

# The association between high hygiene scores and allergic rhinitis in Korean adolescents

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**Background:** Recent studies have proposed that hand-washing can lead to the development of allergic disease by reducing skin epithelial barrier integrity. The purpose of this study was to evaluate the association between personal hygiene practices and allergic rhinitis (AR) in a nationally representative sample of Korean adolescents.

**Methods:** A total of 62,276 adolescent participants (aged 12 to 18 years) were analyzed using the Korea Youth Risk Behavior Web-based Survey, which was conducted in 2017. Participants were asked about the frequency of handwashing considering 5 situations. AR histories throughout life and in the last 12 months were obtained. The associations between AR and hygiene scores were analyzed using multiple logistic regression, with adjustment for possible confounders. Subgroup analyses were conducted for school level, age, economic level, and education level of each parent.

**Results:** The analysis of the general characteristics showed that younger age, increased number of days of physical activity, male sex, living in a large city, high economic level, high education levels of father and mother, nonsmoking

status, and no alcohol consumption were associated with a relatively high hygiene score ( $p < 0.001$ ). The adjusted odds ratio (aOR) of AR was 1.12 (95% confidence interval [CI], 1.06 to 1.18;  $p < 0.001$ ) throughout life and 1.21 (95% CI, 1.14 to 1.29;  $p < 0.001$ ) for the previous 12 months in the highest compared with the lowest hygiene score groups. Consistent results were obtained in the female sex, any school level, middle economic level, and both parents with any education level.

**Conclusion:** The association between high hygiene scores and AR was significant in Korean adolescents after adjustment for several variables. © 2020 ARS-AAOA, LLC.

## Key Words:

allergic rhinitis; hygiene; hand disinfection; socioeconomic factors; adolescent; epidemiology; population surveillance

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Epidemiologic studies have demonstrated a significant increase in allergic diseases over the last century.<sup>1</sup> It is accepted that the recent increase in the prevalence of allergic diseases cannot be explained by genetics alone; it is thought to be a result of changes in the environment and lifestyles.<sup>2</sup> This same time period has been marked by a decrease in the prevalence of bacterial and viral infectious diseases,<sup>3</sup> which was achieved by increased vaccination and antibiotic use as well as by the establishment of living conditions characterized by high hygienic standards.<sup>4</sup>

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Since the “hygiene hypothesis,” which postulates that infection protects against atopy, was proposed by Strachan in 1989,<sup>5</sup> several epidemiological studies have published results supporting this concept, but this concept has evolved over time.<sup>6</sup> An initial study proposed that an inverse relationship between family size/birth order and hay fever/asthma is caused by the frequency of childhood infections.<sup>5</sup> It has been explained that a deficiency in infection in early life results in systemic immune function that increases susceptibility to allergic sensitization.<sup>5,7</sup> However, the concept has evolved and suggests that the reduction in microbial exposure or colonization, rather than microbial infection, increases the prevalence of allergic disease.<sup>6</sup> This evolution was driven by previous cross-sectional and longitudinal studies showing no relationship between the frequency or severity of early childhood infectious illnesses and the later development of allergy, atopic disease, or asthma.<sup>8–11</sup> Environmental exposure to microbial products in the absence of overt infection may have a crucial role in the regulation of allergic immune responses.<sup>12</sup> Therefore, it has been implied that excessive cleanliness reduces microbial stimulation, which is needed to enable normal development of the immune system.<sup>13</sup> These observations suggest an inverse relationship between high living standards and hygiene conditions and an increased risk of developing an allergic disease. The explanation for immunological basis of this has suggested a lack of immune deviation from T helper 2 (Th2) to Th1, caused by the reduced production of Th1-polarizing cytokines by cells involved in the innate immune system in response to stimulation of Toll-like receptors by microbial components.<sup>14</sup>

Recent advances in microbiome and immunologic studies have demonstrated that barrier tissues, such as skin and gut epithelial cells, play an important role in immunoregulation involving the activation of dendritic cells and T cells and innate immunity to allergens.<sup>15</sup> Reduced epithelial function can promote increased penetration of allergens into subepithelial layers involved in antigen recognition mechanisms.<sup>16</sup> In addition, epithelial damage by proteases induces the release of innate cytokines, which act on antigen-presenting cells and innate and adaptive lymphoid cells to promote Th2 differentiation and allergic sensitization.<sup>17,18</sup> Therefore, hygiene habits, such as washing hands using antimicrobial agents, could lead to the development of allergic disease by reducing skin epithelial barrier integrity.<sup>19</sup>

Although the Avon Longitudinal Study of Parents and Children (ALSPAC) study team reported an association between high hygiene scores and wheezing (odds ratio [OR] 1.04; 95% confidence interval [CI], 1.00 to 1.08) and atopic eczema (OR 1.04; 95% CI, 1.01 to 1.07) in children,<sup>20</sup> few studies have shown that personal hygiene conditions relate to allergic disease. This study aimed to evaluate the association between personal hygiene level and AR using a nationally representative sample of Korean adolescents. We hypothesized that a high hygiene

score would be associated with AR independent of the socioeconomic status (SES) levels.

## Subjects and methods

### Study population and data collection

The Institutional Review Board (IRB) of Hallym University approved this study (HALLYM 2019-09-005). Written informed consent was obtained from each participant prior to the survey. Because this web-based survey was performed at schools and included a large number of participants, informed consent from their parents was exempted.

This cross-sectional study analyzed data from the Korea Youth Risk Behavior Web-based Survey (KYRBWS). This study included participants from 1 nation and used statistical methods based on designed sampling and adjusted weighted values. The KYRBWS data collected in 2017 were analyzed. The data were collected by the Korean Centers for Disease Control and Prevention (KCDC). Korean adolescents in grades 7 to 12 voluntarily and anonymously completed the self-administered questionnaire. The validity and reliability of the KYRBWS have been documented in other studies.<sup>21,22</sup> The surveys evaluated the data of South Korean adolescents using a stratified, 2-stage (schools and classes) clustered sampling method based on data from the Education Ministry. Sampling was weighted by statisticians who performed poststratification analyses considering non-response rates and extreme values. The data are available on the website.<sup>23</sup>

Of the 62,276 participants, we excluded the following participants from this study: participants who did not record their age ( $n = 415$ ) and participants who did not record their height or weight ( $n = 1469$ ). Finally, 60,392 participants (males = 30,662; females = 29,730) aged 12 to 18 years were included in this study (Supporting Fig. 1).

### Definition of hygiene score groups

Participants were asked 5 questions regarding personal hygiene. The questions asked if the participants washed their hands with soap in the past 7 days considering the following situations: before a meal at school, after using a toilet at school, before a meal at home, after using a toilet at home, and after coming home from going out. These questions were modified from a previous study's questions regarding children's personal cleanliness.<sup>13</sup> Depending on the level of handwashing in each question, hygiene scores of 3 to 0 were assigned for answers that were “always washed,” “mostly washed,” “sometimes washed,” and “never washed,” respectively. Finally, total hygiene scores were calculated by summing the hygiene scores of the 5 questions. The highest possible score was 15, and the lowest score was 0.

Hygiene scores were classified into 3 groups according to the distribution of participants: lowest score group (T1: total hygiene score = 0 to 9;  $n = 21,250$ ), middle score group (T2: total hygiene score = 10 to 12;  $n = 21,009$ ),

and the highest score group (T3: total hygiene score = 13 to 15;  $n = 18,133$ ; Supporting Fig. 1).

### Definition of AR

Participants were asked about their history of AR, asthma, and atopic dermatitis based on the phase 3 core questionnaire of the International Study of Asthma and Allergies in Children (ISAAC).<sup>24</sup> Based on 2 questions, AR was defined as “AR throughout life” and “AR within 12 months.” In the first question, participants were asked if they were diagnosed with AR at any point in their lifetime. In the second question, those who were diagnosed were also asked whether they were diagnosed by a medical doctor in the previous 12 months. If the participants answered “yes” to the first question, then those participants were defined as “AR throughout life”; the others were considered as “no AR throughout life.” If the participants answered “yes” to the second question, then those participants were defined as “AR within 12 months,” and the others were considered as “no AR within 12 months.”

### Covariates

The days of physical activity were defined as the number of days in the previous week the participant engaged in exercise sufficient in intensity to increase the heart rate or respiration for more than 60 minutes. Sleep durations were recorded by times of falling asleep and waking up. The participants were asked the time they fell asleep and the time they woke up for the past 7 days of weekdays and weekends, respectively. The sleep durations were considered as missing value if sleep durations of weekdays or weekends were  $<0$  hours. Mean sleep duration was calculated by average of weekdays and weekends sleep durations. Body mass index (BMI) was classified into 4 groups according to the Centers for Disease Control and Prevention Guidelines on BMI ( $\text{kg}/\text{m}^2$ ) for Children and Teens<sup>25</sup>: obese  $\geq 95$ th percentile; overweight  $\geq 85$ th percentile and  $<95$ th percentile; healthy weight  $\geq 5$ th percentile and  $<85$ th percentile; and underweight  $<5$ th percentile. Regions of residence were divided into 3 groups according to the administrative district: large city, small city, and rural area. Economic levels were classified into 5 levels from highest to lowest. The education levels of each parent were divided into 4 groups: college graduate or higher; completed high school; completed junior high school or lower; unknown or no parent. The participants were asked to report the number of days they smoked in the previous month; smoking frequency was divided into 3 groups: never, 1 to 19 days per month, and 20 to 30 days per month. The participants were asked to report the number of days they consumed alcohol; alcohol consumption frequency was divided into 3 groups: never, 1 to 5 days per month, and 6 to 30 days per month. Stress level was classified into 5 groups: severe, moderate, mild, a little, and no stress. To identify depression, the participants were asked if they felt depressed enough to stop their daily life for 2 weeks within 12 months and answered yes or no.

Participants were asked if they were diagnosed with asthma or atopic dermatitis at any point in their lifetime. Among those who were diagnosed, they were also asked whether they were diagnosed by a medical doctor in the previous 12 months. Participants were defined as asthma or atopic dermatitis patients if participants were diagnosed at least once in their lifetime.

### Statistical analysis

The general characteristics were compared according to the hygiene score groups. The Rao-Scott chi-square test with sampling weights was used to compare the categorical variables, and linear regression analysis with sampling weights was used to compare the continuous variables.

To calculate the ORs with 95% CIs of AR among the hygiene score groups, crude model (simple model), model 1 (adjusted for age, sex, economic level, region of residence, father's education level, mother's education level, smoking frequency, alcohol consumption frequency, days of physical activity, and obesity), and model 2 (model 1 additionally adjusted for mean sleep duration, stress level, depression, asthma and atopic dermatitis) were analyzed using multiple logistic regression with sampling weights.

For subgroup analyses, we classified the participants according to school level (junior high school and high school), sex (male and female), economic level (highest, middle, and lowest economic level), and education level of each parent (college graduate or higher and completed high school or lower for each parent). In the subgroup analyses, the ORs and 95% CIs of crude, model 1, and model 2 were calculated using multiple logistic regression with sampling weights.

Two-tailed analyses were conducted, and significance was defined as  $p$  values  $<0.05$ . The statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Sampling weights were used to perform complex sampling of the national survey data using a survey procedure (PROC SURVEY).

### Results

The analysis of general characteristics showed that younger age, increased number of days of physical activity, longer sleep duration, male sex, living in a large city, high economic level, high education levels of fathers and mothers, nonsmoking status, no alcohol consumption, less stress level, and no depression were associated with high hygiene scores (each  $p < 0.001$ ; Table 1, Supporting Table 1). An increased prevalence of AR for both throughout life and within 12 months and a decreased prevalence of atopic dermatitis for throughout life were associated with high hygiene scores (each  $p < 0.001$ ).

The OR of AR throughout life was 1.12 (95% CI, 1.06 to 1.18;  $p < 0.001$ ), and the OR of AR within 12 months was 1.21 (95% CI, 1.14 to 1.29;  $p < 0.001$ ) between the T3 group and the T1 group in model 2 (Table 2).

TABLE 1. General characteristics of participants according to the hygiene score

| Characteristics                         | Total           | Hygiene score   |                 |                 | p                   |
|-----------------------------------------|-----------------|-----------------|-----------------|-----------------|---------------------|
|                                         |                 | Group T1        | Group T2        | Group T3        |                     |
| Subjects, n (%)                         | 60,392 (100.0)  | 21,250 (35.4)   | 21,009 (34.9)   | 18,133 (29.8)   |                     |
| Age (years), mean $\pm$ SE              | 15.1 $\pm$ 0.02 | 15.3 $\pm$ 0.03 | 15.2 $\pm$ 0.03 | 14.9 $\pm$ 0.03 | <0.001 <sup>a</sup> |
| Physical activity (days), mean $\pm$ SE | 1.9 $\pm$ 0.02  | 1.6 $\pm$ 0.02  | 1.9 $\pm$ 0.02  | 2.3 $\pm$ 0.02  | <0.001 <sup>a</sup> |
| Sleep duration (hours), mean $\pm$ SE   | 7.15 $\pm$ 0.02 | 7.12 $\pm$ 0.02 | 7.13 $\pm$ 0.02 | 7.23 $\pm$ 0.02 | <0.001 <sup>a</sup> |
| Sex, male, n (%)                        | 30,662 (52.1)   | 10,374 (50.1)   | 10,204 (49.8)   | 10,084 (57.0)   | <0.001 <sup>b</sup> |
| Obesity, n (%)                          |                 |                 |                 |                 | 0.065               |
| Under and normal weight                 | 48,972 (81.4)   | 17,211 (81.3)   | 17,151 (82.1)   | 14,610 (80.8)   |                     |
| Overweight and obese                    | 11,420 (18.6)   | 4,039 (18.7)    | 3,858 (17.9)    | 3,523 (19.2)    |                     |
| Region, large city, n (%)               | 26,852 (43.2)   | 8,907 (41.0)    | 9,450 (43.5)    | 8,495 (45.3)    | <0.001 <sup>b</sup> |
| Economic level, highest, n (%)          | 6,351 (10.7)    | 1,521 (7.4)     | 2,003 (9.7)     | 2,827 (15.7)    | <0.001 <sup>b</sup> |
| Education level, father, n (%)          |                 |                 |                 |                 | <0.001 <sup>b</sup> |
| College or over                         | 30,882 (52.9)   | 10,150 (49.4)   | 10,950 (54.0)   | 9,782 (55.6)    |                     |
| Education level, mother, n (%)          |                 |                 |                 |                 | <0.001 <sup>b</sup> |
| College or over                         | 28,407 (48.3)   | 9,181 (44.2)    | 10,032 (49.0)   | 9,194 (52.2)    |                     |
| Smoking, none, n (%)                    | 56,957 (94.0)   | 19,874 (93.2)   | 19,924 (94.6)   | 17,159 (94.3)   | <0.001 <sup>b</sup> |
| Alcohol, none, n (%)                    | 51,288 (84.3)   | 17,643 (82.5)   | 17,906 (84.6)   | 15,739 (86.1)   | <0.001 <sup>b</sup> |
| Stress level, a little and none, n (%)  | 12,368 (20.2)   | 3,660 (17.1)    | 4,081 (19.2)    | 4,627 (25.1)    | <0.001 <sup>b</sup> |
| Depression, n (%)                       | 14,952 (24.8)   | 5,526 (26.0)    | 5,224 (24.7)    | 4,202 (23.5)    | <0.001 <sup>b</sup> |
| Allergic rhinitis, n (%)                |                 |                 |                 |                 |                     |
| Throughout life                         | 21,201 (36.0)   | 7,191 (34.8)    | 7,560 (36.9)    | 6,450 (36.4)    | <0.001 <sup>b</sup> |
| Within 12 months                        | 11,870 (20.2)   | 3,879 (18.9)    | 4,214 (20.5)    | 3,777 (21.4)    | <0.001 <sup>b</sup> |
| Atopic dermatitis, n (%)                |                 |                 |                 |                 |                     |
| Throughout life                         | 15,132 (25.2)   | 5,528 (26.3)    | 5,389 (25.7)    | 4,215 (23.4)    | <0.001 <sup>b</sup> |
| Within 12 months                        | 4,394 (7.4)     | 1,596 (7.7)     | 1,521 (7.3)     | 1,277 (7.2)     | 0.165               |
| Asthma, n (%)                           |                 |                 |                 |                 |                     |
| Throughout life                         | 5,179 (8.7)     | 1,811 (8.5)     | 1,818 (8.8)     | 1,550 (8.8)     | 0.603               |
| Within 12 months                        | 1,372 (2.3)     | 454 (2.1)       | 475 (2.3)       | 443 (2.4)       | 0.207               |

<sup>a</sup>Linear regression was analyzed with sampling weights, significance at  $p < 0.05$ .

<sup>b</sup>Rao-Scott chi-square test was analyzed with sampling weights, significance at  $p < 0.05$ .

SE = standard error; T1 = lowest score group (hygiene score 0 to 9); T2 = middle score group (hygiene score 10 to 12); T3 = highest score group (hygiene score 13 to 15).

Subgroup analyses according to school level and sex were performed (Fig. 1, Supporting Table 2). In the female group, the ORs of AR throughout life were higher in the T3 group than in the T1 group (junior high school: OR 1.24; 95% CI, 1.11 to 1.38; high school: OR 1.16; 95% CI, 1.05 to 1.29). In the male group, the OR of AR throughout life was higher in the T2 group than in the T1 group but not higher than that in the T3 group. The OR of AR within 12 months were higher in the T3 group than in the T1 group at all school

levels and in both sexes (males, junior high school: OR 1.27; 95% CI, 1.11 to 1.45; females, junior high school: OR 1.21; 95% CI, 1.06 to 1.38; males, high school: OR 1.17; 95% CI, 1.05 to 1.32; females, high school: OR 1.24; 95% CI, 1.10 to 1.41).

Subgroup analyses according to economic levels were analyzed (Fig. 2A, Supporting Table 3). At the middle economic level, the OR of AR throughout life was higher in the T3 group than in the T1 group (OR 1.20; 95% CI,

**TABLE 2.** ORs for allergic rhinitis according to the hygiene score\*

| Hygiene score           | ORs for allergic rhinitis for throughout life |                                            |                                            | ORs for allergic rhinitis within 12 months |                                            |                                            |
|-------------------------|-----------------------------------------------|--------------------------------------------|--------------------------------------------|--------------------------------------------|--------------------------------------------|--------------------------------------------|
|                         | Crude                                         | Model 1 <sup>a</sup>                       | Model 2 <sup>b</sup>                       | Crude                                      | Model 1 <sup>a</sup>                       | Model 2 <sup>b</sup>                       |
| Group T3                | 1.07<br>(95% CI, 1.02–1.12)<br>$p = 0.004$    | 1.08<br>(95% CI, 1.03–1.13)<br>$p = 0.002$ | 1.12<br>(95% CI, 1.06–1.18)<br>$p < 0.001$ | 1.17<br>(95% CI, 1.11–1.24)<br>$p < 0.001$ | 1.17<br>(95% CI, 1.11–1.24)<br>$p < 0.001$ | 1.21<br>(95% CI, 1.14–1.29)<br>$p < 0.001$ |
| Group T2                | 1.09<br>(95% CI, 1.05–1.14)<br>$p < 0.001$    | 1.08<br>(95% CI, 1.04–1.13)<br>$p < 0.001$ | 1.12<br>(95% CI, 1.07–1.18)<br>$p < 0.001$ | 1.11<br>(95% CI, 1.05–1.17)<br>$p < 0.001$ | 1.10<br>(95% CI, 1.04–1.16)<br>$p = 0.001$ | 1.14<br>(95% CI, 1.07–1.21)<br>$p = 0.001$ |
| Group T1<br>(reference) | 1                                             | 1                                          | 1                                          | 1                                          | 1                                          | 1                                          |

\*Logistic regression was analyzed with sampling weights, significance at  $p < 0.05$ .

<sup>a</sup>Model 1 was adjusted for age, sex, economic level, region of residence, father's education level, mother's education level, obesity, smoking, alcohol intake, and physical activity.

<sup>b</sup>Model 2 was adjusted for age, sex, economic level, region of residence, father's education level, mother's education level, obesity, smoking, alcohol intake, physical activity, mean sleep duration, stress level, depression, asthma, and atopic dermatitis.

CI = confidence interval; OR = odds ratio; T1 = lowest score group (hygiene score 0 to 9;  $n = 21,250$ ); T2 = middle score group (hygiene score 10 to 12;  $n = 21,009$ ); T3 = highest score group (hygiene score 13 to 15;  $n = 18,133$ ).

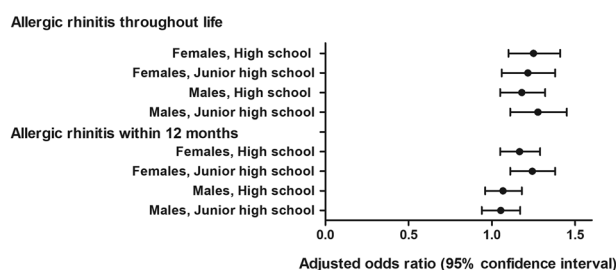
**Subgroup analyses according to school level and sex**

**FIGURE 1.** Adjusted odds ratio for allergic rhinitis according to the hygiene score, stratified by school level and sex using multiple logistic analyses with sampling weight. Model was adjusted for age, sex, economic status, region of residence, father's education level, mother's education level, obesity, smoking, alcohol intake, physical activity, mean sleep duration, stress level, depression, asthma, and atopic dermatitis.

1.11 to 1.29). At the highest economic level, the OR of AR for throughout life was higher in the T2 group than in the T1 group but not higher than that in the T3 group. Statistical significance was not shown at the lowest economic level between hygiene scores and AR for throughout life. The OR of AR within 12 months was higher in the T3 group than in the T1 group at all economic levels (highest economic level: OR 1.20; 95% CI, 1.09 to 1.33; middle economic level: OR 1.23; 95% CI, 1.12 to 1.35; lowest economic level: OR 1.25; 95% CI, 1.00 to 1.50).

For the education levels of each parent (Fig. 2B, Supporting Table 3), the OR of AR for throughout life was higher in the T3 group than in the T1 group for fathers and mothers with all education levels (father, college or over: OR 1.10; 95% CI, 1.02 to 1.18; father, high school or under: OR 1.15; 95% CI, 1.06 to 1.25; mother, college or over: OR 1.08; 95% CI, 1.00 to 1.17; mother, high school or under: OR 1.16; 95% CI, 1.07 to 1.25). The ORs of AR within 12

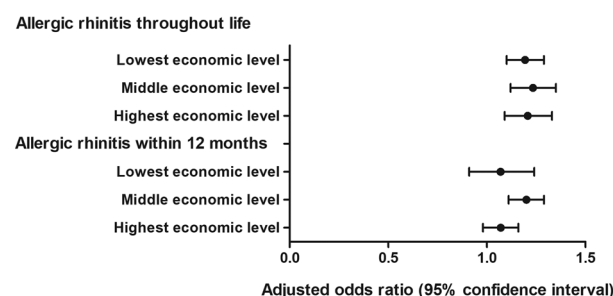
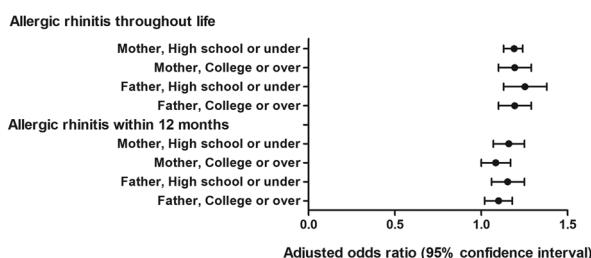
**A Subgroup analyses according to economic level****B Subgroup analyses according to education level of each parent**

**FIGURE 2.** Adjusted odds ratio for allergic rhinitis according to the hygiene score, stratified by economic level (A) and education level of each parent (B) using multiple logistic analyses with sampling weight. Model was adjusted for age, sex, economic level, region of residence, father's education level, mother's education level, obesity, smoking, alcohol intake, physical activity, mean sleep duration, stress level, depression, asthma, and atopic dermatitis.

months were higher in the T3 group than in the T1 group for all education levels for both parents (father, college or over: OR 1.19; 95% CI, 1.10 to 1.29; father, high school or under: OR 1.25; 95% CI, 1.13 to 1.38; mother, college or over: OR 1.21; 95% CI, 1.11 to 1.33; mother, high school or under: OR 1.19; 95% CI, 1.10 to 1.29).

## Discussion

In the present study, higher ORs of AR were observed in participants with relatively high hygiene scores than in those with relatively low hygiene scores. We obtained consistent results in the female, all school levels, middle economic level, and both parents with any education level.

The question of whether the insinuated association between cleanliness and the development of allergic disease can be substantiated in human populations remains. Few studies have shown that personal cleanliness relates to allergic sensitization.<sup>13,26,27</sup> One study in children aged 8 to 11 years reported for the first time that the development of atopic sensitization and asthma was not related to either home or personal cleaning activities.<sup>13</sup> On the other hand, in 2 recent studies, infrequent (once per week or less) baths/showers were protective against aeroallergen sensitization compared to daily baths/showers (adjusted odds ratio [aOR] 0.51; 95% CI, 0.27 to 0.98; aOR 0.688; 95% CI, 0.475 to 0.999; respectively) in adolescents without current allergies.<sup>26,27</sup> This is consistent with our study, but we cannot directly compare our findings because of different age groups, as well as different outcome assessments. In this study, we evaluated AR throughout life and within 12 months, not allergic sensitization. The mechanism mediating the association between personal hygiene and AR is unclear, but we could present the hygiene hypothesis and immunoregulation as a possible mechanism. Adolescent with high hygiene scores would have less contact with infectious agents than those with low hygiene scores as a result of frequent handwashing. Reduction of microbial stimulation leads a lack of immune deviation from Th2 to Th1.<sup>14</sup> Washing hands using antimicrobial agents that have immune modulating properties induces the release of innate cytokines; as a result, they can promote Th2 differentiation and allergic sensitization.<sup>17,18</sup> However, we cannot exclude the possibility that hygiene scores are acting as a substitute measure for some other risk factor that is not associated with the hygiene hypothesis or immunoregulation. Patients with atopic eczema may be more prone to frequent washing hand because of the nature of the condition. Nevertheless, in this study, there was no association with hygiene score group and “atopic dermatitis within 12 months,” and the prevalence of “atopic dermatitis throughout life” was higher in the less frequent handwashing group.

In this study, the association between high hygiene scores and AR was still statistically significant after adjusting for possible confounders, including age, sex, region of residence, obesity, smoking status, alcohol consumption, physical activity, SES, and other allergic diseases. Our previous study showed that the prevalence of AR was influenced by male sex (aOR 1.64; 95% CI, 1.13 to 2.36), a younger age (aOR 1.96; 95% CI, 1.30 to 2.96), and asthma (aOR 4.77; 95% CI, 1.92 to 11.82).<sup>28</sup> Another study showed that high physical activity (aOR 1.15; 95% CI, 1.09 to 1.21) and overweight (aOR 1.12; 95% CI, 1.05 to 1.20) were associated with AR.<sup>29</sup> Active smoking (aOR 1.18; 95% CI, 1.07

to 1.29; aOR 1.57; 95% CI, 1.38 to 0.77; respectively) and passive smoking (aOR 1.12; 95% CI, 1.05 to 1.20; aOR 1.40; 95% CI, 1.28 to 1.53; respectively) were significantly associated with atopic dermatitis<sup>30</sup> and asthma<sup>31</sup> in Korean adolescents. Several studies have reported an association between SES and allergic disease,<sup>32–34</sup> yielding conflicting results. In a Korean study, a high parental education level (father: OR 1.22; 95% CI, 1.11 to 1.34; mother: OR 1.18; 95% CI, 1.07 to 1.30), high family affluence scale (middle: OR 1.11; 95% CI, 1.06 to 1.16; high: OR 1.25; 95% CI, 1.19 to 1.31), and high subjective academic achievement (middle: OR 1.10; 95% CI, 1.03 to 1.17; high-middle: OR 1.26; 95% CI, 1.19 to 1.34; high: OR 1.29; 95% CI, 1.20 to 1.39) were significant risk factors for AR.<sup>32</sup> In another study in South Africa,<sup>33</sup> the prevalence of AR symptoms increased in those with the lowest to highest SES (overall OR for rhinitis symptoms in past year, 1.16; 95% CI, 1.11 to 1.21). On the other hand, there was a decreasing risk of AR with increasing SES after adjustments for confounders ( $p$  for trend = 0.004) in a study from Sweden.<sup>34</sup> Although SES was included as a covariate by adjusting for economic and parental education levels, we could not exclude unknown SES variables related to AR, such as the subjects' living environments, lifestyles, and access to healthcare. We conducted subgroup analyses based on sex, school level, economic level, and educational level of each parent to minimize the influence of other SES variables, which also revealed significant associations between hygiene and AR. The OR of AR within 12 months was higher in the highest hygiene score (T3) group than in the lowest hygiene score (T1) group in all the subgroup analyses.

The advantage of this study is that we used a large representative nationwide sample of adolescents. Our data can easily be compared with other studies using the KYRBWS<sup>23</sup> and ISAAC<sup>24</sup> questionnaires because they share the same standardized methodology. In addition, personal hygiene behaviors suspected of contributing to the hygiene effect were objectively scored. Personal cleanliness was also assessed by the frequency of handwashing after each scenario, as in a previous study<sup>13</sup> in which each condition was slightly different (“after playing outdoors/before meals/after using the toilet/with soap”). Furthermore, the analyses were conducted with adjustment for several covariates, including physical activity, obesity, region of residence, and economic and education levels. A previous study showed that high physical activity and overweight were associated with AR.<sup>29</sup> Several studies have reported an association between SES and AR.<sup>32–34</sup>

In this study, AR was defined based on a self-reported questionnaire without allergic test. We did not assess capture medications or severity of allergic diseases because of a lack of any such information. However, self-reporting may be considered valuable in a large-scale epidemiologic study. The validity and reliability of the KYRBWS have been documented by other studies.<sup>21,22</sup> Moreover, because prevalence of AR within 12 months (20.2%) in this study was similar with those (22.7%) from the

Korea National Health and Nutrition Examination Survey,<sup>28</sup> which defined as being positive for allergen-specific immunoglobulin E (IgE) and reporting at least on subjective allergic symptoms within the last year, the self-report bias was likely minimal. Nevertheless, the association between hygiene scores and allergen sensitization cannot be concluded.

The present study has some limitations. First, hygiene scores were measured depending on only the degree of handwashing in each situation. Regular handwashing is known to be the most effective way to prevent the spread of viral respiratory infections.<sup>35–37</sup> In a previous study, the score for personal cleanliness correlated most strongly with “washing hands” regularly.<sup>13</sup> A meta-analysis showed that improvements in hand hygiene alone resulted in reductions in gastrointestinal and respiratory illness of 31% and 21%, respectively.<sup>38</sup> Second, information on handwashing was collected by a questionnaire instead of examination. Therefore, misclassification and recall bias are likely, although

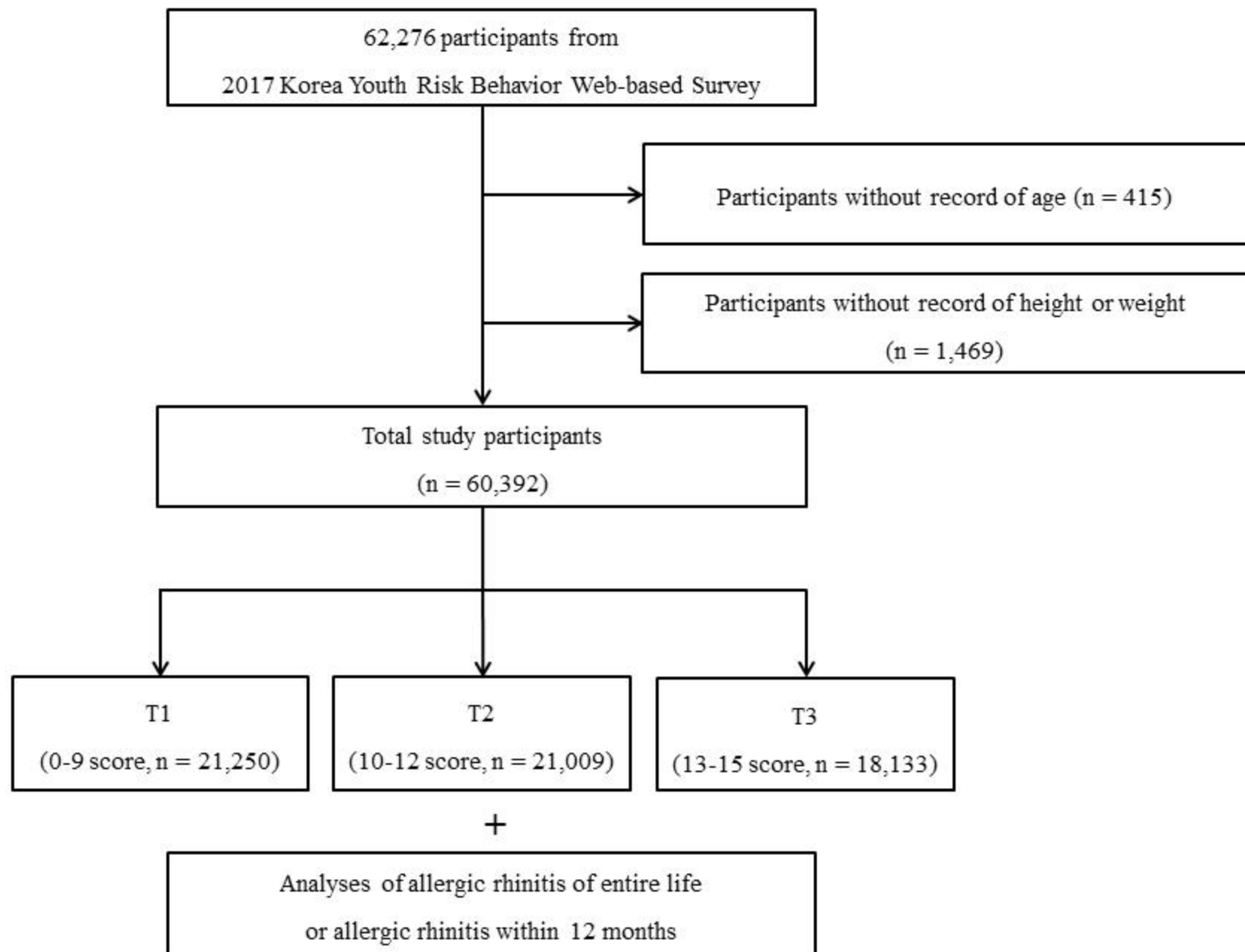
current hygiene-related habits may well reflect past behaviors. Third, because it was a cross-sectional study, it was not possible to determine a clear causal relationship between hygiene scores and AR. Additionally, although we considered several confounding factors, we could not completely exclude the influence of parental allergy history, diet, history of chronic rhinosinusitis and sinus surgery, or family members living together.

## Conclusion

This study showed a significant association between high hygiene score and the prevalence of AR throughout life and within 12 months in Korean adolescents. These relationships persisted even after adjusting for several covariates and in the subgroup analyses. However, this study did not examine cause and effect but interrelationship, because the data in this study were obtained from a cross-sectional survey. 

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**Supplementary File 2.** General characteristics of participants according to the hygiene score

| Characteristics                 | Hygiene score  |                |                  |                  | P-value |
|---------------------------------|----------------|----------------|------------------|------------------|---------|
|                                 | Total          | T1 (0-9 score) | T2 (10-12 score) | T3 (13-15 score) |         |
| Number (n, %)                   | 60,392 (100.0) | 21,250 (35.4)  | 21,009 (34.9)    | 18,133 (29.8)    |         |
| Mean age (yr, mean, SE)         | 15.1 (0.02)    | 15.3 (0.03)    | 15.2 (0.03)      | 14.9 (0.03)      | <0.001* |
| Physical activity (d, mean, SE) | 1.9 (0.02)     | 1.6 (0.02)     | 1.9 (0.02)       | 2.3 (0.02)       | <0.001* |
| Sleep duration (hr, mean, SE)   | 7.15 (0.02)    | 7.12 (0.02)    | 7.13 (0.02)      | 7.23 (0.02)      | <0.001* |
| Sex (n, %)                      |                |                |                  |                  | <0.001† |
| Males                           | 30,662 (52.1)  | 10,374 (50.1)  | 10,204 (49.8)    | 10,084 (57.0)    |         |
| Females                         | 29,730 (47.9)  | 10,876 (49.9)  | 10,805 (50.2)    | 8,049 (43.0)     |         |
| Obesity (n, %)                  |                |                |                  |                  | 0.065   |
| Underweight                     | 3,362 (5.7)    | 1,230 (5.9)    | 1,149 (5.6)      | 983 (5.6)        |         |
| Normal weight                   | 45,610 (75.7)  | 15,981 (75.4)  | 16,002 (76.5)    | 13,627 (75.2)    |         |
| Overweight                      | 8,008 (13.2)   | 2,833 (13.3)   | 2,737 (12.8)     | 2,438 (13.5)     |         |
| Obese                           | 3,412 (5.4)    | 1,206 (5.4)    | 1,121 (5.2)      | 1,085 (5.7)      |         |
| Region, large city (n, %)       |                |                |                  |                  | <0.001† |
| Large city                      | 26,852 (43.2)  | 8,907 (41.0)   | 9,450 (43.5)     | 8,495 (45.3)     |         |
| Small city                      | 28,883 (50.8)  | 10,517 (52.1)  | 10,039 (50.9)    | 8,327 (49.1)     |         |
| Rural area                      | 4,657 (6.1)    | 1,826 (6.9)    | 1,520 (5.6)      | 1,311 (5.6)      |         |
| Economic level (n, %)           |                |                |                  |                  | <0.001† |
| The highest                     | 6,351 (10.7)   | 1,521 (7.4)    | 2,003 (9.7)      | 2,827 (15.7)     |         |
| Middle High                     | 17,712 (29.7)  | 5,709 (27.3)   | 6,346 (30.8)     | 5,657 (31.3)     |         |
| Middle                          | 27,920 (45.9)  | 10,403 (48.6)  | 9,861 (46.5)     | 7,656 (42.1)     |         |
| Middle low                      | 7,009 (11.4)   | 3,013 (13.9)   | 2,357 (10.9)     | 1,639 (8.9)      |         |
| The lowest                      | 1,400 (2.3)    | 604 (2.9)      | 442 (2.1)        | 354 (1.9)        |         |
| Education level, Father (n, %)  |                |                |                  |                  | <0.001† |
| Unknown                         | 12,957 (20.2)  | 4,748 (21.1)   | 4,310 (19.1)     | 3,899 (20.3)     |         |
| Junior high school or under     | 1,111 (1.8)    | 481 (2.1)      | 379 (1.8)        | 251 (1.3)        |         |
| High school                     | 15,442 (25.2)  | 5,871 (27.4)   | 5,370 (25.1)     | 4,201 (22.8)     |         |
| College or over                 | 30,882 (52.9)  | 10,150 (49.4)  | 10,950 (54.0)    | 9,782 (55.6)     |         |
| Education level, Mother (n, %)  |                |                |                  |                  | <0.001† |
| Unknown                         | 12,144 (18.8)  | 4,447 (19.7)   | 4,019 (17.7)     | 3,678 (19.0)     |         |
| Junior high school or under     | 938 (1.5)      | 405 (1.7)      | 321 (1.5)        | 212 (1.2)        |         |
| High school                     | 18,903 (31.5)  | 7,217 (34.4)   | 6,637 (31.9)     | 5,049 (27.6)     |         |
| College or over                 | 28,407 (48.3)  | 9,181 (44.2)   | 10,032 (49.0)    | 9,194 (52.2)     |         |
| Smoking (n, %)                  |                |                |                  |                  | <0.001† |
| None                            | 56,957 (94.0)  | 19,874 (93.2)  | 19,924 (94.6)    | 17,159 (94.3)    |         |
| 1-19 d/mo                       | 1,507 (2.6)    | 585 (2.9)      | 471 (2.3)        | 451 (2.6)        |         |
| 20-30 d/mo                      | 1,928 (3.4)    | 791 (3.9)      | 614 (3.1)        | 523 (3.1)        |         |

|                          |               |               |               |               |         |
|--------------------------|---------------|---------------|---------------|---------------|---------|
| Alcohol (n, %)           |               |               |               |               | <0.001† |
| None                     | 51,288 (84.3) | 17,643 (82.5) | 17,906 (84.6) | 15,739 (86.1) |         |
| 1-5 d/mo                 | 7,322 (12.6)  | 2,925 (14.2)  | 2,508 (12.4)  | 1,889 (11.0)  |         |
| 6-30 d/mo                | 1,782 (3.1)   | 682 (3.3)     | 595 (3.0)     | 505 (2.9)     |         |
| Stress level (n, %)      |               |               |               |               | <0.001† |
| Severe                   | 6,104 (10.0)  | 2,191 (10.2)  | 2,088 (9.7)   | 1,825 (10.0)  |         |
| Moderate                 | 16,267 (26.9) | 6,158 (28.9)  | 5,773 (27.4)  | 4,336 (24.0)  |         |
| Mild                     | 25,653 (42.9) | 9,241 (43.9)  | 9,067 (43.6)  | 7,345 (40.9)  |         |
| A little                 | 9,993 (16.4)  | 3,154 (14.7)  | 3,465 (16.3)  | 3,374 (18.4)  |         |
| No stress                | 2,375 (3.8)   | 506 (2.4)     | 616 (2.9)     | 1,253 (6.7)   |         |
| Depression (n, %)        |               |               |               |               | <0.001† |
| Yes                      | 14,952 (24.8) | 5,526 (26.0)  | 5,224 (24.7)  | 4,202 (23.5)  |         |
| No                       | 45,440 (75.2) | 15,724 (74.0) | 15,785 (75.3) | 13,931 (76.5) |         |
| Allergic rhinitis (n, %) |               |               |               |               |         |
| Throughout life          | 21,201 (36.0) | 7,191 (34.8)  | 7,560 (36.9)  | 6,450 (36.4)  | <0.001† |
| Within 12 mo             | 11,870 (20.2) | 3,879 (18.9)  | 4,214 (20.5)  | 3,777 (21.4)  | <0.001† |
| Atopic dermatitis (n, %) |               |               |               |               |         |
| Throughout life          | 15,132 (25.2) | 5,528 (26.3)  | 5,389 (25.7)  | 4,215 (23.4)  | <0.001† |
| Within 12 mo             | 4,394 (7.4)   | 1,596 (7.7)   | 1,521 (7.3)   | 1,277 (7.2)   | 0.165   |
| Asthma (n, %)            |               |               |               |               |         |
| Throughout life          | 5,179 (8.7)   | 1,811 (8.5)   | 1,818 (8.8)   | 1,550 (8.8)   | 0.603   |
| Within 12 mo             | 1,372 (2.3)   | 454 (2.1)     | 475 (2.3)     | 443 (2.4)     | 0.207   |

SE = standard error

\*Linear regression was analyzed with sampling weights, Significance at  $P < 0.05$

†Rao-Scott Chi-square test was analyzed with sampling weights, Significance at  $P < 0.05$

**Supplementary File 3.** Odds ratio for allergic rhinitis according to the hygiene score stratified by school level and sex

| Hygiene score                            |                  | ORs for allergic rhinitis for throughout life |                  |        |                  |         | ORs for allergic rhinitis within 12 months |         |                  |         |                  |        |
|------------------------------------------|------------------|-----------------------------------------------|------------------|--------|------------------|---------|--------------------------------------------|---------|------------------|---------|------------------|--------|
|                                          | Crude            |                                               | Model 1†         |        | Model 2‡         |         | Crude                                      |         | Model 1†         |         | Model 2‡         |        |
| Junior high school, Males (n = 15,245)   |                  |                                               |                  |        |                  |         |                                            |         |                  |         |                  |        |
| T3                                       | 1.06 (0.98-1.16) | 0.164                                         | 1.02 (0.93-1.12) | 0.653  | 1.05 (0.94-1.17) | 0.373   | 1.24 (1.11-1.39)                           | <0.001* | 1.19 (1.07-1.34) | 0.002*  | 1.27 (1.11-1.45) | 0.001* |
| T2                                       | 1.12 (1.03-1.22) | 0.010*                                        | 1.07 (0.98-1.17) | 0.109  | 1.14 (1.02-1.26) | 0.015*  | 1.22 (1.10-1.37)                           | <0.001* | 1.18 (1.05-1.31) | 0.004*  | 1.31 (1.15-1.48) | 0.001* |
| T1 (ref)                                 | 1                |                                               | 1                |        | 1                |         | 1                                          |         | 1                |         | 1                |        |
| Junior high school, Females (n = 14,817) |                  |                                               |                  |        |                  |         |                                            |         |                  |         |                  |        |
| T3                                       | 1.16 (1.06-1.28) | 0.002*                                        | 1.14 (1.04-1.25) | 0.007* | 1.24 (1.11-1.38) | <0.001* | 1.16 (1.04-1.31)                           | 0.011*  | 1.13 (1.01-1.27) | 0.041*  | 1.21 (1.06-1.38) | 0.006* |
| T2                                       | 1.10 (1.00-1.20) | 0.044*                                        | 1.08 (0.98-1.18) | 0.119  | 1.17 (1.05-1.29) | 0.003*  | 1.03 (0.92-1.15)                           | 0.613   | 1.01 (0.90-1.12) | 0.917   | 1.11 (0.98-1.26) | 0.100  |
| T1 (ref)                                 | 1                |                                               | 1                |        | 1                |         | 1                                          |         | 1                |         | 1                |        |
| High school, Males (n = 15,417)          |                  |                                               |                  |        |                  |         |                                            |         |                  |         |                  |        |
| T3                                       | 1.02 (0.93-1.13) | 0.645                                         | 1.03 (0.93-1.14) | 0.590  | 1.06 (0.96-1.18) | 0.258   | 1.14 (1.02-1.27)                           | 0.018*  | 1.13 (1.02-1.27) | 0.025*  | 1.17 (1.05-1.32) | 0.006* |
| T2                                       | 1.11 (1.02-1.21) | 0.014*                                        | 1.11 (1.02-1.20) | 0.019* | 1.12 (1.02-1.23) | 0.013*  | 1.10 (0.99-1.20)                           | 0.079   | 1.09 (0.98-1.20) | 0.117   | 1.09 (0.98-1.22) | 0.115  |
| T1 (ref)                                 | 1                |                                               | 1                |        | 1                |         | 1                                          |         | 1                |         | 1                |        |
| High school, Females (n = 14,913)        |                  |                                               |                  |        |                  |         |                                            |         |                  |         |                  |        |
| T3                                       | 1.18 (1.08-1.28) | <0.001*                                       | 1.16 (1.06-1.27) | 0.002* | 1.16 (1.05-1.29) | 0.003*  | 1.27 (1.14-1.41)                           | <0.001* | 1.23 (1.10-1.38) | <0.001* | 1.24 (1.10-1.41) | 0.001* |
| T2                                       | 1.08 (1.00-1.17) | 0.049*                                        | 1.07 (0.99-1.16) | 0.098  | 1.08 (0.98-1.18) | 0.116   | 1.13 (1.02-1.25)                           | 0.015*  | 1.12 (1.01-1.24) | 0.025*  | 1.11 (0.94-1.24) | 0.070  |
| T1 (ref)                                 | 1                |                                               | 1                |        | 1                |         | 1                                          |         | 1                |         | 1                |        |

T1: 0-9 score, n = 21,250; T2: 10-12 score, n = 21,009; T3: 13-15 score, n = 18,133

\* Logistic regression was analyzed with sampling weights, Significance at P < 0.05

† Model 1 was adjusted for age, sex, economic status, region of residence, father's education level, mother's education level, obesity, smoking, alcohol intake, and physical activity

‡ Model 2 was adjusted for age, sex, economic status, region of residence, father's education level, mother's education level, obesity, smoking, alcohol intake, physical activity, mean sleep duration, stress level, depression, asthma, and atopic dermatitis

**Supplementary File 4.** Odds ratio for allergic rhinitis according to the hygiene score stratified by economic level and education level of each parent

| Hygiene score                             | ORs for allergic rhinitis for throughout life |        |                  |         |                  |         | ORs for allergic rhinitis within 12 months |         |                  |         |                  |         |
|-------------------------------------------|-----------------------------------------------|--------|------------------|---------|------------------|---------|--------------------------------------------|---------|------------------|---------|------------------|---------|
|                                           | Crude                                         |        | Model 1†         |         | Model 2‡         |         | Crude                                      |         | Model 1†         |         | Model 2‡         |         |
| The highest economic level (n = 24,063)   |                                               |        |                  |         |                  |         |                                            |         |                  |         |                  |         |
| T3                                        | 0.99 (0.92-1.06)                              | 0.765  | 1.02 (0.95-1.09) | 0.602   | 1.07 (0.98-1.16) | 0.127   | 1.12 (1.03-1.22)                           | 0.007*  | 1.16 (1.07-1.26) | 0.001*  | 1.20 (1.09-1.33) | <0.001* |
| T2                                        | 1.09 (1.02-1.17)                              | 0.013* | 1.10 (1.02-1.17) | 0.009*  | 1.15 (1.07-1.24) | <0.001* | 1.13 (1.04-1.22)                           | 0.004*  | 1.14 (1.05-1.24) | 0.002*  | 1.20 (1.10-1.32) | 0.001*  |
| T1 (ref)                                  | 1                                             |        | 1                |         | 1                |         | 1                                          |         | 1                |         | 1                |         |
| Middle economic level (n = 27,920)        |                                               |        |                  |         |                  |         |                                            |         |                  |         |                  |         |
| T3                                        | 1.13 (1.05-1.21)                              | 0.001* | 1.14 (1.06-1.22) | <0.001* | 1.20 (1.11-1.29) | <0.001* | 1.17 (1.07-1.27)                           | <0.001* | 1.18 (1.08-1.28) | <0.001* | 1.23 (1.12-1.35) | <0.001* |
| T2                                        | 1.10 (1.03-1.17)                              | 0.006  | 1.09 (1.02-1.16) | 0.012   | 1.13 (1.05-1.22) | 0.001*  | 1.08 (1.00-1.17)                           | 0.050   | 1.07 (0.99-1.16) | 0.087   | 1.12 (1.02-1.20) | 0.015*  |
| T1 (ref)                                  | 1                                             |        | 1                |         | 1                |         | 1                                          |         | 1                |         | 1                |         |
| The lowest economic level (n = 8,409)     |                                               |        |                  |         |                  |         |                                            |         |                  |         |                  |         |
| T3                                        | 1.05 (0.94-1.16)                              | 0.221  | 1.09 (0.95-1.25) | 0.211   | 1.06 (0.91-1.24) | 0.459   | 1.24 (1.06-1.00)                           | 0.006*  | 1.24 (1.06-1.44) | 0.007*  | 1.25 (1.00-1.50) | 0.016*  |
| T2                                        | 1.05 (0.94-1.16)                              | 0.426  | 1.02 (0.92-1.14) | 0.718   | 1.00 (0.88-1.13) | 0.967   | 1.08 (0.95-1.23)                           | 0.256   | 1.06 (0.92-1.21) | 0.421   | 1.03 (0.88-1.20) | 0.751   |
| T1 (ref)                                  | 1                                             |        | 1                |         | 1                |         | 1                                          |         | 1                |         | 1                |         |
| Father, College or over (n = 30,882)      |                                               |        |                  |         |                  |         |                                            |         |                  |         |                  |         |
| T3                                        | 1.05 (0.99-1.12)                              | 0.113  | 1.06 (1.00-1.13) | 0.055   | 1.10 (1.02-1.18) | 0.010*  | 1.13 (1.05-1.22)                           | 0.001*  | 1.14 (1.06-1.23) | 0.001*  | 1.19 (1.10-1.29) | <0.001* |
| T2                                        | 1.06 (0.99-1.12)                              | 0.079  | 1.06 (1.00-1.13) | 0.056   | 1.10 (1.03-1.17) | 0.006*  | 1.04 (0.98-1.12)                           | 0.221   | 1.05 (0.98-1.12) | 0.179   | 1.09 (1.01-1.17) | 0.034*  |
| T1 (ref)                                  | 1                                             |        | 1                |         | 1                |         | 1                                          |         | 1                |         | 1                |         |
| Father, High school or under (n = 29,510) |                                               |        |                  |         |                  |         |                                            |         |                  |         |                  |         |
| T3                                        | 1.05 (0.97-1.12)                              | 1.124  | 1.10 (1.02-1.19) | 0.010*  | 1.15 (1.06-1.25) | 0.001*  | 1.17 (1.07-1.27)                           | 0.001*  | 1.21 (1.11-1.32) | <0.001* | 1.25 (1.13-1.38) | <0.001* |
| T2                                        | 1.11 (1.04-1.18)                              | 0.002* | 1.11 (1.04-1.18) | 0.001*  | 1.15 (1.07-1.23) | <0.001* | 1.17 (1.07-1.26)                           | <0.001* | 1.17 (1.08-1.26) | <0.001* | 1.21 (1.11-1.33) | <0.001* |
| T1 (ref)                                  | 1                                             |        | 1                |         | 1                |         | 1                                          |         | 1                |         | 1                |         |
| Mother, College or over (n = 28,407)      |                                               |        |                  |         |                  |         |                                            |         |                  |         |                  |         |
| T3                                        | 1.03 (0.97-1.10)                              | 0.325  | 1.05 (0.98-1.12) | 0.200   | 1.08 (1.00-1.17) | 0.039*  | 1.14 (1.06-1.22)                           | 0.001*  | 1.14 (1.06-1.23) | 0.001*  | 1.19 (1.10-1.29) | <0.001* |
| T2                                        | 1.05 (0.99-1.12)                              | 0.132  | 1.05 (0.99-1.12) | 0.109   | 1.08 (1.01-1.16) | 0.027*  | 1.07 (0.99-1.15)                           | 0.075   | 1.07 (1.00-1.16) | 0.061   | 1.11 (1.02-1.20) | 0.019*  |
| T1 (ref)                                  | 1                                             |        | 1                |         | 1                |         | 1                                          |         | 1                |         | 1                |         |
| Mother, High school or under (n = 31,985) |                                               |        |                  |         |                  |         |                                            |         |                  |         |                  |         |

|          |                  |        |                  |        |                  |         |                  |        |                  |         |                  |         |
|----------|------------------|--------|------------------|--------|------------------|---------|------------------|--------|------------------|---------|------------------|---------|
| T3       | 1.06 (0.99-1.13) | 0.104  | 1.11 (1.04-1.19) | 0.002* | 1.16 (1.07-1.25) | <0.001* | 1.15 (1.06-1.25) | 0.001* | 1.20 (1.11-1.31) | <0.001* | 1.24 (1.13-1.20) | <0.001* |
| T2       | 1.11 (1.04-1.18) | 0.002* | 1.11 (1.04-1.18) | 0.001* | 1.16 (1.08-1.24) | <0.001* | 1.12 (1.04-1.21) | 0.004* | 1.12 (1.04-1.21) | 0.004*  | 1.17 (1.07-1.28) | <0.001* |
| T1 (ref) | 1                |        | 1                |        | 1                |         | 1                |        | 1                |         | 1                |         |

T1: 0-9 score, n = 21,250; T2: 10-12 score, n = 21,009; T3: 13-15 score, n = 18,133

\* Logistic regression was analyzed with sampling weights, Significance at  $P < 0.05$

† Model 1 was adjusted for age, sex, economic level, region of residence, father's education level, mother's education level, obesity, smoking, alcohol intake, and physical activity

‡ Model 2 was adjusted for age, sex, economic level, region of residence, father's education level, mother's education level, obesity, smoking, alcohol intake, physical activity, mean sleep duration, stress level, depression, asthma, and atopic dermatitis