

Risk Factors for Current Wheezing and Its Phenotypes Among Elementary School Children

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Summary. Background Accumulating evidence suggests, asthma includes many phenotypes with varying clinical and prognostic features. Epidemiological surveys documented a number of environmental risk factors for the development of asthma and interestingly these differ between and within countries, suggesting that the differences may be related with the different distribution of asthma phenotypes. This study aimed to investigate risk factors of current wheezing (CW) and different wheezing phenotypes in elementary school children. Methods Six thousand nine hundred sixty-three 9- to 11-year-old children of a previous multicenter survey where the methodology of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase-II was used were analyzed. Wheezing phenotypes were defined as wheezing with rhinitis (RW), wheezing with rhinoconjunctivitis (RCW), atopic wheezing (AW), non-atopic wheezing (NAW), and frequent wheezing (FW) (≥ 4 /year wheezing episodes). Results The prevalence of CW was 15.8% and among these, 22.4%, 67.3%, 45.9%, 20.5%, and 79.5% were classified as FW, RW, RCW, AW, and NAW, respectively. History of parental asthma/allergic rhinitis, coexistence of other allergic diseases, presence of mold and dampness in the house lived during the first year of life and maternal smoking in pregnancy were found to be risk factors for most phenotypes (odds ratio (OR) ranged from 1.43 to 3.56). Number of household in the last year (OR = 1.14), prematurity (OR = 2.08), and duration of breastfeeding (OR = 1.02) per additional month were found to be risk factor for FW, AW, and RCW, respectively. Conclusion Beside common risk factors for the development of asthma and its phenotypes, certain risk factors appeared to play a role in the development of phenotypic characteristics of asthma. These findings support our hypothesis that each phenotype has not only different clinical characteristics but also has different roots.

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INTRODUCTION

Various studies have revealed large differences in asthma prevalences across regions, even among people with the same ethnic background.¹ Wide variations are unlikely to be solely explained by genetic factors, and suggest the importance of environmental determinants in the development of asthma.² The finding of different risk factors for asthma/wheezing in previous studies from different regions of the world has been explained mainly by variations in personal and environmental characteristics of different populations.^{3–5} Yet, consideration of asthma as a “single” outcome in statistical risk analyses, rather than a complex set of phenotypes, might have led to identification of different predictors for such conditions in different studies. It is important to note that asthma is, at the best, a syndrome with different risk factors, different prognoses, and different responses to treatment.⁶ The prevalence of phenotypes may vary across countries, even across regions within a given country.^{7,8} Differences in

relative frequencies of asthma phenotypes in different regions and possible variations in predictors of such

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phenotypes might explain the inconsistent findings from asthma-related risk factor studies.

In 2006, a cross-sectional multicenter study based on the same objective markers as proposed by the International Study of Asthma and Allergies in Childhood (ISAAC) Phase-II methodology was performed in Turkey. In this report, we discuss a portion of the results of that study concerning the following research questions among Turkish students aged 10–11 years old:

- (1) Investigation of the risk factors for different phenotypes of wheezing, namely, wheezing with rhinitis (RW), wheezing with rhinoconjunctivitis (RCW), atopic wheezing (AW), non-atopic wheezing (NAW), and frequent wheezing (FW) (≥ 4 /year wheezing episodes).
- (2) To examine the inconsistencies between factors associated with different phenotypes (if any).

MATERIALS AND METHODS

This study is based on a cross-sectional study conducted with the ISAAC Phase-II option B method.⁹ Results were derived from a group of randomly selected school children, residing in the metropolitan areas of five cities, purposefully selected from different geographical regions of Turkey, namely, Van, Manisa, Ankara, Antalya, and Trabzon. The study is not registered by the ISAAC study group as it was conducted after the completion of the ISAAC studies. The study protocol was described in detail elsewhere.¹⁰ In summary, a sample of fifth grade students was selected randomly from the target population (representative of their peers in selected five cities) using a cluster sampling method by the Turkish Institute of Statistics: the selected five cities were considered as strata, and a one-stage cluster sampling was used where individual elementary schools were treated as clusters. Standard questionnaires, including all questions in the ISAAC Phase-II questionnaire modules, were self-completed by parents of students of the selected schools. Presence of current wheezing (CW) was investigated based on a positive answer to the question: “Has your child had wheezing or whistling in the chest in the past 12 months?” Rhinitis symptoms were investigated based on a positive answer to the question: “In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or the flu?” Current allergic rhinoconjunctivitis symptoms were evaluated as “positive” if both of the following questions were answered as “yes”: “In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or the flu?” and “In the past 12 months, has this nose problem been accompanied by itchy watery eyes?” Similarly, symptoms

for current eczema were studied on the basis of positive answers to two questions: “Has your child had this itchy rash at any time in the past 12 months?” and “Has this itchy rash at any time affected any of the following places: folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes.”

Skin Tests

All participants were skin prick tested (SPT) for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternata*, cat, grass mix (*Phleum pratense*, *Poa pratensis*, *Dactylis glomerata*, *Lolium perenne*, *Festuca pratensis*, and *Avena eliator*), tree mix (*Betula verrucosa*, *Alnus glutinosa*, and *Coryllus avellana*), *Olea europea*, horse, and *Blatella germanica*.⁹ Standardized core allergen extracts and controls were provided by Stallergenes (Antony, France), SPT was considered positive if the mean wheal diameter was ≥ 3 mm compared to control.

Flexural Dermatitis

Examination for flexural dermatitis was performed according to an illustrated manual and the presence of dermatitis signs was recorded for the following areas: around the eyes, sides/fronts of the neck, ankles and elbows, and antecubital and popliteal regions.⁹

Definition of Wheezing Phenotypes

A child was defined as AW when he/she was positive to one or more allergens on the SPT; otherwise, he/she was considered as NAW. FW was defined as having at least four wheezing episodes in the past year. RW and RCW were defined as having rhinitis and rhinoconjunctivitis in the past year, respectively, in addition to CW symptoms.

Investigation of Potential Risk Factors (Predictors)

Gender, birth weight, prematurity, history of parental asthma and/or allergic rhinitis, exposure to animal (pets and/or fur) in the first year of life and over the past year, exposure to smoke over the past year, history of maternal smoking during pregnancy and in the first year of life, dampness and mold in the house in the first year of life and over the past year, vaccination history, number of rooms in the house inhabited over the past year, number of household members in the first year of life and in the past year, presence of atopy, presence of flexural dermatitis, family income, duration of breastfeeding, time of weaning period, and number of older siblings were investigated as potential risk factors for CW (in general), and statistical analyses were repeated for individual phenotypes.

Ethical Issues

Written permissions were obtained from the Ethics Committees of the Hacettepe University Medical School, Ministry of Health, the central and provincial directors of the Ministry of Education, and city governors. Written informed consents were obtained from both the students and the parents.

Statistical Analysis

Statistical analyses included frequency and percent distributions, calculation of prevalence rates for wheezing phenotypes and potential risk factors, and group comparisons using chi-squared and Student's *t*-tests, as appropriate. Multivariate logistic regression (LR) models were used to identify significant predictors of CW and five individual phenotypes; adjusted odds ratios (ORs) and relevant 95% confidence intervals (CIs) are presented in tables. All potential risk factors found to be associated with CW in binary analyses and/or in the previous literature were compiled together in the "same" initial model for CW and five individual phenotypes, so that the comparisons between wheezing phenotypes could be made using a consistent approach. This initial model included all potential risk factors presented in Table 1, excluding "having a separate bedroom in the house (*n* was very small), and "the starting month for weaning." Final models were reached by *Backward LR* elimination method to identify the most parsimonious, yet statistically significant, explanatory model for each phenotype of interest, checking for the same set of potential risk factors. SPSS-15 statistical software package (SPSS, Inc., Chicago, IL) was used for the analyses; the *complex samples* module was used to obtain robust estimates, adjusting for the cluster sampling design used. All tables presented are based on weighted analyses, where weights are calculated as inverses of sampling fractions and completion rates.

RESULTS

A total of 70 schools and 244 classes were included in this study. A total of 7,623 questionnaires were distributed to children attending the fifth grade, 7,301 completed questionnaires were returned, and 6,963 accepted to be involved in the physical examination and for the laboratory tests. The overall rate of participation was 91.3% (from 87.0% to 94.4% in different cities). Flexural dermatitis examination and SPT were successfully performed in 79.0% (74.9–83.3% in the five selected cities) and 80.5% (75.2–85.7% in the five cities) of the eligibles, respectively. The average age ($\pm$ SEM) at the time of the survey was 10.8 years, and $50.9 \pm 1.0\%$ of the participants were male. The frequency of "self-reported CW" was $15.8 \pm 1.0\%$.

Results on Prevalence Estimates of Various Phenotypes

In the study population, the prevalence of wheezing phenotypes AW, NAW, FW, RW, and RCW were $2.9 \pm 0.3\%$, $11.3 \pm 0.9\%$, $3.5 \pm 0.4\%$, $10.3 \pm 0.7\%$, and $7.0 \pm 0.7\%$, respectively (Fig. 1).

Prevalence of Potential Risk Factors

Table 1 presents the frequency of the presence of various risk factors among children with different phenotypes of CW. Although some factors are common to all phenotypes, there are variations in relative frequencies across phenotypes. As examples, frequencies of male gender (51.5–56.3%), history of premature birth (2.6–8.2%), history of low birth weight (i.e., $<2,500$ g) (9.7–12.7%), presence of rhinoconjunctivitis (44.3–52.2%), exposure to smoke in the house over the past year (60.4–74.3%), history of maternal smoking during pregnancy (18.5–21.2%), presence of atopy (19.3–21.7%), average duration of breastfeeding (10.4–12.7 months), and history of living in a crowded house (>4 members in the household) over the past year (5.0–6.0%) varied among children with different phenotypes.

Symptoms of rhinoconjunctivitis (45.9%), rhinitis (67.3%) (data not shown), and atopic eczema (17.3%) were significantly common among children with CW. Mean duration of breastfeeding in children with RCW was 12.7 ± 0.7 months, whereas it was 11.2 ± 0.4 months in the CW group. Furthermore, prevalences of maternal asthma and/or allergic rhinitis were 43.5% and 54.7%, respectively, for children with CW and RCW (data not shown).

Risk Modeling of Various Wheezing Phenotypes

It was found that there were differences between risk factors of current wheezing and its phenotypes. Figure 2A presents the factors associated with CW. Rhinoconjunctivitis was significantly associated with CW, with an OR of 2.49 (2.10–2.95) [OR (95% CI)]. Male gender [1.37 (1.11–1.69)], history of parental asthma and/or rhinitis [1.71 (1.32–2.21)], presence of dampness and mold in the house lived in during the first year of life [1.51 (1.12–2.03)] and over the past year [1.98 (1.42–2.76)], living in a one room house [1.85 (1.21–2.82)], monthly family income of <350 US\$ [1.19 (1.03–1.37)], history of maternal smoking during pregnancy [1.53 (1.24–1.87)], exposure to smoke in the house over the past year [1.37 (1.08–1.74)], and presence of atopic dermatitis [2.04 (1.52–2.73)] were (all statistically) significant predictors of CW (Fig. 2A).

Nearly the same set of factors associated with CW was found to be statistically significantly associated with RW and RCW. Male gender [1.34 (1.10–1.62)], history of

TABLE 1—Distribution of Selected Personal, Family, and Health-Related Characteristics of Children Included in the Study by Presence of Current Wheezing and Individual Phenotypes of Current Wheezing

	No current wheezing	Current wheezing	Frequent (≥ 4) wheezing	Wheezing with rhinoconjunctivitis	Wheezing with rhinitis	Atopic wheezing	Non-atopic wheezing
Male gender ¹	49.62 $\pm$ 0.91	56.33 $\pm$ 2.33	51.45 $\pm$ 5.75	54.18 $\pm$ 2.99	56.31 $\pm$ 2.43	56.32 $\pm$ 6.59	54.98 $\pm$ 2.81
Premature birth ¹	4.22 $\pm$ 0.52	3.48 $\pm$ 0.95	4.58 $\pm$ 2.20	3.66 $\pm$ 1.37	3.93 $\pm$ 1.42	8.61 $\pm$ 3.44	2.62 $\pm$ 0.88
Low birth weight ¹	11.03 $\pm$ 0.89	11.38 $\pm$ 1.70	9.73 $\pm$ 2.57	11.80 $\pm$ 2.11	12.89 $\pm$ 2.21	10.61 $\pm$ 3.52	12.75 $\pm$ 1.97
History of allergic disease in either parent ¹	31.16 $\pm$ 1.04	49.70 $\pm$ 2.84	50.43 $\pm$ 4.40	62.12 $\pm$ 3.58	54.26 $\pm$ 3.42	49.61 $\pm$ 5.67	50.29 $\pm$ 3.16
Incomplete vaccination history ¹	18.96 $\pm$ 1.87	25.22 $\pm$ 2.61	36.46 $\pm$ 5.18	29.45 $\pm$ 3.59	28.54 $\pm$ 3.18	24.69 $\pm$ 4.17	26.54 $\pm$ 2.40
Having a separate bedroom in the house ¹	3.43 $\pm$ 0.62	7.38 $\pm$ 1.51	11.81 $\pm$ 3.97	7.62 $\pm$ 2.17	7.45 $\pm$ 1.88	8.09 $\pm$ 3.10	7.96 $\pm$ 1.59
Sharing current bedroom with someone else ¹	79.08 $\pm$ 1.96	80.85 $\pm$ 2.27	84.16 $\pm$ 2.60	85.65 $\pm$ 2.89	82.91 $\pm$ 2.42	76.15 $\pm$ 4.60	81.83 $\pm$ 2.45
History of sharing bedroom with someone in the first year of life ¹	87.79 $\pm$ 1.09	89.07 $\pm$ 1.27	94.81 $\pm$ 1.48	92.85 $\pm$ 1.47	90.01 $\pm$ 1.50	93.28 $\pm$ 2.11	87.20 $\pm$ 1.68
Current exposure to animals/pets ¹	46.10 $\pm$ 1.77	59.56 $\pm$ 3.95	62.26 $\pm$ 3.13	65.16 $\pm$ 2.85	62.68 $\pm$ 3.72	55.63 $\pm$ 6.65	62.17 $\pm$ 3.71
Exposure to animals/pets in the first year of life ¹	56.86 $\pm$ 1.32	68.53 $\pm$ 3.43	70.48 $\pm$ 4.00	75.96 $\pm$ 2.45	72.40 $\pm$ 2.95	63.71 $\pm$ 6.45	71.45 $\pm$ 2.81
Presence of mold or dampness in current house ¹	5.28 $\pm$ 0.49	14.54 $\pm$ 1.37	13.78 $\pm$ 2.71	18.17 $\pm$ 2.28	14.98 $\pm$ 1.95	8.87 $\pm$ 2.72	16.56 $\pm$ 1.65
Presence of mold/dampness in the house lived in during first year of life ¹	9.55 $\pm$ 0.59	20.12 $\pm$ 1.65	18.01 $\pm$ 3.38	23.36 $\pm$ 3.18	20.13 $\pm$ 2.80	19.84 $\pm$ 3.15	21.17 $\pm$ 1.83
Family monthly income of <350 US\$ ¹	42.21 $\pm$ 4.11	53.74 $\pm$ 4.39	67.81 $\pm$ 5.20	61.11 $\pm$ 4.82	58.47 $\pm$ 4.52	52.76 $\pm$ 5.71	55.95 $\pm$ 4.74
History of maternal smoking in the first year of life ¹	17.22 $\pm$ 1.13	22.36 $\pm$ 1.62	23.76 $\pm$ 3.69	25.04 $\pm$ 2.64	23.92 $\pm$ 1.79	21.45 $\pm$ 2.92	22.98 $\pm$ 2.51
History of maternal smoking during pregnancy ¹	11.48 $\pm$ 0.75	18.49 $\pm$ 1.38	21.11 $\pm$ 3.87	21.17 $\pm$ 2.41	20.88 $\pm$ 1.89	18.61 $\pm$ 3.33	18.62 $\pm$ 1.85
Exposure to smoking inside current house ¹	57.43 $\pm$ 1.11	67.76 $\pm$ 2.40	69.00 $\pm$ 5.34	74.34 $\pm$ 2.52	71.64 $\pm$ 2.66	60.43 $\pm$ 5.31	71.62 $\pm$ 2.48
Current rhinoconjunctivitis ¹	19.28 $\pm$ 0.95	45.90 $\pm$ 2.48	52.21 $\pm$ 4.52		68.24 $\pm$ 2.57	44.34 $\pm$ 4.62	46.37 $\pm$ 2.95
Current atopic eczema ¹	6.40 $\pm$ 0.32	17.31 $\pm$ 1.73	21.99 $\pm$ 4.59	21.90 $\pm$ 2.62	19.21 $\pm$ 2.05	14.00 $\pm$ 3.04	18.77 $\pm$ 1.88
Presence of flexural dermatitis ¹	3.74 $\pm$ 0.55	3.06 $\pm$ 0.56	4.00 $\pm$ 1.66	2.64 $\pm$ 0.90	3.41 $\pm$ 0.84	1.90 $\pm$ 0.64	3.13 $\pm$ 0.66
Presence of atopy (>3 mm) ¹	18.63 $\pm$ 1.35	20.50 $\pm$ 2.21	21.66 $\pm$ 3.05	19.30 $\pm$ 2.46	18.07 $\pm$ 1.53		
Duration of breastfeeding (in months) ²	11.64 $\pm$ 0.23	11.20 $\pm$ 0.44	10.43 $\pm$ 0.51	12.67 $\pm$ 0.70	11.60 $\pm$ 0.53	10.59 $\pm$ 0.82	11.62 $\pm$ 0.55
Starting month for weaning ²	5.83 $\pm$ 0.09	6.11 $\pm$ 0.14	6.14 $\pm$ 0.37	6.44 $\pm$ 0.25	6.16 $\pm$ 0.22	5.94 $\pm$ 0.21	6.20 $\pm$ 0.17
Number of household members in current house ²	5.01 $\pm$ 0.09	5.29 $\pm$ 0.13	5.93 $\pm$ 0.21	5.47 $\pm$ 0.14	5.33 $\pm$ 0.13	5.04 $\pm$ 0.23	5.37 $\pm$ 0.13
Number of household members in the house lived in during infancy ²	5.03 $\pm$ 0.11	5.40 $\pm$ 0.13	6.00 $\pm$ 0.22	5.74 $\pm$ 0.15	5.53 $\pm$ 0.14	5.00 $\pm$ 0.25	5.50 $\pm$ 0.15
Number of older siblings ²	1.17 $\pm$ 0.06	1.36 $\pm$ 0.08	1.65 $\pm$ 0.16	1.46 $\pm$ 0.10	1.37 $\pm$ 0.08	1.24 $\pm$ 0.16	1.36 $\pm$ 0.08

¹Percentages $\pm$ SEM.²Mean $\pm$ SEM.

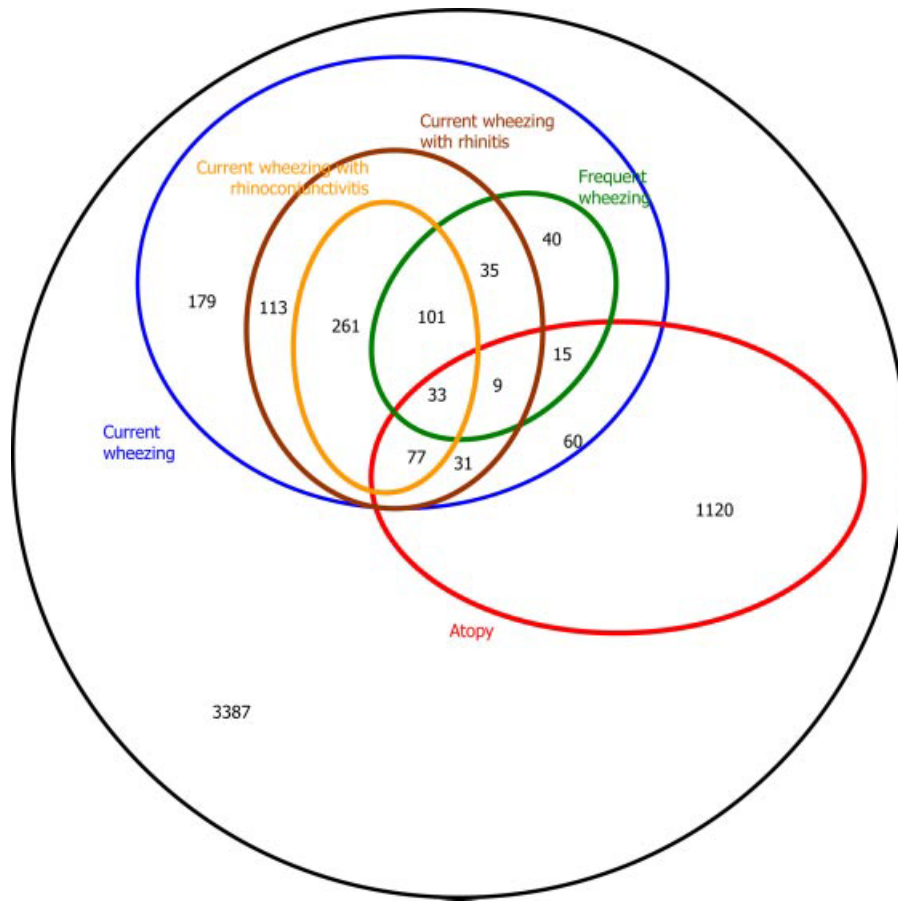


Fig. 1. Number of children with current wheezing and individual phenotypes in the study group (calculations were performed on 5,461 individuals with complete set of data). —, Current wheezing; —, wheezing with rhinitis; —, wheezing with rhinoconjunctivitis; —, frequent wheezing; —, atopy; and —, study population.

parental asthma and/or rhinitis [2.26 (1.72–2.97)], presence of dampness and mold in the house lived in during the first year of life [1.61 (1.06–2.43)] and over the past year [1.95 (1.29–2.94)], living in a one room house [2.04 (1.30–3.19)], monthly family income of <350 US\$ [1.54 (1.25–1.90)], history of maternal smoking during pregnancy [1.85 (1.37–2.52)], exposure to smoke in the house over the past year [1.74 (1.27–2.39)], and presence of atopic dermatitis [2.71 (2.03–3.61)] were associated with RW. History of parental asthma and/or rhinitis [3.23 (2.25–4.63)], presence of dampness and mold in the house lived in during the first year of life [2.03 (1.30–3.17)] and over the past year [2.18 (1.37–3.48)], living in a one room house [2.13 (1.15–3.93)], monthly family income of <350 US\$ [1.65 (1.25–2.18)], history of maternal smoking during pregnancy [1.88 (1.28–2.77)], exposure to smoke in the house over the past year [2.04 (1.43–2.91)], and presence of atopic dermatitis [2.76 (1.88–4.06)] were associated with RCW. Additionally, duration of breastfeeding [1.02 (1.00–1.03)] per additional month was found to be independent risk factors for RCW (Fig. 2B,C).

Some risk factors of CW, such as male gender, presence of dampness and mold in the house lived in during the first year of life, number of rooms in the current house, exposure to maternal smoking, and presence of atopic dermatitis were not found as significant predictors of FW. However, history of parental asthma and/or rhinitis [1.78 (1.23–2.56)], presence of dampness and mold in the house lived over the past year [2.21 (1.28–3.81)], monthly family income of <350 US\$ [2.00 (1.32–3.04)], presence of rhinoconjunctivitis [3.56 (2.62–4.86)], and number of household members [1.14 (1.08–1.21)] were associated with FW (Fig. 2D).

History of asthma and/or rhinitis in either parent [1.87 (1.13–3.11)], exposure to maternal smoking during pregnancy [1.72 (1.05–2.83)], and coexistence of rhinoconjunctivitis [2.95 (2.02–4.32)] were found to be statistically significantly associated with AW, while history of premature birth increased the odds ratio of AW 2.08 (1.05–4.13) times (Fig. 2E). Male gender [1.26 (1.00–1.59)], rhinoconjunctivitis [2.49 (2.10–2.95)], history of parental asthma and/or rhinitis [1.74 (1.30–2.32)], presence of dampness and mold in the house lived

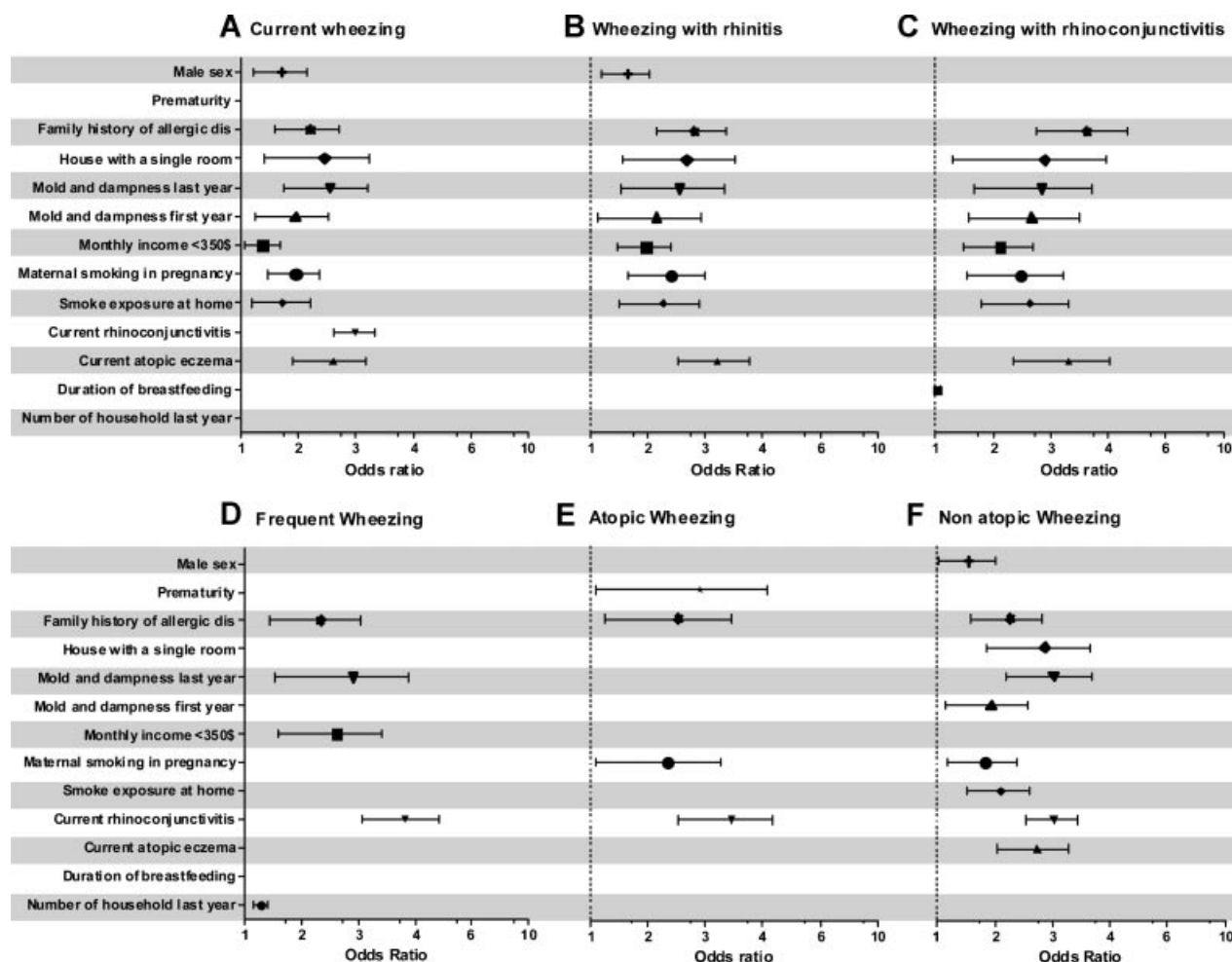


Fig. 2. Risk factors of current wheezing and different wheezing phenotypes. A: Current wheezing; (B) wheezing with rhinitis; (C) wheezing with rhinoconjunctivitis; (D) frequent wheezing; (E) atopic wheezing; and (F) non-atopic wheezing.

in during the first year of life [1.48 (1.06–2.08)] and over the past year [2.44 (1.73–3.44)], living in a one room house [2.24 (1.48–3.39)], history of maternal smoking during pregnancy [1.43 (1.08–1.89)], exposure to smoke in the house over the past year [1.63 (1.28–2.09)], and presence of atopic dermatitis [2.16 (1.63–2.88)] were all statistically significant predictors of NAW. The same risk factors found to be associated with CW were also found significantly associated with NAW, except low family monthly income (Fig. 2F).

DISCUSSION

The most important asset of this study to a priori literature on CW among school children is the finding that different phenotypes of CW might be associated with different personal or environmental characteristics. The most consistent and significant predictors of CW were identified as male gender, presence of allergic rhinitis and/or asthma in either parent, exposure to smoke, presence of rhinoconjunctivitis or atopic dermatitis, and parental

report of presence of dampness or mold in the house. Neither atopy nor flexural dermatitis was found to be associated with any phenotype of CW.

Atopic wheezing was found to exist in 2.9% of the study population, corresponding to 20.5% of all CW cases. In ISAAC Phase-II studies in other countries, prevalence of atopic wheezing was found to range between 0.2% and 13.4% and prevalence of AW increases in parallel to the developmental status of countries.⁷ Relatively low prevalence of AW in our study can be explained by level of developmental status in our country.

Risk Factors of CW

Male gender was a significant risk factor for CW and this could be due to our a priori knowledge that the risk of wheezing is higher in boys than girls especially in the first 10 years of life because of their narrower airways.¹¹

Family history is known to be the most important risk factor for allergic diseases in childhood and was appeared to be a consistent risk factor for all wheezing phenotypes

studied in our population. Although a Mendelian inheritance does not exist, presence of allergic diseases in parents increases the risk of allergic diseases in their children.¹² Furthermore, asthma prevalence is higher in monozygotic twins than in dizygotics, and twin studies suggest that approximately 60% of susceptibility is due to genetic factors.¹³

Several longitudinal and cross-sectional studies have reported that prenatal and postnatal exposure to smoke increased risk of wheezing and asthma in childhood independently.¹⁴ In our study, exposure to smoke during pregnancy and past 1 year were found as independent risk factors for CW. Smoke may cause such conditions by leading to premature birth, underdevelopment of the lung in prenatal period and increase of bronchial hyper-reactivity in postnatal period.^{15,16}

In this study, presence of rhinoconjunctivitis was found to be an independent risk factor for CW, as shown in the previous reports.¹⁷ This situation can be explained by coexistence of asthma and allergic rhinitis, similarities in histological structures, inflammatory mechanisms, and anatomical proximity.¹⁸

Presence of mold and dampness, based on parental self-reports, was found to be a significant risk factor for CW, regardless of the time of exposure (i.e., during the first year of life or over the past year). Mold and dampness are known to promote bacterial and house dust mite growth, and release of volatile organic compounds (VOCs), may irritate respiratory systems.¹⁹ It is thought that exposure to mold and dampness in the house in the first year of life may lead to development of CW through release of endotoxins. Repeated exposure to endotoxins might induce Th cell type switching from Th1 to Th2.²⁰ Exposure to mold and dampness over the past year may cause bronchial hyper-reactivity through VOCs and endotoxins leading to CW.²¹

Low family monthly income, living in a one room house are known to be indicators of low socioeconomic status (SES), were found to increase the chance of CW. Previous studies have also suggested that morbidity and mortality of asthma are both higher among children with lower SES²² through its association with passive smoking, low birth weight, presence of mold and dampness in the house, indoor air pollution, frequent infections, cockroach exposure, and/or obesity.²³

Differences of Wheezing Phenotypes

Prevalence of rhinoconjunctivitis was thought to reflect prevalence of allergic rhinitis better than prevalence of rhinitis.²⁴ Therefore, RCW was accepted as a separate phenotype and separate statistical analyses were conducted for this particular phenotype and it was found that increase in duration of breastfeeding was a risk factor for only this phenotype. Sears et al.²⁵ found that duration of breastfeeding increases the prevalence of atopy and

asthma, independent of the family history of asthma and allergic rhinitis. Kuyucu et al.²⁶ revealed that the association between duration of breastfeeding and presence of atopy in children varies with the atopic status of the mother: atopy risk in children decreases only in situations where the mother is non-atopic and breastfeeds her child for long periods. Review of ISAAC Phase-II studies revealed that breastfeeding was generally not associated with allergy; the protective effect of it from wheezing was different in rich and poor countries; and its effect on wheezing was associated with wheezing phenotype.²⁷ Accordingly, the association between breastfeeding duration and RCW in our study population is likely to be explained by the confounding effect of atopic disease in the mothers, rather than the duration of breastfeeding per se.

High number of household members living in the house was found to be a risk factor for only FW. Most striking finding differentiating FW from AW and NAW was the dominance of unfavorable environmental factors (low monthly income, mold and dampness, and crowd). Living under unfavorable environmental condition may lead to FW by increasing risk of exposure to triggers of wheezing.⁸ This result suggests that unfavorable environmental conditions affect frequency of wheezing in addition to development of wheezing.

Premature birth was a predictor of AW. The literature provides some evidence, although inconclusive, on the association between premature birth and asthma. In a meta-analysis published in 2006, preterm birth was found to increase the risk of asthma by 1.07 (1.07–1.08) and was linked with immaturity of the lungs and environmental factors, although the biological basis for such a link has not been completely explained.²⁸ Late effects of prematurity on the immune system are not fully understood, either. The response of an immune system to environmental factors could be different due to maturity of the immune system and, thus, immaturity of immune system could lead to atopic wheezing in children with history of premature birth.

Atopy in premature children could also be explained by the hygiene hypothesis: given that such children are more likely to be overprotected and to be raised in more hygienic environments than their full gestational counterparts. No environmental risk factor, except for maternal smoking during pregnancy, has been indicated as a significant risk factor for AW, suggesting that development of AW may stem from the intrauterine period.

In our population, factors identified as risk factors for NAW were similar to those identified for CW, except for low family monthly income. This finding could be, at least partially, explained by the fact that almost 80% of our participants with CW were non-atopic.

When risk factors of AW and NAW are compared it is recognized that AW is more likely to have genetic

predictors, whereas NAW is linked with both genetic and environmental factors. Similarly, clinical features and risk factors of AW and NAW were previously reported to be different from each other.^{29–31}

Strengths and Limitations of the Study

As a limitation of the study, data were mainly based on parental self-reports and atopy was the only objective marker used to confirm the symptoms. Also, the cross-sectional design of the study limits its ability to study temporality assumption for the associations studied. Given that no standard classification is available for wheezing phenotypes in children of this age, we classified phenotypes based on daily practices of pediatric allergy professionals. In order to minimize this limitation, we referred to expert panel opinion in classifying wheezing phenotypes.

On the other hand, the study stands as an asset to allergic disease literature in the sense that data were obtained from a multicenter study, representing the general childhood population, had a high response rate, used internationally proven methods, and provided objective evidence from SPT.

This study is novel in its approach to investigate risk factors of CW by modeling risk factors of individual CW phenotypes in childhood. Significance of different phenotypes has gained popularity in approaching individuals with asthma and recently, the concept of phenotype-specific treatment modalities was proposed.^{32,33} Our findings suggest that, besides common predictors of CW, some factors could have higher/lower impact on development of some phenotypes rather than the others. Future studies are clearly warranted to clarify this issue.

CONCLUSION

In this study, parental asthma and/or allergic rhinitis and coexistence of rhinoconjunctivitis were the most consistent and significant predictors for CW and its different phenotypes among school-aged children. As a remarkable finding, different wheezing phenotypes seemed to have different risk factors. Identification of phenotype-specific risk factors for CW in children has the potential to offer a novel solution for primary prevention and/or treatment of CW.

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