



Effect of triclosan on the pathogenesis of allergic diseases among children

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Abstract

Background Few studies have assessed associations between allergic diseases and antibacterial agents in Taiwanese children.

Objective This study aimed to investigate the association of triclosan (TCS) exposure with allergic diseases among pre-schoolers, disease-specific IgE titers, and a child's sex.

Methods Pediatric data were obtained from the Childhood Environment and Allergic Diseases Study (CEAS; 2010) cohort, and their urine and blood samples were used to analyze TCS and IgE concentrations (age 3 group). Three years later, clinical data were obtained again from the age 3 group (age 6 group). Correlations of TCS levels at ages 3 and 6 years with IgE levels and allergic diseases were evaluated.

Results The TCS levels were higher at age 3 than at age 6 (geometric mean, 1.05 ng/ml vs 0.37 ng/ml). TCS levels were positively correlated with serum IgE levels at ages 3 and 6 years. Asthma and atopic dermatitis were significantly associated with TCS (adjusted OR 1.14, 95% confidence interval [CI] 1.01–1.29; OR 1.22, 95% CI 1.05–1.41). Sex-stratified analysis revealed that TCS levels were positively correlated with IgE levels among boys in the age 6 group and significantly associated with asthma, allergic rhinitis, and atopic dermatitis among boys.

Significance TCS exposure is associated with IgE levels and a potentially high risk of pediatric atopic disorders.

Keywords Triclosan · IgE levels · Allergic diseases

Introduction

In Taiwan, atopic dermatitis prevalence appears to have increased considerably over the past decades. The prevalence of atopic dermatitis was 6.7% among infants aged 6 months in

2005 and 7.9% among children aged 18 months in 2007. In 6–7-year-old school children in Taipei, atopic dermatitis prevalence significantly increased in 2007 (29.8%) compared with that in 1994 (23.9%) and 2002 (26.3%) [1–3]. Numerous early-life environmental exposures have been identified as risk factors for the pathogenesis of asthma and eczema among children, including environmental tobacco smoke (ETS), air pollution, aeroallergens, microbial diversity, and environmental compounds [4]. The “hygiene hypothesis,” referring to the lack

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of exposure to microorganisms, could explain how the allergy epidemic, observed after World War II, might be an underlying factor for this increasing trend in allergic diseases [5]. Based on this hypothesis, recent studies have focused on exposure to antimicrobial agents and preservatives, including paraben and triclosan (TCS) [6, 7]. TCS inhibits fatty acid synthesis by inhibiting enoyl reductase [8]. TCS potentially alters the bacterial flora of the skin, oral mucosa, and intestines [9–11], thus impairing normal maturation of the immune system [7, 12–14]. The United States Food and Drug Administration prohibited the use of TCS in over-the-counter consumer washing products in 2016, partly because of concerns regarding its potential teratogenic effects; however, TCS is still commercially used in toothpastes, body lotions, cosmetics, toys, textiles, and kitchenware [15]. TCS use is permitted in cosmetic products in Taiwan, Canada, the United States, and China at <0.3% concentration [16]. TCS exposure primarily occurs through oral intake and dermal absorption [17]. TCS has been detected in human urine, blood, plasma, and milk; the brain; adipose tissue; and the liver [18, 19]. After ingestion or absorption, TCS is glucuronidated and primarily excreted through the urine. A large proportion of the absorbed TCS is eliminated within 24 h, mostly through urine [20]. Because this chemical agent does not persist in the body, its urinary concentrations reflect single-use exposure [21]. Allergic diseases including hay fever, food allergies, and allergic asthma result from hypersensitive immune responses to typically harmless substances in the environment. A study using a mouse model of asthma reported that TCS enhances the allergic response [22]. The United States National Health and Nutrition Examination Surveys (NHANES) reported a positive correlation between TCS and allergic sensitization. A cross-sectional study in the United States reported that propyl parabens and TCS exposure are associated with allergic sensitization among children [22]. Another study on children in Norway reported that higher urine TCS levels are associated with allergic sensitization and allergic rhinitis [23]. Using data from children and adolescents aged 6–18 years from the NHANES conducted from 2005 to 2006, researchers reported an increased probability of elevated immunoglobulin E (IgE) with an increase in urine TCS levels [24]. However, no studies have investigated the association between TCS exposure and allergies among children in Taiwan. Therefore, this study aimed to investigate the association of postnatal TCS exposure with allergic diseases among preschoolers, disease-specific IgE titers, and a child's sex.

Materials and methods

Study population

In total, 453 3-year-old kindergarten children with available urine and blood specimens were selected from the

Childhood Environment and Allergic Diseases Study (CEAS) cohort in 2010 in Taiwan. To be enrolled in the study, no significant differences were required to be observed between the original cohort and the final participants. Complete enrollment in the study required complete monitoring of TCS exposure monitoring based on urinary TCS metabolite levels and total serum IgE levels. These children are hereafter referred to as “age 3.” Three years later, the second set of clinical data was obtained from the age 3 group, hereafter, referred to as “age 6.” After excluding patients lost to follow-up ($n = 84$), those with missing blood or urine data ($n = 103$), and those with missing outcome data ($n = 66$), 200 children were included in the age 6 group. TCS metabolites were measured in urine samples, and serum IgE levels were determined in blood samples. Parents were interviewed in accordance with a standardized questionnaire on basic demographics and environmental exposures of the child. Information on asthma was also obtained. Written informed consent was obtained from all parents. This study was approved by Taipei Hospital's Institutional Review Board (TH-IRB-0016–0019).

Questionnaire survey

The parents of the children in the age 3 and 6 groups were all asked to complete a questionnaire on basic demographic characteristics, parental history of allergic diseases, alcohol and drug use, diets and supplements, and smoke exposure during pregnancy. For the age 3 and 6 groups, an International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was used to obtain data on the children's allergic symptoms and information regarding the duration of breast feeding, number of older siblings, furry pets, carpets, incense use at home, fungi on the walls at home, and tobacco smoke exposure.

Urine collection and TCS analysis

Participants were asked to collect their first morning voids at home on the same day as the follow-up visit. The urine samples were frozen at -80°C in 2-mL polypropylene tubes until analyzed, and a modification of the automated high-performance liquid chromatography–tandem mass spectrometry method was used to determine the TCS concentration [25]. For concentrations below the detection limits, a value of half the limit of detection (LOD) was assigned. All concentrations were determined through duplicate analysis. Urine creatinine levels were analyzed using an enzymatic assay in accordance with the manufacturer's instructions (Cayman Chemical, Ann Arbor, MI, USA) [26]. All statistical models were adjusted for urine creatinine levels.

Measurement of total IgE levels

Total serum IgE levels were determined as a sensitization indicator. Allergic sensitization against perennial allergens (German cockroach, dog, cat, and rabbit), seasonal allergens, and food allergens (egg white, milk, and crab) was assessed through skin prick tests and specific serum IgE titers. A subject was considered to have aeroallergens or food sensitivity if an aeroallergen or food-specific IgE was ≥ 0.35 KU/l. A subject was considered to lack sensitivity if specific IgE to aeroallergens or foods was not detected.

Case definition

In the clinical setting, experienced pediatric allergists performed standardized history and clinical examination among participants with parent-reported doctor-diagnosed atopic dermatitis, allergic rhinitis, and asthma based on the ISAAC questionnaire. These atopic dermatitis cases were further confirmed in accordance with the diagnostic criteria of Hanifin and Rajka [27], and allergic rhinitis was further confirmed in accordance with Allergic Rhinitis and its Impact on Asthma guidelines [28]. Asthma was diagnosed by pediatric allergists on the basis of the following three criteria: (i) recurrence of at least two of three symptoms, namely, cough, wheeze, and shortness of breath, within the previous 12 months without having a cold; (ii) diagnosis of asthma with ongoing treatment; and (iii) response to treatment with β_2 -agonists or inhaled corticosteroids [29].

Statistical analysis

Because of the significant deviation from the normal distribution, log transformation was performed for serum total IgE and TCS levels before further analysis. All log-transformed data herein were normally distributed, and no significant outliers were noted. Correlations between TCS and IgE levels at different stages were analyzed through multivariate linear regression analysis. Associations between TCS levels and allergic diseases were analyzed through logistic regression analysis. Potential confounders identified from literature reviews, including infant sex, premature birth, maternal education and occupation, alcohol consumption during pregnancy, family income, parental history of atopy, duration of breast feeding, early consumption of solid food, carpets at home, fungi on walls at home, and urine specific gravity, were considered covariates for the multivariate models, as determined using a directed acyclic graph. p values < 0.05 were considered statistically significant. Statistical analysis was performed using the SAS software version 9.1 (SAS Institute, Cary, NC, USA).

Results

Basic demographic characteristics of the study population are indicated in Table 1. In mothers, most populations belonged to the following categories: For the age 3 group, 83.6% of mothers were aged < 34 years, 69.0% of mothers had no college degree, and 64.0% of mothers had no history of atopy. In children, most populations belonged to the following categories: in the age 3 group, most children weighed ≥ 2500 g, 90.7% of them had a gestational age of ≥ 37 weeks, and parity was < 2 in 83.7% of them. However, no significant differences were observed in the demographic data between children in the age 3 and 6 groups. The minimum and maximum percentages of urinary TCS levels $\geq$ LOD among each category at age 3 were 59.5 and 73.0%, respectively, and at age 6 were 27.3 and 66.7%, respectively. No significant differences were observed between each category in the age 3 and 6 groups; however, age 3 exhibited higher percentages in all categories than age 6 did.

The geometric means of TCS levels were 1.05 ng/ml at age 3 and 0.37 ng/ml at age 6 (Table 2). The minimum and maximum TCS levels at age 3 were 0.15 and 3829.74 ng/ml, respectively, and at age 6, 0.15 and 542.55 ng/ml, respectively. The percentage of subjects in whom TCS levels were $>$ LOD was greater at age 3, 66.45%, than at age 6, 33.00%.

Correlations between TCS levels and total IgE levels

Urine TCS levels were significantly correlated with IgE levels at ages 3 and 6. On adjusting for urinary creatinine levels, maternal age, maternal education, maternal history of atopy, breast feeding, and ETS exposure, urine TCS levels were positively correlated with serum IgE levels in the age 3 ($\beta = 44.56$ KU/l, $p = 0.002$) and age 6 ($\beta = 75.76$ KU/l, $p < 0.045$) groups. Interestingly, on adjusting for urine creatinine, maternal age, maternal education, maternal history of atopy, breast feeding, and ETS exposure, sex-stratified analysis revealed that urine TCS levels were positively correlated with IgE levels among boys ($\beta = 62.90$, $p = 0.002$) and girls ($\beta = 87.08$, $p = 0.001$) at age 3; however, a positive correlation was observed only among boys at age 6 ($\beta = 78.94$, $p = 0.013$; Table 3).

Associations between TCS levels and allergic diseases

After adjustments for urinary creatinine levels, maternal age, maternal education, maternal history of atopy, breast feeding, and ETS exposure, asthma and atopic dermatitis in the age 3 group were significantly correlated with urinary

Table 1 Demographic characteristics of the study population and percentage within each category with urine triclosan concentrations $\geq$ limit of detection (LOD = 0.29 ng/ml).

Characteristics		% of <i>n</i> = 453	Triclosan % $\geq$ LOD	% of <i>n</i> = 200	Triclosan % $\geq$ LOD
<i>Mother</i>					
Maternal age	<34 years	83.6	66.7	82.7	32.8
	$\geq$ 34 years	16.4	67.7	17.3	28.6
Maternal education	<College	69.0	69.1	65.9	34.5
	$\geq$ College	31.0	64.5	34.1	31.6
Maternal history of atopy	No	64.0	68.6	62.3	35.
	Yes	36.0	64.7	37.7	23.3
<i>Children</i>					
Gender	Male	56.5	64.8	60.5	35.5
	Female	43.5	69.0	39.5	29.1
Birth weight	<2500 g	4.7	72.2	3.8	66.7
	$\geq$ 2500 g	95.3	67.0	96.8	33.3
Gestational age	<37 weeks	9.3	59.5	7.8	33.3
	$\geq$ 37 weeks	90.7	68.2	92.2	30.8
Parity	<2	83.7	67.1	83.8	32.9
	$\geq$ 2	16.2	73.0	16.2	29.6
<i>Environmental factors</i>					
Breast feeding	No	22.8	69.7	22.3	24.3
	Yes	77.2	67.5	77.7	36.4
Incensing at home	No	45.7	68.2	42.1	33.3
	Yes	54.3	69.0	57.9	31.6
ETS exposure	No	52.9	67.8	50.0	35.2
	Yes	47.1	64.9	50.0	28.4
Family income per year	<600,000 NT dollars	31.9	64.6	30.1	27.3
	600,000–1,500,000 NT dollars	59.3	68.1	63.0	35.9
	>1,500,000 NT dollars	8.8	64.5	6.8	30.0

ETS environmental tobacco smoke, NT New Taiwan dollars.

* $p < 0.05$.**Table 2** Distribution of triclosan levels (ng/ml) at ages 3 and 6.

	>LOD (%)	Minimum	Maximum	GM (GSD)
<i>Age 3</i>				
Triclosan	66.45	0.15	3829.74	1.05 (7.20)
<i>Age 6</i>				
Triclosan	33.00	0.15	542.55	0.37 (4.75)

ND nondetectable, LOD limit of detection = 0.29 ng/ml, LOQ limit of quantification = 0.97 ng/ml, GM geometric mean, GSD geometric standard deviation.

TCS levels (adjusted odds ratio [OR] 1.14, 95% confidence interval [CI] 1.01–1.29; OR 1.22, 95% CI 1.05–1.41). Sex-stratified analysis revealed that urinary TCS levels in the age 3 group were only significantly associated with asthma (OR 1.25, 95% CI 1.07–1.47), allergic rhinitis (OR 1.18, 95% CI 1.02–1.37), and atopic dermatitis (OR 1.25, 95% CI 1.04–1.50) among boys (Table 4).

After adjustments for urinary creatinine levels, maternal age, maternal education, maternal history of atopy, breast feeding, and ETS exposure, allergen sensitization caused by dust mites was significantly associated with urinary TCS levels in the age 3 (OR 1.13, 95% CI 1.01–1.27) and age 6 (OR 1.18, 95% CI 1.02–1.35) groups. Sex-stratified analysis revealed that only dust mites among boys at age 3 (OR 1.16, 95% CI 1.01–1.33) and age 6 (OR 1.22, 95% CI 1.01–1.46) were significantly associated with urine TCS levels (Table 5), suggesting that dust mites significantly increase urine TCS exclusively among boys.

Associations among the three types of allergic diseases and urine TCS levels at age 6 are summarized in Table 6. After adjustments for urinary creatinine levels, maternal age, maternal education, maternal history of atopy, breast feeding, and ETS exposure, only atopic dermatitis was significantly associated with urinary TCS levels in the age 6 group (OR 1.26, 95% CI 1.02–1.55; Table 6).

Table 3 Regression coefficients β (95% CI) for total IgE (KU/l) at ages 3 and 6 in accordance with urine Ln-Triclosan levels at ages 3 and 6 stratified by sex.

	<i>n</i>	Unadjusted β OR (95% CI)	<i>p</i> value	adjusted β^a OR (95% CI)	<i>p</i> value
<i>Age 3</i>	453	40.27 (11.26 to 69.28)	0.007*	44.56 (16.00 to 73.12)	0.002**
Boys	256	43.31 (3.68 to 82.93)	0.032*	62.90 (24.17 to 101.62)	0.002*
Girls	197	69.21 (49.28 to 89.14)	<0.001*	87.08 (61.51 to 112.65)	<0.001*
<i>Age 6</i>	200	91.51 (27.11 to 155.90)	0.006*	75.76 (1.90 to 149.61)	0.045*
Boys	121	83.04 (4.03 to 162.06)	0.040*	78.94 (17.48 to 140.40)	0.013*
Girls	79	65.85 (−59.14 to 190.84)	0.291	1.31 (−175.90 to 178.53)	0.988

p* < 0.05^aAdjusted for urine creatinine, maternal age, maternal education, maternal history of atopy, breast feeding, and ETS exposure.Table 4** Associations between allergic diseases at ages 3 and 6 and urine triclosan levels (ng/ml) at age 3 stratified by sex (*n* = 453).

	Age 3 Ln-Triclosan	
Asthma adjusted OR (95% CI) ^a	Age 3	1.14 (1.01–1.29)*
	Boys	1.25 (1.07–1.47)*
	Girls	0.95 (0.76–1.19)
Asthma adjusted OR (95% CI) ^a	Age 6	0.94 (0.79–1.11)
	Boys	1.04 (0.85–1.28)
	Girls	0.68 (0.45–1.04)
Allergic rhinitis adjusted OR (95% CI) ^a	Age 3	1.12 (0.99–1.26)
	Boys	1.18 (1.02–1.37)*
	Girls	0.99 (0.80–1.23)
Allergic rhinitis adjusted OR (95% CI) ^a	Age 6	1.01 (0.86–1.20)
	Boys	1.14 (0.91–1.42)
	Girls	0.80 (0.56–1.14)
Atopic dermatitis adjusted OR (95% CI) ^a	Age 3	1.22 (1.05–1.41)*
	Boys	1.25 (1.04–1.50)*
	Girls	1.15 (0.89–1.48)
Atopic dermatitis adjusted OR (95% CI) ^a	Age 6	1.00 (0.83–1.21)
	Boys	1.07 (0.86–1.33)
	Girls	0.82 (0.54–1.25)

OR odds ratio, CI confidence interval.

**p* < 0.05^aAdjusted for urine creatinine, maternal age, maternal education, maternal history of atopy, breast feeding, and ETS exposure.

Discussion

TCS levels among children

Here urine geometric mean TCS levels among children in the age 3 and 6 groups were 1.05 and 0.37 ng/ml, respectively. The reported urine TCS levels among

children from India, China, and the United States were 9.55, 7.52, and 8.20 ng/ml [30], respectively, which are higher than the corresponding levels determined herein. Geometric mean urinary TCS concentration among children and adolescents in the United States (NHANES 2003–2004) was 13 µg/l, which was significantly higher than that among adults. Urine TCS levels generally decrease with age [31]. Multiple factors may result in differences in TCS levels. Different geographical areas; assessment sites, including the skin, blood, or urine; exposure routes; duration; exposure levels; and laboratory methods may account for this inconsistency [15]. Furthermore, genetic factors may impact the metabolism of these compounds [32].

Correlations between TCS levels and total IgE levels

Our study indicates that TCS exposure potentially increases IgE levels, causing high susceptibility to allergic diseases. Several epidemiological studies have reported that urine TCS levels during pregnancy and in early childhood are associated with biomarkers of altered immune function, including increased levels of IgE, cytokines, and other inflammatory markers [32–37]. An experimental study in mice reported that dermal exposure to TCS increased the frequency of immune system biomarkers including B cells, T cells, and natural killer cells in skin lymph nodes [38].

Sex-based differences in correlations between TCS and IgE levels

Herein, TCS levels were positively correlated with IgE levels, particularly among boys. TCS has a novel mechanism of action, potentially serving as an endocrine disruptor [39]. TCS suppresses thyroid hormone [40] and is estrogenic [41] in mammalian models [42]. Sexual dimorphism is hypothesized to be associated with estrogenic activity and

Table 5 Associations between allergen sensitivity at ages 3 and 6 and urine triclosan levels (ng/ml) at age 3 stratified by sex ($n = 453$).

		Age 3 Ln-Triclosan	
Dust mite adjusted OR (95% CI) ^a	Age 3	1.13 (1.01–1.27)*	
	Boys	1.16 (1.01–1.33)*	
	Girls	1.06 (0.86–1.30)	
Dust mite adjusted OR (95% CI) ^a	Age 6	1.18 (1.02–1.35)*	
	Boys	1.22 (1.01–1.46)*	
	Girls	1.07 (0.75–1.36)	
Cockroach adjusted OR (95% CI) ^a	Age 3	1.24 (0.96–1.60)	
	Boys	1.19 (0.89–1.59)	
	Girls	1.37 (0.80–2.36)	
Cockroach adjusted OR (95% CI) ^a	Age 6	1.48 (0.74–2.95)	
	Boys	1.26 (0.22–7.20)	
	Girls	1.40 (0.69–2.82)	
Dog adjusted OR (95% CI) ^a	Age 3	1.40 (0.88–2.22)	
	Boys	1.35 (0.85–2.16)	
	Girls	—	
Dog adjusted OR (95% CI) ^a	Age 6	1.08 (0.37–3.12)	
	Boys	1.26 (0.22–7.20)	
	Girls	—	
Milk adjusted OR (95% CI) ^a	Age 3	1.44 (0.92–2.27)	
	Boys	1.67 (0.90–3.07)	
	Girls	0.98 (0.36–2.66)	
Milk adjusted OR (95% CI) ^a	Age 6	1.17 (0.56–2.43)	
	Boys	1.13 (0.49–2.60)	
	Girls	0.94 (0.36–2.45)	
Egg adjusted OR (95% CI) ^a	Age 3	0.96 (0.40–2.29)	
	Boys	0.91 (0.37–2.22)	
	Girls	—	
Egg adjusted OR (95% CI) ^a	Age 6	0.88 (0.29–2.65)	
	Boys	0.89 (0.32–2.44)	
	Girls	—	
Crab adjusted OR (95% CI) ^a	Age 3	0.92 (0.44–1.92)	
	Boys	1.34 (0.64–2.80)	
	Girls	—	
Crab adjusted OR (95% CI) ^a	Age 6	0.88 (0.29–2.65)	
	Boys	0.89 (0.32–2.44)	
	Girls	—	

OR odds ratio, CI confidence interval.

* $p < 0.05$ ^aAdjusted for urine creatinine, maternal age, maternal education, maternal history of atopy, breast feeding, and ETS exposure.

increased triclosan sensitization risk [22]. Heightened immunity among women renders them more susceptible to autoimmune conditions and allergies than men [43]. In children, asthma incidence is higher in boys than in girls, with increased atopy, wheezing, serum IgE level, and asthma medication use [44–46].

Table 6 Associations between allergic diseases across three categories of urinary triclosan levels (ng/ml) in the age 6 group ($n = 200$).

		Age 6 Triclosan	
Asthma adjusted OR (95% CI) ^a	Age 6	1.18 (0.96–1.46)	
	Boys	1.30 (0.96–1.77)	
	Girl	1.04 (0.74–1.48)	
Allergic rhinitis adjusted OR (95% CI) ^a	Age 6	1.14 (0.89–1.46)	
	Boys	1.16 (0.85–1.58)	
	Girl	1.17 (0.82–1.67)	
Atopic dermatitis adjusted OR (95% CI) ^a	Age 6	1.26 (1.02–1.55)*	
	Boys	1.31 (0.96–1.77)	
	Girl	1.35 (0.93–1.96)	

OR odds ratio, CI confidence interval.

* $p < 0.05$ ^aAdjusted for urine creatinine, maternal age, maternal education, maternal history of atopy, breast feeding, and ETS exposure.

Associations between TCS levels and allergic diseases

Herein asthma and atopic dermatitis were significantly associated with urinary TCS levels in the age 3 group. Among Norwegian children, TCS levels were associated with allergic sensitization, especially inhalant and seasonal allergens, but not food allergens. Current rhinitis was associated with the highest TCS levels; however, no association was observed for current asthma. These results are consistent with those of recent studies and provide additional evidence for the association between TCS and allergies [39]. Frequent use of antimicrobial household products is reportedly associated with current wheezing and current allergic rhinitis [47]. TCS exposure alone is not allergenic; however, exposure to a known allergen enhances the hypersensitivity response to that allergen, implying that TCS exposure potentially augments the allergic response to other environmental allergens [48]. These findings further indicate that environmental exposure to TCS during early childhood potentially influences allergic sensitization.

Sex-based differences in the association between TCS levels and allergic diseases

This study indicates that urinary TCS levels in the age 3 group are significantly associated with asthma, allergic rhinitis, and atopic dermatitis among boys, and only allergic sensitization due to dust mites among boys in the age 3 and 6 groups was significantly associated with urinary TCS levels in the age 3 group. Another animal study reported positive associations between TCS and Th2 cytokines [interleukin (IL)-4 and IL-13] and dust mite-specific IgE concentrations among sensitized mice [38]. Allergic disease

is more prevalent among men than among women [49], although the mechanism of this sex dependence remains unclear. Because men are at a higher risk of allergic diseases in general, they may be more susceptible to the effects of a second risk factor such as antimicrobial exposure.

Study limitations

This study has several limitations. First, this study used spot urinary TCS levels as a proxy for TCS exposure instead of personal air monitoring. Although urine TCS metabolites have a short half-life (7–14 h) and have the potential for significant daily variations in exposure during chronic exposure, they provide a useful measure of TCS exposure [50]. Moreover, this study measured TCS levels more than once. Second, there may have been a potential selection bias with respect to differences in sociodemographic characteristics among participants. Except for higher maternal education, statistical data of the participants lost to follow-up are not significantly different from those completing follow-up evaluation. Therefore, a selection bias, if any, would be nonsignificant. Finally, the 200 subjects overlapped between the age 3 and 6 groups; therefore, in these subjects, measures of TCS exposure, IgE levels, and health-related outcomes were repeatedly obtained. Additional studies are required to use the generalized estimating equation method to investigate the associations between TCS and allergic diseases.

The strengths of this study are its population-based prospective cohort study design and exposure assessment of objective biomarkers at different stages. Cohort studies potentially offer further insights into the timing of exposure relative to disease onset and minimize recall bias. Aside from maternal self-reporting information from ISAAC questionnaires, asthma was further confirmed by a physician in accordance with standard diagnostic criteria. Urine biomarkers offer a more direct measure of individual exposure by integrating ingestion, inhalation, and dermal absorption. Moreover, urinary TCS concentrations were determined through ultra-performance liquid chromatography–tandem mass spectrometry with high validity. Therefore, the assessment of the exposure is reliable. Moreover, TCS levels may change with age and different conditions because of their short half-life and rapid excretion after exposure.

Conclusions

Early-life TCS exposure is associated with IgE and may increase the risk of the development of atopic disorders among children. Preventive measures should be introduced as early as possible for young children to prevent subsequent development of allergic diseases. Further studies

with more specific subpopulations categorized by the degree of exposure may increase the consistency and generalizability of the current findings.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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