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Risk of Dental Discoloration and Enamel Dysplasia in Children Exposed to Tetracycline and Its Derivatives

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Purpose: To examine the risk of dental abnormalities after exposure to tetracycline and its derivatives (TCs) in Korean children.
Materials and Methods: Children aged 0–17 years with a claim for prescriptions of TCs between 2002 and 2015 were identified from the Sample Research Database 2.0 of the National Health Insurance Service. Children not exposed to TCs were selected as the control group by matching sex and age (1:4). Cumulative incidence rate and relative risk of dental abnormalities after TCs exposure were investigated.
Results: The 10-year cumulative incidence rate in the 0–12 years group was 3.1% [95% confidence interval (CI), 2.3–3.9]. The 10-year cumulative incidence rates were 7.0%, 1.9%, and 1.6% in the 0–7, 8–12, and 13–17 years age groups (95% CI: 4.7–9.3, 1.2–2.6, and 1.3–1.9, respectively). There was no significant difference in the risk of dental abnormalities according to TC exposure among the age groups of 0–7 years [adjusted hazard ratio (aHR)=1.0], 8–12 years (aHR=1.1), and 13–17 years (aHR=1.2).
Conclusion: Short-term exposure to TCs does not appear to increase the risk of dental abnormalities in children aged 0–7 and 0–12 years. Restrictions on the use of TCs in children aged 8–12 years, in some countries, may warrant consideration.

Key Words: Tooth abnormalities, tooth discoloration, tetracyclines, dental care for children, Korea

INTRODUCTION

Tetracycline and its derivatives (TCs) have been widely used worldwide since Duggar, et al. discovered chlortetracycline (trade name Aureomycin in relation to its yellow color) in 1945 from the "ultra-mold" *Streptomyces aureofaciens*.[1] This class of broad-spectrum antibiotics is not only prescribed for scrub typhus and Rocky Mountain spotted fever, but it also has antibacterial activity against various infections, including those caused by *Bacillus anthracis*, *Borrelia species*, and *Plasmodium falciparum*.[2] However, since Shwachman, et al.[3] reported dental discoloration in approximately 5% of 300 newborns and children who had been prescribed chlortetracycline or oxytetracycline (10–20 mg/kg/day) for >1 year in 1956, a number of reports have raised concerns regarding dental discoloration and enamel dysplasia (hereafter referred to as dental abnormalities). Under this background, in 1963, the United States Food and Drug Administration issued a statement that TCs should not be prescribed to children under the age of 8 years and pregnant or lactating women, allowing limited use only when the potential benefits outweighed the risks.[4-6] In addition, in some countries, such as South Korea and the United Kingdom, health authorities have limited the use of TCs in children aged 8–11 years, making clinicians hesitant when prescribing these antibiotics.[7]

However, these inexpensive and desirable antibiotics are use-

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ful and effective both for the indications mentioned above and macrolide-resistant *Mycoplasma pneumoniae* (MRMP) and are often used as first-line drugs of choice.[8-11] Moreover, recent dental abnormalities-related studies have reported that the risk of dental abnormalities is not as high as the risk reported in previous literature when the actual period of use is <14–21 days. In particular, newer TCs, such as doxycycline or tigecycline, reportedly pose a lower risk than first-generation TCs.[12-16] However, there are no large-scale observational studies to support this, and the relative risk compared with that of the general population is not precisely known.

We examined the attributable risk of dental abnormalities in Korean children exposed to TCs and compared it with that in children not exposed to TCs using nationwide population-based data. Further, we investigated whether there is a higher risk of dental abnormalities in children aged 8–12 years and compared it with that in children aged 13–17 years, who have no age restrictions on TCs use. The cumulative incidence of dental abnormalities was also assessed.

MATERIALS AND METHODS

Data source

We used the Sample Research Database 2.0 maintained by the National Health Insurance Service (NHIS), a universal single payer in Korea. The NHIS subscribers and Medicare recipients who maintained their qualifications as of 2006 were eligible for this cohort. Among them, a cohort was constructed by stratifying age, sex, subscriber classification, insurance decile, and region of one million people, approximately 2% of the total population in Korea. This cohort provides information on socioeconomic status (including death and disability), diagnoses by International Classification of Diseases, 10th edition (ICD-10) codes, prescription codes for medications, and medical resource utilization between 2002 and 2015.

Study design

This study was designed as a population-based retrospective cohort study. Children aged 0–17 years with a claim for TCs prescription between January 2002 and December 2015 were included. We examined the cumulative incidence rate of dental abnormalities after exposure to TCs and their relative risk in comparison with an unexposed population. The age groups were divided as follows: 0–7 years, 8–12 years, and 13–17 years. The 13–17 years age group was set as a reference for age comparison. Moreover, children and adolescents without TCs prescriptions were selected as the TCs-unexposed group through 1:4 exact matching for age and sex. The exclusion criteria for the TCs-exposed group were as follows: 1) cases where TCs were prescribed in 2002 (washout period); 2) cases where the first input date of the diagnosis code of dental abnormalities was earlier than the date of the first TCs prescription; 3) cases in which a diagnosis code for dental abnormalities was registered within 6 months of the date of the first TCs prescription; and 4) death within 6 months of the date of the first TCs prescription. This study was approved by the Institutional Review Board (IRB) of Yonsei Medical University, and the need for informed consent was waived because this was a de-identified population-based study (IRB No. 4-2020-0316).

Cases definition

Dental abnormalities were defined as cases with a diagnosis code for dental discoloration or dental enamel dysplasia (ICD-10 codes: K03.6, K03.7, K00.8, K00.4, K00.5, and K00.9). A pediatric dental professional (CM Kang) selected the codes. TCs exposure was defined as an Anatomical Therapeutic Chemical (ATC) code corresponding to TCs administered systemically for at least 1 day. Detailed ICD-10 codes for dental abnormalities and ATC codes for systemic TCs are listed in Supplementary Table 1 and Supplementary Table 2 (only online), respectively.

Statistical analyses

Characteristics of the study population including sex, age, and underlying diseases were obtained from the database. The ICD-10 codes for each underlying disease are presented in Supplementary Table 3 (only online). We defined the presence of an underlying disease as any diagnosis according to ICD-10 codes within 6 months before the first prescription date of TCs. The characteristics of the study population in each age group are presented as percentages for categorical variables and mean (±SD) values for continuous variables. As a primary outcome, the attributable risk of dental abnormalities in children exposed to TCs was compared with that in children not exposed to TCs. The 1: max 4 exact matching for age and sex was used to reduce selection bias between the TCs-exposed and TCs-unexposed groups. A stratified Cox hazards regression model was used to analyze the relative risk of dental abnormalities. Underlying disease was adjusted as a confounding variable. As secondary outcomes, cumulative incidence rates of dental abnormalities according to age groups were calculated using Kaplan–Meier estimation with log-rank test after Bonferroni's correction. For age comparisons within the exposed group, sex and underlying disease were adjusted. A two-sided p value of <0.05 was considered to be statistically significant. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC, USA) and GraphPad Prism version 9.1.0 (GraphPad Software, La Jolla, CA, USA).

RESULTS

Of the 996095 individuals in the sample cohort, 248385 had a prescription for TCs for at least 1 day. Of these, 233554 were excluded for the following reasons: age ≥18 years at the time of the first TCs prescription (n=202840), TCs prescription in

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2002 (n=29432), dental abnormality before TCs prescription (n=756), and dental abnormality or death within 6 months after TCs prescription (n=526). Finally, 14831 individuals were included, and 201 of them (1.4%) were diagnosed with dental abnormalities. Next, 59324 control individuals not exposed to TCs were selected based on age and sex 1:4 matching (Fig. 1). The baseline characteristics of the TCs-exposed and TCs-unexposed groups are shown in Table 1. In both the TCs-exposed and TCs-unexposed groups, the male to female ratio was 1.1:1. Only 2.7% of the TCs-exposed group and 2.1% of the TCs-unexposed group had at least one underlying disease. A total of 14831 individuals with at least one claim for a TCs prescription were identified. The 13–17 years age group had the highest number of cases [12649 (85.3%)], followed by the 8–12 years age group with 1695 cases (11.4%) and those under 8 years with 487 cases (3.3%). The duration of TCs prescription differed according to age group, with 5.4 days (SD, 11.0) for those under 8 years, 15.6 days (SD, 36.0) for those aged 8–12 years, and 21.4 days (SD, 39.8) for those aged 13–17 years (p< 0.001). When the number of prescriptions by year was compared, the annual number of TCs prescriptions for children aged 0–12 years decreased significantly from 375.6 to 54.0 around 2008, the year when the Drug Utilization Review (DUR) was collectively applied in Korea (p<0.001). Among the prescribed TCs (n=14867), doxycycline was the most common [10087 cases (67.8%)], followed by minocycline [3770 cases (25.4%)], tetracycline [1009 cases (6.8%)], and oxytetracycline [1 case (0.01%)]. Detailed ATC codes, generic name codes, and generic name of TCs categories are described in Supplementary Table 2 (only online).

Cumulative incidence rates of dental abnormalities

The 5-year and 10-year cumulative incidence rates of dental abnormalities after TCs exposure in the 0–12 years age group were 2.1% [95% confidence interval (CI), 1.5–2.7] and 3.1% (95% CI, 2.3–3.9), respectively (Fig. 2A). Regarding age group, the 5-year and 10-year cumulative incidence rates of dental abnormalities in the 0–7 years age group were the highest at 4.7% (95% CI, 2.8–6.6) and 7.0% (95% CI, 4.7–9.3), respectively, which were significantly higher than 0.9% (95% CI, 0.7–1.1) and 1.6% (95% CI, 1.3–1.9), respectively, in the 13–17 years age group (p<0.001). Meanwhile, the 5-year and 10-year cumulative incidence rates of dental abnormalities in the 8–12 years age group were 1.3% (95% CI, 0.7–1.9) and 1.9% (95% CI, 1.2–2.6),

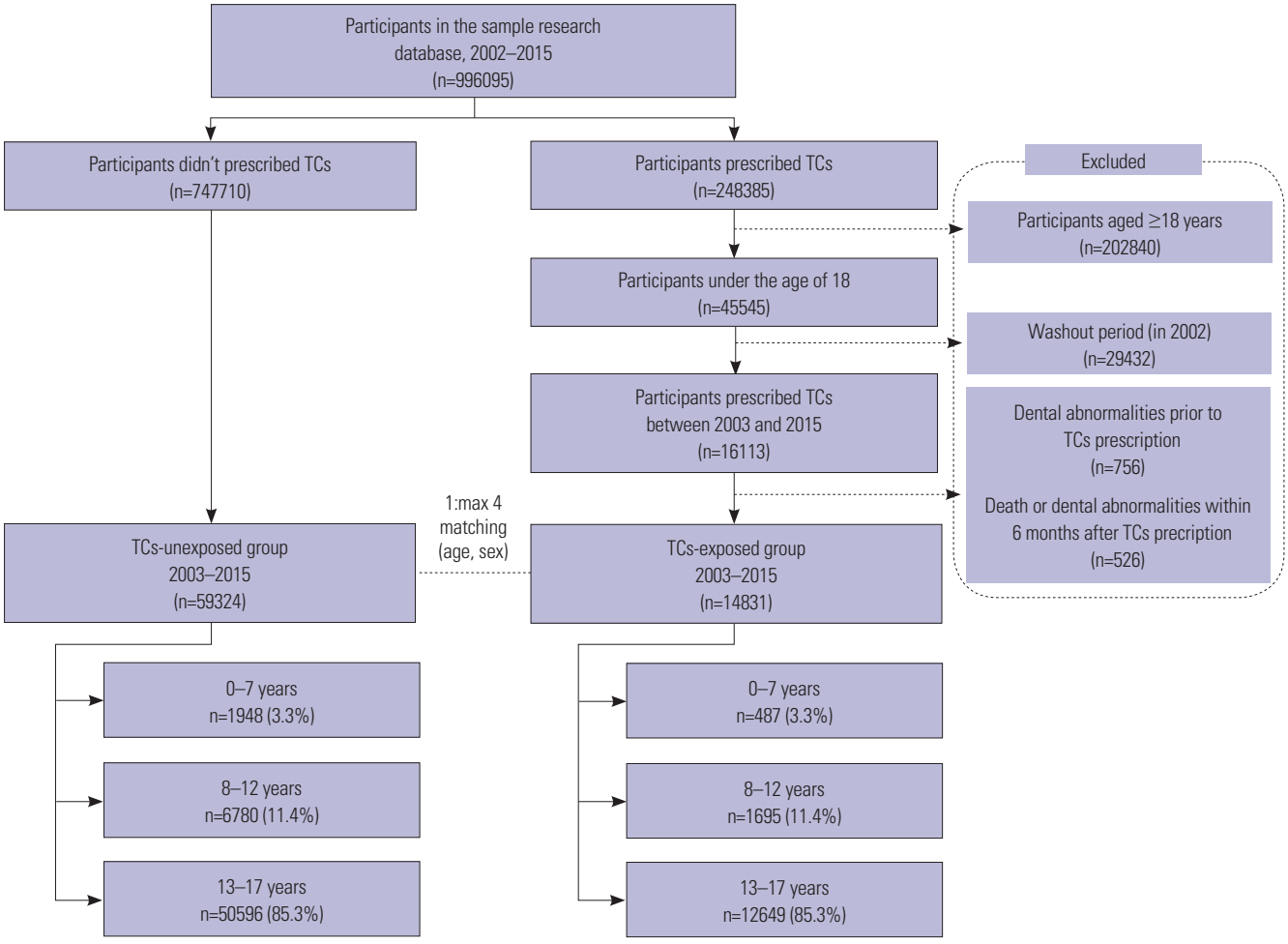

Fig. 1. Flow diagram for selection of the study population. TCs, tetracycline and its derivatives.

Table 1. Characteristics of the Study Population and Controls after 1:4 Exact Matching for Age and Sex

Characteristics	Age 0–7 years		Age 8–12 years		Age 13–17 years	
	TCs-exposed (n=487)	TCs-unexposed (n=1948)	TCs-exposed (n=1695)	TCs-unexposed (n=6780)	TCs-exposed (n=12649)	TCs-unexposed (n=50596)
Age (yr)	4.6±1.8	4.6±1.8	11.0±1.3	11.0±1.3	15.3±1.4	15.3±1.4
Sex, female	221 (45.4)	884 (45.4)	941 (55.5)	3764 (55.5)	6027 (47.7)	24108 (47.7)
Underlying disease	6 (1.2)	29 (1.5)	38 (2.2)	108 (1.6)	354 (2.8)	1107 (2.2)
Neurologic and neuromuscular	0 (0)	3 (0.2)	2 (0.1)	5 (0.1)	17 (0.1)	57 (0.1)
Cardiovascular	0 (0)	2 (0.1)	0 (0)	6 (0.1)	26 (0.2)	85 (0.2)
Respiratory	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Genitourinary	0 (0)	2 (0.1)	1 (0.1)	2 (0.03)	18 (0.1)	35 (0.1)
Gastrointestinal	4 (0.8)	6 (0.3)	15 (0.9)	57 (0.8)	108 (0.9)	394 (0.8)
Hematologic or immunologic	0 (0)	9 (0.5)	4 (0.2)	3 (0.04)	11 (0.1)	27 (0.05)
Metabolic	0 (0)	4 (0.2)	7 (0.4)	11 (0.2)	101 (0.8)	265 (0.5)
Malignancy	0 (0)	3 (0.2)	2 (0.1)	5 (0.1)	29 (0.2)	77 (0.2)
Prematurity and neonatal	2 (0.4)	2 (0.1)	0 (0)	0 (0)	1 (0.01)	1 (0.01)
Other congenital or genetic defect	0 (0)	2 (0.1)	10 (0.6)	24 (0.4)	79 (0.6)	263 (0.5)
Miscellaneous chronic disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Duration of TCs treatment (day)†	5.4±11.0		15.6±36.0		21.4±39.8	
≤7 days	417 (85.6)		997 (58.8)		5958 (47.1)	
8–14 days	45 (9.2)		297 (17.5)		2469 (19.5)	
15–28 days	17 (3.5)		205 (12.1)		1936 (15.3)	
>28 days	8 (1.6)		196 (11.6)		2286 (18.1)	
Duration from index date‡ to last follow-up§ (yr)	10.7±2.6	10.7±2.4	9.3±3.1	9.4±3.1	6.8±3.6	6.8±3.6

TCs, tetracycline and its derivatives.
Data are presented as mean±standard deviation or n (%).
*Diagnostic codes input within 6 months before the first TCs prescription; †From date of the first prescription of *TCs to last prescription date; ‡Date of the first TCs prescription. For unexposed group, the first TCs prescription date of the matched exposed group was used; §Date when a dental abnormalities diagnosis code was entered for the first time or the date of death or last date of study duration (December 31, 2021).

respectively, and there were no significant differences when compared with those in the 13–17 years age group (p=0.67) (Fig. 2B). When the 0–7 years age group was divided into 0–3 years and 4–7 years subgroups, there were no significant differences for 5-year and 10-year cumulative incidence rates between the two subgroups [5.1% (95% CI, 1.4–8.7) and 9.5% (95% CI, 4.5–14.3), respectively, in the 0–3 years age group; 4.6% (95% CI, 2.4–6.8) and 6.1% (95% CI, 3.5–8.5), respectively, in the 4–7 years age group] (Fig. 2C).

When analyzing the dental abnormalities by the duration of TCs prescription, there was no significant difference in dental abnormalities according to the prescription days in both the 0–7 year age group and the 8–12 year age group (Fig. 2D and E). When the risk of dental abnormalities according to age was analyzed by including only individuals with a prescription of ≤14 days, the 0–7 years group had a significantly higher risk than the 8–12 years and 13–17 years groups (p<0.001) (Fig. 2F).

Next, the 13–17 years age group was set as the reference, with no age restriction for TCs prescription, and the risk of dental abnormalities after TCs exposure was evaluated according to age group. The relative risk in the 0–7 years age group was significantly higher [adjusted hazard ratio (aHR)=4.5] than the reference age group (95% CI, 3.1–6.5, p<0.001). There was no difference in the risk of dental deformities between the 0–3 years group and the 4–7 years group. Meanwhile, the risk of dental abnormalities in the 8–12 years age group was aHR=1.3 (95% CI, 0.9–1.9, p=0.25), which was higher than that in the 13–17 years age group, but the difference was not statistically significant (Fig. 3A).

Attributable risk for dental abnormalities after TCs exposure

The cumulative incidence rates of dental abnormalities according to 10000 person-years in each age group are shown in Table 2. In the TCs-exposed group, the 0–7 years age group showed the highest rate of 67.0 per 10000 person–years, while the 8–12 years and 13–17 years age groups showed the rate of 19.6 per 10000 person–years and 15.8 per 10000 person–years, respectively. When analyzing the relative risk of dental abnormalities according to TCs exposure, there was no significant difference in the risk in the 0–7 years age group, the 8–12 years age group, and the 13–17 years age group [aHR=1.0 (95% CI, 0.7–1.5), p=0.87 in the 0–7 years age group; aHR=1.1 (95% CI, 0.8–1.7), p=0.55 in the 8–12 years age group; aHR=1.2 (95% CI, 1.0–1.4), p=0.10 in the 13–17 years age group] (Fig. 3B).

Regarding the age subgroups, the incidence of dental abnor-

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malities in the 0–3 years age group with TCs exposure seemed to be higher than that in the 0–3 years age group without TCs exposure; however, the difference was not statistically significant [aHR=1.4 (95% CI, 0.7–2.5), p=0.35]. There was no difference in the incidence of dental abnormalities in the 4–7 years age group according to TCs exposure [aHR=0.9 (95% CI, 0.6–

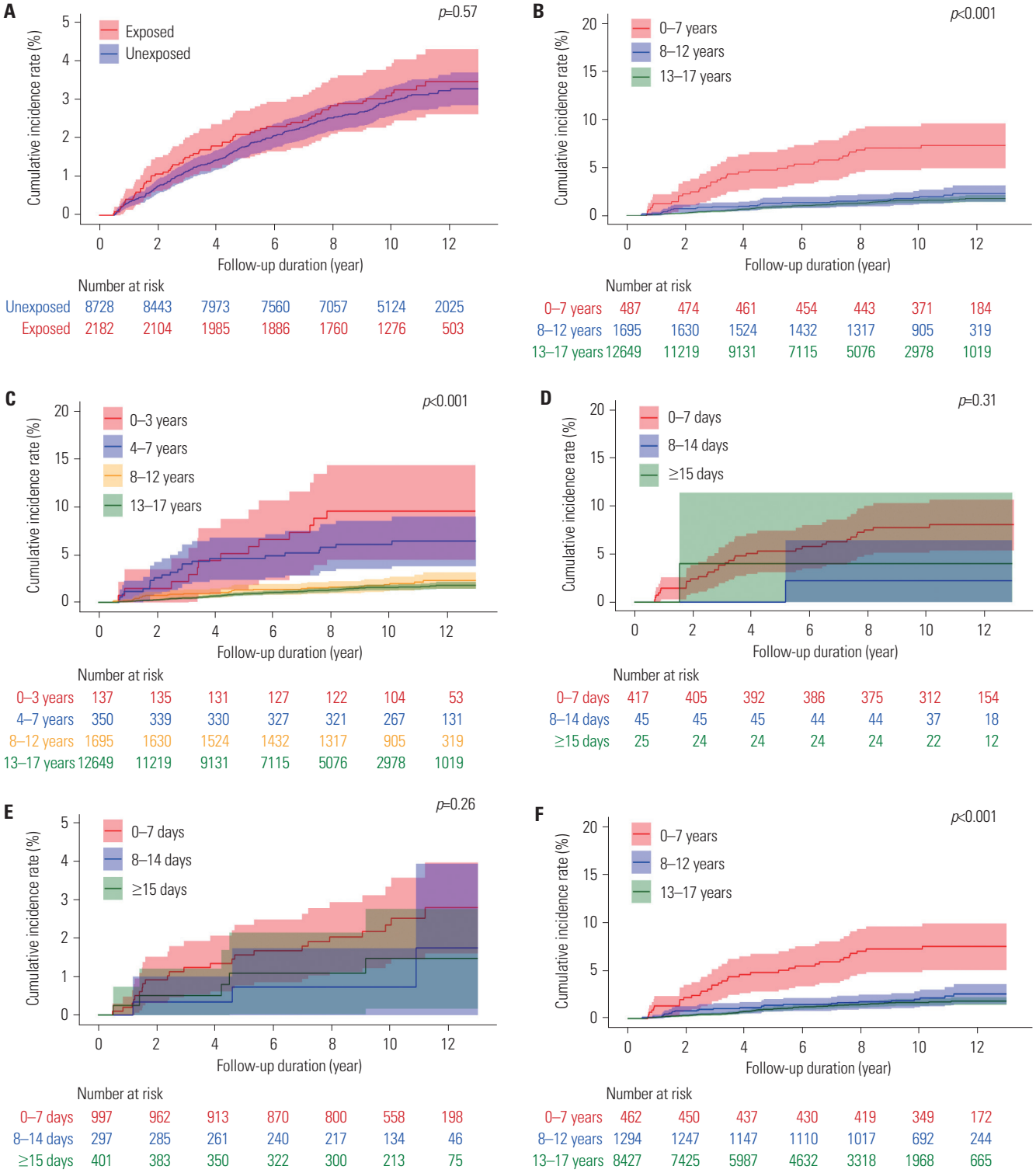

Fig. 2. Cumulative incidence rate of dental abnormalities after TCs prescription. (A) Incidence of dental abnormalities in children aged 0–12 years. (B and C) Incidence of dental abnormalities according to age group in children aged 0–17 years with TCs exposure. (D) Comparison of the incidence of dental abnormalities according to cumulative prescription days (0–7 days/8–14 days/≥15 days) in children aged 0–7 years. (E) Comparison of the incidence of dental abnormalities according to cumulative prescription days (0–7 days/8–14 days/≥15 days) in children aged 8–12 years. (F) Incidence of dental malformations according to age in children aged 0–17 years exposed to TCs for <15 days. TCs, tetracycline and its derivatives.

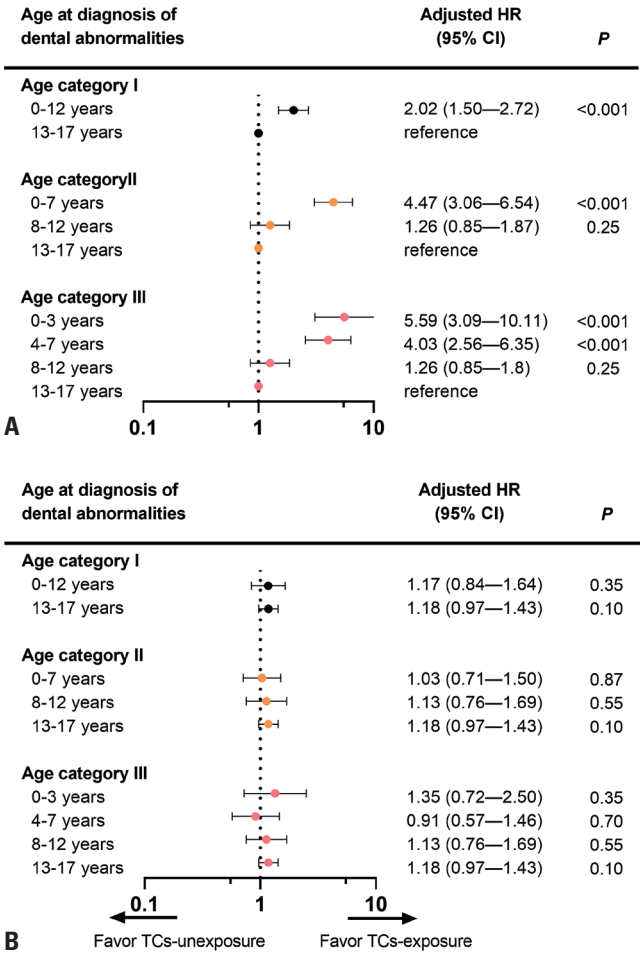

Fig. 3. Risk of dental abnormalities according to age groups in children with TCs exposure. (A) Adjusted hazard ratio of dental abnormalities according to age groups in children with TCs exposure (reference group: 13–17 years age). (B) Adjusted hazard ratio of dental abnormalities according to TC exposure. TCs, tetracycline and its derivatives; CI, confidence interval.

1.5), p=0.70] (Fig. 3B).

DISCUSSION

This population-based study showed the real-world incidence of dental abnormalities in Korean children after TCs exposure. The incidence of dental abnormalities in the 0–7 years age group with TCs exposure was not significantly different from that in the 0–7 years age group without TCs exposure. The occurrence of dental abnormalities after TCs exposure was the highest in the 0–7 years age group; however, there was no difference in the incidence of dental abnormalities in the 8–12 years age group, compared with that in the 13–17 years age group, the age at which TCs use is permitted in Korea.

We found no significant difference in the incidence of dental abnormalities between the TCs-exposed and the TCs-unexposed groups, even in 0–3 years and 4–7 years age subgroups.

Table 2. Cumulative Incidence Rate and Relative Risk of Dental Abnormalities after TCs Exposure

Age groups	Cumulative incidence rate per 10000 person-year		aHR*	95% CI	*p* value
	TCs-exposed	TCs-unexposed			
0–7 years	67.04	64.38	1.03	0.71–1.50	0.87
0–3 years	88.23	64.78	1.35	0.72–2.50	0.35
4–7 years	58.71	64.22	0.91	0.57–1.46	0.70
8–12 years	19.59	17.18	1.13	0.76–1.69	0.55
13–17 years	15.77	13.41	1.18	0.97–1.43	0.10

TCs, tetracycline and its derivatives; aHR, adjusted hazard ratio; CI, confidence interval.
*A stratified Cox hazards regression model adjusted underlying disease was used.

This finding suggests that the actual risk of dental abnormalities attributable to TCs, exceeding the baseline natural incidence at these ages, may be absent or minimal. In addition, the 10-year cumulative incidence of dental abnormalities in the 0–12 years old group was 3.1% in our study, which was lower than the 4%–90% reported in previous studies conducted between the 1950s and the 1970s.[3,4,17,18] Two possible explanations can be proposed for this phenomenon. First, the prescription duration of TCs in our study (98% of TCs exposure ≤28 days) was not sufficiently long, as in the previous studies. Grossman, et al.[4] reported that permanent dental staining occurred in proportion to the course of TCs use in a study of 160 children who were followed up from newborn stage; however, the risk of staining was low or negligible if TCs were used fewer than five times. Wallman and Hilton[17] also reported that the severity of dental discoloration is correlated with birth weight, gestational age, and tetracycline dosage, including the length of treatment. Second, newer generations of TCs, such as doxycycline, which was the most frequently prescribed type of TCs in our study, may have had less impact on the extent of dental abnormalities. It is known that TCs attach to calcium ion to form a tetracycline-calcium orthophosphate complex, thereby inhibiting proper dental mineralization.[19,20] However, in the case of doxycycline, research indicates that it has less avidity to calcium and causes less dental discoloration than the first-generation TCs (tetracycline or oxytetracycline).[21,22] Cross, et al.[2] suggested in their systematic review that there is no correlation between permanent dental discoloration and the use of doxycycline in children when the drug is given for up to 14 days. In this context, the American Academy of Pediatrics recently announced in 2018 that doxycycline can be safely used for up to 21 days for all indications, regardless of age.[23] Our findings emphasized the safety of short-course use of TCs in children under 8 or 12 years of age, as suggested by recent studies and guidelines, based on large-scale population-based data.

Notably, there was no difference in the incidence of dental abnormalities after TCs exposure in the 8–12 years age group, compared with that in the 13–17 years age group. Moreover, our data showed that prescriptions of TCs have declined sharply

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since 2008, when the Food and Drug Administration in Korea started real-time feedback on age-restricted TCs prescriptions through the DUR program. This indicates that many clinicians hesitate to prescribe these medications, even though domestic and international guidelines have recommended since 2008 that TCs, especially doxycycline, can be prescribed regardless of age, if indicated for use.[7,23,24] Therefore, easing of age restrictions in children aged 8–12 years by health authorities will help clinicians select an appropriate treatment for several infectious diseases, such as MRMP, which is especially prevalent among adolescents, particularly in Asia.[9,11]

Our study has several limitations. First, since the data are based on a database established for the main purpose of claiming medical billing for the NHIS, the claimed diagnosis may be underestimated or overestimated, and some unclaimed prescriptions may have been omitted. However, the bias can be eliminated when analyzing attributable risk. Second, it was difficult to collect data regarding accurate prescription doses and cumulative doses. Rather, as 85.6% of the study population were exposed to TCs within 1 week, the safety of TC use can be emphasized when the cumulative dose is not high. Third, it was not possible to analyze the severity and clinical course of the actual dental abnormalities in detail; therefore, we tried to select a diagnostic code that only dentists prescribe. Moreover, cases of enamel dysplasia were almost absent in the 0–7 years group (n=6), which made it difficult to conduct a direct comparison between the TC-exposed and TC-unexposed groups. Lastly, this study was conducted on Korean children, so it does not represent the risk of dental abnormalities in other ethnicities, including Caucasian children.

Nevertheless, to our knowledge, this study is significant because it is the largest population-based study to observe dental abnormalities in children and adolescents who received TCs prescriptions. In addition, our study has the strength of not only observing the long-term cumulative incidence rate through follow-up for several years but also analyzing the attributable risk of dental abnormalities according to TCs exposure by using age- and sex-matched controls.

In conclusion, the incidence of dental abnormalities did not increase in the 0–7 years age group with short-term TCs exposure. No additional risk was found with TCs exposure in the 8–12 years group. Theoretically, the potential for additional risk still exists; therefore, larger, well-designed studies are needed in the future.

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AUTHOR CONTRIBUTIONS

Conceptualization: Ji-Man Kang. Data curation: Seo Jung Kim, Eun Hwa Kim, and Myeongjee Lee. Formal analysis: Seo Jung Kim, Eun Hwa Kim, Myeongjee Lee, Min Young Kim, and Inkyung Jung. Funding acquisition: Ji-Man Kang. Investigation: Seo Jung Kim, Eun Hwa Kim, Myeongjee Lee. Methodology: Seo Jung Kim, Eun Hwa Kim, Myeongjee Lee, and Chung-Min Kang. Project administration: Ji-Man Kang. Resources: Ji-Man Kang. Software: Eun Hwa Kim and Myeongjee Lee. Supervision: Ji-Man Kang, Jong Gyun Ahn, Baek Jee Yeon, Ji Young Lee, Jae Hee Shin, Sung Min Lim, and Inkyung Jung. Validation: Seo Jung Kim, Eun Hwa Kim, and Myeongjee Lee. Visualization: Seo Jung Kim, Eun Hwa Kim, and Min Young Kim. Writing—original draft: Seo Jung Kim and Ji-Man Kang. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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