frequency of visiting a dental clinic for a dental check-up. In particular, the question in the questionnaire on the number of teeth was as follows: "How many teeth do you have now? Please note that fixed prostheses are counted, but prostheses that have been removed are not counted. Moreover, please note that people have 28 permanent teeth in general, but some people have 29 to 32 permanent teeth because one to four wisdom teeth may be present." Educational status was selected as a proxy for SES, and it was classified into the following three groups according to participants' age at completion of education: high educational status group (> 19 years of age at completion of college or another institution of higher learning), middle educational status group (≤ 18 and > 15 years of age at completion of senior high school), and low educational status group (≤ 15 years of age at completion of junior high school). This categorization was used because people in Japan generally graduate from high and junior high school at 18 and 15 years of age, respectively.

For the calculation of sucrose and alcohol consumption, a brief self-administered questionnaire on diet history (BDHQ: brief self-administered diet history questionnaire) was used (Sasaki et al. 1998a, b, 2000). This questionnaire, BDHQ, which has been available since 2001, was used to conduct a survey on the frequency of the consumption of 58 foods and beverages. The estimated amounts of consumption of these foods and beverages, as well as the intake of energy and selected nutrients, were then calculated using an ad hoc computer algorithm based on the Standard Tables of Food Composition in Japan. This questionnaire has been widely used in epidemiological surveillance for nutritional assessment in Japan from the time it was publicly available (Ishikawa et al. 2013, 2019a, b; Tabata et al. 2020; Matsunaga et al. 2020; Yoshihara et al. 2020; Suthuvoravut et al. 2020).

Statistical analyses

One-way analysis of variance and chi-square test were performed to analyze the distribution of quantitative and qualitative characteristics. Univariate logistic regression analysis was conducted to calculate the crude odds ratios (ORs) for determining the risk of having fewer than 20 teeth. Next, the representative variables that were found to be significant in the univariate analysis ($P < 0.05$) were included in the multivariate logistic regression analysis to examine the associations between various characteristics and having fewer than 20 teeth and to estimate the resultant adjusted ORs and 95% confidence intervals (CIs). Statistical significance was set at $P < 0.05$. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Table 1 shows the distribution of clinical parameters, age, parity, alcohol and sucrose consumption, educational status, history of cancer, presence of hypertension, diabetes mellitus, and dyslipidemia, smoking habits, stressful life events during the previous month, daily brushing habits, and dental check-ups according to groups with fewer than 20 or 20 or more teeth. Participants with fewer than 20 teeth were significantly older and had significantly higher parity than those with 20 or more teeth. Alcohol consumption was much higher among participants with 20 or more teeth than among those with fewer than 20 teeth. Sucrose consumption did not vary significantly between groups. The results of the chi-square test showed significant differences in the distribution of parameters between the groups. Educational status, hypertension, diabetes mellitus, stressful life events during the previous month, daily brushing habits, and dental check-ups showed significantly different distributions between the groups. The distributions of a history of cancer, dyslipidemia, and smoking habits did not significantly differ between groups.

Table 2 shows the significant variables considered in the univariate logistic regression analysis, including parity, dental check-ups, daily brushing habits, age, educational status, hypertension, diabetes mellitus, stressful life events during the previous month, and alcohol consumption, as well as the significant variables identified in the multivariate logistic regression analysis. Model 1 is the multivariate logistic regression analysis adjusted for representative variables that were significant in the univariate analysis ($P < 0.05$). Model 2 is the multivariate logistic regression analysis adjusted for smoking habits and representative variables that were significant in the univariate analysis. Parity, dental check-ups, daily brushing habits, age, and educational status were independent factors for having fewer than 20 teeth in both models. Alcohol consumption was a significant factor for having fewer than 20 teeth in Model 1, and current smoking was a significant independent factor for having fewer than 20 teeth in Model 2. Compared to nulliparous women, women with two, three, and four completed pregnancies had a 2.485-fold, 2.844-fold, and 4.305-fold increased risk of having fewer than 20 teeth, respectively. Therefore, two or more completed pregnancies were a significant independent risk factor for having fewer than 20 teeth compared with nulliparity.

Table 1. Characteristics of participants.

		Number of teeth				
		< 20		≥ 20		
		n	Mean ± SD	n	Mean ± SD	P value†
Age (years)		1,289	70.1±10.8	2,424	55.1 ± 9.8	< 0.001*
Parity		1,349	2.7 ± 1.1	2,505	2.3 ± 0.9	< 0.001*
Alcohol consumption (g/day)		982	2.1 ± 11.3	2,112	3.6 ± 11.2	0.001*
Sucrose consumption (g/day)		982	21.7 ± 10.1	2,112	22.3 ± 9.1	0.082
		n	%	n	%	P value‡
Educational status	High	174	13.6	591	24.0	< 0.001*
	Middle	637	49.6	1,460	59.3	
	Low	472	36.8	411	16.7	
History of cancer	No	1,274	94.4	2,389	95.4	0.205
	Yes	75	5.6	116	4.6	
Hypertension	No	783	58.0	1,976	78.9	< 0.001*
	Yes	566	42.0	529	21.1	
Diabetes mellitus	No	1,221	90.5	2,392	95.5	< 0.001*
	Yes	128	9.5	113	4.5	
Dyslipidemia	No	1,255	93.0	2,332	93.1	0.942
	Yes	94	7.0	173	6.9	
Current smoker	No	824	89.9	1,951	89.8	0.363
	Yes	93	10.1	221	10.2	
Stressful life events during the previous month	None	85	6.4	78	3.1	< 0.001*
	Few	394	29.8	434	17.4	
	Some	643	48.7	1,473	59.2	
	Many	199	15.1	504	20.2	
Frequency of brushing per day	0	171	13.1	496	19.9	< 0.001*
	1	566	43.3	1,448	58.0	
	2	529	40.5	550	22.0	
	3	41	3.1	3	0.1	
Dental check-ups	No	1,228	91.0	2,111	84.3	< 0.001*
	Yes	121	9.0	394	15.7	

SD, standard deviation.
†P value according to Student's *t*-test.
‡P value according to Chi-square test.
*statistically significant.

Discussion

The present study comprehensively examined the risk factors for having fewer than 20 teeth among the general female population in Japan. The results showed that higher parity, especially, two or more completed pregnancies, was a significant independent risk factor for having fewer than 20 teeth. To the best of our knowledge, only nine studies have reported the association between parity and the number of teeth (Stalp and Zuhrt 1979; Rundgren and Osterberg 1987; Wysokińska-Miszczuk 1987; Christensen et al. 1998; Scheutz et al. 2002; Russell et al. 2008; Ueno et al. 2013; Han et al. 2017; Oziegbe and Schepartz 2019). Among these studies, only one, which was conducted in Korea, investigated the association between parity and having fewer than 20 teeth (Han et al. 2017). In that survey, the presence of birth history, older age, current smoker, low educational level, and lack of hormone replacement therapy were identified as significant risk factors for having fewer than 20 teeth. However, oral health habits, such as frequency of tooth brushing and dental check-ups, were not included for the statistical adjustment of variables, although poor oral health habits were powerful risk factors for having fewer than 20 teeth. Furthermore, the Korean study did not report whether increasing parity increased the risk of having fewer than 20 teeth (Han et al. 2017). However, our present study revealed that a higher parity and poor oral health-related factors were independent risk factors for having fewer than 20 teeth in women, after statistically adjusting for well-known risk factors of tooth loss such as oral

Table 2. Crude and adjusted odds ratios and 95% confidence intervals for variables associated with having fewer than 20 teeth.

Variable	Number of teeth (< 20)					
			Model 1[#1]		Model 2[#2]	
	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (0.95% CI)	P value
Parity						
0	1		1		1	
1	2.906 (1.567-5.390)	0.001*	2.074 (0.877-4.905)	0.097	2.180 (0.862-5.515)	0.100
2	2.876 (1.626-5.087)	< 0.001*	2.448 (1.112-5.392)	0.026*	2.485 (1.063-5.812)	0.036*
3	4.047 (2.281-7.181)	< 0.001*	2.508 (1.132-5.557)	0.023*	2.844 (1.206-6.702)	0.017*
≥ 4	10.68 (5.843-19.52)	< 0.001*	3.807 (1.610-8.997)	0.002*	4.305 (1.694-10.94)	0.002*
Dental check-ups No (vs. yes)	1.894 (1.527-2.350)	< 0.001*	1.448 (1.083-1.934)	0.012*	1.579 (1.130-2.206)	0.007*
Frequency of brushing per day						
3	1		1		1	
2	1.134 (0.929-1.384)	0.216	1.052 (0.799-1.385)	0.718	1.107 (0.811-1.512)	0.523
1	2.790 (2.259-3.445)	< 0.001*	1.658 (1.227-2.239)	0.001*	1.601 (1.138-2.251)	0.007*
0	39.64 (12.12-129.7)	< 0.001*	11.821 (2.004-69.72)	0.006*	13.22 (1.422-122.9)	0.023*
Age (per 1-year increase)	1.135 (1.126-1.145)	< 0.001*	1.134 (1.122-1.147)	< 0.001*	1.140 (1.125-1.154)	< 0.001*
Educational status						
High	1		1			
Middle	1.482 (1.222-1.797)	< 0.001*	1.425 (1.093-1.856)	0.009*	1.537 (1.141-2.072)	0.005*
Low	3.901 (3.147-4.834)	< 0.001*	1.399 (1.028-1.903)	0.033*	1.509 (1.062-2.146)	0.022*
Current smoker Yes (vs. no)	0.889 (0.689-1.146)	0.363			1.830 (1.213-2.760)	0.004*
History of cancer Yes (vs. no)	1.212 (0.900-1.634)	0.206				
Hypertension Yes (vs. no)	2.700 (2.337-3.120)	< 0.001*	1.033 (0.834-1.279)	0.767	1.151 (0.904-1.466)	0.255
Diabetes mellitus Yes (vs. no)	2.219 (1.707-2.884)	< 0.001*	1.101 (0.756-1.604)	0.615	0.946 (0.620-1.445)	0.798
Dyslipidemia Yes (vs. no)	1.010 (0.778-1.310)	0.942				
Stressful life events during the last month						
None	1				1	
Few	0.833 (0.595-1.166)	0.287	1.544 (0.918-2.597)	0.102	1.843 (1.025-3.314)	0.041*
Some	0.401 (0.291-0.552)	< 0.001*	1.229 (0.744-2.031)	0.420	1.318 (0.749-2.317)	0.338
Many	0.362 (0.256-0.513)	< 0.001*	1.584 (0.919-2.729)	0.098	1.743 (0.950-3.199)	0.073
Alcohol consumption (g/day) (per 1-g increase)	0.985 (0.976-0.994)	0.001*	1.011 (1.003-1.020)	0.011*	1.009 (0.999-1.018)	0.065
Sucrose consumption (g/day) (per 1-g increase)	0.993 (0.985-1.001)	0.082				

OR, odds ratio; CI, confidence interval.

[#1]Adjusted for representative variables that were significant in univariate analysis (P < 0.05).

[#2]Adjusted for smoking and representative variables that were significant in univariate analysis (P < 0.05).

*statistically significant.

health habits. Our study also revealed that compared with nulliparous women, women with two, three, and four completed pregnancies had a 2.485-, 2.844-, and 4.305-fold increased risk of having fewer than 20 teeth, respectively. The Korean study revealed that the presence of the parity, regardless of the number of parities, was a risk factor for having fewer than 20 teeth, while the present study revealed the precise number of parities that were associated with the risk of having fewer than 20 teeth in Japanese women. Comparing our study and the previous Korean study methodologically, the present study provides a higher quality of evidence indicating a higher parity as an independent risk factor for having fewer than 20 teeth; this finding makes our study notable.

Moreover, in Japan, to the best of our knowledge, only one study has investigated the association between tooth loss and parity (Ueno et al. 2013). The results of that study revealed that the number of teeth significantly declined with increasing parity. However, a sample size of 649 is relatively small, and the study confirmed only the statistical trend that the higher the number of parities, the fewer the number of the teeth. The study did not survey the threshold value of the number of parities that significantly affected tooth loss. Furthermore, systemic diseases such as diabetes mellitus, which is a strong risk factor for periodontal disease that can lead to tooth loss, were not statistically adjusted for among the variables examined in that Japanese study. In contrast, our study included 3,854 participants, which was six times more than the sample size included in the previous Japanese study. Furthermore, we revealed that a higher parity, especially, two or more parities, was an independent risk factor for having fewer than 20 teeth after adjusting for various confounding factors of tooth loss. The present study provides more robust evidence that higher

parity is a risk factor for having fewer than 20 teeth in the Japanese female population than that revealed in the previous Japanese study. Our study is the ninth study to determine the association between parity and tooth number worldwide; however, our study is the largest study in the general female population in Japan. It is the first to comprehensively investigate the risk factors (parity, oral health status, and SES) for having fewer than 20 teeth, among the general female population in Japan, and is the first to identify parity, using precise numbers, as risk factors for having fewer than 20 teeth.

Why higher parity is an independent risk factor for having fewer than 20 teeth has not been definitively answered; however, one possibility is that periodontal disease, which is one of the most common diseases associated with tooth loss, worsens during pregnancy. It has been reported that gingival inflammatory symptoms worsen during pregnancy (Taani et al. 2003; Gürsoy et al. 2008). Increased hormone levels during pregnancy lead to increased susceptibility to gingival inflammation without a clear association with the amount of dental plaque (Gürsoy et al. 2008), and pregnant women have been found to be more susceptible to develop periodontal disease than non-pregnant women (Taani et al. 2003; Russell et al. 2010; Gil et al. 2019). Past surveys have also reported that approximately 40% of pregnant women were found to have periodontal disease (Vamos et al. 2015; Bui et al. 2019). It is understandable that if periodontal disease is aggravated during every pregnancy, then the risk of tooth loss may increase for every delivery. However, the association between parity and tooth loss may not be directly causal. In other words, dentists' approach to management during pregnancy may be the cause for tooth loss. Although dental treatment has been shown to be safe during pregnancy (Newnham et al. 2009; Morelli et al. 2018), the possibility that dentists may choose to alter treatment plans for pregnant women or to delay treatment until after parturition has been reported in past studies (Pistorius et al. 2003; Morelli et al. 2018). Furthermore, Pistorius et al. (2003) reported that only 54.6% of surveyed dentists felt that they were sufficiently informed and educated about the treatment of pregnant patients. Therefore, the challenge associated with the management by dentists is thought to be one of the explanations for the association between higher parity and fewer teeth. Furthermore, the patients' awareness of and behavior toward oral health during pregnancy, postpartum, and parenting have the potential to cause tooth loss. It is well known that many pregnant women hesitate to visit the dental clinic (Ressler-Maerlender et al. 2005; George et al. 2012). It has also been reported that the lack of general awareness of the importance of oral health during pregnancy and the deep-rooted misunderstanding that dental treatments during pregnancy may adversely affect the unborn baby (Ressler-Maerlender et al. 2005; George et al. 2012). Furthermore, barriers to accessing care can lead to the hesitation for receiving oral care during pregnancy (Wasylko et al. 1998; Boggess and Edelstein 2006; George et al. 2012). Therefore, despite the availability of public dental service for dental check-up during pregnancy worldwide, the rates of usage of this service is generally low (George et al. 2012). Moreover, during the postpartum and parenting, women may not consider the need to visit the dental clinic as a priority because of being busy with child rearing. Those multiple factors could explain our present result of higher parity as an independent risk factor for having fewer than 20 teeth. However, the explanation for the association between higher parity and having fewer than 20 teeth could not be achieved scientifically and, thus, further studies are needed to verify this.

This study had several limitations. First, the number of remaining teeth was determined using a self-reported questionnaire as compared to confirming by clinical examination. Furthermore, questionnaires on the number of teeth did not mention presence of fixed bridge pontics, dental implants, or supernumerary teeth. Therefore, non-natural teeth such as the fixed bridge pontics, dental implants, and supernumerary teeth as natural teeth may have counted for some participants. However, the fact that we determined the number of remaining teeth using only self-reported questionnaire should not be problematic because several surveys have reported finding a close correlation between the number of self-reported teeth and that determined in a clinical examination (Buhlin et al. 2002; Ueno et al. 2018). Nonetheless, some discrepancies in the tooth count may exist. Second, since we did not have baseline data, it was not possible to compare participants with non-participants; therefore, the final sample (3,854 women) may not be representative of the original target population (8,298 women). Third, as the data were collected in 2005, the previous socioeconomic and lifestyle situations of the participants may differ from those in the present study. Therefore, our findings may not be a generalization of the present population. Finally, selection bias was noted for variables included in the statistical analysis. The questionnaire used in this study included many items on lifestyle-related factors, medical history, oral health status and habits, SES, and dietary intake. However, we did not include all these variables in the statistical analysis because we selected only those that were associated with tooth loss.

In conclusion, this cross-sectional study—the largest study conducted to date—revealed that higher parity, especially, more than two pregnancies, increases the risk of having fewer than 20 teeth among Japanese women. Our results emphasize the importance of good oral health habits in women, especially, during pregnancy and in the postpartum period, to maintain 20 or more teeth.

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Conflict of Interest

The authors declare no conflict of interest.

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