



Risk of Dental Discoloration and Enamel Dysplasia in Children with Exposure to Tetracycline and its Derivatives: A Retrospective, Population-based Study in Korea, 2002-2015



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Background

- ✓ Tetracycline and its derivatives (hereafter referred to as TCs) is a broad-spectrum antibiotics and widely used worldwide against various infections.
- ✓ Dental discoloration and enamel dysplasia (hereafter referred to as dental abnormalities) prohibited use of TCs to lactating women or children under the age of 8 years in USA and 12 years in South Korea and United Kingdom.

Objectives

- ✓ To examine 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.
- ✓ To investigated whether there was a higher risk of dental abnormalities in children aged 8-12 years and compared it with that in children aged 13-17 years, who had no age restriction concerning TCs use. The cumulative incidence of dental abnormalities was also assessed.

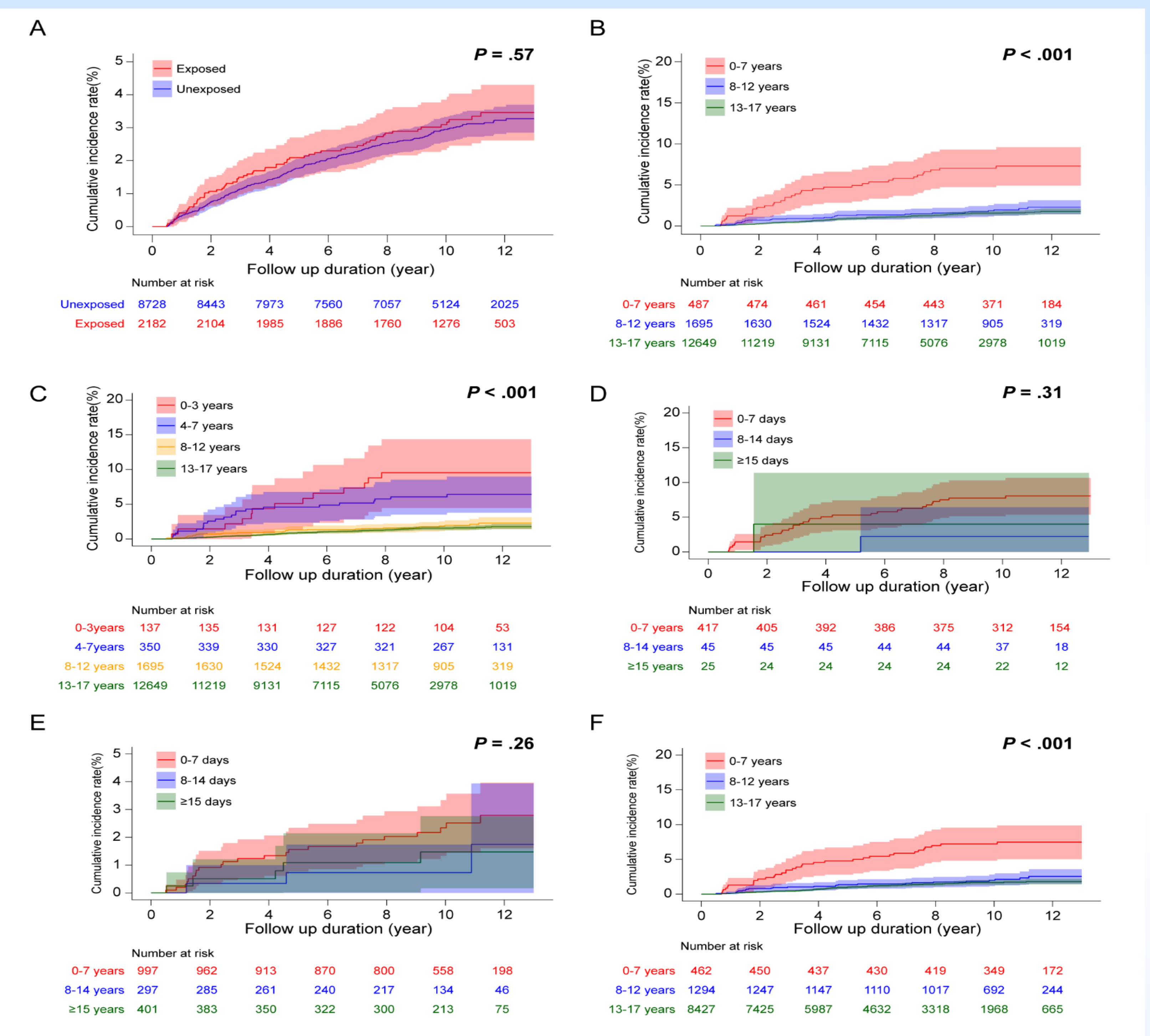
Methods

- ✓ Data source: Data of one million people from sample Research Database 2.0, received from National Health Insurance Service (NHIS), a universal single payer in Korea.
- ✓ Subjects: Children aged 0-17 years with a claim for TCs prescription between January 2002 and December 2015. TCs-exposed group : 14,831 TCs-unexposed group : 59,324 (1:4 exact matching for age and sex)

- ✓ Outcomes: Cumulative incidence rate of dental abnormalities after exposure to TCs according to age groups. Cumulative incidence rate of dental abnormalities after exposure to TCs according to prescription duration. Relative risk of dental abnormalities after TCs-exposure in comparison with the TCs-unexposed group according to age groups. Relative risk of dental abnormalities in the TCs-exposed group according to age groups.
 - Age groups were divided as follows: 0-7 years, 8-12 years, and 13-17 years(reference for age comparison)
 - Prescription duration divided as follows: 0-7 days, 8-14 days, ≥15 days

Results

Cumulative incidence rate of dental abnormalities after TCs prescription



- (A) Incidence of dental abnormalities in children aged 0-12 years
- (B) (C) Incidence of dental abnormalities according to age groups 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

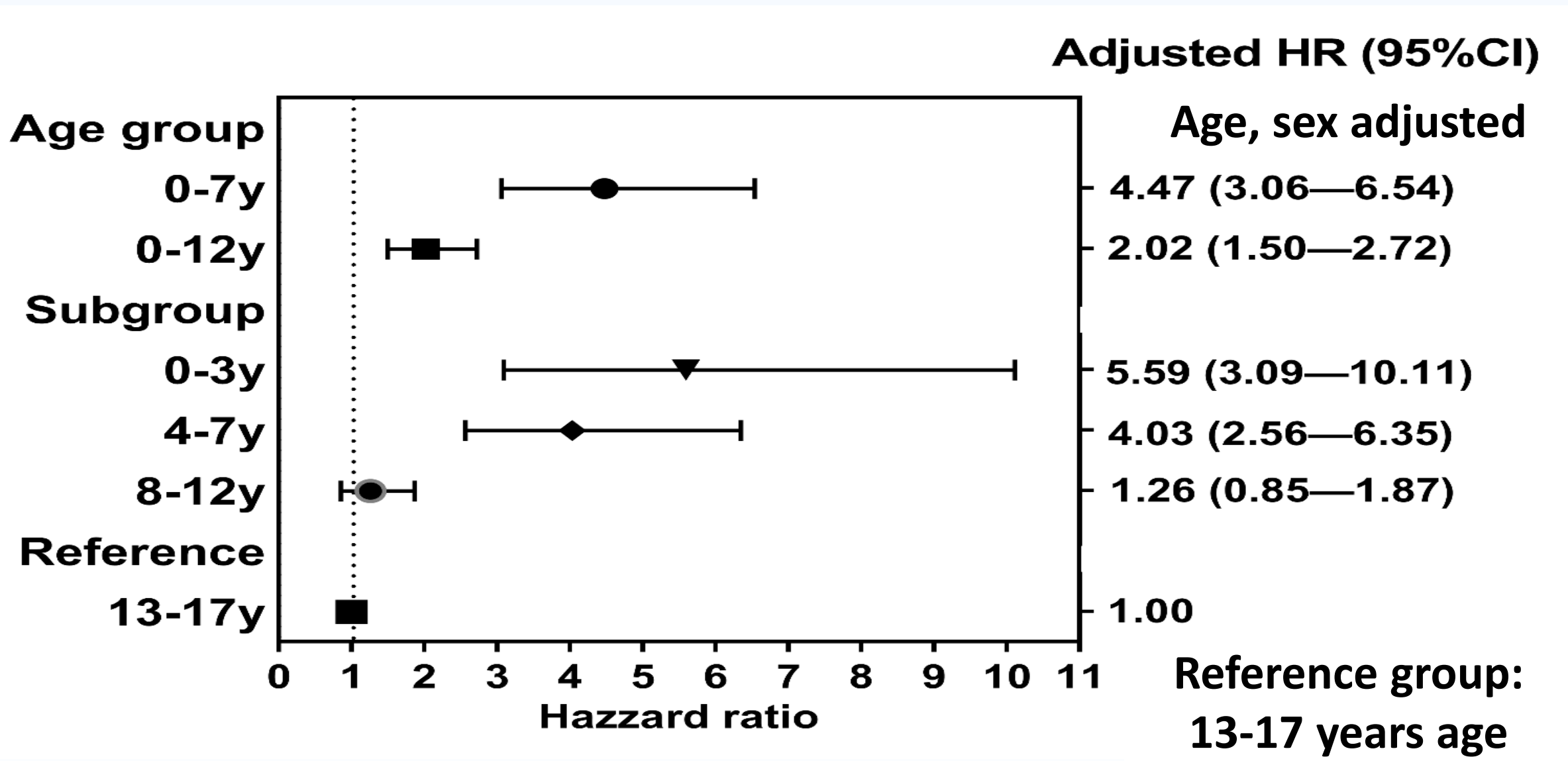
Number of prescriptions by type of TCs

Among the prescribed TCs (n = 14 867), doxycycline was the most common (10,087 cases [67.8%]), followed by minocycline (3 770 cases [25.4%]), tetracycline (1 009 cases [6.8%]), and oxytetracycline (1 case [0.01%]).

Cumulative incidence rate and relative risk of dental abnormalities after TCs exposure

Age groups	Cumulative incidence rate per 10 000 person-year		aHR	95% CI	P
	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

Adjusted relative risk of dental abnormalities according to age groups in the TCs-exposure group



Characteristics of study participants and controls

	Age 0-7		Age 8-12		Age 13-17	
	TCs-exposed (N=487)	TCs-unexposed (N=1,948)	TCs-exposed (N=1,695)	TCs-unexposed (N=6,780)	TCs-exposed (N=12,649)	TCs-unexposed (N=50,596)
Mean age (year ± SD)	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 (N, %)	221 (45.4)	884 (45.4)	941 (55.5)	3,764 (55.5)	6,027 (47.7)	24,108 (47.7)
Duration of TCs treatment (days ± SD)	5.4±11		15.6±36		21.4±40	
≤ 7 days (N, %)	417 (85.6)		997 (58.8)		5,958 (47.1)	
8-14 days (N, %)	45 (9.2)		297 (17.5)		2,469 (19.5)	
15-28 days (N, %)	17 (3.5)		205 (12.1)		1,936 (15.3)	
> 28 days (N, %)	8 (1.6)		196 (11.6)		2,286 (18.1)	

Summary of Results

- ✓ 10-year cumulative incidence rate of dental abnormalities after TCs exposure in the 0-12 years age group was 3.1% (95% confidence interval [CI], 2.3-3.9%) not significantly higher than non-exposure group.
- ✓ 10-year cumulative incidence rate of dental abnormalities was highest in the 0-7 years age group 7.0% (95% CI, 4.7-9.3%) which was significantly higher than 1.6% (95% CI, 1.3-1.9%) in the 13-17 years age group (P < .001) But in the 8-12 years age group, 10-year cumulative incidence rate was 1.9% (95% CI, 1.2-2.6%) and there were no significant differences compared with those in the 13-17 years age group (P = .67)
- ✓ There was no significant difference in incidence rate of dental abnormalities according to the prescription days.
- ✓ When the risk of dental abnormalities according to age was analyzed by including only participants with the 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 < .001)
- ✓ The relative risk of dental abnormalities according to TCs exposure, there was no significant difference in the risk in all age groups.
- ✓ The relative risk in the 0-7 years age group was 4.5 (95% CI, 3.1-6.5, P < .001) which is significantly higher than the reference age group (13-17 years age group). But in the 8-12 years age group, the relative risk of dental abnormalities was 1.3 (95% CI, 0.9-1.9, P = .25), which was higher than that in the reference age group (13-17 years age group), but the difference was not statistically significant

Conclusion

- ✓ In our population-based study, no significant increase in the risk of dental abnormalities after short-term TCs use (98%, ≤ 28 days) was observed in children aged 0-7 and 8-12 years.
- ✓ No additional risk of dental abnormalities in children aged 8-12 years was observed compared with that in children aged 13-17 years.
- ✓ Restrictions on the use of TCs in children aged 8-12 years, in some countries, need to be reconsidered.