

LETTERS TO THE EDITOR

Association of antimicrobial household exposure with development of allergic rhinitis in Korea

To the Editor

Antimicrobial chemicals are used in consumer products. Typical antimicrobial chemicals include triclosan (TCS) and its congener triclocarban (TCC).¹ TCS exhibits endocrine-disruptor activity² and affects thyroid hormone and estrogen³ and androgen levels.⁴ Urinary TCS concentrations in children were associated with allergic sensitization,⁵ with higher TCS concentrations being associated with increased risk of current rhinitis.

Various types of antimicrobial household products (AHPs) are in wide use. In Korea, TCS or TCC is found in laundry detergents, soaps, hand washes, and toothpastes.⁶ These products are commonly labeled "antimicrobial."

Our cross-sectional study in 2012 reported that parental use of AHPs was associated with wheezing and allergic rhinitis symptoms in children aged 0-13 years.⁷ In this study, we followed up with these children who attended elementary school in 2012 to examine the relationship between parental use of AHPs and development of allergic rhinitis.

The protocols of the 2012 study were reported previously.⁷ The target population was 4081 children who were first-grade elementary school students (6-8 years) in 2012. Written consent forms and questionnaires were delivered by the children to their parents asking whether they wished to voluntarily participate in the study. In total, 1538 students in 30 elementary schools were tracked from 2012 to 2017 and 220 of them were excluded due to missing values. Comparison of 1318 children (32.3%) with all information available and 2763 children loss to follow-up is shown in Table S1. Relationships between parental use of AHPs and allergic rhinitis of children in 2012 are shown in Tables S2 and S3. Results of these relationships by combining prevalent and incident cases into a single outcome variable are shown in Tables S4 and S5. Because 401 of 1318 children (30.4%) had a baseline diagnosis of allergic rhinitis, 917 children with no baseline diagnosis of allergic rhinitis were included. This study was approved by the Seoul Medical Center Institutional Review Board (IRB no. 2017-05-006).

Baseline characteristics of children, including any diagnosis of allergic diseases (allergic rhinitis, asthma, and atopic dermatitis) and parental use of AHPs, were collected by questionnaires. During follow-up, questions addressed demographic characteristics and diagnosis of allergic diseases.

Parental use of AHPs was provided previously.⁷ Ten selected products labeled "antimicrobial" or "antibacterial" were examined. In this study, we used information on three of the 10 products because these products were significantly associated with allergic rhinitis

in the preliminary analysis (Table S5). The three products and the frequency of use by parents were soaps (49.3%), hand sanitizers (59.4%), and dishwashing detergents (67.9%). We scored product frequency of use as follows: 0 = not at all, 1 = less than once per week, 2 = approximately once per week, 3 = more than once per week, and 4 = every day. Antimicrobial exposure (AE) scores were produced by summing the scores of each product, which ranged from 0 to 12.

The International Study of Asthma and Allergies in Childhood questionnaire was used to assess allergic disease in the children during the baseline and follow-up surveys. Asthma, allergic rhinitis, and atopic dermatitis were defined based on diagnoses by physicians.

Antimicrobial exposure score was classified into two categories based on its median value of 5. Data were analyzed using a chi-square test, the Cochran-Mantel-Haenszel test, and univariable and multivariable logistic regression. The multivariable regression models used stepwise method with entry levels of 0.10 and stay levels of 0.05. Odds ratios (ORs) for the AE score groups in the model were reported with 95% confidence intervals (CIs). Significance was set at $P < 0.05$, and the SAS 9.4 software (SAS Institute Inc, Cary, NC, USA) was used for statistical analyses.

The average age of children was 7.0 ± 0.1 years in the baseline survey. The average AE score was 5.7 ± 4.2 . AE score groups classified by the median value were not associated with any of the baseline characteristics (Table 1).

During the follow-up survey, 235 of 917 children (25.6%) were diagnosed with allergic rhinitis. The incidence was higher in children who were male and who had parents with a history of allergic disease (Table 2). The incidence was higher in those who had been diagnosed with asthma or dermatitis in the baseline survey. Baseline AE score groups were marginally associated with the incidence of allergic rhinitis.

The results of the univariable and multivariable logistic regression analyses are presented in Table 3. Children with AE scores $\geq$ median value were more likely to have allergic rhinitis than those with AE scores $<$ median value (adjusted odds ratios, aOR = 1.37, 95% CI = 1.01-1.87).

Antimicrobial exposure score groups were significantly associated with the development of allergic rhinitis in children during the follow-up. The findings are similar to our cross-sectional study in 2012. In that study, dose-dependent relationships were observed between AE score groups and the allergic rhinitis and wheezing symptoms of children aged 0-13 years.⁷ The findings of this study

TABLE 1 Characteristics of children not previously diagnosed with allergic rhinitis by baseline antimicrobial exposure score

		Antimicrobial exposure score ^a		P-value ^b
		<Median	≥Median	
Sex				
Female	500 (54.5)	224 (53.6)	276 (55.3)	0.602
Male	417 (45.5)	194 (46.4)	223 (44.7)	
Birth order				
First	435 (47.4)	191 (45.7)	244 (48.9)	0.542
Second	410 (85.1)	191 (45.7)	219 (43.9)	
≥Third	72 (7.9)	36 (8.6)	36 (7.2)	
Duration of breastfeeding				
None	79 (8.6)	36 (8.6)	43 (8.6)	0.966
<6 mo	371 (44.3)	171 (40.9)	200 (40.1)	
≥6 mo	467 (50.9)	211 (50.5)	256 (51.3)	
Parental history of allergic disease				
No	646 (70.4)	295 (70.6)	351 (70.3)	0.939
Yes	271 (29.6)	123 (29.4)	148 (29.7)	
Parental smoking status				
No	470 (51.3)	224 (53.6)	246 (49.3)	0.196
Yes	447 (48.7)	194 (46.4)	253 (50.7)	
Food allergy symptoms at first year of life				
No	830 (90.5)	379 (90.7)	451 (90.4)	0.882
Yes	87 (9.5)	39 (9.3)	48 (9.6)	
Diagnosis of asthma				
No	871 (95.0)	395 (94.5)	476 (95.4)	0.537
Yes	46 (5.0)	23 (5.5)	23 (4.6)	
Diagnosis of atopic dermatitis				
No	676 (73.7)	303 (72.5)	373 (74.7)	0.438
Yes	241 (26.3)	115 (27.5)	126 (25.3)	

^aChi-square test.^bMedian value of antimicrobial exposure score calculated by three antimicrobial household products was 5.

imply that parental use of AHPs may be associated with development of allergic rhinitis in elementary schoolchildren.

We calculated AE score using three AHP uses by parents because each of them was associated with allergic rhinitis of children in the preliminary analysis (Table S5). AE score by the 10 products was not significantly associated with development of allergic rhinitis. This may be because small sample size and AE by the 10 products can have diluted effects on development of allergic rhinitis in children.

Antimicrobial compounds are contained in various consumer products. In Korea, about 37% of consumer products (laundry detergent, soap, hand washes, and toothpaste) highlighted as "antimicrobial" were found to contain these compounds.⁶ These indicate that the frequency of AHP uses may be associated with AE, especially to TCS and TCC.

AHPs may contain other antimicrobial agents. Ethylenediaminetetraacetic acid (EDTA) is found in some consumer

TABLE 2 Incidence of allergic rhinitis during a 5-year follow-up survey by subject characteristics and antimicrobial exposure scores at baseline

	Allergic rhinitis ^a	
	Yes (%)	P-value ^b
Sex		
Female	110 (22.0)	0.006
Male	125 (30.0)	
Birth order		
First	124 (28.5)	0.149
Second	96 (23.4)	
≥Third	15 (20.8)	
P for trend ^c	0.055	
Duration of breastfeeding		
None	16 (20.3)	0.465
<6 mo	94 (25.3)	
≥6 mo	125 (26.8)	
P for trend ^c	0.262	
Parental history of allergic disease		
No	135 (20.9)	<0.001
Yes	100 (36.9)	
Parental smoking status		
No	129 (27.4)	0.196
Yes	106 (23.7)	
Food allergy symptoms in first year of life		
No	207 (24.9)	0.141
Yes	28 (32.2)	
Any previous diagnosis of asthma		
No	214 (24.6)	0.001
Yes	21 (45.7)	
Any previous diagnosis of atopic dermatitis		
No	152 (22.5)	<0.001
Yes	83 (34.4)	
Antimicrobial exposure score ^d		
<Median	95 (22.7)	0.066
≥Median	140 (28.1)	

^aA "yes" response indicates diagnosis of allergic rhinitis by a doctor before the 5-year follow-up.^bChi-square test.^cMantel-Haenszel chi-square test.^dMedian value of antimicrobial exposure score calculated by three antimicrobial household products was 5.

products.⁸ In occupational settings, associations between tetrasodium EDTA and work-related asthma and/or rhinitis have been reported.⁹ Chloroxylenol is a compound used as a preservative in consumer products. Chloroxylenol in soaps and hand creams has been associated with contact dermatitis.¹⁰

This study had several limitations. Because the recruitment did not involve a random sampling process, it cannot be considered

TABLE 3 Associations between antimicrobial exposure scores and development of allergic rhinitis in children

Antimicrobial exposure score ^a	OR (95% CI)	P-value	aOR (95%CI) ^b	P-value
<Median	1.00			
≥Median	1.33 (0.98-1.79)	0.066	1.37 (1.01-1.87)	0.046

aOR, adjusted odds ratio; OR, crude odds ratio.

^aMedian value of antimicrobial exposure score calculated by three antimicrobial household products was 5.

^bAdjusted for sex, birth order, parental history of allergic disease, and baseline diagnosis of asthma and atopic dermatitis by stepwise selection procedures.

representative of the child population of Seoul. There might have been selection biases due to loss to follow-up. Although we included data on several demographic factors, there may have been other confounders. We examined parental use of AHPs labeled “antimicrobial” or “antibacterial.” The parents may have misclassified their exposure if products containing antimicrobial chemicals did not have appropriate labeling. Because we did not measure use of AHPs during follow-up, there may have been variation in AE as a result of changes in by parental use of these products over time. Future studies should ensure consistent assessment of the parental use of AHPs and use objective methods such as biomarkers to confirm associations between AE and allergic disease in children.

Conclusively, baseline AE score groups were significantly associated with the incidence of allergic rhinitis in children. This finding implies that parental use of AHPs may be associated with development of allergic rhinitis.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Additional File

TABLE S1 Comparison of 2763 children lost to follow up and 1318 children with all information available

	Follow-up loss children (%)	Included children (%)	<i>P</i> -value*
Sex			
Female	1332 (48.2)	687 (52.1)	0.019
Male	1431 (51.8)	631 (47.9)	
Birth order			
First	1510 (55.4)	672 (51.0)	0.008
Second	1009 (37.0)	555 (42.1)	
≥Third	205 (7.5)	91 (6.9)	
Missing	39	0	
Duration of breastfeeding			
None	259 (9.5)	110 (8.3)	0.499
<6 months	1122 (41.1)	545 (41.4)	
≥6 months	1352 (49.5)	663 (50.3)	
Missing	30	0	
Parental history of allergic disease			
No	1622 (60.1)	808 (61.3)	0.470
Yes	1076 (39.9)	510 (38.7)	
Missing	65	0	
Parental smoking status			
No	1441 (52.9)	687 (52.1)	0.643
Yes	1283 (47.1)	631 (47.9)	
Missing	39	0	
Food allergy symptoms in first year of life			
No	2450 (89.5)	1176 (89.2)	0.805
Yes	288 (10.5)	142 (10.8)	
Missing	25	0	
Any previous diagnosis of asthma			
No	2529 (92.7)	1225 (92.9)	0.783
Yes	199 (7.3)	93 (7.1)	
Missing	35	0	
Any previous diagnosis of atopic dermatitis			
No	1847 (69.2)	902 (68.4)	0.647
Yes	824 (30.8)	416 (31.6)	
Missing	92	0	
Any previous diagnosis of allergic rhinitis			
No	1832 (67.8)	917 (69.6)	0.263
Yes	869 (32.2)	401 (30.4)	
Missing	62	0	
Antimicrobial exposure score**			
< Median	1171 (48.9)	625 (47.4)	0.390
≥ Median	1224 (51.1)	693 (52.6)	
Missing	368	0	

Missing values are not included for a percentage of number in each variable and for chi-square test.

*Chi-square test.

**Median value of antimicrobial exposure score calculated by 10 antimicrobial household products was 14.

TABLE S2 Characteristics of 1318 children by allergic rhinitis ever diagnosis at baseline

	Total	Allergic rhinitis* Yes (%)	P-value**
Sex			
Female	687	187 (27.2)	0.008
Male	631	214 (33.9)	
Birth order			
First	672	237 (35.3)	<0.001
Second	555	145 (26.1)	
≥Third	91	19 (20.9)	
P for trend***		<0.001	
Duration of breastfeeding			
None	110	31 (28.2)	0.584
<6 months	545	174 (31.9)	
≥6 months	663	196 (29.6)	
P for trend***		0.762	
Parental history of allergic disease			
No	808	162 (20.0)	<0.001
Yes	510	239 (46.9)	
Parental smoking status			
No	687	217 (31.6)	0.339
Yes	631	184 (29.2)	
Food allergy symptoms in first year of life			
No	1176	346 (29.4)	0.023
Yes	142	55 (38.7)	
Any previous diagnosis of asthma			
No	1225	354 (28.9)	<0.001
Yes	93	47 (50.5)	
Any previous diagnosis of atopic dermatitis			
No	902	226 (25.1)	<0.001
Yes	416	175 (42.1)	
Antimicrobial exposure score****			
< Median	625	161 (25.8)	<0.001
≥ Median	693	240 (34.6)	

* A “yes” response indicates diagnosis of allergic rhinitis by a doctor at baseline.

** Chi-square test.

*** Mantel–Haenszel chi-square test.

**** Median value of antimicrobial exposure score calculated by 10 antimicrobial household products was 14.

TABLE S3 Relationships between antimicrobial exposure scores and allergic rhinitis ever diagnosis of children at baseline (n = 1318)

Antimicrobial exposure score [*]	OR (95%CI)	<i>P</i> -value	aOR (95%CI) ^{**}	<i>P</i> -value
< Median	1.00			
≥ Median	1.53 (1.20-1.94)	<0.001	1.45 (1.12-1.87)	0.004

OR, crude odds ratio; aOR, adjusted odds ratio.

^{*}Median value of antimicrobial exposure score calculated by 10 antimicrobial household products was 14.

^{**}Adjusted for sex, birth order, parental history of allergic disease, and baseline diagnosis of asthma and atopic dermatitis by stepwise selection procedures.

TABLE S4 Relationships between antimicrobial exposure scores and combined cases of allergic rhinitis of children before and after follow up based on 1318 children in 2012

Antimicrobial exposure score *	Allergic rhinitis Yes (%) **	OR (95%CI)	P-value	aOR (95%CI) ***	P-value
< Median (n = 625)	271 (43.4)	1.00			
≥ Median (n = 693)	265 (52.7)	1.45 (1.17-1.81)	<0.001	1.39 (1.10-1.75)	0.006

OR, crude odds ratio; aOR, adjusted odds ratio.

* Median value of antimicrobial exposure score calculated by 10 antimicrobial household products was 14.

** Combining prevalent cases in 2012 and incident cases in 2017 of allergic rhinitis ever diagnosis into a single outcome variables based on 1318 children studied in 2012.

*** Adjusted for sex, birth order, parental history of allergic disease, and baseline diagnosis of asthma and atopic dermatitis by stepwise selection procedures.

TABLE S5 Relationships between use of each antimicrobial household product and combined cases of allergic rhinitis of children before and after follow up based on 1318 children in 2012

Antimicrobial household product	Total	Yes (%) [*]	OR (95%CI)	P-value	aOR (95%CI) ^{**}	P-value
Toothpaste						
No	815	385 (47.2)				
Yes	503	251 (49.9)	1.11 (0.89-1.39)	0.348	1.08 (0.85-1.38)	0.517
Soap						
No	633	282 (44.5)				
Yes	685	354 (51.7)	1.33 (1.07-1.65)	0.010	1.32 (1.05-1.67)	0.019
Hand sanitizer						
No	508	218 (42.9)				
Yes	810	418 (51.6)	1.42 (1.14-1.77)	0.002	1.39 (1.09-1.77)	0.008
Dishwashing detergent						
No	400	171 (42.8)				
Yes	918	465 (50.7)	1.38 (1.09-1.74)	0.008	1.40 (1.08-1.80)	0.011
Fungicide						
No	717	324 (45.2)				
Yes	601	312 (51.9)	1.31 (1.05-1.63)	0.015	1.26 (1.00-1.59)	0.052
Laundry detergent						
No	538	246 (45.7)				
Yes	780	390 (50.0)	1.19 (0.95-1.48)	0.127	1.16 (0.91-1.47)	0.223
Deodorant						
No	841	399 (47.4)				
Yes	477	237 (49.7)	1.09 (0.87-1.37)	0.434	1.06 (0.83-1.35)	0.622
Aerosol cleaners						
No	590	272 (46.1)				
Yes	728	364 (50.0)	1.17 (0.94-1.45)	0.160	1.11 (0.88-1.40)	0.382
Wet wipes						
No	406	182 (44.8)				
Yes	912	454 (49.8)	1.22 (0.97-1.54)	0.097	1.16 (0.90-1.49)	0.258
Household pesticides						
No	753	373 (49.5)				
Yes	565	263 (46.5)	0.89 (0.71-1.10)	0.283	0.94 (0.74-1.19)	0.585

OR, crude odds ratio; aOR, adjusted odds ratio.

^{*}Combining prevalent cases in 2012 and incident cases in 2017 of allergic rhinitis ever diagnosis into a single outcome variables based on 1318 children studied in 2012.

^{**}Adjusted for sex, birth order, parental history of allergic disease, and baseline diagnosis of asthma and atopic dermatitis by stepwise selection procedures.

P-value <0.05 are in bold.