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## Multimorbidities of asthma, allergies, and airway illnesses in childhood: Chance or not chance?

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### ABSTRACT

**Objectives:** We investigated patterns of multimorbidities among asthma, allergies, and respiratory illnesses in preschool children. We investigated multimorbidities of lifetime asthma, allergic rhinitis, eczema, food allergy, pneumonia, and ear infections; and multimorbidities of current (in the last year before the survey) wheeze, dry cough, rhinitis, eczema, and common cold during childhood. We further analyzed whether prevalences of these multimorbidities were due to chance. **Methods:** A cross-sectional study was conducted in 72 kindergartens of Shanghai, China. Parents of preschool children were surveyed with a modified ISAAC questionnaire. Observed prevalences (OPs), expected prevalences (EPs), absolute excess comorbidities (AECs), and relative excess comorbidities (RECs) of various combinations of illnesses were calculated to indicate whether the combined illnesses were related. **Results:** We analyzed questionnaires for children aged 4–6 years, whose 13,335 questionnaires were the majority of the total 15,266 returned questionnaires (response rate: 85.3%). The studied illnesses were common. For children who had more than three lifetime or current illnesses, OPs tended to be higher than EPs. Most OPs and EPs were higher in boys than in girls, and were higher in children with a family history of atopy (FHA) than in children without FHA. AECs and RECs between boys and girls as well as between children with and without FHA were substantially different. **Conclusions:** Our findings suggest that multimorbidities among childhood asthma, allergies, and respiratory illnesses are likely not random, but rather share etiology. Specific patterns of childhood asthma multimorbidities perhaps differ between boys and girls and between children with and without FHA.

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### Introduction

Asthma, a common respiratory disease among children [1,2], adversely affects life quality and is an economic burden for a family [2]. The prevalence of childhood asthma worldwide has increased, especially in developing countries [1–4]. Therefore, treatment and prevention of asthma is urgent for public health agencies [2]. Many epidemiological studies [5–19] have noted that asthma is strongly associated with rhinitis and eczema. The association of asthma with rhinitis is so strong [5,6,17,18] that rhinitis is a predictor of asthma among young adults [5,11,17]. One study has reported that treating allergic rhinitis decreased the risk of emergency department visits and hospitalizations for asthma [20]. Other studies have found that asthma comorbidities are related to sex [13,15] and family history of atopy (FHA) [15,19,21], and that the association between asthma and allergic rhinitis is

stronger in males than females [13]. Still, our understanding of childhood multimorbidities for asthma, allergies, and respiratory illnesses is far from thorough [19,22]. Few studies have analyzed whether the prevalence proportions for these comorbidities are the result of chance, and/or selection bias, and/or the same cause [23]. Shared causation for co-existing illnesses could explain those multimorbidity prevalences for which the proportions of prevalence from chance and bias have been excluded [19]. Also, there have been few studies of asthma multimorbidities with such diseases as pneumonia [24], food allergy [25,26], ear infections [27,28], and common colds [29]. This is especially true for China [30].

In this paper, as a part of the China, Children, Homes, Health (CCHH) study in Shanghai [4,31], we described the “allergic march” issue and reported multimorbidities both singularly and in combinations of asthma,

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allergies, and respiratory illnesses among preschool children aged 4–6 years. We used an analysis similar to that described in Pinart et al.'s study [19] to estimate how much of multimorbidity prevalences were the consequence of chance and how much were not due to chance. Firstly, we reported multimorbidities for pairs of the studied illnesses. Secondly, as in previous studies [5–19], we investigated multimorbidities of asthma, allergic rhinitis, and eczema (lifetime-ever) as well as multimorbidities of wheeze, rhinitis, and eczema in the year prior to the survey (current). Thirdly, we further analyzed multimorbidities of lifetime-ever asthma, allergic rhinitis, eczema, pneumonia, food allergy, and ear infections, as well as multimorbidities of current wheezing, dry cough, rhinitis, eczema, and common cold (3 times). We also investigated these multimorbidities for children stratified according to sex and FHA. We hypothesized that substantial proportions of multimorbidity prevalences are not a result of chance and that multimorbidities of the studied illnesses might be significantly different between boys and girls as well as between children with FHA and children without FHA.

Materials and methods

Ethics statement

The questionnaire and detailed proposal for the CCHH study in Shanghai were approved by the ethical committee in the School of Public Health, Fudan University, Shanghai, China (International Registered Number: IRB00002408 & FWA00002399). We informed potential participants of the purpose, proposal details, and potential concerns of the study by oral presentation or written explanation. All participants verbally consented for themselves and for their preschool children for whom they responded to questionnaires, and voluntarily responded to the survey. The Fudan ethical committee approved the procedure for obtaining consent.

Questionnaire and definition

From April 2011 to April 2012, the cross-sectional study (CCHH-Phase one) on associations between preschool children's health status and both indoor environment and family lifestyles was conducted in Shanghai city. A total of 72 kindergartens were randomly chosen in five districts. Then, 17,898 questionnaires were distributed to the children's parents or guardians at teacher–parent meetings in the kindergartens, or by post to the teachers who distributed the questionnaires along with a handout explanation and guidance (one child, one questionnaire).

Table 1. Question and prevalence for each illness (N = 13,335).

| Illness                                      | Question                                                                                                                                            | Prevalence, n (%)        |
|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Lifetime-ever (lifetime)                     |                                                                                                                                                     |                          |
| Asthma                                       | Has your child been diagnosed with asthma by a doctor?                                                                                              | 1342 (10.3)              |
| Allergic rhinitis                            | Has your child been diagnosed with hay fever or allergic rhinitis by a doctor?                                                                      | 1624 (12.6)              |
| Eczema                                       | Has your child ever had eczema (an itchy rash is coming and going for at least 6 months)?                                                           | 2856 (22.9)              |
| Food allergy                                 | Has the child had allergic irritations such as eczema, nettle rash, diarrhea, or swollen lips or eyes caused by the listed foods at any time?       | 2014 (19.0)              |
| Pneumonia                                    | Has your child been diagnosed with pneumonia by a doctor?                                                                                           | 4335 (33.6)              |
| Ear infections                               | Has your child ever had ear infections?                                                                                                             | 1443 (11.1)              |
| In the last year before the survey (current) |                                                                                                                                                     |                          |
| Wheezing                                     | Has your child had wheezing or whistling in the chest in the last 12 months?                                                                        | 2858 (21.7)              |
| Dry cough                                    | In the last 12 months, has your child had a dry cough at night for more than 2 weeks, apart from a cough associated with a cold or chest infection? | 2569 (19.5)              |
| Rhinitis symptoms                            | In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when he/she did not have a cold or the flu?        | 5532 (42.7)              |
| Common cold                                  | In the past 12 months, how many times has your child had a cold?                                                                                    | 5548 (43.6) <sup>a</sup> |
| Eczema                                       | Has your child had eczema at any time in the last 12 months?                                                                                        | 1695 (13.2)              |

Note. <sup>a</sup>The child had a cold equal to or more than 3 times in the last year.

We obtained 15,266 completed and valid questionnaires for children aged 1–8 years (response rate: 85.3%). We selected the 13,335 children aged 4–6 years for analyses of multimorbidity prevalences. We excluded younger and older children from analyses because their numbers were small [31]. Figure S1 shows the selection of samples for different analyses. Our previous articles provide additional information about the CCHH study in China [4] and in Shanghai [31,32].

The questions for children's health were from the questionnaire developed by the International Study of Asthma and Allergies in Childhood (ISAAC) [33]. Table 1 shows questions for illnesses discussed in the present study. Children were considered to have had an illness when their questionnaires were answered "Yes" to the corresponding question. Family history of atopy (FHA) was defined as asthma, eczema, and/or allergic nose or eye problems in the child's sibling, parent, or grandparent. Multimorbidity was defined as the co-existence of two or more of the illnesses during lifetime-ever (lifetime) or in the last year before the survey (current) [34].

**Table 2.** Correlations between two illnesses.

| Illness                                      | Gamma's correlation coefficient <sup>a</sup> |        |              |              |               |                                              |              |                   |             |              |
|----------------------------------------------|----------------------------------------------|--------|--------------|--------------|---------------|----------------------------------------------|--------------|-------------------|-------------|--------------|
|                                              | Lifetime-ever (lifetime)                     |        |              |              |               | In the last year before the survey (current) |              |                   |             |              |
|                                              | Allergic rhinitis                            | Eczema | Food allergy | Pneumonia    | Ear infection | Wheeze                                       | Dry cough    | Rhinitis symptoms | Common cold | Eczema       |
| Lifetime-ever (lifetime)                     |                                              |        |              |              |               |                                              |              |                   |             |              |
| Asthma                                       | <b>0.672</b>                                 | 0.424  | 0.389        | <b>0.558</b> | 0.224         | <b>0.824</b>                                 | <b>0.508</b> | <b>0.573</b>      | 0.342       | 0.334        |
| Allergic rhinitis                            |                                              | 0.470  | <b>0.526</b> | 0.391        | 0.314         | 0.490                                        | 0.377        | <b>0.766</b>      | 0.327       | 0.465        |
| Eczema                                       |                                              |        | <b>0.705</b> | 0.195        | 0.284         | 0.350                                        | 0.288        | 0.385             | 0.192       | <b>1.000</b> |
| Food allergy                                 |                                              |        |              | 0.191        | 0.212         | 0.366                                        | 0.293        | 0.365             | 0.216       | <b>0.718</b> |
| Pneumonia                                    |                                              |        |              |              | 0.199         | 0.304                                        | 0.318        | 0.291             | 0.184       | 0.181        |
| Ear infections                               |                                              |        |              |              |               | 0.097                                        | 0.142        | 0.181             | 0.154       | 0.197        |
| In the last year before the survey (current) |                                              |        |              |              |               |                                              |              |                   |             |              |
| Wheezing                                     |                                              |        |              |              |               |                                              | 0.486        | 0.424             | 0.391       | 0.315        |
| Dry cough                                    |                                              |        |              |              |               |                                              |              | 0.459             | 0.435       | 0.286        |
| Rhinitis symptoms                            |                                              |        |              |              |               |                                              |              |                   | 0.243       | 0.369        |
| Common cold (≥3 times)                       |                                              |        |              |              |               |                                              |              |                   |             | 0.213        |

Note. <sup>a</sup>All *p*-values are <0.001, and coefficients which are higher than 0.500 are bold.

### Statistical analysis

Statistical analysis was performed using SPSS 19.0 (IBM, Armonk, New York, USA). Pearson's chi-square test was used to determine the statistical significances of prevalence differences between subgroups (boys vs. girls; or children with FHA vs. children without FHA). Gamma's test for correlation was used to calculate correlation coefficients (*G*) between each two illnesses for which the variables were dichotomous (Yes vs. No) [35]. Observed prevalence (OP) was calculated as the proportion of children in the sample who had had the illness. The expected prevalence (EP) was the prevalence assuming that the illnesses occur independently of each other; it is therefore the prevalence of a given multimorbidity due to chance. EP is given by

$$EP = \prod_{i=1}^n P_i \cdot \prod_{j=n+1}^N (1 - P_j) \quad (1 \leq n < N)$$

where  $P_i$  is prevalence of the illness  $i$  in the total sample children;  $P_j$  is prevalence of illness  $j$  in the total sample children;  $N$  is the total number of selected illnesses for analyses of various multimorbidities;  $n$  is the number of co-existing illnesses. When  $n = N$ ,  $EP = \prod_{i=1}^N P_i$ ; when  $n = 0$ ,  $EP = \prod_{i=1}^N (1 - P_i)$ . Absolute excess comorbidity (AEC), calculated as OP minus EP, is the prevalence of multimorbidities that are not the result of chance [19]. Relative excess comorbidity (REC), calculated as OP divided by EP, is a metric of differences between OP and EP among various multimorbidities with different numbers of co-existing illnesses. Pearson's chi-square test was used to determine the statistical significances of the extent (REC) to which the observed comorbidity departed from the expected comorbidity if those illnesses only co-existed due to chance by plotting standardized residuals (the null hypothesis is  $REC = 1$ ) [19]. Significances in all statistical analyses are indicated by *p*-value <0.05.

### Results

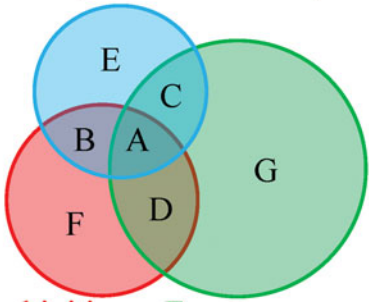
#### Prevalences of studied illnesses

Doctor-diagnosed asthma and other respiratory and/or allergic illnesses were common among children aged 4–6 years in Shanghai. The proportion of children who had ever had pneumonia was 33.6%, making pneumonia the most frequently reported lifetime-ever respiratory disease (Table 1). More than 40% of the children had had current rhinitis symptoms and common colds (initis sy. There were no notable differences in prevalences between those children for whom data were missing for some illnesses (Table 1) and for whom all data with respect to three lifetime and current illnesses were available (Table S1), as well as for whom all data with respect to six lifetime illnesses and five current illnesses were available (Table S2). Boys had significantly higher prevalences of lifetime asthma and allergic rhinitis and current wheezing and rhinitis symptoms than girls (*p*-value <0.001). Children with FHA had significantly higher prevalences of all studied illnesses than children without FHA (*p*-value <0.001) (Table S2).

#### Correlations of studied illnesses

Children who had had any one of the studied illnesses had significantly higher prevalences of all other illnesses than other children (Table S3). Correlations between any two illnesses were generally high (Table 2). Because lifetime eczema included current eczema, correlation coefficient between lifetime and current eczema was equal to 1.000. Except for this coefficient, the high correlations for pairs included wheezing with doctor-diagnosed asthma (correlation coefficient: 0.824); rhinitis symptoms with allergic rhinitis (0.766); and food allergy with eczema (lifetime: 0.705; current: 0.718).

Asthma (N = 1215, 10.2%)



Allergic rhinitis (N = 1505, 12.6%) Eczema (N = 2691, 22.6%)

| Item | n    | OP     | [AEC, REC]                 |
|------|------|--------|----------------------------|
| A    | 206  | 1.730  | [1.438, <b>5.937</b> ###]  |
| B    | 231  | 1.940  | [0.942, <b>1.944</b> ###]  |
| C    | 269  | 2.259  | [0.245, 1.122]             |
| D    | 406  | 3.409  | [0.845, <b>1.329</b> ##]   |
| E    | 509  | 4.274  | [-2.625, <b>0.620</b> ###] |
| F    | 622  | 5.559  | [-3.225, <b>0.633</b> ###] |
| G    | 1810 | 15.199 | [-2.528, <b>0.857</b> ###] |

**Figure 1.** Multimorbidities of lifetime asthma, allergic rhinitis, and eczema. OP, observed prevalence; AEC, absolute excess comorbidity; REC, relative excess comorbidity. The corresponding expected prevalences (EPs) are shown in Table S4. ##0.001 ≤ *p*-value < 0.01; ###*p*-value < 0.001 in the Pearson's chi-square test for the extent of difference between OPs and EPs (the null hypothesis is REC = 1). Bold indicates statistical significance.

Multimorbidities of lifetime asthma, allergic rhinitis, and eczema

The multimorbidities of lifetime asthma with allergic rhinitis and eczema are presented as Venn diagrams among all children (Figure 1), stratified by sex (Figure 2), and stratified by FHA (Figure 3). Most OPs for possible multimorbidities of asthma, allergic rhinitis, and eczema were higher than EPs (AECs > 0 and RECs > 1); and all RECs for possible multimorbidities were significantly higher than 1.000 except for comorbidity of asthma and eczema (Figure 1). Most of boys' OPs were significantly higher than girls' OPs, whereas the RECs for boys were not notably different from girls' RECs with the exception of three-disease multimorbidity, which was higher for girls (Figure 2). All OPs in children with FHA were significantly higher, whereas all RECs in these children were notably lower than in children without FHA (Figure 3). Except for the three disease multimorbidities, the highest AEC and REC were for multimorbidities of asthma and allergic rhinitis in all various sample groups; and all of

these RECs were significantly higher than 1.000 except for among children with FHA.

Multimorbidities of six lifetime illnesses

A Venn diagram shows parts of the multimorbidity combinations with their RECs (Figure 4), and all data regarding OPs, EPs, AECs, and RECs of 55 possible multimorbidities for the six illnesses are provided in Table S5. Generally, the greater the number of co-existing illnesses, the more likely the RECs were higher than 1.000. All RECs for five and four illnesses were higher than 1.000 (Figure 4 and Table S5). About half of RECs for multimorbidities of three illnesses were higher than 1.000, whereas most of RECs for multimorbidities for two illnesses were lower than 1.000. Most of RECs for multimorbidities involving allergic rhinitis and eczema were significantly departed from 1.000 (Figure 4 and Table S5). The highest RECs were for multimorbidity of asthma, pneumonia, allergic rhinitis, eczema, and food allergy (REC = 37.750). For four illnesses, the highest REC (8.040) was for multimorbidity of asthma, allergic rhinitis, eczema, and food allergy. For three illnesses, the highest REC (3.266) was for multimorbidity of asthma, allergic rhinitis, and food allergy. For two illnesses, the highest REC (1.591) was for comorbidity of eczema and food allergy.

With respect to boys and girls (Figure S2 and Table S6), the trends in OPs, EPs, AECs, and RECs for various multimorbidities of illnesses were similar in boys and in girls to those of total children. However, most OPs and EPs were higher in boys than in girls (Table S6). For six, five, and four illnesses, most RECs in boys were lower than in girls, whereas most AECs in boys were higher than in girls. For three and two illnesses, most RECs in boys were similar to those in girls, whereas most AECs in boys were lower than in girls.

With respect to children with and without FHA (Figure S2 and Table S7), most OPs and EPs in FHA children were significantly higher than in non-FHA children. However, AECs and RECs were generally greater for children without FHA than children with FHA. The higher the number of co-existing illnesses, the larger the differences in RECs. The REC for multimorbidities of six illnesses in children without FHA was substantially higher than in children with FHA (396.0 vs. 15.4), although the REC (396.0) for children without FHA was not statistically significant. Most RECs for multimorbidities of five and four illnesses were higher in children without FHA than in children with FHA. Most RECs for multimorbidities of three and two illnesses were similar in children with FHA and in children without FHA.

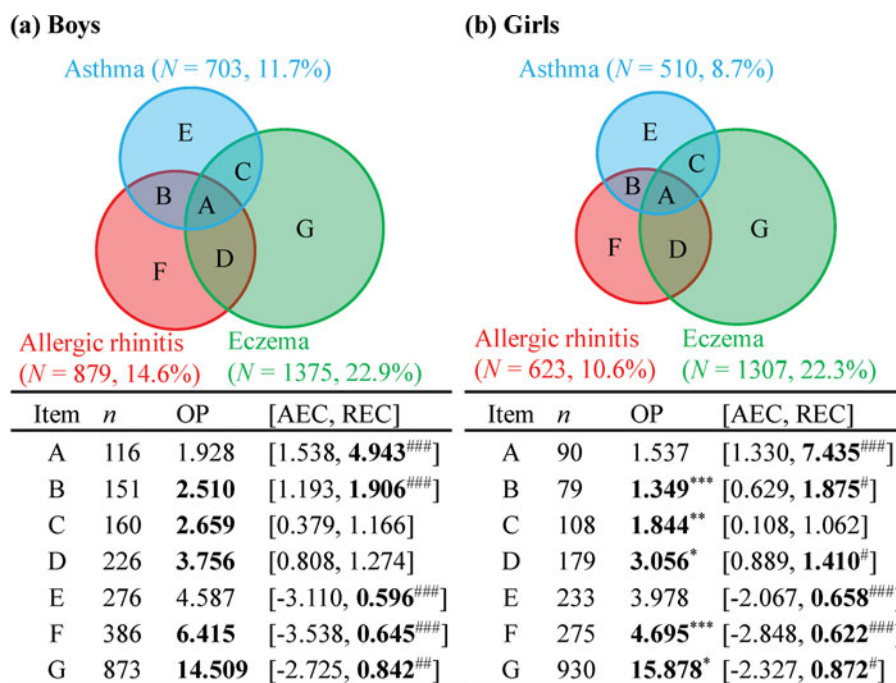


**Figure 2.** Multimorbidities of lifetime asthma, allergic rhinitis, and eczema, stratified by sex. OP, observed prevalence; AEC, absolute excess comorbidity; REC, relative excess comorbidity. The corresponding expected prevalences (EPs) are shown in Table S4. \* $0.01 \leq p\text{-value} < 0.05$ ; \*\* $0.001 \leq p\text{-value} < 0.01$ ; \*\*\* $p\text{-value} < 0.001$  in the Pearson's chi-square test for differences of OPs between boys and girls. # $0.01 < p\text{-value} < 0.05$ ; ## $0.001 \leq p\text{-value} < 0.01$ ; ### $p\text{-value} < 0.001$  in the Pearson's chi-square test for the extent of differences between OPs and EPs (the null hypothesis is  $REC = 1$ ). Bold indicates statistical significance.

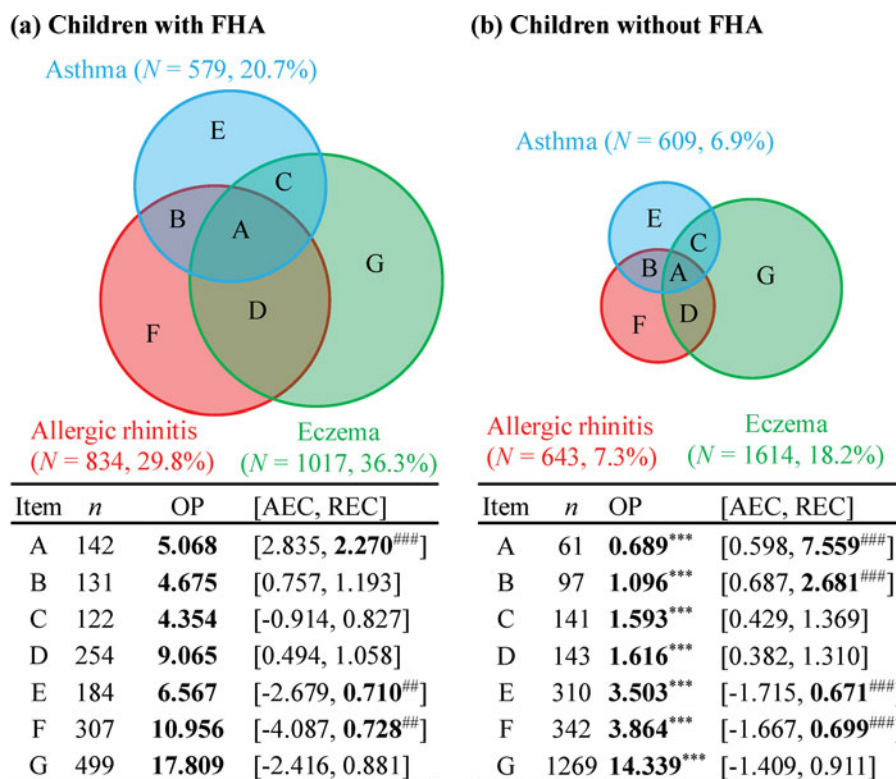


**Figure 3.** Multimorbidities of lifetime asthma, allergic rhinitis, and eczema, stratified by family history of atopy (FHA). OP, observed prevalence; AEC, absolute excess comorbidity; REC, relative excess comorbidity. The corresponding expected prevalences (EPs) are shown in Table S4. \*\*\* $p\text{-value} < 0.001$  in the Pearson's chi-square test for differences of OPs between children with FHA and children without FHA. ## $0.001 \leq p\text{-value} < 0.01$ ; ### $p\text{-value} < 0.001$  in the Pearson's chi-square test for the extent of difference between OPs and EPs (the null hypothesis is  $REC = 1$ ). Bold indicates statistical significance.

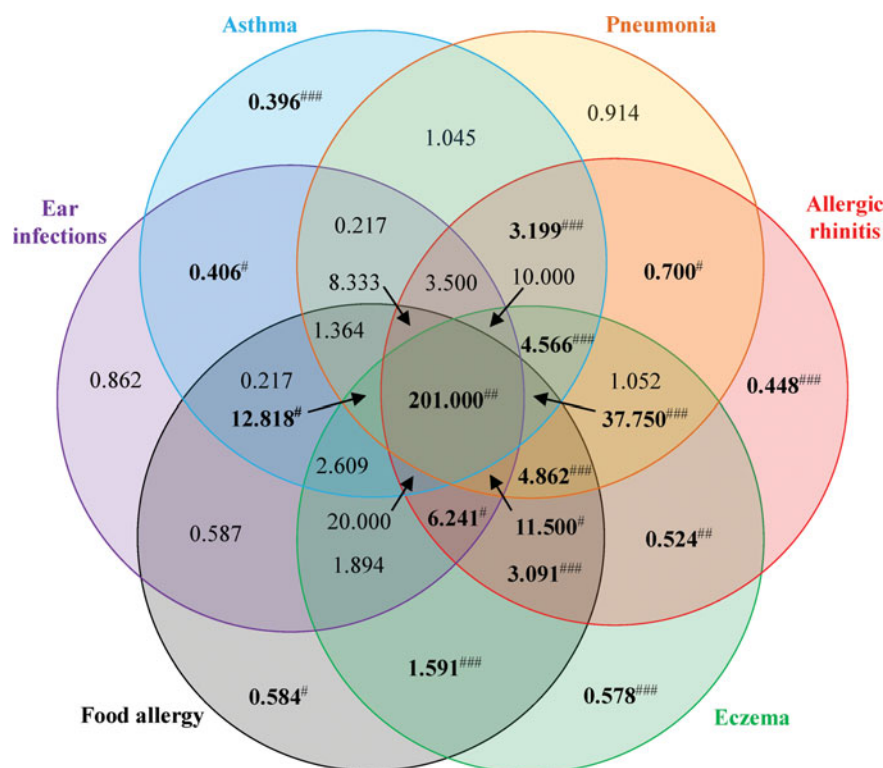


**Figure 4.** Relative excess comorbidities (RECs) for the various multimorbidities of six lifetime illnesses. #  $0.01 \leq p\text{-value} < 0.05$ ; ##  $0.001 \leq p\text{-value} < 0.01$ ; ###  $p\text{-value} < 0.001$  in the Pearson's chi-square test for the extent of differences between observed prevalences and expected prevalences (the null hypothesis is  $\text{REC} = 1$ ). Bold indicates statistical significance. Table S5 shows more related information.

For all children, those RECs which were significantly different from 1.000 were for multimorbidities involving allergic rhinitis and eczema than for multimorbidities involving other illnesses in various subgroups.

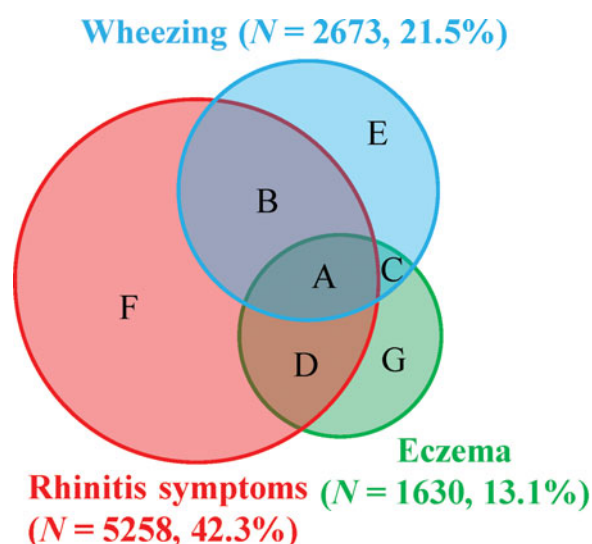
### Multimorbidities of current wheezing, rhinitis symptoms, and eczema

Three-morbidity Venn diagrams were constructed for current wheezing, rhinitis symptoms, and eczema among all children (Figure 5), stratified by sex (Figure 6), and stratified by FHA (Figure 7). OPs for all three symptoms and for any two symptoms were higher than the corresponding EPs ( $\text{AECs} > 0$  and  $\text{RECs} > 1$ ) except for comorbidity of wheeze and eczema in all children (Figure 5). Stratified by sex or FHA, OPs for boys were higher than for girls, whereas boys' RECs were not significantly different from those of girls (Figure 6). All OPs in FHA children were higher than EPs ( $\text{AECs} > 0$  and  $\text{RECs} > 1$ ), whereas all RECs in these children were lower than in non-FHA children (Figure 7). The highest AEC and REC for two illnesses was for comorbidity of wheezing and rhinitis symptoms in various sample groups; and all of these RECs were significantly higher than 1.000 except for among children with FHA. The lowest AEC and REC was for comorbidity of wheeze and eczema.

### Multimorbidities of five current illnesses

A Venn diagram also was constructed for parts of RECs for various multimorbidities of current wheeze, dry cough, rhinitis, eczema, and common cold (heeze, dry (Figure 8). Table S9 shows all data regarding OPs, EPs, RECs, and AECs of 32 possible multimorbidities for the five illnesses. Most of these RECs were significantly different than 1.000. Most RECs for four illnesses were significantly higher than 1.000. Half of RECs for multimorbidities of three illnesses were higher than 1.000. However, most RECs for two illnesses were lower than 1.000. For four illnesses, the highest REC (19.382) was for multimorbidities of wheezing, dry cough, rhinitis symptoms, and eczema. For three illnesses, half of RECs were higher than 1.000 and the highest REC (6.715) was for multimorbidities of dry cough, rhinitis symptoms, and eczema. For two illnesses, the highest REC (3.718) was for dry cough and eczema.

Most OPs, EPs, AECs, and RECs for various multimorbidities of these illnesses did not differ between boys and girls (Figure S3 and Table S10). Most OPs and EPs for various multimorbidities of five current illnesses were significantly higher in FHA children than in non-FHA children, whereas RECs for multimorbidities of more than three illnesses were lower in FHA children than in non-FHA children (Figure S3 and Table S11).



| Item | n    | OP     | [AEC, REC]                 |
|------|------|--------|----------------------------|
| A    | 370  | 2.979  | [1.783, <b>2.491</b> ###]  |
| B    | 1227 | 9.879  | [1.964, <b>1.248</b> ###]  |
| C    | 158  | 1.272  | [-0.357, 0.781]            |
| D    | 587  | 4.726  | [0.366, 1.084]             |
| E    | 918  | 7.391  | [-3.390, <b>0.686</b> ###] |
| F    | 3074 | 24.750 | [-4.113, <b>0.857</b> ###] |
| G    | 515  | 4.147  | [-1.793, <b>0.698</b> ###] |

**Figure 5.** Multimorbidities of current wheezing, rhinitis symptoms, and eczema. OP, observed prevalence; AEC, absolute excess comorbidity; REC, relative excess comorbidity. The corresponding expected prevalences (EPs) are shown in Table S8. ###*p*-value <0.001 in the Pearson's chi-square test for the extent of differences between observed prevalences and expected prevalences (the null hypothesis is REC = 1). Bold indicates statistical significance.

## Discussion

In this study, we have compared OPs with EPs for childhood multimorbidities regarding asthma, allergies, and respiratory illnesses both lifetime and currently. Our findings for prevalences of multimorbidities of lifetime asthma, allergic rhinitis, and eczema, as well as for prevalences of multimorbidities of current wheeze, rhinitis symptoms, and eczema, were substantially consistent with what has been reported for other countries or regions [5–19].

With respect to lifetime multimorbidities, a study from Ireland reported that 2.2% of children aged 6–9 years in 2002 and 2.0% of them in 2007 had multimorbidities of lifetime asthma, allergic rhinitis, and eczema [14], compared to about 1.7% in our study. The ISAAC worldwide study in 1994–1997 found that 15% of asthmatic

children aged 6–7 years and 40% of asthmatic children aged 13–14 years were diagnosed allergic rhinitis during lifetime [34], compared to 36.0% in our study. Among French children aged 9–11 years in 1999–2000, 20.7% of children with food allergy and 9.6% of children without food allergy were diagnosed asthma during lifetime [25], compared to 32.7% and 17.6% in our study, respectively. In this study as well as 49.6% had food allergy (in our study: 38.2%) and 19.2% of children without food allergy were diagnosed with allergic rhinitis (in our study: 16.1%), respectively. Umapathy et al. [28] found that ear infections were significantly associated with asthma and allergic rhinitis, but not with eczema and food allergy among children aged 6–6.5 years from East Berkshire district of the United Kingdom. Our finding, that ear infections were comorbid with eczema and food allergy as well as with asthma and allergic rhinitis, differed from that in the Umapathy et al.'s study.

With respect to current multimorbidities, Yuksel et al. from western Turkey reported that 31.5% of children with current rhinitis symptoms and 11.8% of children without rhinitis symptoms had current wheezing among children aged 3–17 years in 2000 [12], compared to 30.5% and 15.1% in our study. Moreover, in the Yuksel et al.' study [12], 28.1% of children with eczema and 14.0% of children without eczema had current wheezing, lower than the 32.4% and 20.0% in our study. Among Irish children aged 6–9 years, 3.2% in 2002 and 4.1% in 2007 had multimorbidities of current wheezing, rhinitis, and eczema [14], compared to the 3.0% observed prevalence in our study. Among children aged 3–5 years in Portugal in 2007, 68.5% of children with wheezing and 35.4% of children without wheezing had rhinitis symptoms [9], compared to 59.9% and 37.7% in our study. In Sweden, 7.5% of 2916 children aged 12 years in 2006–2008 simultaneously had our study. In among wheezing, rhinitis, and eczema [15], compared to 18.9% in our study. In Seoul, Korea, 2.5%, 4.7%, and 8.7% of children aged 0–13 years in 2010 simultaneously had eczema and asthma, or asthma and rhinitis symptoms, or eczema and allergic rhinitis [16], compared to 9.9%, 1.3%, and 4.7% in our study. Among 8-year-old children in United Kingdom, Deliu et al. found that children with rhinitis had significantly higher risk for other asthma-associated symptoms [17]. A systematic review published in 2012 has also concluded that both the intensity and duration of rhinitis might be correlated with the development and remission of asthma, and that allergic rhinitis possibly affects asthma control in children [18]. This review suggests that these diseases should be approached together with respect to their diagnosis and treatment. This viewpoint is supported by our findings that most RECs for multimorbidities of asthma and allergic rhinitis

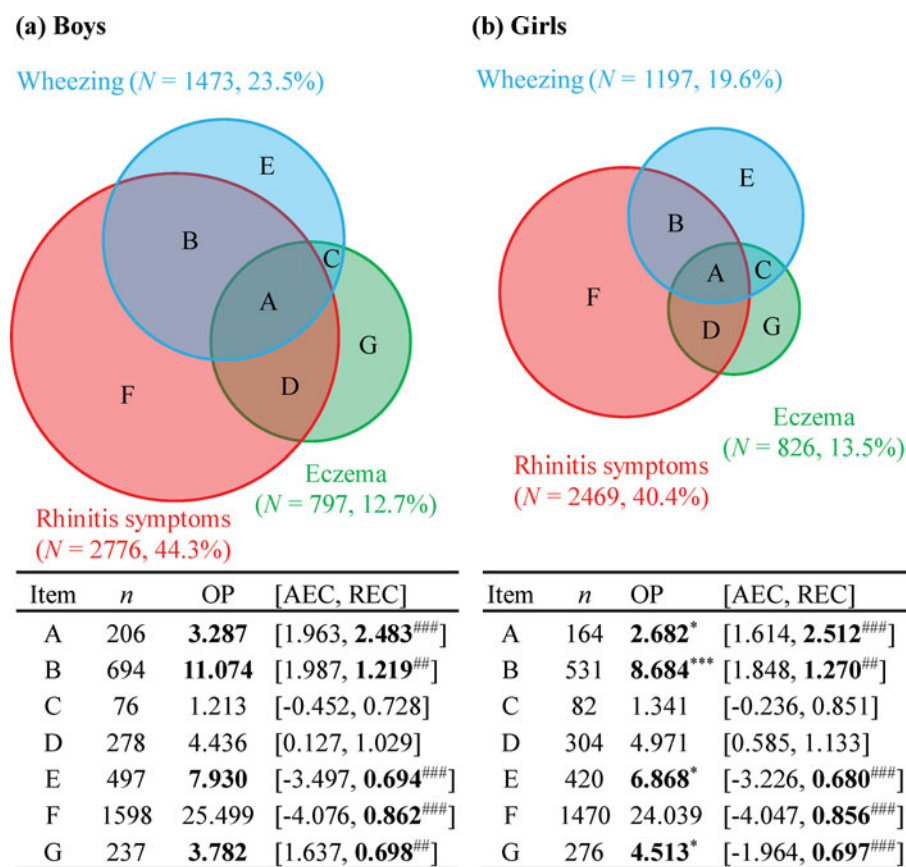


**Figure 6.** Multimorbidities of current wheezing, rhinitis symptoms, and eczema, stratified by sex. OP, observed prevalence; AEC, absolute excess comorbidity; REC, relative excess comorbidity. The corresponding expected prevalences (EPs) are shown in Table S8. \* $0.01 \leq p$ -value  $< 0.05$ ; \*\*\* $p$ -value  $< 0.001$  in the Pearson's chi-square test for differences of OPs between boys and girls. ## $0.001 \leq p$ -value  $< 0.01$ ; ### $p$ -value  $< 0.001$  in the Pearson's chi-square test for the extent of difference between OPs and EPs (the null hypothesis is  $REC = 1$ ). Bold indicates statistical significance.

were significantly higher than 1.000 in various sample groups.

To our best knowledge, while many previous studies analyzed OPs for asthma multimorbidities, most of these studies did not include EPs in their analyses [5–17]. Recently, Pinart et al. [19] calculated EPs for current comorbidities of asthma, allergic rhinitis, and eczema, and also introduced AECs and RECs to compare EPs and OPs. This analysis makes it possible to distinguish multimorbidities that might share the same cause (AECs) from those more likely to be randomly related by chance (EPs). The statistics OP, EP, and AEC are a function of an illness's prevalence and independent of the number of co-existing illnesses, and therefore insufficient to compare various comorbidities when there are different numbers of co-existing illnesses. REC has been introduced to compare various comorbidities when there are different numbers of co-existing illnesses [19]. To compare our findings with those of other studies [5–19], we used these statistics to analyze comorbidities of lifetime asthma, allergic rhinitis, and eczema as well as their corresponding current symptoms at the first step of this study. In Pinart et al.'s

study [19], EPs of a pair of diseases were calculated as the product of OPs of the two diseases minus the product of EPs of three diseases. Although we calculated EPs of pairs as simply the product of the two OPs, we obtained essentially the same EPs. Our OPs and EPs differed from those of Pinart et al. [19], perhaps because the definitions of asthma and rhinitis [36] from the Pinart et al.'s study differed from those used in the present study. Nonetheless, our AECs and RECs trended similarly. In agreement with Pinart et al. [19], we found that (1) RECs for multimorbidity of asthma, rhinitis, and eczema were notably higher than RECs for multimorbidities of other combinations of these diseases; and (2) REC for comorbidity of asthma and rhinitis among preschool children was notably higher than RECs for comorbidities of any other two illnesses. These findings indicate that multimorbidities of asthma, allergic rhinitis, and eczema were notably more common than expected by chance, suggesting that these illnesses perhaps shared the same cause. We also found that the higher the number of co-existing illnesses, the higher the RECs of various comorbidities. This finding also provides evidence that multimorbidities are likely not random, but

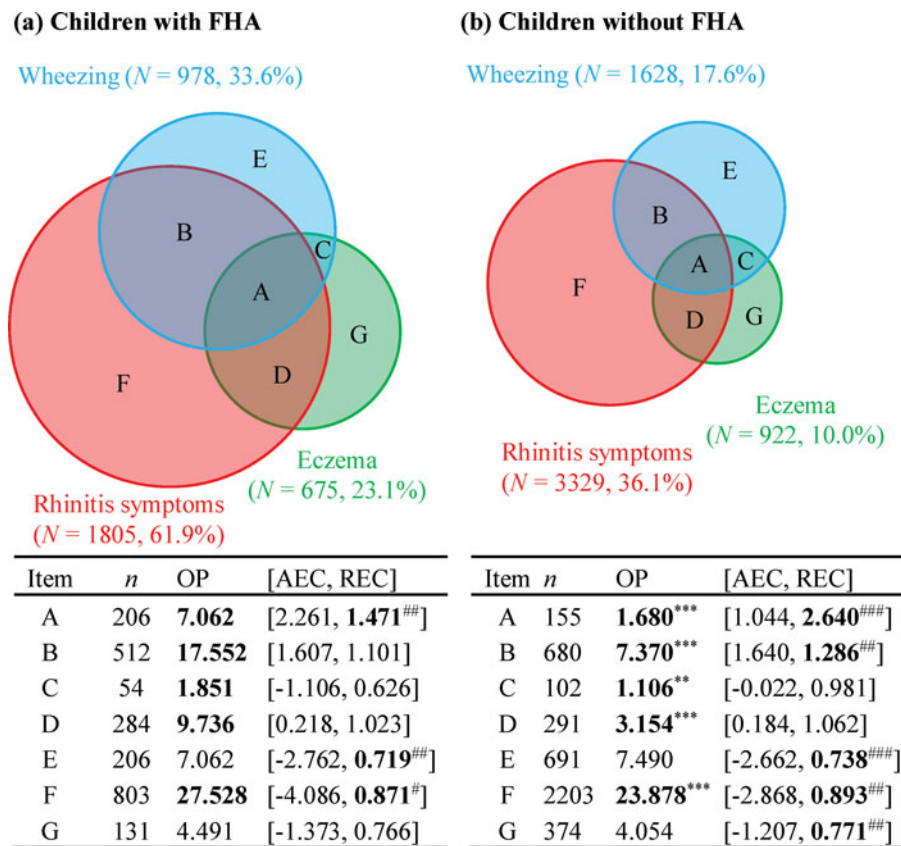


**Figure 7.** Multimorbidities of current wheezing, rhinitis symptoms, and eczema, stratified by family history of atopy (FHA). OP, observed prevalence; AEC, absolute excess comorbidity; REC, relative excess comorbidity. The corresponding expected prevalences (EPs) are shown in Table S8. <sup>\*\*</sup> $0.001 \leq p\text{-value} < 0.01$ ; <sup>\*\*\*</sup> $p\text{-value} < 0.001$  in the Pearson's chi-square test for differences of OPs between children with FHA and children without FHA. <sup>#</sup> $0.01 \leq p\text{-value} < 0.05$ ; <sup>##</sup> $0.001 \leq p\text{-value} < 0.01$ ; <sup>###</sup> $p\text{-value} < 0.001$  in the Pearson's chi-square test for the extent of differences between OPs and EPs (the null hypothesis is  $\text{REC} = 1$ ). Bold indicates statistical significance.

rather than our studied illnesses share a similar etiology, consistent with what was reported by Pinart et al. [19].

Our results also suggested that in addition to asthma, allergic rhinitis, and eczema, many other diseases, such as pneumonia, food allergy, ear infections, and common cold during childhood perhaps had potential associations as has been suggested in other studies [24–29]. Our finding that most OPs for one illness were lower than their corresponding EPs ( $\text{AECs} < 0$  and  $\text{RECs} < 1$ ) also implies that common etiology might exist for these diseases.

Stratification by sex and FHA yielded higher OPs and EPs for boys than girls, and for FHA children than for non-FHA children. However, most RECs showed reverse trends both for gender and FHA. Our findings for OPs according to gender and FHA are consistent with those of a study in Sweden [15]. These differences in OPs, EPs, AECs, and RECs, between boys and girls, as well as between FHA children and non-FHA children, indicates that children of different genders or with different family backgrounds of health had different multimorbidities of these illnesses. In particular, more RECs that were significantly different from 1.000 were found in children

without FHA than in children with FHA. However, to our best knowledge, although many studies found that gender and FHA are significantly associated with prevalences of asthma, allergies, and respiratory illnesses [2–4,9,15,24,32], no study has previously reported differences in multimorbidities for these illnesses among children with different sexes and FHA backgrounds. More studies need to be conducted to test this finding and its implications.

Several studies [19,37,38] have tried to find mechanisms to explain multimorbidities. Pinart et al. [19] found that the presence of IgE sensitization accounts for 38% of comorbidities of asthma, allergic rhinitis, and eczema. Lee et al. found that two co-existing illnesses tend to display a higher correlation of reaction flux rate, corresponding to enzyme-encoding gene co-expression, and a higher comorbidity than those without a metabolic link [37]. They also showed how the structure and function of the human metabolic network might influence multimorbidities [37]. A recent study found that rhinoviruses, the main cause of common colds, could induce interleukin-25 in lung epithelial cells, thus worsening asthma attacks [38].

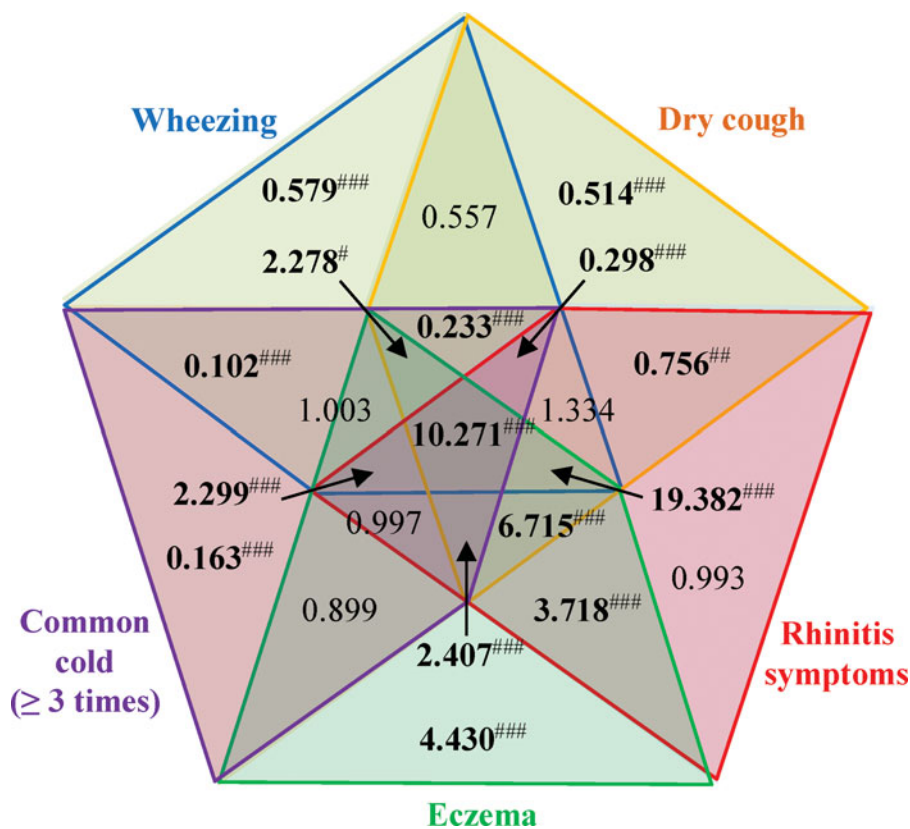


**Figure 8.** Relative excess comorbidities (RECs) for the various multimorbidities of five current illnesses. #  $0.01 \leq p\text{-value} < 0.05$ ; ##  $0.001 \leq p\text{-value} < 0.01$ ; ###  $p\text{-value} < 0.001$  in the Pearson's chi-square test for the extent of difference between observed prevalences and expected prevalences (the null hypothesis is  $REC = 1$ ). Bold indicates statistical significance. Tables S9 shows more related information.

This is consistent with our findings that children who had a common cold  $\geq 3$  times had a two-fold higher risk for reported wheeze than children with common cold  $< 3$  times.

This study has limitations. Firstly, as in all questionnaire-based cross-sectional studies, we cannot make causal inferences about the studied multimorbidities. We also cannot provide biological interpretations for the differences in the studied multimorbidities between children with different sexes and FHA backgrounds. Secondly, prevalences of all illnesses were based on responses from the children's parents or guardians and therefore could have recalled and/or reported error or bias. In particular, we note that our question for food allergy included eczema, and might have led to this kind of error but the correlation coefficients between food allergy and lifetime and current eczema were not equal to 1.000 (Table 2, lifetime: 0.705; current: 0.718). Thirdly, the definitions for some illnesses, particularly for food allergy and ear infections, in the questionnaire were not very specific. The definition of eczema also did not say that the disease should be diagnosed by a doctor. Fourthly, since it is difficult to exactly diagnose asthma among children younger than 6 years old [39], our analyses that included doctor-diagnosed asthma

among 4- and 5-year-old children might have low reliability. Moreover, the original ISAAC questionnaire for the child's illnesses was validated for children aged 6–7 years and 13–14 years [40], but not for children aged 4–6 years. Fifthly, the sample sizes for analyses of multimorbidities for six lifetime illnesses were small, especially among children with FHA. Our sample sizes for some other items were also not always sufficient to draw conclusions.

This study also has several strengths. Firstly, this study of 13,335 multistage hierarchical sampled preschool children is presently one of the largest cross-sectional studies of children's asthma and other illnesses in China [4]. Secondly, our high response rate (85.3%) makes it likely that the present study gives a valid, reliable picture of comorbidities among Shanghai preschool children. Thirdly, the improved ISAAC questionnaire we used has been validated in studies for children younger than 6 years old in several other countries [41] and in other cities of China [4,31,32]. Fourthly, for the first time, we provided abundant data for various multimorbidities of asthma and other illnesses, and further stratified the samples by gender and FHA in China. We also used EP, AEC, and REC as pioneered in a recent study [19] so that trends in China could be compared to those in Europe. We also

broadened Pinart et al.'s approach to analyze for possible causation among more than three illnesses. Thus our results add insight into comorbidities regarding asthma, allergies, and respiratory illnesses, and give a useful reference to facilitate diagnosis, intervention, and prevention of these illnesses.

## Conclusions

Various multimorbidities of asthma, allergic rhinitis, and eczema among Shanghai preschool children are consistent with those of most previous studies. Multimorbidities of asthma, allergies, and respiratory illnesses were notably more common than expected by chance, indicating that these illnesses perhaps shared the same etiology. Boys and girls, as well as children with FHA and without FHA, appeared to have substantial differences with respect to the co-existence of the studied illnesses.

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## Declaration of interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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# Supporting Information

## Contents

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**Table S11.** Multimorbidities of five current illnesses, stratified by family history of atopy.

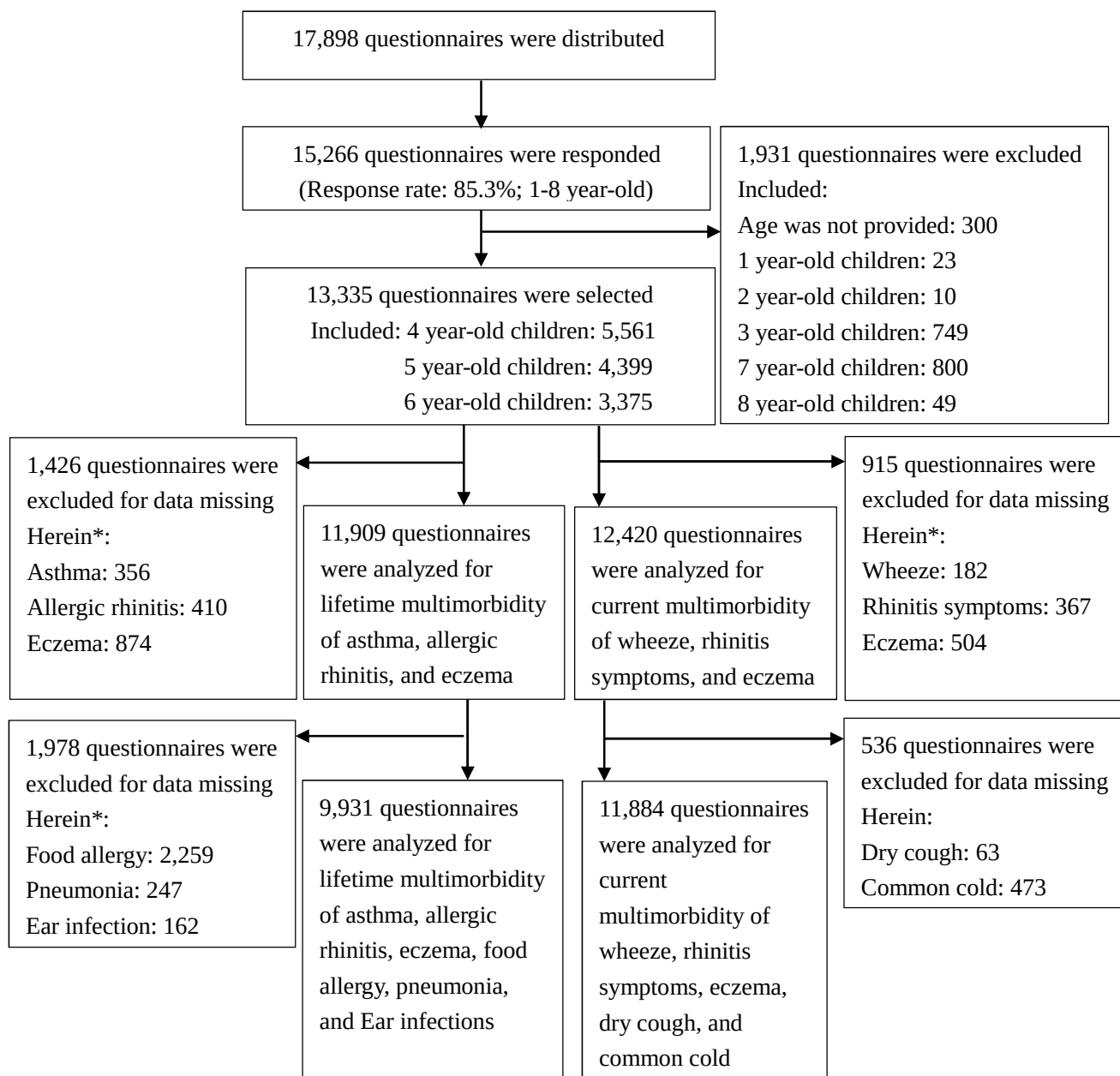


**Figure S1.** Flowchart for the selection of samples in different analyses. \* Because some questionnaires simultaneously missed data for different illnesses, the summarized amounts of data-missed questionnaires for different illnesses would more than the total excluded questionnaires for data missing.

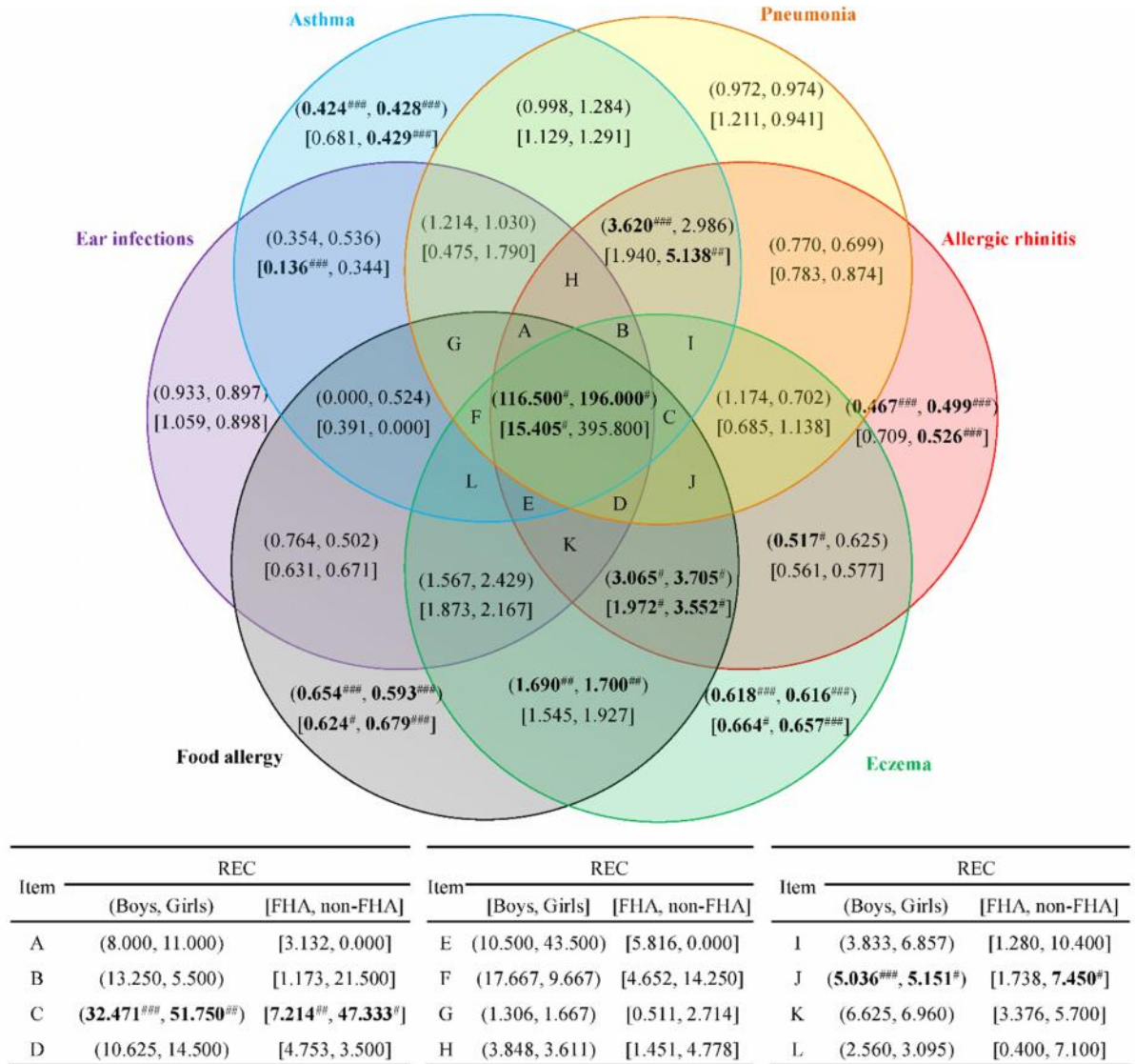


**Figure S2.** Relative excess comorbidities (RECs) for the various multimorbidities of six lifetime illnesses, stratified by sex and family history of atopy (FHA). Data in parentheses are RECs in boys and in girls; data in brackets are RECs in children with and without FHA, respectively. <sup>#</sup> 0.01 ≤ *p*-value <0.05; <sup>##</sup> 0.001 ≤ *p*-value <0.01; <sup>###</sup> *p*-value <0.001 in the Pearson's chi-square test for the extent of differences between observed prevalences and expected prevalences (the null hypothesis is REC=1). Bold indicates statistical significance. Tables S7 and S8 show more related information.

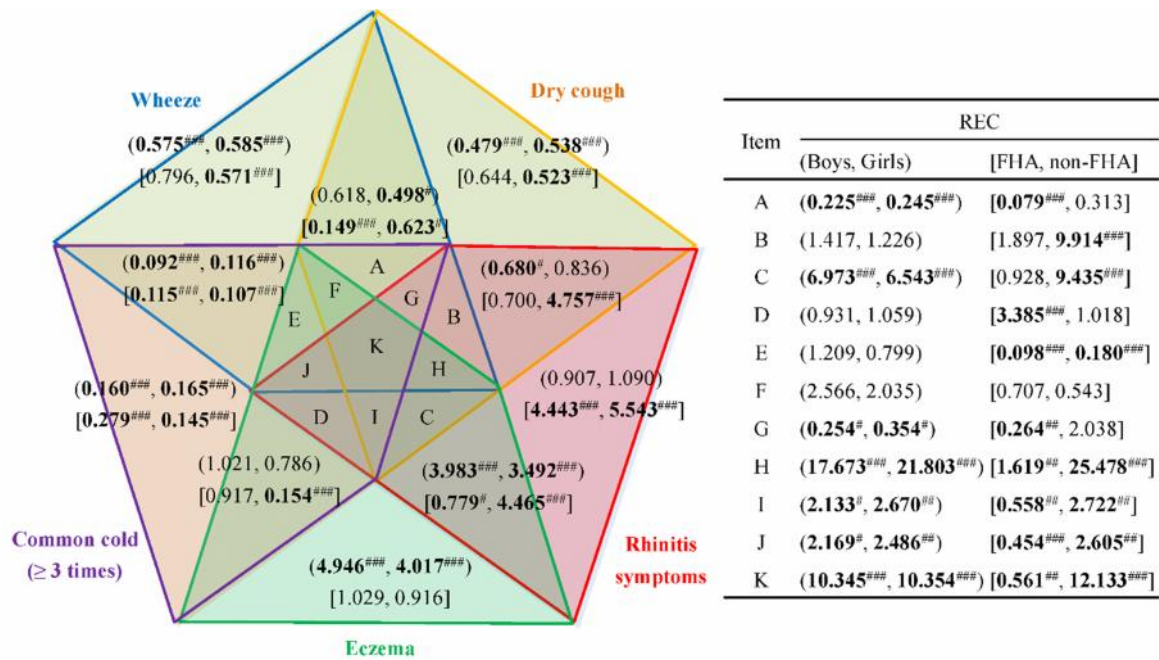


**Figure S3.** Relative excess comorbidities (RECs) for the various multimorbidities of five current illnesses, stratified by sex and family history of atopy (FHA). Data in parentheses are RECs in boys and in girls; data in brackets are RECs in children with and without FHA, respectively. <sup>#</sup> 0.01 ≤ *p*-value < 0.05; <sup>##</sup> 0.001 ≤ *p*-value < 0.01; <sup>###</sup> *p*-value < 0.001 in the Pearson's chi-square test for the extent of differences between observed prevalences and expected prevalences (the null hypothesis is REC=1). Bold indicates statistical significance. Tables S10 and S11 show more related information.

**Table S1.** Prevalence of three lifetime and current illnesses among those children who had no missing data in the questionnaire for these illnesses <sup>a</sup>.

| Illness                                                                             | Total, <i>n</i> (%) | Sex, <i>n</i> (%)  |                    |                 | Family history of atopy (FHA), <i>n</i> (%) |                    |                 |
|-------------------------------------------------------------------------------------|---------------------|--------------------|--------------------|-----------------|---------------------------------------------|--------------------|-----------------|
|                                                                                     |                     | Boys               | Girls              | <i>p</i> -value | Yes                                         | No                 | <i>p</i> -value |
| Lifetime-ever (Lifetime) (Valid sample size: <i>N</i> =11,909)                      |                     |                    |                    |                 |                                             |                    |                 |
| Asthma                                                                              | 1215 (10.2)         | <b>703 (11.7)</b>  | <b>510 (8.7)</b>   | < <b>0.001</b>  | <b>579 (20.7)</b>                           | <b>609 (6.9)</b>   | < <b>0.001</b>  |
| Allergic rhinitis                                                                   | 1505 (12.6)         | <b>879 (14.6)</b>  | <b>623 (10.6)</b>  | < <b>0.001</b>  | <b>834 (29.8)</b>                           | <b>643 (7.3)</b>   | < <b>0.001</b>  |
| Eczema                                                                              | 2691 (22.6)         | 1375 (22.9)        | 1307 (22.3)        | 0.484           | <b>1017 (36.3)</b>                          | <b>1614 (18.2)</b> | < <b>0.001</b>  |
| In the last year before the survey (Current) (Valid sample size: <i>N</i> = 12,420) |                     |                    |                    |                 |                                             |                    |                 |
| Wheeze                                                                              | 2673 (21.5)         | <b>1473 (23.5)</b> | <b>1197 (19.6)</b> | < <b>0.001</b>  | <b>978 (33.6)</b>                           | <b>1628 (17.6)</b> | < <b>0.001</b>  |
| Rhinitis symptoms                                                                   | 5258 (42.3)         | <b>2776 (44.3)</b> | <b>2469 (40.4)</b> | < <b>0.001</b>  | <b>1805 (61.9)</b>                          | <b>3329 (36.1)</b> | < <b>0.001</b>  |
| Eczema                                                                              | 1630 (13.1)         | 797 (12.7)         | 826 (13.5)         | 0.193           | <b>675 (23.1)</b>                           | <b>922 (10.0)</b>  | < <b>0.001</b>  |

<sup>a</sup> Bold indicates statistical significance.

**Table S2.** Prevalences of six lifetime illnesses and five current illnesses among children who had no missing data in the questionnaire for these illnesses<sup>a</sup>.

| Illness                                                                            | Total, <i>n</i> (%) | Sex, <i>n</i> (%)  |                    |                  | Family history of atopy (FHA), <i>n</i> (%) |                    |                  |
|------------------------------------------------------------------------------------|---------------------|--------------------|--------------------|------------------|---------------------------------------------|--------------------|------------------|
|                                                                                    |                     | Boys               | Girls              | <i>p</i> -value  | Yes                                         | No                 | <i>p</i> -value  |
| Lifetime-ever (Lifetime) (Valid sample size: <i>N</i> = 9931)                      |                     |                    |                    |                  |                                             |                    |                  |
| Asthma                                                                             | 884 (9.5)           | <b>511 (10.8)</b>  | <b>372 (8.1)</b>   | <b>&lt;0.001</b> | <b>418 (19.9)</b>                           | <b>446 (6.3)</b>   | <b>&lt;0.001</b> |
| Allergic rhinitis                                                                  | 1100 (11.8)         | <b>645 (13.7)</b>  | <b>452 (9.8)</b>   | <b>&lt;0.001</b> | <b>611 (29.0)</b>                           | <b>470 (6.7)</b>   | <b>&lt;0.001</b> |
| Eczema                                                                             | 1855 (19.9)         | 949 (20.1)         | 900 (19.6)         | 0.523            | <b>695(33.0)</b>                            | <b>1122 (15.9)</b> | <b>&lt;0.001</b> |
| Food allergy                                                                       | 1755 (18.8)         | 893 (18.9)         | 858 (18.7)         | 0.753            | <b>666 (31.7)</b>                           | <b>1062 (15.1)</b> | <b>&lt;0.001</b> |
| Pneumonia                                                                          | 3037 (32.5)         | 1576 (33.4)        | 1452 (31.6)        | 0.063            | <b>912 (43.3)</b>                           | <b>2066 (29.3)</b> | <b>&lt;0.001</b> |
| Ear infection                                                                      | 1007 (10.8)         | 490 (10.4)         | 514 (11.2)         | 0.213            | <b>301 (14.3)</b>                           | <b>686 (9.7)</b>   | <b>&lt;0.001</b> |
| In the last year before the survey (Current) (Valid sample size: <i>N</i> = 11884) |                     |                    |                    |                  |                                             |                    |                  |
| Wheeze                                                                             | 2591 (21.8)         | <b>1424 (23.7)</b> | <b>1164 (19.9)</b> | <b>&lt;0.001</b> | <b>960 (33.7)</b>                           | <b>1565 (17.8)</b> | <b>&lt;0.001</b> |
| Dry cough                                                                          | 2362 (19.9)         | 1165 (19.4)        | 1191 (20.4)        | 0.204            | <b>839 (29.5)</b>                           | <b>1484 (16.9)</b> | <b>&lt;0.001</b> |
| Rhinitis symptoms                                                                  | 5190 (42.9)         | <b>2693 (44.9)</b> | <b>2393 (40.9)</b> | <b>&lt;0.001</b> | <b>652 (22.9)</b>                           | <b>893 (10.2)</b>  | <b>&lt;0.001</b> |
| Common cold (≥ 3 times)                                                            | 1576 (43.7)         | 2624 (43.7)        | 2557 (43.7)        | 0.960            | <b>1544 (54.3)</b>                          | <b>3543 (40.3)</b> | <b>&lt;0.001</b> |
| Eczema                                                                             | 5098 (13.3)         | 773 (12.9)         | 796 (13.6)         | 0.250            | <b>1765 (62.0)</b>                          | <b>3214 (36.6)</b> | <b>&lt;0.001</b> |

<sup>a</sup> Bold indicates statistical significance.

**Table S3.** Multimorbidities of two illnesses.

| Illness                                      | Category | Prevalence, <i>n</i> (%) <sup>a</sup> |             |              |              |             |                |                                              |             |                   |                         |             |
|----------------------------------------------|----------|---------------------------------------|-------------|--------------|--------------|-------------|----------------|----------------------------------------------|-------------|-------------------|-------------------------|-------------|
|                                              |          | Lifetime-ever (Lifetime)              |             |              |              |             |                | In the last year before the survey (Current) |             |                   |                         |             |
|                                              |          | Asthma                                | Hay fever   | Eczema       | Food allergy | Pneumonia   | Ear infections | Wheeze                                       | Dry cough   | Rhinitis symptoms | Common cold (≥ 3 times) | Eczema      |
| Lifetime-ever (Lifetime)                     |          |                                       |             |              |              |             |                |                                              |             |                   |                         |             |
| Asthma                                       | Yes      |                                       | 465 (36.0)  | 495 (39.5)   | 322 (32.7)   | 791 (60.5)  | 204 (15.7)     | 880 (66.7)                                   | 513 (38.7)  | 925 (70.4)        | 775 (59.5)              | 281 (21.9)  |
|                                              | No       |                                       | 1125 (9.9)  | 2289 (20.9)  | 1651 (17.6)  | 3439 (30.3) | 1205 (10.5)    | 1871 (16.2)                                  | 1980 (17.1) | 4456 (39.2)       | 4651 (41.8)             | 1383 (12.3) |
| Allergic rhinitis                            | Yes      | 465 (29.2)                            |             | 925 (48.0)   | 464 (38.2)   | 802 (50.8)  | 281 (17.7)     | 644 (40.2)                                   | 514 (31.9)  | 1303 (81.5)       | 918 (58.2)              | 403 (25.7)  |
|                                              | No       | 827 (7.5)                             |             | 1116 (13.8)  | 1474 (16.1)  | 3413 (31.1) | 1127 (10.1)    | 2096 (18.7)                                  | 1962 (17.5) | 4066 (36.9)       | 4476 (41.4)             | 1230 (11.2) |
| Eczema                                       | Yes      | 495 (17.8)                            | 627 (22.8)  |              | 925 (45.3)   | 1120 (40.6) | 437 (15.8)     | 900 (32.0)                                   | 773 (27.4)  | 1611 (58.1)       | 1410 (51.2)             | 1695 (61.4) |
|                                              | No       | 757 (8.0)                             | 905 (9.6)   |              | 1002 (12.6)  | 2947 (31.5) | 897 (9.5)      | 1965 (18.5)                                  | 1649 (17.3) | 3579 (38.1)       | 3830 (41.6)             | 0 (0.0)     |
| Food allergy                                 | Yes      | 322 (16.3)                            | 464 (23.9)  | 627 (40.9)   |              | 775 (39.7)  | 287 (14.6)     | 620 (31.1)                                   | 526 (26.3)  | 1096 (55.6)       | 1001 (51.3)             | 613 (31.4)  |
|                                              | No       | 662 (7.9)                             | 751 (8.9)   | 2122 (20.0)  |              | 2577 (30.9) | 843 (10.0)     | 1472 (17.3)                                  | 1393 (16.4) | 3092 (36.8)       | 3313 (40.5)             | 585 (7.0)   |
| Pneumonia                                    | Yes      | 791 (18.7)                            | 802 (19.0)  | 1120 (27.5)  | 775 (23.1)   |             | 589 (13.8)     | 1235 (28.9)                                  | 1136 (26.5) | 2223 (52.3)       | 2086 (49.7)             | 675 (16.1)  |
|                                              | No       | 517 (6.1)                             | 777 (9.3)   | 1637 (20.4)  | 1176 (17.0)  |             | 814 (9.7)      | 1512 (17.8)                                  | 1340 (15.7) | 3135 (37.6)       | 3294 (40.5)             | 975 (11.8)  |
| Ear infections                               | Yes      | 204 (14.5)                            | 281 (20.0)  | 437 (32.8)   | 287 (25.4)   | 589 (42.0)  |                | 350 (24.6)                                   | 339 (23.7)  | 710 (50.6)        | 704 (50.5)              | 243 (17.6)  |
|                                              | No       | 1096 (9.7)                            | 1303 (11.5) | 2333 (21.4)  | 1682 (18.1)  | 3664 (32.6) |                | 2432 (21.2)                                  | 2175 (18.9) | 4696 (41.5)       | 4753 (42.7)             | 1407 (12.5) |
| In the last year before the survey (Current) |          |                                       |             |              |              |             |                |                                              |             |                   |                         |             |
| Wheeze                                       | Yes      | 880 (32.0)                            | 644 (23.5)  | 900 (33.8)   | 620 (29.6)   | 1235 (45.0) | 350 (12.6)     |                                              | 969 (34.3)  | 1667 (59.9)       | 1656 (59.5)             | 541 (19.7)  |
|                                              | No       | 439 (4.3)                             | 957 (9.5)   | 1910 (19.7)  | 1374 (16.3)  | 3043 (30.4) | 1072 (10.6)    |                                              | 1567 (15.3) | 3790 (37.7)       | 3842 (39.2)             | 1131 (11.3) |
| Dry cough                                    | Yes      | 513 (20.6)                            | 514 (20.8)  | 773 (31.9)   | 526 (27.4)   | 1136 (45.9) | 339 (13.5)     | 969 (38.2)                                   |             | 1556 (62.1)       | 1559 (61.9)             | 476 (19.3)  |
|                                              | No       | 812 (7.8)                             | 1098 (10.6) | 2048 (20.6)  | 1472 (17.1)  | 3148 (30.5) | 1093 (10.5)    | 1855 (17.6)                                  |             | 3920 (37.8)       | 3940 (39.0)             | 1200 (11.7) |
| Rhinitis symptoms                            | Yes      | 925 (17.2)                            | 1303 (24.3) | 1611 (31.0)  | 1096 (26.2)  | 2223 (41.5) | 710 (13.1)     | 1667 (30.5)                                  | 1556 (28.4) |                   | 2712 (50.4)             | 974 (18.3)  |
|                                              | No       | 389 (5.3)                             | 296 (4.1)   | 1164 (16.7)  | 875 (14.2)   | 2025 (28.0) | 694 (9.5)      | 1115 (15.1)                                  | 948 (12.8)  |                   | 2697 (38.3)             | 676 (9.4)   |
| Common cold (≥ 3 times)                      | Yes      | 775 (14.3)                            | 918 (17.0)  | 1410 (26.9)  | 1001 (23.2)  | 2086 (38.8) | 704 (12.9)     | 1656 (30.1)                                  | 1559 (28.4) | 2712 (50.1)       |                         | 870 (16.2)  |
|                                              | No       | 528 (7.6)                             | 659 (9.4)   | 1343 (20.0)  | 950 (16.3)   | 2112 (30.4) | 691 (9.8)      | 1126 (15.9)                                  | 959 (13.5)  | 2665 (38.0)       |                         | 773 (11.2)  |
| Eczema                                       | Yes      | 281 (16.9)                            | 403 (24.7)  | 1695 (100.0) | 613 (51.2)   | 675 (40.9)  | 243 (14.7)     | 541 (32.4)                                   | 476 (28.4)  | 974 (59.0)        | 870 (53.0)              |             |
|                                              | No       | 1003 (9.2)                            | 1163 (10.7) | 1064 (10.0)  | 1339 (14.7)  | 3510 (32.4) | 1138 (10.4)    | 2203 (20.0)                                  | 1996 (18.0) | 4341 (39.9)       | 4496 (42.2)             |             |

<sup>a</sup> All *p*-values in the Pearson's chi-square test are <0.001.

**Table S4.** Expected prevalences (%) of multimorbidities of lifetime asthma, allergic rhinitis, and eczema <sup>a</sup>.

| Number of co-occurred illnesses (Total possible combinations) | Asthma | Allergic rhinitis | Eczema | Total  | Stratified by sex |        | Stratified by FHA |             |
|---------------------------------------------------------------|--------|-------------------|--------|--------|-------------------|--------|-------------------|-------------|
|                                                               |        |                   |        |        | Boys              | Girls  | With FHA          | Without FHA |
| 3 (1)                                                         | +      | +                 | +      | 0.291  | 0.390             | 0.207  | 2.232             | 0.091       |
|                                                               | +      | +                 | -      | 0.998  | 1.317             | 0.720  | 3.918             | 0.409       |
| 2 (3)                                                         | +      | -                 | +      | 2.014  | 2.280             | 1.736  | 5.268             | 1.164       |
|                                                               | -      | +                 | +      | 2.564  | 2.948             | 2.167  | 8.571             | 1.234       |
|                                                               | +      | -                 | -      | 8.784  | 7.697             | 6.045  | 9.246             | 5.218       |
|                                                               | -      | +                 | -      | 6.899  | 9.953             | 7.544  | 15.043            | 5.532       |
| 1 (3)                                                         | -      | -                 | +      | 17.727 | 17.234            | 18.205 | 20.225            | 15.748      |
|                                                               | -      | -                 | -      | 60.725 | 58.181            | 63.377 | 35.498            | 70.605      |

<sup>a</sup> “+” denotes that the disease has occurred among the surveyed children; “-” denotes that the disease has not occurred among the surveyed children. FHA: family history of atopy.

**Table S5.** Multimorbidities of six lifetime illnesses <sup>a</sup>.

| Number of co-existed illnesses (Total possible combinations) | Comorbidity (+: Yes; -: No) |           |                   |        |              |                | Total (N=9931)  |        |        |         |                             |
|--------------------------------------------------------------|-----------------------------|-----------|-------------------|--------|--------------|----------------|-----------------|--------|--------|---------|-----------------------------|
|                                                              | Asthma                      | Pneumonia | Allergic rhinitis | Eczema | Food allergy | Ear infections | Sample size (n) | OP (%) | EP (%) | AEC (%) | REC                         |
| 6 (1)                                                        | +                           | +         | +                 | +      | +            | +              | 20              | 0.201  | 0.001  | 0.200   | <b>201.000<sup>#</sup></b>  |
| 5 (6)                                                        | +                           | +         | +                 | +      | +            | -              | 45              | 0.453  | 0.012  | 0.441   | <b>37.750<sup>###</sup></b> |
|                                                              | +                           | +         | +                 | +      | -            | +              | 6               | 0.060  | 0.006  | 0.054   | <b>10.000</b>               |
|                                                              | +                           | +         | +                 | -      | +            | +              | 5               | 0.050  | 0.006  | 0.044   | <b>8.333</b>                |
|                                                              | +                           | +         | -                 | +      | +            | +              | 14              | 0.141  | 0.011  | 0.130   | <b>12.818<sup>#</sup></b>   |
|                                                              | +                           | -         | +                 | +      | +            | +              | 6               | 0.060  | 0.003  | 0.057   | <b>20.000</b>               |
|                                                              | -                           | +         | +                 | +      | +            | +              | 16              | 0.161  | 0.014  | 0.147   | <b>11.500<sup>#</sup></b>   |
| 4 (15)                                                       | +                           | +         | +                 | +      | -            | -              | 24              | 0.242  | 0.053  | 0.189   | <b>4.566<sup>#</sup></b>    |
|                                                              | +                           | +         | +                 | -      | +            | -              | 21              | 0.211  | 0.049  | 0.162   | <b>4.306<sup>#</sup></b>    |
|                                                              | +                           | +         | +                 | -      | -            | +              | 9               | 0.091  | 0.026  | 0.065   | <b>3.500</b>                |
|                                                              | +                           | +         | -                 | +      | +            | -              | 34              | 0.342  | 0.091  | 0.251   | <b>3.758<sup>##</sup></b>   |
|                                                              | +                           | +         | -                 | +      | -            | +              | 10              | 0.101  | 0.048  | 0.053   | 2.104                       |
|                                                              | +                           | +         | -                 | -      | +            | +              | 6               | 0.060  | 0.044  | 0.016   | <b>1.364</b>                |
|                                                              | +                           | -         | +                 | +      | +            | -              | 20              | 0.201  | 0.025  | 0.176   | <b>8.040<sup>#</sup></b>    |
|                                                              | +                           | -         | +                 | +      | -            | +              | 6               | 0.060  | 0.013  | 0.047   | 4.615                       |
|                                                              | +                           | -         | +                 | -      | +            | +              | 1               | 0.010  | 0.012  | -0.002  | 0.833                       |
|                                                              | +                           | -         | -                 | +      | +            | +              | 6               | 0.060  | 0.023  | 0.037   | <b>2.609</b>                |
|                                                              | -                           | +         | +                 | +      | +            | -              | 56              | 0.564  | 0.116  | 0.448   | <b>4.862<sup>###</sup></b>  |
|                                                              | -                           | +         | +                 | +      | -            | +              | 9               | 0.091  | 0.061  | 0.030   | 1.492                       |
|                                                              | -                           | +         | +                 | -      | +            | +              | 6               | 0.060  | 0.056  | 0.004   | 1.071                       |
|                                                              | -                           | +         | -                 | +      | +            | +              | 27              | 0.272  | 0.105  | 0.167   | 2.590                       |
|                                                              | -                           | -         | +                 | +      | +            | +              | 18              | 0.181  | 0.029  | 0.152   | <b>6.241<sup>#</sup></b>    |
| 3 (20)                                                       | +                           | +         | +                 | -      | -            | -              | 67              | 0.675  | 0.211  | 0.464   | <b>3.199<sup>###</sup></b>  |
|                                                              | +                           | +         | -                 | +      | -            | -              | 55              | 0.554  | 0.393  | 0.161   | 1.410                       |
|                                                              | +                           | +         | -                 | -      | +            | -              | 28              | 0.282  | 0.366  | -0.084  | 0.770                       |
|                                                              | +                           | +         | -                 | -      | -            | +              | 20              | 0.201  | 0.191  | 0.010   | <b>1.052</b>                |
|                                                              | +                           | -         | +                 | +      | -            | -              | 13              | 0.131  | 0.109  | 0.022   | 1.202                       |
|                                                              | +                           | -         | +                 | -      | +            | -              | 17              | 0.171  | 0.053  | 0.118   | 3.226                       |
|                                                              | +                           | -         | +                 | -      | -            | +              | 5               | 0.050  | 0.053  | -0.003  | 0.943                       |
|                                                              | +                           | -         | -                 | +      | +            | -              | 13              | 0.131  | 0.189  | -0.058  | 0.693                       |
|                                                              | +                           | -         | -                 | +      | -            | +              | 7               | 0.070  | 0.099  | -0.029  | 0.707                       |
|                                                              | +                           | -         | -                 | -      | +            | +              | 2               | 0.020  | 0.092  | -0.072  | <b>0.217</b>                |
|                                                              | -                           | +         | +                 | +      | -            | -              | 46              | 0.463  | 0.500  | -0.037  | 0.926                       |
|                                                              | -                           | +         | +                 | -      | +            | -              | 49              | 0.493  | 0.466  | 0.027   | 1.058                       |
|                                                              | -                           | +         | +                 | -      | -            | +              | 27              | 0.272  | 0.244  | 0.028   | 1.115                       |
|                                                              | -                           | +         | -                 | +      | +            | -              | 149             | 1.500  | 0.866  | 0.634   | <b>1.732<sup>##</sup></b>   |
|                                                              | -                           | +         | -                 | +      | -            | +              | 27              | 0.272  | 0.453  | -0.181  | 0.600                       |
|                                                              | -                           | +         | -                 | -      | +            | +              | 27              | 0.272  | 0.422  | -0.150  | 0.645                       |
|                                                              | -                           | -         | +                 | +      | +            | -              | 74              | 0.745  | 0.241  | 0.504   | <b>3.091<sup>###</sup></b>  |
|                                                              | -                           | -         | +                 | +      | -            | +              | 10              | 0.101  | 0.126  | -0.025  | 0.802                       |
|                                                              | -                           | -         | +                 | -      | +            | +              | 8               | 0.081  | 0.117  | -0.036  | 0.692                       |
|                                                              | -                           | -         | -                 | +      | +            | +              | 41              | 0.413  | 0.218  | 0.195   | <b>1.894</b>                |

**Table S5.** Continued.

| Number of co-existed illnesses (Total possible combinations) | Comorbidity (+: Yes; -: No) |           |                   |        |              |                | Total (N=9931)  |        |        |         | REC                        |
|--------------------------------------------------------------|-----------------------------|-----------|-------------------|--------|--------------|----------------|-----------------|--------|--------|---------|----------------------------|
|                                                              | Asthma                      | Pneumonia | Allergic rhinitis | Eczema | Food allergy | Ear infections | Sample size (n) | OP (%) | EP (%) | AEC (%) |                            |
| 2 (15)                                                       | +                           | +         | -                 | -      | -            | -              | 164             | 1.651  | 1.580  | 0.071   | 1.045                      |
|                                                              | +                           | -         | +                 | -      | -            | -              | 43              | 0.433  | 0.439  | -0.006  | 0.986                      |
|                                                              | +                           | -         | -                 | +      | -            | -              | 29              | 0.292  | 0.815  | -0.523  | <b>0.358<sup>###</sup></b> |
|                                                              | +                           | -         | -                 | -      | +            | -              | 24              | 0.242  | 0.760  | -0.518  | <b>0.318<sup>###</sup></b> |
|                                                              | +                           | -         | -                 | -      | -            | +              | 16              | 0.161  | 0.397  | -0.236  | <b>0.406<sup>#</sup></b>   |
|                                                              | -                           | +         | +                 | -      | -            | -              | 140             | 1.410  | 2.014  | -0.604  | <b>0.700<sup>#</sup></b>   |
|                                                              | -                           | +         | -                 | +      | -            | -              | 199             | 2.004  | 3.739  | -1.735  | 0.536                      |
|                                                              | -                           | +         | -                 | -      | +            | -              | 196             | 1.974  | 3.485  | -1.511  | 0.566                      |
|                                                              | -                           | +         | -                 | -      | -            | +              | 168             | 1.692  | 1.822  | -0.130  | 0.929                      |
|                                                              | -                           | -         | +                 | +      | -            | -              | 54              | 0.544  | 1.039  | -0.495  | <b>0.524<sup>##</sup></b>  |
|                                                              | -                           | -         | +                 | -      | +            | -              | 55              | 0.554  | 0.968  | -0.414  | <b>0.572<sup>#</sup></b>   |
|                                                              | -                           | -         | +                 | -      | -            | +              | 36              | 0.363  | 0.506  | -0.143  | 0.717                      |
|                                                              | -                           | -         | -                 | +      | +            | -              | 284             | 2.860  | 1.798  | 1.062   | <b>1.591<sup>###</sup></b> |
|                                                              | -                           | -         | -                 | +      | -            | +              | 74              | 0.745  | 0.940  | -0.195  | 0.793                      |
|                                                              | -                           | -         | -                 | -      | +            | +              | 51              | 0.514  | 0.876  | -0.362  | <b>0.587</b>               |
| 1 (6)                                                        | +                           | -         | -                 | -      | -            | -              | 129             | 1.299  | 3.281  | -1.982  | <b>0.396<sup>###</sup></b> |
|                                                              | -                           | +         | -                 | -      | -            | -              | 1366            | 13.755 | 15.051 | -1.296  | <b>0.914</b>               |
|                                                              | -                           | -         | +                 | -      | -            | -              | 186             | 1.873  | 4.182  | -2.309  | <b>0.448<sup>###</sup></b> |
|                                                              | -                           | -         | -                 | +      | -            | -              | 446             | 4.491  | 7.766  | -3.275  | <b>0.578<sup>###</sup></b> |
|                                                              | -                           | -         | -                 | -      | +            | -              | 420             | 4.229  | 7.237  | -3.008  | <b>0.584<sup>###</sup></b> |
|                                                              | -                           | -         | -                 | -      | -            | +              | 324             | 3.263  | 3.785  | -0.522  | <b>0.862</b>               |
| 0 (1)                                                        | -                           | -         | -                 | -      | -            | -              | 3859            | 38.858 | 31.259 | 7.599   | 1.243                      |

<sup>a</sup> Data in red have been presented in the Figure 1; “+” denotes that the disease has occurred among the surveyed children; “-” denotes that the disease has not occurred among the surveyed children.

<sup>#</sup>  $0.01 \leq p\text{-value} < 0.05$ ; <sup>##</sup>  $0.001 \leq p\text{-value} < 0.01$ ; <sup>###</sup>  $p\text{-value} < 0.001$  in the Pearson’s chi-square test for the extent of differences between OPs and EPs (the null hypothesis is REC=1). Bold indicates statistical significance.

**Table S6.** Multimorbidities of six lifetime illnesses, stratified by sex <sup>a</sup>.

| Number of co-existed illnesses (Total possible combinations) | Asthma | Pneumonia | Allergic rhinitis | Eczema | Food allergy | Ear infections | Boys (N = 4714) |              |        |         |                             | Girls (N = 4591) |                           |        |         |                            |
|--------------------------------------------------------------|--------|-----------|-------------------|--------|--------------|----------------|-----------------|--------------|--------|---------|-----------------------------|------------------|---------------------------|--------|---------|----------------------------|
|                                                              |        |           |                   |        |              |                | Sample size (n) | OP (%)       | EP (%) | AEC (%) | REC                         | Sample size (n)  | OP (%)                    | EP (%) | AEC (%) | REC                        |
| 6 (1)                                                        | +      | +         | +                 | +      | +            | +              | 11              | 0.233        | 0.002  | 0.231   | <b>116.500<sup>#</sup></b>  | 9                | 0.196                     | 0.001  | 0.195   | <b>196.000<sup>#</sup></b> |
| 5 (6)                                                        | +      | +         | +                 | +      | +            | -              | 26              | 0.552        | 0.017  | 0.535   | <b>32.471<sup>###</sup></b> | 19               | 0.414                     | 0.008  | 0.406   | <b>51.750<sup>##</sup></b> |
|                                                              | +      | +         | +                 | +      | -            | +              | 5               | 0.106        | 0.008  | 0.098   | <b>13.250</b>               | 1                | 0.022                     | 0.004  | 0.018   | <b>5.500</b>               |
|                                                              | +      | +         | +                 | -      | +            | +              | 3               | 0.064        | 0.008  | 0.056   | <b>8.000</b>                | 2                | 0.044                     | 0.004  | 0.040   | <b>11.000</b>              |
|                                                              | +      | +         | -                 | +      | +            | +              | 10              | 0.212        | 0.012  | 0.200   | 17.667                      | 4                | 0.087                     | 0.009  | 0.078   | 9.667                      |
|                                                              | +      | -         | +                 | +      | +            | +              | 2               | 0.042        | 0.004  | 0.038   | 10.500                      | 4                | 0.087                     | 0.002  | 0.085   | 43.500                     |
|                                                              | -      | +         | +                 | +      | +            | +              | 8               | 0.170        | 0.016  | 0.154   | <b>10.625</b>               | 8                | 0.174                     | 0.012  | 0.162   | <b>14.500</b>              |
| 4 (15)                                                       | +      | +         | +                 | +      | -            | -              | 13              | 0.276        | 0.072  | 0.204   | <b>3.833</b>                | 11               | 0.240                     | 0.035  | 0.205   | <b>6.857</b>               |
|                                                              | +      | +         | +                 | -      | +            | -              | <b>16</b>       | <b>0.339</b> | 0.067  | 0.272   | <b>5.060<sup>#</sup></b>    | <b>5</b>         | <b>0.109<sup>*</sup></b>  | 0.033  | 0.076   | 3.303                      |
|                                                              | +      | +         | +                 | -      | -            | +              | 6               | 0.127        | 0.033  | 0.094   | <b>3.848</b>                | 3                | 0.065                     | 0.018  | 0.047   | 3.611                      |
|                                                              | +      | +         | -                 | +      | +            | -              | <b>23</b>       | <b>0.488</b> | 0.106  | 0.382   | <b>4.604<sup>#</sup></b>    | <b>11</b>        | <b>0.240<sup>*</sup></b>  | 0.075  | 0.165   | 3.200                      |
|                                                              | +      | +         | -                 | +      | -            | +              | 4               | 0.085        | 0.053  | 0.032   | 1.604                       | 6                | 0.131                     | 0.041  | 0.090   | 3.195                      |
|                                                              | +      | +         | -                 | -      | +            | +              | 3               | 0.064        | 0.049  | 0.015   | <b>1.306</b>                | 3                | 0.065                     | 0.039  | 0.026   | <b>1.667</b>               |
|                                                              | +      | -         | +                 | +      | +            | -              | 11              | 0.233        | 0.034  | 0.199   | 6.853                       | 9                | 0.196                     | 0.018  | 0.178   | 10.889                     |
|                                                              | +      | -         | +                 | +      | -            | +              | 3               | 0.064        | 0.017  | 0.047   | 3.765                       | 3                | 0.065                     | 0.010  | 0.055   | 6.500                      |
|                                                              | +      | -         | +                 | -      | +            | +              | 1               | 0.021        | 0.015  | 0.006   | 1.400                       | 0                | 0.000                     | 0.009  | -0.009  | 0.000                      |
|                                                              | +      | -         | -                 | +      | +            | +              | 3               | 0.064        | 0.025  | 0.039   | <b>2.560</b>                | 3                | 0.065                     | 0.021  | 0.044   | <b>3.095</b>               |
|                                                              | -      | +         | +                 | +      | +            | -              | 33              | 0.700        | 0.139  | 0.561   | <b>5.036<sup>###</sup></b>  | 22               | 0.479                     | 0.093  | 0.386   | <b>5.151<sup>#</sup></b>   |
|                                                              | -      | +         | +                 | +      | -            | +              | 6               | 0.127        | 0.069  | 0.058   | 1.841                       | 3                | 0.065                     | 0.051  | 0.014   | 1.275                      |
|                                                              | -      | +         | +                 | -      | +            | +              | 3               | 0.064        | 0.064  | 0.000   | 1.000                       | 3                | 0.065                     | 0.048  | 0.017   | 1.354                      |
|                                                              | -      | +         | -                 | +      | +            | +              | 9               | 0.191        | 0.102  | 0.089   | 1.873                       | 17               | 0.370                     | 0.108  | 0.262   | 3.426                      |
|                                                              | -      | -         | +                 | +      | +            | +              | 10              | 0.212        | 0.032  | 0.180   | <b>6.625</b>                | 8                | 0.174                     | 0.025  | 0.149   | <b>6.960</b>               |
| 3 (20)                                                       | +      | +         | +                 | -      | -            | -              | <b>49</b>       | <b>1.039</b> | 0.287  | 0.752   | <b>3.620<sup>###</sup></b>  | <b>20</b>        | <b>0.436<sup>**</sup></b> | 0.146  | 0.290   | <b>2.986</b>               |
|                                                              | +      | +         | -                 | +      | -            | -              | <b>36</b>       | <b>0.764</b> | 0.455  | 0.309   | 1.679                       | <b>19</b>        | <b>0.414<sup>*</sup></b>  | 0.327  | 0.087   | 1.266                      |
|                                                              | +      | +         | -                 | -      | +            | -              | 15              | 0.318        | 0.421  | -0.103  | 0.755                       | 13               | 0.283                     | 0.308  | -0.025  | 0.919                      |
|                                                              | +      | +         | -                 | -      | -            | +              | 12              | 0.255        | 0.210  | 0.045   | <b>1.214</b>                | 8                | 0.174                     | 0.169  | 0.005   | <b>1.030</b>               |
|                                                              | +      | -         | +                 | +      | -            | -              | 5               | 0.106        | 0.144  | -0.038  | 0.736                       | 8                | 0.174                     | 0.077  | 0.097   | 2.260                      |

**Table S6.** Continued.

| Number of co-existed illnesses (Total possible combinations) | Asthma | Pneumonia | Allergic rhinitis | Eczema | Food allergy | Ear infection | Boys (N = 4714) |        |        |         |                      | Girls (N = 4591) |         |        |         |                     |
|--------------------------------------------------------------|--------|-----------|-------------------|--------|--------------|---------------|-----------------|--------|--------|---------|----------------------|------------------|---------|--------|---------|---------------------|
|                                                              |        |           |                   |        |              |               | Sample size (n) | OP (%) | EP (%) | AEC (%) | REC                  | Sample size (n)  | OP (%)  | EP (%) | AEC (%) | REC                 |
|                                                              | +      | -         | +                 | -      | +            | -             | 15              | 0.318  | 0.133  | -0.127  | 2.391                | 2                | 0.044** | 0.072  | 0.142   | 0.611               |
|                                                              | +      | -         | +                 | -      | -            | +             | 3               | 0.064  | 0.066  | -0.610  | 0.970                | 2                | 0.044   | 0.040  | -0.380  | 1.100               |
|                                                              | +      | -         | -                 | +      | +            | -             | 5               | 0.106  | 0.211  | -0.522  | 0.502                | 8                | 0.174   | 0.163  | -0.471  | 1.067               |
|                                                              | +      | -         | -                 | +      | -            | +             | 4               | 0.085  | 0.105  | -0.270  | 0.810                | 3                | 0.065   | 0.089  | -0.170  | 0.730               |
|                                                              | +      | -         | -                 | -      | +            | +             | 0               | 0.000  | 0.097  | -0.546  | 0.000                | 2                | 0.044   | 0.084  | -0.498  | 0.524               |
|                                                              | -      | +         | +                 | +      | -            | -             | 33              | 0.700  | 0.596  | -1.655  | 1.174                | 13               | 0.283** | 0.403  | -1.572  | 0.702               |
|                                                              | -      | +         | +                 | -      | +            | -             | 29              | 0.615  | 0.552  | -1.846  | 1.114                | 20               | 0.436   | 0.380  | -0.927  | 1.147               |
|                                                              | -      | +         | +                 | -      | -            | +             | 18              | 0.382  | 0.275  | 0.006   | 1.389                | 9                | 0.196   | 0.208  | -0.067  | 0.942               |
|                                                              | -      | +         | -                 | +      | +            | -             | 71              | 1.506  | 0.875  | -0.574  | 1.721 <sup>#</sup>   | 78               | 1.699   | 0.853  | -0.327  | 1.992 <sup>#</sup>  |
|                                                              | -      | +         | -                 | +      | -            | +             | 12              | 0.255  | 0.436  | -0.465  | 0.585                | 15               | 0.327   | 0.467  | -0.277  | 0.700               |
|                                                              | -      | +         | -                 | -      | +            | +             | 9               | 0.191  | 0.404  | -0.209  | 0.473                | 17               | 0.370   | 0.441  | -0.015  | 0.839               |
|                                                              | -      | -         | +                 | +      | +            | -             | 40              | 0.849  | 0.277  | 1.204   | 3.065 <sup>#</sup>   | 34               | 0.741   | 0.200  | 1.292   | 3.705 <sup>##</sup> |
|                                                              | -      | -         | +                 | +      | -            | +             | 5               | 0.106  | 0.138  | -0.148  | 0.768                | 5                | 0.109   | 0.110  | -0.141  | 0.991               |
|                                                              | -      | -         | +                 | -      | +            | +             | 5               | 0.106  | 0.128  | -0.190  | 0.828                | 3                | 0.065   | 0.104  | -0.476  | 0.625               |
|                                                              | -      | -         | -                 | +      | +            | +             | 15              | 0.318  | 0.203  | -0.127  | 1.567                | 26               | 0.566   | 0.233  | 0.142   | 2.429               |
| 2 (15)                                                       | +      | +         | -                 | -      | -            | -             | 85              | 1.803  | 1.807  | -0.610  | 0.998                | 79               | 1.721   | 1.340  | -0.380  | 1.284               |
|                                                              | +      | -         | +                 | -      | -            | -             | 21              | 0.445  | 0.572  | -0.522  | 0.778                | 21               | 0.457   | 0.315  | -0.471  | 1.451               |
|                                                              | +      | -         | -                 | +      | -            | -             | 14              | 0.297  | 0.907  | -0.270  | 0.327 <sup>###</sup> | 15               | 0.327   | 0.707  | -0.170  | 0.463               |
|                                                              | +      | -         | -                 | -      | +            | -             | 15              | 0.318  | 0.840  | -0.546  | 0.379 <sup>#</sup>   | 9                | 0.196   | 0.667  | -0.498  | 0.294 <sup>#</sup>  |
|                                                              | +      | -         | -                 | -      | -            | +             | 7               | 0.148  | 0.418  | -1.655  | 0.354                | 9                | 0.196   | 0.366  | -1.572  | 0.536               |
|                                                              | -      | +         | +                 | -      | -            | -             | 86              | 1.824  | 2.370  | -1.846  | 0.770                | 53               | 1.154** | 1.652  | -0.927  | 0.699               |
|                                                              | -      | +         | -                 | +      | -            | -             | 99              | 2.100  | 3.755  | 0.006   | 0.559                | 98               | 2.135   | 3.707  | -0.067  | 0.576 <sup>#</sup>  |
|                                                              | -      | +         | -                 | -      | +            | -             | 77              | 1.633  | 3.479  | -0.574  | 0.469                | 118              | 2.570** | 3.497  | -0.327  | 0.735               |
|                                                              | -      | +         | -                 | -      | -            | +             | 82              | 1.739  | 1.733  | -0.465  | 1.003                | 85               | 1.851   | 1.918  | -0.277  | 0.965               |
|                                                              | -      | -         | +                 | +      | -            | -             | 29              | 0.615  | 1.189  | -0.209  | 0.517 <sup>#</sup>   | 25               | 0.545   | 0.872  | -0.015  | 0.625               |
|                                                              | -      | -         | +                 | -      | +            | -             | 30              | 0.636  | 1.101  | 1.204   | 0.578                | 25               | 0.545   | 0.822  | 1.292   | 0.663               |
|                                                              | -      | -         | +                 | -      | -            | +             | 16              | 0.339  | 0.548  | -0.148  | 0.619                | 20               | 0.436   | 0.451  | -0.141  | 0.967               |

**Table S6.** Continued.

| Number of co-existed illnesses (Total possible combinations) | Asthma | Pneumonia | Allergic rhinitis | Eczema | Food allergy | Ear infection | Boys (N = 4714) |        |        |         |                            | Girls (N = 4591) |        |        |         |                            |
|--------------------------------------------------------------|--------|-----------|-------------------|--------|--------------|---------------|-----------------|--------|--------|---------|----------------------------|------------------|--------|--------|---------|----------------------------|
|                                                              |        |           |                   |        |              |               | Sample size (n) | OP (%) | EP (%) | AEC (%) | REC                        | Sample size (n)  | OP (%) | EP (%) | AEC (%) | REC                        |
|                                                              | -      | -         | -                 | +      | +            | -             | 139             | 2.949  | 1.745  | -0.190  | <b>1.690<sup>##</sup></b>  | 144              | 3.137  | 1.845  | -0.476  | <b>1.700<sup>#</sup></b>   |
|                                                              | -      | -         | -                 | +      | -            | +             | 34              | 0.721  | 0.869  | -0.127  | 0.830                      | 40               | 0.871  | 1.012  | 0.142   | 0.861                      |
|                                                              | -      | -         | -                 | -      | +            | +             | 29              | 0.615  | 0.805  | -0.610  | <b>0.764</b>               | 22               | 0.479  | 0.955  | -0.380  | <b>0.502</b>               |
| 1 (6)                                                        | +      | -         | -                 | -      | -            | -             | 72              | 1.527  | 3.604  | -2.077  | <b>0.424<sup>###</sup></b> | 57               | 1.242  | 2.901  | -1.659  | <b>0.428<sup>###</sup></b> |
|                                                              | -      | +         | -                 | -      | -            | -             | 684             | 14.510 | 14.928 | -0.418  | <b>0.972</b>               | 680              | 14.812 | 15.204 | -0.392  | <b>0.974</b>               |
|                                                              | -      | -         | +                 | -      | -            | -             | 104             | 2.206  | 4.725  | -2.519  | <b>0.467<sup>###</sup></b> | 82               | 1.786  | 3.576  | -1.790  | <b>0.499<sup>###</sup></b> |
|                                                              | -      | -         | -                 | +      | -            | -             | 218             | 4.625  | 7.488  | -2.863  | <b>0.618<sup>###</sup></b> | 227              | 4.944  | 8.023  | -3.079  | <b>0.616<sup>###</sup></b> |
|                                                              | -      | -         | -                 | -      | +            | -             | 214             | 4.540  | 6.937  | -2.397  | <b>0.654<sup>###</sup></b> | 206              | 4.487  | 7.570  | -3.083  | <b>0.593<sup>###</sup></b> |
|                                                              | -      | -         | -                 | -      | -            | +             | 152             | 3.224  | 3.455  | -0.231  | <b>0.933</b>               | 171              | 3.725  | 4.151  | -0.426  | <b>0.897</b>               |
| 0 (1)                                                        | -      | -         | -                 | -      | -            | -             | 1904            | 40.390 | 29.766 | 10.624  | 1.357                      | 1942             | 42.300 | 32.911 | 9.389   | 1.285                      |

<sup>a</sup> Data in red have been presented in the Figure 2; “+” denotes that the disease has occurred among the surveyed children; “-” denotes that the disease has not occurred among the surveyed children.

\*  $0.01 \leq p\text{-value} < 0.05$ ; \*\*  $0.001 \leq p\text{-value} < 0.01$ ; \*\*\*  $p\text{-value} < 0.001$  in the Pearson’s chi-square test for differences of OPs between boys and girls.

<sup>#</sup>  $0.01 \leq p\text{-value} < 0.05$ ; <sup>##</sup>  $0.001 \leq p\text{-value} < 0.01$ ; <sup>###</sup>  $p\text{-value} < 0.001$  in the Pearson’s chi-square test for the extent of differences between OPs and EPs (the null hypothesis is REC=1). Bold indicates statistical significance.

**Table S7.** Multimorbidities of six lifetime illnesses, stratified by family history of atopy <sup>a</sup>.

| Number of co-existed illnesses (Total possible combinations) | Asthma | Pneumonia | Allergic rhinitis | Eczema | Food allergy | Ear infections | Children with family history of atopy (N = 2104) |        |        |         |                     | Children without family history of atopy (N = 7048) |                      |        |         |                     |
|--------------------------------------------------------------|--------|-----------|-------------------|--------|--------------|----------------|--------------------------------------------------|--------|--------|---------|---------------------|-----------------------------------------------------|----------------------|--------|---------|---------------------|
|                                                              |        |           |                   |        |              |                | Sample size (n)                                  | OP (%) | EP (%) | AEC (%) | REC                 | Sample size (n)                                     | OP (%)               | EP (%) | AEC (%) | REC                 |
| 6 (1)                                                        | +      | +         | +                 | +      | +            | +              | 12                                               | 0.570  | 0.037  | 0.533   | 15.405 <sup>#</sup> | 8                                                   | 0.114 <sup>***</sup> | 0.000  | 0.114   | 395.800             |
| 5 (6)                                                        | +      | +         | +                 | +      | +            | -              | 34                                               | 1.616  | 0.224  | 1.392   | 7.214 <sup>##</sup> | 10                                                  | 0.142 <sup>***</sup> | 0.003  | 0.139   | 47.333 <sup>#</sup> |
|                                                              | +      | +         | +                 | +      | -            | +              | 2                                                | 0.095  | 0.081  | 0.014   | 1.173               | 3                                                   | 0.043                | 0.002  | 0.041   | 21.500              |
|                                                              | +      | +         | +                 | -      | +            | +              | 5                                                | 0.238  | 0.076  | 0.162   | 3.132               | 0                                                   | 0.000 <sup>***</sup> | 0.002  | -0.002  | 0.000               |
|                                                              | +      | +         | -                 | +      | +            | +              | 9                                                | 0.428  | 0.092  | 0.336   | 4.652               | 4                                                   | 0.057 <sup>***</sup> | 0.004  | 0.053   | 14.250              |
|                                                              | +      | -         | +                 | +      | +            | +              | 6                                                | 0.285  | 0.049  | 0.236   | 5.816               | 0                                                   | 0.000 <sup>***</sup> | 0.001  | -0.001  | 0.000               |
|                                                              | -      | +         | +                 | +      | +            | +              | 15                                               | 0.713  | 0.150  | 0.563   | 4.753               | 1                                                   | 0.014 <sup>***</sup> | 0.004  | 0.010   | 3.500               |
| 4 (15)                                                       | +      | +         | +                 | +      | -            | -              | 13                                               | 0.618  | 0.483  | 0.135   | 1.280               | 11                                                  | 0.156 <sup>***</sup> | 0.015  | 0.141   | 10.400              |
|                                                              | +      | +         | +                 | -      | +            | -              | 10                                               | 0.475  | 0.455  | 0.020   | 1.044               | 11                                                  | 0.156 <sup>**</sup>  | 0.014  | 0.142   | 11.143              |
|                                                              | +      | +         | +                 | -      | -            | +              | 5                                                | 0.238  | 0.164  | 0.074   | 1.451               | 3                                                   | 0.043 <sup>***</sup> | 0.009  | 0.034   | 4.778               |
|                                                              | +      | +         | -                 | +      | +            | -              | 18                                               | 0.856  | 0.548  | 0.308   | 1.562               | 16                                                  | 0.227 <sup>***</sup> | 0.037  | 0.190   | 6.135 <sup>#</sup>  |
|                                                              | +      | +         | -                 | +      | -            | +              | 3                                                | 0.143  | 0.197  | -0.054  | 0.726               | 7                                                   | 0.099                | 0.023  | 0.076   | 4.304               |
|                                                              | +      | +         | -                 | -      | +            | +              | 2                                                | 0.095  | 0.186  | -0.091  | 0.511               | 4                                                   | 0.057                | 0.021  | 0.036   | 2.714               |
|                                                              | +      | -         | +                 | +      | +            | -              | 14                                               | 0.665  | 0.293  | 0.372   | 2.270               | 6                                                   | 0.085 <sup>***</sup> | 0.006  | 0.079   | 14.167              |
|                                                              | +      | -         | +                 | +      | -            | +              | 4                                                | 0.190  | 0.105  | 0.085   | 1.810               | 2                                                   | 0.028 <sup>*</sup>   | 0.004  | 0.024   | 7.000               |
|                                                              | +      | -         | +                 | -      | +            | +              | 0                                                | 0.000  | 0.099  | -0.099  | 0.000               | 1                                                   | 0.014                | 0.004  | 0.010   | 3.500               |
|                                                              | +      | -         | -                 | +      | +            | +              | 1                                                | 0.048  | 0.120  | -0.072  | 0.400               | 5                                                   | 0.071                | 0.010  | 0.061   | 7.100               |
|                                                              | -      | +         | +                 | +      | +            | -              | 33                                               | 1.568  | 0.902  | 0.666   | 1.738               | 21                                                  | 0.298 <sup>***</sup> | 0.040  | 0.258   | 7.450 <sup>#</sup>  |
|                                                              | -      | +         | +                 | +      | -            | +              | 4                                                | 0.190  | 0.324  | -0.134  | 0.586               | 4                                                   | 0.057                | 0.024  | 0.033   | 2.375               |
|                                                              | -      | +         | +                 | -      | +            | +              | 5                                                | 0.238  | 0.305  | -0.067  | 0.780               | 1                                                   | 0.014 <sup>***</sup> | 0.023  | -0.009  | 0.609               |
|                                                              | -      | +         | -                 | +      | +            | +              | 8                                                | 0.380  | 0.368  | 0.012   | 1.033               | 19                                                  | 0.270                | 0.060  | 0.210   | 4.500 <sup>#</sup>  |
|                                                              | -      | -         | +                 | +      | +            | +              | 14                                               | 0.665  | 0.197  | 0.468   | 3.376               | 4                                                   | 0.057 <sup>***</sup> | 0.010  | 0.047   | 5.700               |
| 3 (20)                                                       | +      | +         | +                 | -      | -            | -              | 40                                               | 1.901  | 0.980  | 0.921   | 1.940               | 29                                                  | 0.411 <sup>***</sup> | 0.080  | 0.331   | 5.138 <sup>#</sup>  |
|                                                              | +      | +         | -                 | +      | -            | -              | 26                                               | 1.236  | 1.182  | 0.054   | 1.046               | 26                                                  | 0.369 <sup>***</sup> | 0.210  | 0.159   | 1.757               |
|                                                              | +      | +         | -                 | -      | +            | -              | 14                                               | 0.665  | 1.114  | -0.449  | 0.597               | 13                                                  | 0.184 <sup>***</sup> | 0.197  | -0.013  | 0.934               |
|                                                              | +      | +         | -                 | -      | -            | +              | 4                                                | 0.190  | 0.400  | -0.210  | 0.475               | 15                                                  | 0.213                | 0.119  | 0.094   | 1.790               |

Table S7. Continued.

| Number of co-existed illnesses (Total possible combinations) | Asthma | Pneumonia | Allergic rhinitis | Eczema | Food allergy | Ear infection | Children with family history of atopy (N = 2104) |        |        |         |                      | Children without family history of atopy (N = 7048) |          |        |         |                     |
|--------------------------------------------------------------|--------|-----------|-------------------|--------|--------------|---------------|--------------------------------------------------|--------|--------|---------|----------------------|-----------------------------------------------------|----------|--------|---------|---------------------|
|                                                              |        |           |                   |        |              |               | Sample size (n)                                  | OP (%) | EP (%) | AEC (%) | REC                  | Sample size (n)                                     | OP (%)   | EP (%) | AEC (%) | REC                 |
|                                                              | +      | -         | +                 | +      | -            | -             | 10                                               | 0.475  | 0.632  | -0.121  | 0.752                | 3                                                   | 0.043*** | 0.036  | 0.065   | 1.194               |
|                                                              | +      | -         | +                 | -      | +            | -             | 10                                               | 0.475  | 0.596  | -0.024  | 0.797                | 7                                                   | 0.099*** | 0.034  | -0.021  | 2.912               |
|                                                              | +      | -         | +                 | -      | -            | +             | 4                                                | 0.190  | 0.214  | -0.243  | 0.888                | 0                                                   | 0.000*** | 0.021  | -0.047  | 0.000               |
|                                                              | +      | -         | -                 | +      | +            | -             | 10                                               | 0.475  | 0.718  | -0.163  | 0.662                | 3                                                   | 0.043*** | 0.090  | 0.017   | 0.478               |
|                                                              | +      | -         | -                 | +      | -            | +             | 2                                                | 0.095  | 0.258  | -0.148  | 0.368                | 5                                                   | 0.071    | 0.054  | -0.051  | 1.315               |
|                                                              | +      | -         | -                 | -      | +            | +             | 2                                                | 0.095  | 0.243  | -0.612  | 0.391                | 0                                                   | 0.000**  | 0.051  | 0.031   | 0.000               |
|                                                              | -      | +         | +                 | +      | -            | -             | 28                                               | 1.331  | 1.943  | -0.453  | 0.685                | 18                                                  | 0.255*** | 0.224  | 0.059   | 1.138               |
|                                                              | -      | +         | +                 | -      | +            | -             | 29                                               | 1.378  | 1.831  | 0.102   | 0.753                | 19                                                  | 0.270*** | 0.211  | 0.029   | 1.280               |
|                                                              | -      | +         | +                 | -      | -            | +             | 16                                               | 0.760  | 0.658  | 0.501   | 1.155                | 11                                                  | 0.156*** | 0.127  | 0.736   | 1.228               |
|                                                              | -      | +         | -                 | +      | +            | -             | 57                                               | 2.709  | 2.208  | -0.461  | 1.227                | 91                                                  | 1.291*** | 0.555  | -0.080  | 2.326 <sup>#</sup>  |
|                                                              | -      | +         | -                 | +      | -            | +             | 7                                                | 0.333  | 0.794  | -0.368  | 0.419                | 18                                                  | 0.255    | 0.335  | -0.046  | 0.761               |
|                                                              | -      | +         | -                 | -      | +            | +             | 8                                                | 0.380  | 0.748  | 1.148   | 0.508                | 19                                                  | 0.270    | 0.316  | 0.245   | 0.854               |
|                                                              | -      | -         | +                 | +      | +            | -             | 49                                               | 2.329  | 1.181  | -0.140  | 1.972 <sup>#</sup>   | 24                                                  | 0.341*** | 0.096  | -0.001  | 3.552 <sup>#</sup>  |
|                                                              | -      | -         | +                 | +      | -            | +             | 6                                                | 0.285  | 0.425  | -0.115  | 0.671                | 4                                                   | 0.057**  | 0.058  | -0.027  | 0.983               |
|                                                              | -      | -         | +                 | -      | +            | +             | 6                                                | 0.285  | 0.400  | 0.421   | 0.713                | 2                                                   | 0.028*** | 0.055  | 0.168   | 0.509               |
|                                                              | -      | -         | -                 | +      | +            | +             | 19                                               | 0.903  | 0.482  | 0.310   | 1.873                | 22                                                  | 0.312*** | 0.144  | 0.323   | 2.167               |
| 2 (15)                                                       | +      | +         | -                 | -      | -            | -             | 57                                               | 2.709  | 2.399  | -0.142  | 1.129                | 101                                                 | 1.433*** | 1.110  | 0.078   | 1.291               |
|                                                              | +      | -         | +                 | -      | -            | -             | 24                                               | 1.141  | 1.283  | -1.167  | 0.889                | 19                                                  | 0.270*** | 0.192  | -0.223  | 1.406               |
|                                                              | +      | -         | -                 | +      | -            | -             | 8                                                | 0.380  | 1.547  | -0.888  | 0.246 <sup>#</sup>   | 20                                                  | 0.284    | 0.507  | -0.307  | 0.560               |
|                                                              | +      | -         | -                 | -      | +            | -             | 12                                               | 0.570  | 1.458  | -2.714  | 0.391 <sup>#</sup>   | 12                                                  | 0.170**  | 0.477  | -0.189  | 0.356 <sup>#</sup>  |
|                                                              | +      | -         | -                 | -      | -            | +             | 9                                                | 0.428  | 3.142  | -0.856  | 0.136 <sup>###</sup> | 7                                                   | 0.099**  | 0.288  | -0.150  | 0.344               |
|                                                              | -      | +         | +                 | -      | -            | -             | 65                                               | 3.089  | 3.945  | -2.190  | 0.783                | 73                                                  | 1.036*** | 1.186  | -1.121  | 0.874               |
|                                                              | -      | +         | -                 | +      | -            | -             | 54                                               | 2.567  | 4.757  | -2.153  | 0.540 <sup>##</sup>  | 141                                                 | 2.001    | 3.122  | -0.894  | 0.641 <sup>##</sup> |
|                                                              | -      | +         | -                 | -      | +            | -             | 49                                               | 2.329  | 4.482  | -0.043  | 0.520 <sup>##</sup>  | 144                                                 | 2.043    | 2.937  | 0.099   | 0.696 <sup>##</sup> |
|                                                              | -      | +         | -                 | -      | -            | +             | 33                                               | 1.568  | 1.611  | -1.118  | 0.973                | 132                                                 | 1.873    | 1.774  | -0.229  | 1.056               |
|                                                              | -      | -         | +                 | +      | -            | -             | 30                                               | 1.426  | 2.544  | -1.114  | 0.561                | 22                                                  | 0.312*** | 0.541  | -0.140  | 0.577               |
|                                                              | -      | -         | +                 | -      | +            | -             | 27                                               | 1.283  | 2.397  | -0.197  | 0.535                | 26                                                  | 0.369*** | 0.509  | -0.009  | 0.725               |

**Table S7.** Continued.

| Number of co-existed illnesses (Total possible combinations) | Asthma | Pneumonia | Allergic rhinitis | Eczema | Food allergy | Ear infection | Children with family history of atopy (N = 2104) |               |        |         |               | Children without family history of atopy (N = 7048) |                  |        |         |                 |
|--------------------------------------------------------------|--------|-----------|-------------------|--------|--------------|---------------|--------------------------------------------------|---------------|--------|---------|---------------|-----------------------------------------------------|------------------|--------|---------|-----------------|
|                                                              |        |           |                   |        |              |               | Sample size (n)                                  | OP (%)        | EP (%) | AEC (%) | REC           | Sample size (n)                                     | OP (%)           | EP (%) | AEC (%) | REC             |
|                                                              | -      | -         | +                 | -      | -            | +             | <b>14</b>                                        | <b>0.665</b>  | 0.862  | 1.577   | 0.771         | <b>21</b>                                           | <b>0.298*</b>    | 0.307  | 1.242   | 0.971           |
|                                                              | -      | -         | -                 | +      | +            | -             | <b>94</b>                                        | <b>4.468</b>  | 2.891  | -0.326  | <b>1.545</b>  | <b>182</b>                                          | <b>2.582***</b>  | 1.340  | 0.028   | <b>1.927###</b> |
|                                                              | -      | -         | -                 | +      | -            | +             | 15                                               | 0.713         | 1.039  | -0.361  | 0.686         | 59                                                  | 0.837            | 0.809  | -0.250  | 1.035           |
|                                                              | -      | -         | -                 | -      | +            | +             | 13                                               | 0.618         | 0.979  | -0.121  | <b>0.631</b>  | 36                                                  | 0.511            | 0.761  | 0.065   | <b>0.671</b>    |
| 1 (6)                                                        | +      | -         | -                 | -      | -            | -             | <b>45</b>                                        | <b>2.139</b>  | 3.142  | -1.00   | <b>0.681</b>  | <b>81</b>                                           | <b>1.149**</b>   | 2.679  | -1.530  | <b>0.429###</b> |
|                                                              | -      | +         | -                 | -      | -            | -             | <b>246</b>                                       | <b>11.692</b> | 9.657  | 2.04    | <b>1.211</b>  | <b>1095</b>                                         | <b>15.536***</b> | 16.515 | -0.979  | <b>0.941</b>    |
|                                                              | -      | -         | +                 | -      | -            | -             | <b>77</b>                                        | <b>3.660</b>  | 5.165  | -1.51   | <b>0.709</b>  | <b>106</b>                                          | <b>1.504***</b>  | 2.862  | -1.358  | <b>0.526###</b> |
|                                                              | -      | -         | -                 | +      | -            | -             | 87                                               | 4.135         | 6.229  | -2.09   | <b>0.664#</b> | 349                                                 | 4.952            | 7.534  | -2.582  | <b>0.657###</b> |
|                                                              | -      | -         | -                 | -      | +            | -             | <b>77</b>                                        | <b>3.660</b>  | 5.869  | -2.21   | <b>0.624#</b> | <b>339</b>                                          | <b>4.810*</b>    | 7.088  | -2.278  | <b>0.679###</b> |
|                                                              | -      | -         | -                 | -      | -            | +             | <b>47</b>                                        | <b>2.234</b>  | 2.110  | 0.12    | <b>1.059</b>  | <b>271</b>                                          | <b>3.845***</b>  | 4.281  | -0.436  | <b>0.898</b>    |
| 0 (1)                                                        | -      | -         | -                 | -      | -            | -             | <b>453</b>                                       | <b>21.530</b> | 12.646 | 8.88    | 1.703         | <b>3330</b>                                         | <b>47.247***</b> | 39.850 | 7.397   | 1.186           |

<sup>a</sup> Data in red have been presented in the Figure 2; “+” denotes that the disease has occurred among the surveyed children; “-” denotes that the disease has not occurred among the surveyed children.

\*  $0.01 \leq p\text{-value} < 0.05$ ; \*\*  $0.001 \leq p\text{-value} < 0.01$ ; \*\*\*  $p\text{-value} < 0.001$  in the Pearson’s chi-square test for differences of OPs between boys and girls.

#  $0.01 \leq p\text{-value} < 0.05$ ; ##  $0.001 \leq p\text{-value} < 0.01$ ; ###  $p\text{-value} < 0.001$  in the Pearson’s chi-square test for the extent of differences between OPs and EPs (the null hypothesis is REC=1). Bold indicates statistical significance.

**Table S8.** Expected prevalences (%) of multimorbidities of current wheeze, rhinitis symptoms, and eczema <sup>a</sup>.

| Number of co-occurred illnesses (Total possible combinations) | Wheeze | Rhinitis symptoms | Eczema | Total  | Stratified by sex |        | Stratified by FHA |             |
|---------------------------------------------------------------|--------|-------------------|--------|--------|-------------------|--------|-------------------|-------------|
|                                                               |        |                   |        |        | Boys              | Girls  | With FHA          | Without FHA |
| 3 (1)                                                         | +      | +                 | +      | 1.196  | 1.324             | 1.068  | 4.801             | 0.636       |
|                                                               | +      | +                 | -      | 7.915  | 9.087             | 6.836  | 15.946            | 5.731       |
| 2 (3)                                                         | +      | -                 | +      | 1.629  | 1.665             | 1.577  | 2.958             | 1.127       |
|                                                               | -      | +                 | +      | 4.360  | 4.309             | 4.386  | 9.518             | 2.970       |
|                                                               | +      | -                 | -      | 10.782 | 11.428            | 10.095 | 9.824             | 10.152      |
| 1 (3)                                                         | -      | +                 | -      | 28.863 | 29.575            | 28.086 | 31.614            | 26.746      |
|                                                               | -      | -                 | +      | 5.939  | 5.419             | 6.477  | 5.864             | 5.260       |
| 0 (1)                                                         | -      | -                 | -      | 39.361 | 37.193            | 41.475 | 19.476            | 47.378      |

<sup>a</sup> “+” denotes that the disease has occurred among the surveyed children; “-” denotes that the disease has not occurred among the surveyed children. FHA: family history of atopy.

**Table S9.** Multimorbidities of five current illnesses <sup>a</sup>.

| Number of co-occurred illnesses<br>(Total possible combinations) | Comorbidity (+: Yes; -: No) |           |                   |        |                         | Total (N = 11884) |        |        |         | REC                         |
|------------------------------------------------------------------|-----------------------------|-----------|-------------------|--------|-------------------------|-------------------|--------|--------|---------|-----------------------------|
|                                                                  | Wheeze                      | Dry cough | Rhinitis symptoms | Eczema | Common cold (≥ 3 times) | Sample size (n)   | OP (%) | EP (%) | AEC (%) |                             |
| 5 (1)                                                            | +                           | +         | +                 | +      | +                       | 132               | 1.111  | 0.108  | 1.003   | <b>10.271<sup>###</sup></b> |
| 4 (5)                                                            | +                           | +         | +                 | +      | -                       | 321               | 2.701  | 0.139  | 2.562   | <b>19.382<sup>###</sup></b> |
|                                                                  | +                           | +         | +                 | -      | +                       | 25                | 0.210  | 0.705  | -0.495  | <b>0.298<sup>###</sup></b>  |
|                                                                  | +                           | +         | -                 | +      | +                       | 39                | 0.328  | 0.144  | 0.184   | <b>2.278<sup>#</sup></b>    |
|                                                                  | +                           | -         | +                 | +      | +                       | 119               | 1.001  | 0.435  | 0.566   | <b>2.299<sup>###</sup></b>  |
|                                                                  | -                           | +         | +                 | +      | +                       | 111               | 0.934  | 0.388  | 0.546   | <b>2.407<sup>###</sup></b>  |
| 3 (10)                                                           | +                           | +         | +                 | -      | -                       | 144               | 1.212  | 0.908  | 0.304   | <b>1.334</b>                |
|                                                                  | +                           | +         | -                 | +      | -                       | 131               | 1.102  | 0.185  | 0.917   | <b>5.941<sup>###</sup></b>  |
|                                                                  | +                           | +         | -                 | -      | +                       | 26                | 0.219  | 0.939  | -0.720  | <b>0.233<sup>###</sup></b>  |
|                                                                  | +                           | -         | +                 | +      | -                       | 426               | 3.585  | 0.561  | 3.024   | <b>6.391<sup>###</sup></b>  |
|                                                                  | +                           | -         | +                 | -      | +                       | 57                | 0.480  | 2.838  | -2.358  | <b>0.169<sup>###</sup></b>  |
|                                                                  | +                           | -         | -                 | +      | +                       | 69                | 0.581  | 0.580  | 0.001   | <b>1.003</b>                |
|                                                                  | -                           | +         | +                 | +      | -                       | 399               | 3.357  | 0.500  | 2.857   | <b>6.715<sup>###</sup></b>  |
|                                                                  | -                           | +         | +                 | -      | +                       | 44                | 0.370  | 2.529  | -2.159  | <b>0.146<sup>###</sup></b>  |
|                                                                  | -                           | +         | -                 | +      | +                       | 49                | 0.412  | 0.516  | -0.104  | 0.798                       |
|                                                                  | -                           | -         | +                 | +      | +                       | 185               | 1.557  | 1.562  | -0.005  | <b>0.997</b>                |
| 2 (10)                                                           | +                           | +         | -                 | -      | -                       | 80                | 0.673  | 1.209  | -0.536  | <b>0.557<sup>##</sup></b>   |
|                                                                  | +                           | -         | +                 | -      | -                       | 328               | 2.760  | 3.657  | -0.897  | <b>0.755<sup>##</sup></b>   |
|                                                                  | +                           | -         | -                 | +      | -                       | 313               | 2.634  | 0.747  | 1.887   | <b>3.528<sup>###</sup></b>  |
|                                                                  | +                           | -         | -                 | -      | +                       | 46                | 0.387  | 3.778  | -3.391  | <b>0.102<sup>###</sup></b>  |
|                                                                  | -                           | +         | +                 | -      | -                       | 293               | 2.465  | 3.259  | -0.794  | <b>0.756<sup>##</sup></b>   |
|                                                                  | -                           | +         | -                 | +      | -                       | 283               | 2.381  | 0.665  | 1.716   | <b>3.579<sup>#</sup></b>    |
|                                                                  | -                           | +         | -                 | -      | +                       | 20                | 0.168  | 3.367  | -3.199  | <b>0.050<sup>###</sup></b>  |
|                                                                  | -                           | -         | +                 | +      | -                       | 889               | 7.481  | 2.012  | 5.469   | <b>3.718<sup>###</sup></b>  |
|                                                                  | -                           | -         | +                 | -      | +                       | 169               | 1.422  | 10.181 | -8.759  | <b>0.140<sup>###</sup></b>  |
|                                                                  | -                           | -         | -                 | +      | +                       | 222               | 1.868  | 2.079  | -0.211  | <b>0.899</b>                |
| 1 (5)                                                            | +                           | -         | -                 | -      | -                       | 335               | 2.819  | 4.867  | -2.048  | <b>0.579<sup>###</sup></b>  |
|                                                                  | -                           | +         | -                 | -      | -                       | 265               | 2.230  | 4.337  | -2.107  | <b>0.514<sup>###</sup></b>  |
|                                                                  | -                           | -         | +                 | -      | -                       | 1548              | 13.026 | 13.117 | -0.091  | <b>0.993</b>                |
|                                                                  | -                           | -         | -                 | +      | -                       | 1410              | 11.865 | 2.678  | 9.187   | <b>4.430<sup>###</sup></b>  |
|                                                                  | -                           | -         | -                 | -      | +                       | 263               | 2.213  | 13.551 | -11.338 | <b>0.163<sup>###</sup></b>  |
| 0 (1)                                                            | -                           | -         | -                 | -      | -                       | 3143              | 26.447 | 17.458 | 8.989   | 1.515                       |

<sup>a</sup> Data in red have been presented in the Figure 3; “+” denotes that the disease has occurred among the surveyed children; “-” denotes that the disease has not occurred among the surveyed children.

<sup>#</sup>  $0.01 \leq p\text{-value} < 0.05$ ; <sup>##</sup>  $0.001 \leq p\text{-value} < 0.01$ ; <sup>###</sup>  $p\text{-value} < 0.001$  in the Pearson’s chi-square test for the extent of differences between OPs and EPs (the null hypothesis is REC=1). Bold indicates statistical significance.

**Table S10.** Multimorbidities of five current illnesses, stratified by sex <sup>a</sup>.

| Number of co-occurred illnesses (Total possible combinations) | Comorbidity (+: Yes; -: No) |           |                   |        |                         | Boys (N = 5998) |              |        |         |                             | Girls (N = 5851) |                            |        |         |                             |
|---------------------------------------------------------------|-----------------------------|-----------|-------------------|--------|-------------------------|-----------------|--------------|--------|---------|-----------------------------|------------------|----------------------------|--------|---------|-----------------------------|
|                                                               | Wheeze                      | Dry cough | Rhinitis symptoms | Eczema | Common cold (≥ 3 times) | Sample size (n) | OP (%)       | EP (%) | AEC (%) | REC                         | Sample size (n)  | OP (%)                     | EP (%) | AEC (%) | REC                         |
| 5 (1)                                                         | +                           | +         | +                 | +      | +                       | 72              | 1.200        | 0.116  | 1.084   | <b>10.345<sup>###</sup></b> | 60               | 1.025                      | 0.099  | 0.926   | <b>10.354<sup>###</sup></b> |
| 4 (5)                                                         | +                           | +         | +                 | +      | -                       | 159             | 2.651        | 0.150  | 2.501   | <b>17.673<sup>###</sup></b> | 162              | 2.769                      | 0.127  | 2.642   | <b>21.803<sup>###</sup></b> |
|                                                               | +                           | +         | +                 | -      | +                       | 12              | 0.200        | 0.786  | -0.586  | <b>0.254<sup>###</sup></b>  | 13               | 0.222                      | 0.627  | -0.405  | <b>0.354<sup>#</sup></b>    |
|                                                               | +                           | +         | -                 | +      | +                       | 22              | 0.367        | 0.143  | 0.224   | <b>2.566<sup>#</sup></b>    | 17               | 0.291                      | 0.143  | 0.148   | <b>2.035<sup>#</sup></b>    |
|                                                               | +                           | -         | +                 | +      | +                       | 63              | 1.050        | 0.484  | 0.566   | <b>2.169<sup>#</sup></b>    | 56               | 0.957                      | 0.385  | 0.572   | <b>2.486<sup>#</sup></b>    |
|                                                               | -                           | +         | +                 | +      | +                       | 48              | 0.800        | 0.375  | 0.425   | <b>2.133<sup>#</sup></b>    | 62               | 1.060                      | 0.397  | 0.663   | <b>2.670<sup>#</sup></b>    |
| 3 (10)                                                        | +                           | +         | +                 | -      | -                       | <b>86</b>       | <b>1.434</b> | 1.012  | 0.422   | <b>1.417<sup>#</sup></b>    | <b>58</b>        | <b>0.991<sup>*</sup></b>   | 0.808  | 0.183   | <b>1.226<sup>#</sup></b>    |
|                                                               | +                           | +         | -                 | +      | -                       | 74              | 1.234        | 0.184  | 1.050   | <b>6.707<sup>###</sup></b>  | 56               | 0.957                      | 0.184  | 0.773   | <b>5.201<sup>###</sup></b>  |
|                                                               | +                           | +         | -                 | -      | +                       | 13              | 0.217        | 0.964  | -0.747  | <b>0.225<sup>###</sup></b>  | 13               | 0.222                      | 0.906  | -0.684  | <b>0.245<sup>###</sup></b>  |
|                                                               | +                           | -         | +                 | +      | -                       | <b>256</b>      | <b>4.268</b> | 0.623  | 3.645   | <b>6.851<sup>###</sup></b>  | <b>170</b>       | <b>2.905<sup>***</sup></b> | 0.496  | 2.409   | <b>5.857<sup>###</sup></b>  |
|                                                               | +                           | -         | +                 | -      | +                       | 28              | 0.467        | 3.265  | -2.798  | <b>0.143<sup>###</sup></b>  | 29               | 0.496                      | 2.446  | -1.950  | <b>0.203<sup>###</sup></b>  |
|                                                               | +                           | -         | -                 | +      | +                       | 43              | 0.717        | 0.593  | 0.124   | <b>1.209<sup>#</sup></b>    | 26               | 0.444                      | 0.556  | -0.112  | <b>0.799<sup>#</sup></b>    |
|                                                               | -                           | +         | +                 | +      | -                       | 202             | 3.368        | 0.483  | 2.885   | <b>6.973<sup>###</sup></b>  | 196              | 3.350                      | 0.512  | 2.838   | <b>6.543<sup>###</sup></b>  |
|                                                               | -                           | +         | +                 | -      | +                       | <b>13</b>       | <b>0.217</b> | 2.530  | -2.313  | <b>0.086<sup>###</sup></b>  | <b>31</b>        | <b>0.530<sup>**</sup></b>  | 2.523  | -1.993  | <b>0.210<sup>###</sup></b>  |
|                                                               | -                           | +         | -                 | +      | +                       | 21              | 0.350        | 0.460  | -0.110  | 0.761                       | 28               | 0.479                      | 0.574  | -0.095  | 0.834                       |
|                                                               | -                           | -         | +                 | +      | +                       | 87              | 1.450        | 1.557  | -0.107  | <b>0.931<sup>#</sup></b>    | 96               | 1.641                      | 1.550  | 0.091   | <b>1.059<sup>#</sup></b>    |
| 2 (10)                                                        | +                           | +         | -                 | -      | -                       | 46              | 0.767        | 1.242  | -0.475  | <b>0.618<sup>#</sup></b>    | 34               | 0.581                      | 1.167  | -0.586  | <b>0.498<sup>#</sup></b>    |
|                                                               | +                           | -         | +                 | -      | -                       | <b>170</b>      | <b>2.834</b> | 4.206  | -1.372  | <b>0.674<sup>###</sup></b>  | <b>158</b>       | <b>2.700<sup>*</sup></b>   | 3.151  | -0.451  | 0.857                       |
|                                                               | +                           | -         | -                 | +      | -                       | 180             | 3.001        | 0.764  | 2.237   | <b>3.928<sup>###</sup></b>  | 132              | 2.256                      | 0.717  | 1.539   | <b>3.146<sup>###</sup></b>  |
|                                                               | +                           | -         | -                 | -      | +                       | 22              | 0.367        | 4.006  | -3.639  | <b>0.092<sup>###</sup></b>  | 24               | 0.410                      | 3.535  | -3.125  | <b>0.116<sup>###</sup></b>  |
|                                                               | -                           | +         | +                 | -      | -                       | 133             | 2.217        | 3.259  | -1.042  | <b>0.680<sup>#</sup></b>    | 159              | 2.717                      | 3.251  | -0.534  | <b>0.836<sup>#</sup></b>    |
|                                                               | -                           | +         | -                 | +      | -                       | 140             | 2.334        | 0.592  | 1.742   | <b>3.943<sup>###</sup></b>  | 143              | 2.444                      | 0.739  | 1.705   | <b>3.307<sup>###</sup></b>  |
|                                                               | -                           | +         | -                 | -      | +                       | <b>9</b>        | <b>0.150</b> | 3.104  | -2.954  | <b>0.048<sup>###</sup></b>  | <b>11</b>        | <b>0.188<sup>*</sup></b>   | 3.646  | -3.458  | <b>0.052<sup>###</sup></b>  |
|                                                               | -                           | -         | +                 | +      | -                       | 479             | 7.986        | 2.005  | 5.981   | <b>3.983<sup>###</sup></b>  | 408              | 6.973                      | 1.997  | 4.976   | <b>3.492<sup>###</sup></b>  |
|                                                               | -                           | -         | +                 | -      | +                       | 79              | 1.317        | 10.510 | -9.193  | <b>0.125<sup>###</sup></b>  | 90               | 1.538                      | 9.846  | -8.308  | <b>0.156<sup>###</sup></b>  |
|                                                               | -                           | -         | -                 | +      | +                       | 117             | 1.951        | 1.910  | 0.041   | <b>1.021<sup>#</sup></b>    | 103              | 1.760                      | 2.240  | -0.480  | <b>0.786<sup>#</sup></b>    |

**Table S10.** Continued.

| Number of co-occurred illnesses (Total possible combinations) | Comorbidity (+: Yes; -: No) |           |                   |        |                         | Boys (N = 5998) |              |        |         |                            | Girls (N = 5851) |                          |        |         |                            |
|---------------------------------------------------------------|-----------------------------|-----------|-------------------|--------|-------------------------|-----------------|--------------|--------|---------|----------------------------|------------------|--------------------------|--------|---------|----------------------------|
|                                                               | Wheeze                      | Dry cough | Rhinitis symptoms | Eczema | Common cold (≥ 3 times) | Sample size (n) | OP (%)       | EP (%) | AEC (%) | REC                        | Sample size (n)  | OP (%)                   | EP (%) | AEC (%) | REC                        |
| 1 (5)                                                         | +                           | -         | -                 | -      | -                       | <b>178</b>      | <b>2.968</b> | 5.161  | -2.193  | <b>0.575<sup>###</sup></b> | <b>156</b>       | <b>2.666<sup>*</sup></b> | 4.554  | -1.888  | <b>0.585<sup>###</sup></b> |
|                                                               | -                           | +         | -                 | -      | -                       | <b>115</b>      | <b>1.917</b> | 3.999  | -2.082  | <b>0.479<sup>###</sup></b> | <b>148</b>       | <b>2.529<sup>*</sup></b> | 4.698  | -2.169  | <b>0.538<sup>###</sup></b> |
|                                                               | -                           | -         | +                 | -      | -                       | 737             | 12.287       | 13.540 | -1.253  | <b>0.907</b>               | 809              | 13.827                   | 12.685 | 1.142   | <b>1.090</b>               |
|                                                               | -                           | -         | -                 | +      | -                       | 730             | 12.171       | 2.461  | 9.710   | <b>4.946<sup>###</sup></b> | 678              | 11.588                   | 2.885  | 8.703   | <b>4.017<sup>###</sup></b> |
|                                                               | -                           | -         | -                 | -      | +                       | 124             | 2.067        | 12.898 | -10.831 | <b>0.160<sup>###</sup></b> | 137              | 2.341                    | 14.227 | -11.886 | <b>0.165<sup>###</sup></b> |
| 0 (1)                                                         | -                           | -         | -                 | -      | -                       | 1540            | 25.675       | 16.616 | 9.059   | 1.545                      | 1588             | 27.141                   | 18.330 | 8.811   | 1.481                      |

<sup>a</sup> Data in red have been presented in the Figure 4; “+” denotes that the disease has occurred among the surveyed children; “-” denotes that the disease has not occurred among the surveyed children.

\*  $0.01 \leq p\text{-value} < 0.05$ ; \*\*  $0.001 \leq p\text{-value} < 0.01$ ; \*\*\*  $p\text{-value} < 0.001$  in the Pearson’s chi-square test for differences of OPs between boys and girls.

#  $0.01 \leq p\text{-value} < 0.05$ ; ##  $0.001 \leq p\text{-value} < 0.01$ ; ###  $p\text{-value} < 0.001$  in the Pearson’s chi-square test for the extent of differences between OPs and EPs (the null hypothesis is REC=1). Bold indicates statistical significance.

**Table S11.** Multimorbidities of five current illnesses, stratified by family history of atopy <sup>a</sup>.

| Number of co-occurred illnesses (Total possible combinations) | Comorbidity (+: Yes; -: No) |           |                   |        |                         | Children with family history of atopy (N = 2845) |              |        |         |                            | Children without family history of atopy (N = 8785) |                            |        |         |                             |
|---------------------------------------------------------------|-----------------------------|-----------|-------------------|--------|-------------------------|--------------------------------------------------|--------------|--------|---------|----------------------------|-----------------------------------------------------|----------------------------|--------|---------|-----------------------------|
|                                                               | Wheeze                      | Dry cough | Rhinitis symptoms | Eczema | Common cold (≥ 3 times) | Sample size (n)                                  | OP (%)       | EP (%) | AEC (%) | REC                        | Sample size (n)                                     | OP (%)                     | EP (%) | AEC (%) | REC                         |
| 5 (1)                                                         | +                           | +         | +                 | +      | +                       | <b>81</b>                                        | <b>2.847</b> | 5.077  | -2.230  | <b>0.561<sup>##</sup></b>  | <b>48</b>                                           | <b>0.546<sup>***</sup></b> | 0.045  | 0.501   | <b>12.133<sup>###</sup></b> |
| 4 (5)                                                         | +                           | +         | +                 | +      | -                       | <b>166</b>                                       | <b>5.835</b> | 3.604  | 2.231   | <b>1.619<sup>##</sup></b>  | <b>150</b>                                          | <b>1.707<sup>***</sup></b> | 0.067  | 1.640   | <b>25.478<sup>###</sup></b> |
|                                                               | +                           | +         | +                 | -      | +                       | <b>10</b>                                        | <b>0.351</b> | 1.331  | -0.980  | <b>0.264<sup>##</sup></b>  | <b>14</b>                                           | <b>0.159<sup>**</sup></b>  | 0.078  | 0.081   | <b>2.038</b>                |
|                                                               | +                           | +         | -                 | +      | +                       | <b>19</b>                                        | <b>0.668</b> | 0.945  | -0.277  | <b>0.707</b>               | <b>19</b>                                           | <b>0.216<sup>***</sup></b> | 0.398  | -0.182  | <b>0.543</b>                |
|                                                               | +                           | -         | +                 | +      | +                       | <b>67</b>                                        | <b>2.355</b> | 5.190  | -2.835  | <b>0.454<sup>###</sup></b> | <b>51</b>                                           | <b>0.581<sup>***</sup></b> | 0.223  | 0.358   | <b>2.605<sup>##</sup></b>   |
|                                                               | -                           | +         | +                 | +      | +                       | <b>60</b>                                        | <b>2.109</b> | 3.780  | -1.671  | <b>0.558<sup>##</sup></b>  | <b>50</b>                                           | <b>0.569<sup>***</sup></b> | 0.209  | 0.360   | <b>2.722<sup>##</sup></b>   |
| 3 (10)                                                        | +                           | +         | +                 | -      | -                       | 42                                               | 1.476        | 0.778  | 0.698   | <b>1.897</b>               | 101                                                 | 1.150                      | 0.116  | 1.034   | <b>9.914<sup>###</sup></b>  |
|                                                               | +                           | +         | -                 | +      | -                       | <b>57</b>                                        | <b>2.004</b> | 4.273  | -2.269  | <b>0.469<sup>###</sup></b> | <b>68</b>                                           | <b>0.774<sup>***</sup></b> | 0.590  | 0.184   | 1.312                       |
|                                                               | +                           | +         | -                 | -      | +                       | 7                                                | 0.246        | 3.112  | -2.866  | <b>0.079<sup>###</sup></b> | 19                                                  | 0.216                      | 0.690  | -0.474  | <b>0.313<sup>###</sup></b>  |
|                                                               | +                           | -         | +                 | +      | -                       | <b>180</b>                                       | <b>6.327</b> | 3.033  | 3.294   | <b>2.086<sup>###</sup></b> | <b>236</b>                                          | <b>2.686<sup>***</sup></b> | 0.330  | 2.356   | <b>8.139<sup>###</sup></b>  |
|                                                               | +                           | -         | +                 | -      | +                       | <b>21</b>                                        | <b>0.738</b> | 2.209  | -1.471  | <b>0.334<sup>###</sup></b> | <b>35</b>                                           | <b>0.398<sup>*</sup></b>   | 0.385  | 0.013   | 1.034                       |
|                                                               | +                           | -         | -                 | +      | +                       | <b>34</b>                                        | <b>1.195</b> | 12.132 | -10.937 | <b>0.098<sup>###</sup></b> | <b>31</b>                                           | <b>0.353<sup>***</sup></b> | 1.959  | -1.606  | <b>0.180<sup>###</sup></b>  |
|                                                               | -                           | +         | +                 | +      | -                       | <b>134</b>                                       | <b>4.710</b> | 5.077  | -0.367  | <b>0.928</b>               | <b>257</b>                                          | <b>2.925<sup>***</sup></b> | 0.310  | 2.615   | <b>9.435<sup>###</sup></b>  |
|                                                               | -                           | +         | +                 | -      | +                       | 12                                               | 0.422        | 3.604  | -3.182  | <b>0.117<sup>###</sup></b> | 32                                                  | 0.364                      | 0.362  | 0.002   | 1.006                       |
|                                                               | -                           | +         | -                 | +      | +                       | <b>30</b>                                        | <b>1.054</b> | 1.331  | -0.277  | 0.792                      | <b>17</b>                                           | <b>0.194<sup>***</sup></b> | 1.840  | -1.646  | <b>0.105<sup>###</sup></b>  |
|                                                               | -                           | -         | +                 | +      | +                       | <b>91</b>                                        | <b>3.199</b> | 0.945  | 2.254   | <b>3.385<sup>###</sup></b> | <b>92</b>                                           | <b>1.047<sup>***</sup></b> | 1.028  | 0.019   | <b>1.018</b>                |
| 2 (10)                                                        | +                           | +         | -                 | -      | -                       | 22                                               | 0.773        | 5.190  | -4.417  | <b>0.149<sup>###</sup></b> | 56                                                  | 0.637                      | 1.022  | -0.385  | <b>0.623<sup>#</sup></b>    |
|                                                               | +                           | -         | +                 | -      | -                       | 67                                               | 2.355        | 3.780  | -1.425  | <b>0.623<sup>#</sup></b>   | 254                                                 | 2.891                      | 0.571  | 2.320   | <b>5.063<sup>###</sup></b>  |
|                                                               | +                           | -         | -                 | +      | -                       | <b>101</b>                                       | <b>3.550</b> | 0.778  | 2.772   | <b>4.563<sup>###</sup></b> | <b>199</b>                                          | <b>2.265<sup>***</sup></b> | 2.902  | -0.637  | 0.780                       |
|                                                               | +                           | -         | -                 | -      | +                       | 14                                               | 0.492        | 4.273  | -3.781  | <b>0.115<sup>###</sup></b> | 32                                                  | 0.364                      | 3.394  | -3.030  | <b>0.107<sup>###</sup></b>  |
|                                                               | -                           | +         | +                 | -      | -                       | 62                                               | 2.179        | 3.112  | -0.933  | <b>0.700</b>               | 224                                                 | 2.550                      | 0.536  | 2.014   | <b>4.757<sup>###</sup></b>  |
|                                                               | -                           | +         | -                 | +      | -                       | <b>83</b>                                        | <b>2.917</b> | 3.033  | -0.116  | 0.962                      | <b>198</b>                                          | <b>2.254<sup>*</sup></b>   | 2.726  | -0.472  | 0.827                       |
|                                                               | -                           | +         | -                 | -      | +                       | 6                                                | 0.211        | 2.209  | -1.998  | <b>0.096<sup>###</sup></b> | 14                                                  | 0.159                      | 3.187  | -3.028  | <b>0.050<sup>###</sup></b>  |
|                                                               | -                           | -         | +                 | +      | -                       | <b>269</b>                                       | <b>9.455</b> | 12.132 | -2.677  | <b>0.779<sup>#</sup></b>   | <b>597</b>                                          | <b>6.796<sup>***</sup></b> | 1.522  | 5.274   | <b>4.465<sup>###</sup></b>  |
|                                                               | -                           | -         | +                 | -      | +                       | 47                                               | 1.652        | 5.077  | -3.425  | <b>0.325<sup>###</sup></b> | 118                                                 | 1.343                      | 1.780  | -0.437  | 0.754                       |
|                                                               | -                           | -         | -                 | +      | +                       | <b>94</b>                                        | <b>3.304</b> | 3.604  | -0.300  | <b>0.917</b>               | <b>122</b>                                          | <b>1.389<sup>***</sup></b> | 9.048  | -7.659  | <b>0.154<sup>###</sup></b>  |

**Table S11.** Continued.

| Number of co-occurred illnesses (Total possible combinations) | Comorbidity (+: Yes; -: No) |           |                   |        |                         | Children with family history of atopy (N = 2845) |        |        |         |                      | Children without family history of atopy (N = 8785) |                       |        |         |                      |
|---------------------------------------------------------------|-----------------------------|-----------|-------------------|--------|-------------------------|--------------------------------------------------|--------|--------|---------|----------------------|-----------------------------------------------------|-----------------------|--------|---------|----------------------|
|                                                               | Wheeze                      | Dry cough | Rhinitis symptoms | Eczema | Common cold (≥ 3 times) | Sample size (n)                                  | OP (%) | EP (%) | AEC (%) | REC                  | Sample size (n)                                     | OP (%)                | EP (%) | AEC (%) | REC                  |
| 1 (5)                                                         | +                           | -         | -                 | -      | -                       | 72                                               | 2.531  | 3.181  | -0.650  | 0.796                | 252                                                 | 2.869                 | 5.028  | -2.159  | 0.571 <sup>###</sup> |
|                                                               | -                           | +         | -                 | -      | -                       | 48                                               | 1.687  | 2.619  | -0.932  | 0.644                | 217                                                 | 2.470 <sup>*</sup>    | 4.722  | -2.252  | 0.523 <sup>###</sup> |
|                                                               | -                           | -         | +                 | -      | -                       | 235                                              | 8.260  | 1.859  | 6.401   | 4.443 <sup>###</sup> | 1284                                                | 14.616 <sup>***</sup> | 2.637  | 11.979  | 5.543 <sup>###</sup> |
|                                                               | -                           | -         | -                 | +      | -                       | 299                                              | 10.510 | 10.211 | 0.299   | 1.029                | 1079                                                | 12.282 <sup>*</sup>   | 13.403 | -1.121  | 0.916                |
|                                                               | -                           | -         | -                 | -      | +                       | 59                                               | 2.074  | 7.436  | -5.362  | 0.279 <sup>###</sup> | 199                                                 | 2.265                 | 15.673 | -13.408 | 0.145 <sup>###</sup> |
| 0 (1)                                                         | -                           | -         | -                 | -      | -                       | 356                                              | 12.513 | 6.258  | 6.255   | 2.000                | 2720                                                | 30.962 <sup>***</sup> | 23.217 | 7.745   | 1.334                |

<sup>a</sup> Data in red have been presented in the Figure 4; “+” denotes that the disease has occurred among the surveyed children; “-” denotes that the disease has not occurred among the surveyed children.

\*  $0.01 \leq p\text{-value} < 0.05$ ; \*\*  $0.001 \leq p\text{-value} < 0.01$ ; \*\*\*  $p\text{-value} < 0.001$  in the Pearson’s chi-square test for differences of OPs between boys and girls.

#  $0.01 \leq p\text{-value} < 0.05$ ; ##  $0.001 \leq p\text{-value} < 0.01$ ; ###  $p\text{-value} < 0.001$  in the Pearson’s chi-square test for the extent of differences between OPs and EPs (the null hypothesis is REC=1). Bold indicates statistical significance.