



Article

Relationship between the Use of Parabens and Allergic Diseases in Japanese Adults—A Cross-Sectional Study

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Abstract: It currently remains unclear whether parabens, which are preservatives added to cosmetics, shampoos, and personal care products that exhibit biocidal activities, exert allergic effects in adults. The aim of the present study was to examine the relationship between the use of parabens and the prevalence of allergic diseases in Japanese adults. This population-based cross-sectional study comprised 2005 participants aged 40 years or older living in Shika Town in Japan who answered a self-administered questionnaire on allergic diseases and the daily use of household goods. The information obtained was then analyzed to assess the exposure to parabens (response rate: 77.9%). The prevalence of nasal allergies, atopic conjunctivitis, and total allergies was significantly higher in women who used parabens. These differences remained significant after adjustments for confounding factors including age, body mass index, smoking, alcohol, exercise, sleep, income, education, and marital status. No relationship between the prevalence of atopic dermatitis and the

use of parabens was observed in men or women. However, the present results demonstrated that the prevalence of nasal allergies and atopic conjunctivitis was associated with use of parabens in women, suggesting that parabens may induce allergic responses.

Keywords: allergy; asthma; atopic conjunctivitis; nasal allergies; paraben; triclosan

1. Introduction

A decrease of early childhood exposure to substances in the environment including bacteria leads to an increase in susceptibility to allergies and atopy in later life (hygiene hypothesis) [1,2]. The prevalence of allergic diseases, including asthma, nasal allergies, and allergic dermatitis, is increasing worldwide, which can be explained by the hygiene hypothesis based on the relationship of atopy, allergy, and asthma to environmental and microbial exposure. Triclosan, an antibacterial and antifungal agent added to personal care and medical products including toothpaste and soap, has been shown to affect immune systems and induce allergic effects on the basis of the hygiene hypothesis [3–5]. Parabens are preservatives that are also added to cosmetics, shampoos, and personal care products for their biocidal activities [6], and, unlike triclosan, only limited information is available on the effects of parabens on allergy. However, it is well known that parabens increase local skin sensitivity as an antiseptic and is involved in the increased prevalence of allergic contact dermatitis [7,8]; however, few studies have reported the systemic allergic effects of parabens on allergic diseases such as asthma. The relationship between the use of parabens and allergic diseases in adults has not yet been fully elucidated.

The only study to examine the relationship between exposure to parabens and the prevalence of atopy was a National Health and Nutrition Examination Survey (NHANES). A cross-sectional study was conducted on 860 children aged between 6 and 18 years, and the findings obtained showed significantly higher odds of aeroallergen sensitization with increased urinary levels of propyl and butyl parabens [5,9]. To the best of our knowledge, epidemiological studies have yet to be performed on adults to support the relationship observed between systemic allergic responses and paraben use in children.

We conducted a cohort study named the Shika study in Shika Town of Ishikawa prefecture in Japan from 2011 [10,11]. Shika Town is located in Ishikawa prefecture, which is a rural area of Japan, and it has approximately 22,000 residents. The subjects of the study were residents of two districts (model 1 districts: Horimatsu district and Higashimasuho district) at the starting point. We added residents of another two districts (model 2 districts: Tsuchida district and Togi district) to the study as subjects from 2016. The association between health (life-style diseases such as hypertension, allergy diseases, chronic pain, mental health, and so on) and lifestyle, nutrition, etc., was investigated in adults (more than 40 years old). We also started investigating the effect of parabens contained in household goods such as cosmetics on health (allergy) in adults of the model 2 districts from 2016 and in babies and toddlers in the whole area of Shika Town from 2017.

The present cross-sectional study was conducted as part of the Shika study. We herein conducted a complete survey of a general population in Japan in an attempt to clarify the relationship between the use of parabens and the prevalence of allergic diseases, including asthma, nasal allergies, allergic dermatitis, and conjunctivitis, among adults.

2. Materials and Methods

2.1. Study Design and Subjects

The present study was a cross-sectional study and conducted as a part of the Shika study in 2016. We selected two model districts, Tsuchida district (n = 1420 (2016)) and Togi district (n = 1381 (2016)),

from four model districts in Shika Town because their population demographics are similar to those of Shika Town. A questionnaire was provided to all residents aged 40 years and older ($n = 2801$) in the two model districts by trained interviewers. A total of 2183 questionnaires were returned, with the responses of 2014 questionnaires being complete (response rate: 77.9%). Since 9 out of 2014 subjects reported the use of triclosan, the questionnaires of 2005 subjects (average age and standard deviation: 64.7 and 12.9 years) were ultimately analyzed in the present study. The present study was conducted between November and December 2016.

2.2. Assessment Instruments and Definitions

We used a self-administered questionnaire handed to subjects by interviewers who were trained using standardized procedures; they explained the study and how to complete the questionnaire. A few days later, the completed forms, which were placed in sealed envelopes [11], were collected.

Allergic diseases were defined using questions shown below. "Do you have hand eczema or severe skin problems now?", "Have you ever had asthma?", "Do you have nasal allergy containing pollinosis?", and "Do you have atopic dermatitis?". Information on the use of parabens and triclosan was obtained from questions on the daily use of household goods such as cosmetics, skin ointments, hand or body creams and lotions, shampoos, soaps, toothpastes, sunscreen, eyewash, oral cleaning solution, and bath additives. We asked the subjects about the use of each household good and the frequency of its use. For example, "Did you use soap to wash your body in the last 3 days?" and "Please tell us how frequently you use soap." (1: 1–2 times per 3 days; 2: 1 time per day; 3: more than 2 times per day). The inclusion of parabens in household goods was confirmed using photos of labels which participants took or information on the Internet.

2.3. Demographics

Data on the general demographic characteristics, including age, sex, height, weight, current smoker/non-smoker status, alcohol intake, exercise habit, hours slept per day, household income, education level, and marital states, were also collected. We used the questions mentioned below in the present study. "Please tell us about your smoking habits." (1: smoker; 2: ex-smoker; 3: non-smoker), "How often do you drink per week?" (1: 7 days; 2: 5–6 days; 3: 3–4 days; 4: 1–2 days; 5: 2–3 days per month; 6: almost no drinking; 7: cessation of drinking; 8: no drinking), "How often do you perform exercise per week?" (1: 7 days; 2: 5–6 days; 3: 3–4 days; 4: 1–2 days; 5: zero), "What is your average sleeping time in the last month?", "What was your family's total income last year?" (1: less than 2 million yen; 2: 2–4 million yen; 3: 4–6 million yen; 4: 6–8 million yen; 5: 8–10 million yen; 6: 10–12 million yen; 7: more than 12 million yen; 8: unclear), "How many years did you attend school after you have entered elementary school?", and "Are you married?" (1: single; 2: have spouse now; 3: had spouse previously). Body mass index (BMI) was calculated from height and weight.

2.4. Statistical Analysis

The Student's *t*-test was used for continuous variables and the chi-squared test was used for categorical variables in order to analyze differences between the groups of independent variables (men and women; subjects with and without allergic diseases). Subjects with more than one of the following allergic diseases: asthma, nasal allergies, atopic dermatitis, atopic conjunctivitis, food allergies, and drug allergies were categorized into total allergies. A Cochran–Armitage test was employed for trend analysis on the relationship between the frequency of using general household goods in daily life and that of using individual paraben-containing household goods. A logistic regression analysis was conducted in order to estimate the independent impact of each variable (age, BMI, smoking, alcohol intake, exercise habits, sleep, income, education, marital status, and paraben use) on the prevalence of allergic diseases. Hypothesis testing involved two-sided tests, and $p < 0.05$ was considered to be significant. All analyses were performed using SPSS (Version 24.0, IBM Japan, Tokyo, Japan).

2.5. Ethics Statement

This study was approved by the Medical Ethics Committee of Kanazawa University (examination number 2184-1). All subjects provided written informed consent to participate in the present study.

3. Results

3.1. Subject Characteristics

Table 1 shows the characteristics of subjects who participated in the present study. Comparisons of variables between men and women revealed a significantly higher prevalence of nasal allergies and total allergies and a lower prevalence of atopic conjunctivitis in men than in women. Height, weight, BMI, the percentage of current smokers, frequency of alcohol intake, hours slept, education level, and the percentage of those who were single were significantly higher in men, while age and income were significantly higher in women. A markedly higher percentage (35.3%) of women used household goods containing parabens than men (18.5%).

3.2. Relationship between the Frequency of Using Household Goods in Daily Life and That of Using Paraben-Containing Goods

Table 2 shows the relationship between the frequency of using household goods in daily life and that of using paraben-containing goods. A significant positive relationship was demonstrated by the trend analysis of the use of cosmetics, hand or body creams and lotions, shampoos, soaps, toothpastes, and sunscreens in women, while only the use of toothpastes in men demonstrated a significant positive relationship (Table 2).

3.3. Comparison of the Prevalence of Allergic Diseases between Subjects Who Did and Did Not Use Household Goods Containing Parabens

We compared the prevalence of asthma, nasal allergies, atopic dermatitis, atopic conjunctivitis, and total allergies between subjects who did and did not use household goods containing parabens (Table 3). The prevalence of nasal allergies among women was significantly higher among those using goods containing parabens (23.3%) than those who did not (13.4%). The prevalence of atopic conjunctivitis and total allergies, but not asthma or atopic dermatitis, was significantly higher in women using goods containing parabens than in those who did not. No significant differences were observed in the prevalence of any allergic diseases in men who did and did not use goods containing parabens (Table 3).

The logistic regression analysis with adjustments for age, BMI, smoking, alcohol, exercise, sleep, income, education, and marital status revealed that the relationship between the use of parabens and the prevalence of nasal allergies and atopic conjunctivitis remained significant (Table 4). Furthermore, associations were observed among the prevalence of asthma, BMI, and smoking, and also the use of parabens in women (Table 4).

Table 1. Subject characteristics in the present study.

Sex	Men (n = 891)		Women (n = 1114)		<i>p</i> Value ⁽³⁾
	Average or Percentage	SD	Average or Percentage	SD	
Age (years)	63.9	12.4	65.3	13.2	0.013
Height (cm)	166.5	6.85	152.7	6.89	0.000
Weight (kg)	65.7	10.3	52.6	9.19	0.000
BMI (kg/cm ²)	23.6	3.00	22.5	3.47	0.000
Asthma prevalence (%)	7.10	-	6.84	-	0.824
Nasal allergy prevalence (%)	26.0	-	17.0	-	0.000
Atopic dermatitis prevalence (%)	2.54	-	2.42	-	0.864
Atopic conjunctivitis prevalence (%)	4.91	-	7.40	-	0.028
Total allergy prevalence (%)	34.8	-	28.9	-	0.008
Current smoker prevalence (%)	30.8	-	6.40	-	0.000
Alcohol drinking frequency per week ⁽¹⁾	2.94	1.80	4.41	1.25	0.000
Exercise frequency per week ¹⁾	3.91	1.47	3.95	1.42	0.515
Sleep (hours)	7.10	1.43	6.91	1.40	0.004
Household Income ⁽²⁾	3.60	2.25	3.83	2.46	0.042
Educational carrier (years)	11.8	2.89	11.5	2.61	0.017
Marital status (1, single; 2, married or married in the past)	1.91	0.292	1.96	0.185	0.000
Use of parabens (%)	18.5	-	35.3	-	0.000

⁽¹⁾ 1, 7 days; 2, 5–6 days; 3, 3–4 days; 4, 1–2 days; 5, almost zero; ⁽²⁾ 1, less than 2 million; 2, 2–4 million; 3, 4–6 million; 4, 6–8 million; 5, 8–10 million; 6, 10–12 million; 7, more than 12 million;

⁽³⁾ *p* values were calculated using the Student's *t*-test or the chi-squared test to compare averages or frequencies between men and women.

Table 2. Relationship between the frequency of use of household goods and parabens. Number of subjects reporting the frequency of use of household goods in paraben users (upper row). Percentage of paraben users in the subjects who reported the frequencies of household goods in each category (%) ⁽¹⁾ (lower row).

Sex	Men					Women					
	Household Goods	no Use	1-2 Times per 3 Days	Everyday	More Than 2 Times per Day	<i>p</i> for Trend ⁽²⁾	No Use	1-2 Times per 3 Days	Everyday	More Than 2 Times per Day	<i>p</i> for Trend
Cosmetics		152	2	2	0	0.964	103	47	229	8	0.000
		19.5	25.0	18.2	0.0	-	22.9	43.1	45.8	47.1	-
Skin Ointments		141	3	10	3	0.225	323	20	22	16	0.215
		20.3	9.7	17.5	13.0	-	37.1	44.4	29.7	30.8	-
Hand or Body Creams and Lotions		134	9	14	1	0.278	220	45	89	32	0.037
		18.7	24.3	24.6	16.7	-	34.2	38.5	41.2	41.6	-
Shampoos		8	63	90	3	0.076	8	159	222	3	0.009
		9.0	20.0	20.0	20.0	-	19.0	33.8	39.3	30.0	-
Soaps		27	16	37	83	0.068	42	30	76	240	0.002
		18.2	14.4	14.6	23.5	-	29.4	30.3	30.6	40.7	-
Toothpastes		10	9	79	66	0.025	15	8	110	258	0.000
		10.6	18.8	19.1	21.6	-	14.7	27.6	34.9	40.6	-
Sunscreen		159	1	0	1	0.918	211	40	133	3	0.000
		19.9	11.1	0.0	50.0	-	30.9	40.8	48.4	33.3	-
Eyewash		156	2	2	1	0.875	369	3	5	1	0.072
		19.4	28.6	22.2	16.7	-	36.8	37.5	23.8	12.5	-
Oral Cleaning Solution		138	8	6	10	0.065	319	25	28	11	0.225
		18.7	22.2	15.4	41.7	-	36.4	48.1	31.8	25.6	-
Bath Additives		116	24	24	0	0.596	250	59	77	0	0.449
		19.9	17.9	18.6	0.0	-	35.6	36.0	40.1	0.0	-

⁽¹⁾ The percentage was calculated as follows. If there are 90 male paraben users among 449 male subjects who used shampoos everyday, the percentage is calculated as 20%. ⁽²⁾ *p* values were calculated by the Cochran-Armitage test in order to examine the relationship between the subjects who reported the frequency of household goods and those reporting the frequency of household goods containing parabens. The *p* for the trend represents *p* values for the trend analysis.

Table 3. Comparisons of allergic diseases between subjects using and not using household goods containing parabens.

Sex	Men					Women				
	Use of parabens (+)		(-)			(+)		(-)		
	N	Prevalence	N	Prevalence	<i>p</i> Value ⁽¹⁾	N	Prevalence	N	Prevalence	<i>p</i> Value ⁽¹⁾
Asthma	10	6.06	51	7.35	0.563	27	6.96	46	6.77	0.909
Nasal Allergies	39	23.6	186	26.5	0.445	90	23.3	93	13.4	0.000
Atopic Dermatitis	3	1.82	19	2.71	0.512	12	3.10	14	2.03	0.275
Atopic Conjunctivitis	5	3.18	36	5.31	0.267	49	13.35	27	4.09	0.000
Total Allergies	46	29.3	241	36.0	0.111	148	40.9	142	22.2	0.000

⁽¹⁾ *p* values were calculated using the chi-squared test in order to compare the prevalence of allergic diseases between subjects using and not using household goods containing parabens.

Table 4. Logistic regression analysis of allergic diseases with explanatory variables including paraben use in women.

Disease	Asthma				Nasal Allergies			Atopic Dermatitis			Atopic Conjunctivitis			Total Allergies						
	Variables	exp(β)	Confidence Interval	<i>p</i> Value	exp(β)	Confidence Interval	<i>p</i> Value	exp(β)	Confidence Interval	<i>p</i> Value	exp(β)	Confidence Interval	<i>p</i> Value	exp(β)	Confidence Interval	<i>p</i> Value				
Age	0.994	0.962	1.027	0.714	1.036	1.013	1.059	0.002	1.018	0.960	1.080	0.548	1.018	0.985	1.053	0.290	1.022	1.002	1.042	0.027
BMI	0.925	0.858	0.998	0.044	0.991	0.937	1.048	0.750	0.990	0.834	1.174	0.908	1.076	0.971	1.192	0.162	0.987	0.938	1.038	0.613
Smoking	2.926	1.106	7.743	0.031	1.257	0.581	2.717	0.561	0.000	0.000	0.000	0.995	0.891	0.248	3.206	0.860	1.540	0.775	3.059	0.218
Alcohol	1.000	0.788	1.269	0.999	0.847	0.713	1.006	0.058	0.894	0.643	1.243	0.505	0.946	0.738	1.213	0.662	0.935	0.810	1.078	0.355
Exercise	0.802	0.617	1.041	0.098	1.059	0.912	1.231	0.452	0.495	0.246	0.996	0.049	0.980	0.776	1.236	0.863	0.999	0.876	1.138	0.983
Sleep	0.920	0.707	1.197	0.534	1.057	0.873	1.280	0.571	1.191	0.759	1.869	0.446	1.269	0.944	1.707	0.115	1.054	0.897	1.239	0.520
Income	1.068	0.861	1.324	0.551	0.996	0.866	1.147	0.960	1.076	0.717	1.615	0.723	0.886	0.721	1.088	0.247	0.979	0.866	1.108	0.741
Education	1.002	0.867	1.159	0.974	0.934	0.849	1.027	0.158	0.873	0.709	1.074	0.198	1.073	0.933	1.233	0.326	0.978	0.901	1.062	0.600
Marital Status	0.589	0.071	4.870	0.624	1.570	0.570	4.319	0.383	0.000	0.000	0.000	0.997	1.249	0.252	6.193	0.785	1.129	0.427	2.989	0.806
Parabens	1.985	1.057	3.727	0.033	2.069	1.368	3.128	0.001	1.153	0.297	4.476	0.837	2.748	1.428	5.285	0.002	2.558	1.782	3.673	0.000

4. Discussion

Our study had a high response rate (77.9%) to a survey of a community-based sample in a Japanese population, and the comprehensive survey was conducted with the residents of the areas based on the basic resident register, thereby minimizing selection bias, to survey the symptoms of allergy and the use of parabens. To the best of our knowledge, this is the first study to analyze the relationship between the use of parabens and the prevalence of allergic diseases in Japanese adults.

Parabens are contained in household goods, including cosmetics, shampoos, and personal care products, as preservatives. Triclosan is used as an antibacterial agent for personal care and medical products. Although parabens have been shown to increase the prevalence of allergic contact dermatitis [7,12], limited information is currently available on the relationship between the use of parabens and allergies including asthma, nasal allergies, and hay fever. Previous studies reported that triclosan possessed endocrine-disrupting and, potentially, immune-modulating properties [3,13,14] in addition to allergy-inducing effects [4,15,16]. Therefore, the use of triclosan as an ingredient in antibacterial soaps was banned by the EU in 2015 and by the US Food and Drug Administration (FDA) in 2016. The Ministry of Health, Labor and Welfare in Japan also supported the decision of the FDA, immediately announcing a change in soaps with triclosan to those without it. Since the present study was performed after the announcement by the Ministry of Health, Labor and Welfare in Japan, 9 of the 2014 subjects who participated used products containing triclosan. Given the administrative measures, the known effects of triclosan in inducing allergies were the reason why we excluded these subjects from the analysis.

Since cosmetics, hand creams or lotions, sunscreen, and other products are applied to a large area of the skin and not washed off for a long time, the parabens in these products are more likely to be absorbed [6]. According to Soni et al. [17], the average daily exposure to parabens is 76 mg, which includes 50 mg derived from household goods, such as cosmetics, creams, lotions, soaps, and shampoos, 25 mg from pharmaceuticals, and 1 mg from the diet. A study on adult women in Sweden revealed a relationship between the use of household goods, including cosmetics and body creams and lotions, and urinary levels of parabens [18]. The present results showed higher frequencies in the use of cosmetics, hand or body creams and lotions, shampoos, and soaps among household goods containing parabens by women and are consistent with the findings of Soni et al. [17] and Larsson et al. [18]. To the best of our knowledge, the present study is the first to show a positive relationship between paraben use and the prevalence of nasal allergies. This is attributed to the limited number of epidemiological studies that have investigated paraben use and the prevalence of allergic diseases in adult populations, because nasal allergies, including cedar pollinosis, are common characteristics in adults, but are rare in children in Japan. We also noted a relationship between the prevalence of atopic ocular conjunctivitis in women and the use of household goods containing parabens. Taken together with the higher exposure of women to parabens, the results regarding allergic diseases only in women suggest that parabens induce allergic responses that subsequently lead to nasal allergies and atopic ocular conjunctivitis. On the other hand, eye drops, oral washes, creams, and gels containing parabens as a preservative have been demonstrated to have adverse effects on conjunctivitis [19,20]. Based on our results on allergic responses in the eyes and nose, the increases observed in the prevalence of nasal and ocular allergic diseases appear to be attributed to the higher sensitivities of the local immune systems of the nasal and ocular organs in women to parabens, which are mainly added to cosmetics, face creams, lotions, and shampoos. Detailed etiologies can be obtained from pathophysiological examinations of the nasal and conjunctive mucosa.

In the present study, no significant association between the use of parabens and allergic diseases was observed in men. Parabens are considered to be mainly absorbed through the skin [17]. It may be difficult to absorb parabens from shampoo or soap because they are washed out soon after they are used. The number of men who used household goods that are applied for a long time (cosmetics, skin ointments, hand or body creams and lotions, and sunscreen) was very small (Table 2). Therefore, the concentrations of parabens absorbed in men may be very low, and parabens did not affect allergic

diseases in men. Further study, such as the measurement of parabens in urine, is needed to elucidate the lack of effect of parabens on allergic diseases in men.

Univariate analysis demonstrated no significant relationship between the use of parabens and asthma. However, intriguingly, logistic regression analysis demonstrated a significant positive relationship. Previous studies reported that one of the important risk factors for asthma in women is being overweight or obese [21–25]. Furthermore, smoking contributes to the development of asthma in men and women [26,27]. Based on the effects of obesity and smoking on asthma in women, adjustments for these confounding factors may result in a positive relationship being observed between paraben use and the prevalence of asthma. A longitudinal study is needed to examine the causal relationship between parabens and asthma after excluding confounding factors.

The prevalence of nasal allergies was higher among men than women in the present study. If parabens have adverse effects on nasal allergy, the prevalence of nasal allergy should have been higher in women than in men, considering that larger amounts of parabens were used by women than by men. However, the prevalence of nasal allergy was higher in men than in women. This may be explained by a higher heritability of allergy in men [24,28,29]. The interaction between the heritability of allergy and the use of parabens should be analyzed to explain this inconsistency [30,31].

The strengths of our study were the high response rate (77.9%) to this survey from a community-based sample in a Japanese population and that a comprehensive survey was conducted among the residents of the areas based on the basic resident register, thereby minimizing the selection bias to survey the symptoms of allergy and the use of parabens. To the best of our knowledge, this is the first study to analyze the relationship between the use of parabens and the prevalence of allergic diseases in Japanese adults.

Our study had some limitations. Since it was a cross-sectional design, we could not directly infer causal relationships. Furthermore, our data, including the determination of allergy, were based on self-reports, not objective data from medical records and blood tests. Additionally, we investigated the use of parabens based on the questionnaire only. In order to objectively assess exposure to parabens, urinary levels of parabens need to be measured [5]. We also need to perform longitudinal research with data based on objective diagnoses of allergic diseases and objective examinations of exposure to parabens in order to demonstrate causal relationships.

5. Conclusions

The prevalence of nasal allergies and atopic conjunctivitis was associated with the use of parabens in women, whereas a relationship was not observed between the prevalence of atopic dermatitis and the use of parabens in men or women. The results obtained from women indicate that parabens may induce allergic responses. Increases in the prevalence of nasal and ocular allergic diseases appear to be attributed to the higher sensitivities of the local immune systems of the nasal and ocular organs in women to parabens, which are mainly added to cosmetics, face creams and lotions, and shampoos. In order to demonstrate causal relationships, we need to perform longitudinal research with data based on objective diagnoses of allergic diseases and objective examinations of exposure to parabens.

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