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Synergistic effect of multiple indoor allergen sources on atopic symptoms in primary school children[☆]

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Abstract

Accumulating data show that the complex modern indoor environment contributes to increasing prevalence of atopic diseases. However, the dose–response relationship between allergic symptoms and complexity of indoor environmental allergen sources (IEAS) has not been clearly evaluated before. Therefore, we designed this study to investigate the overall effect of multiple IEAS on appearance of asthma (AS), allergic rhinitis (AR), and eczema (EC) symptoms in 1472 primary school children. Among various IEAS analyzed, only stuffed toys, cockroaches, and mold patches fit the model of ‘more IEAS, higher odds ratio (OR) of association’. The association of IEAS and AR increased stepwise as more IEAS appeared in the environment (1.71, 2.47, to 2.86). In AS and EC, the association was significant only when all three IEAS were present (1.42, 1.98, to 4.11 in AS; 1.40, 1.76, to 2.95 in EC). These results showed that different IEAS had a synergistic effect on their association with atopic symptoms and also suggest that there is a dose–response relationship between kinds of IEAS and risk of appearance of atopic diseases.

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1. Introduction

Over the past 40 years, the morbidity and prevalence of asthma (AS) have progressively increased, and many reports on the association between AS and common indoor environmental allergens have been published (Davies et al., 1998; Liccardi et al., 2001; Lamphear et al., 2001). Indeed, there are good reasons for considering a causal relationship between exposure to indoor environmental allergens and AS. Studies from England, Australia, France, Denmark, the United States, and Germany have all demonstrated that children growing up in houses with greater than 2 µg of Group I mite allergen per gram of dust are at risk for developing positive skin-test responses and serum IgE antibodies (Korsgaard, 1983; Lau et al., 1985; Palmer et al., 1999).

On the other hand, several groups have failed to find a clear dose–response relationship between symptoms of AS and current exposure to indoor allergens (Platts-Mills et al., 1995; Lau et al., 2000).

The majority of atopic children are sensitized to more than one allergen, and a graded effect has been observed with the risk of atopic disease in the child increasing with the number of positive skin-prick-test reactions (Wang and Chen, 1992; Arshad et al., 2001). Unfortunately, few have explored the effect of interaction of various indoor environmental allergen sources (IEAS) on the appearance of atopic symptoms. We hypothesized that there must be such interaction, and explored with the following study.

2. Material and methods

We selected one of the primary schools from the list afforded by the Educational Department of the Government of Kaohsiung City. All students in Grades 2–5

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without any major systemic disease were included in this study. After watching the videotape of symptoms and signs of typical atopic diseases, all children answered the questionnaire of self-reported symptoms. Later, parents were requested to answer another more detailed structural questionnaire, which, as well as signed informed consent, was collected by teachers of the school. In this questionnaire, the parents confirmed the self-reported symptoms of their children and also reported whether there were any doctor-diagnosed atopic diseases. All of these questionnaires were collected in 2 weeks. The study was reviewed and approved by the Institution of Review Board of the National Health Research Institute in Taiwan.

2.1. Parameters assessed in the questionnaire

The questionnaire had three parts: part 1 was the demographic data, which included date of birth, sex, age, grade, and education level of the parents; part 2 was the adopted Revised Chinese edition of the ISAAC questionnaire (Committee TISOAaAiCIS, 1998); part 3 contained questions about the IEAS of each home. Symptoms and disease status in the previous 12 months were assessed from the core ISAAC questionnaires. Symptoms of AS, allergic rhinitis (AR), and eczema (EC) in the past 12 months were defined as positive responses to selected questions. If the student visited a physician because of these symptoms and was diagnosed as having atopic diseases, then this student was classified as having “doctor-diagnosed” atopic symptoms. Parents of the children completed information regarding the IEAS. The data collected were presence of stuffed toys, cockroaches, mold patches, floor blankets, passive tobacco smoking exposure, and exposure to incense.

2.2. Statistical analysis

The primary dependent variables in this analysis were atopic symptoms and doctor-diagnosed atopic symptoms of AS, AR, and EC. Initially, χ^2 test models were used to analyze the association of each IEAS with the appearance of each atopic symptom. Next, generalized linear models (logistic regression) were used to analyze the adjusted effect of each IEAS with the appearance of each atopic symptom. Finally, a logistic model was designed to analyze the synergistic effect of various IEAS on their association with various atopic symptoms.

3. Results

3.1. Response rates to the questionnaires

One thousand five hundred ninety-eight questionnaires were delivered to the 7- to 12-year-old students in the school. Responses were obtained from parents of

Table 1

Frequencies of questionnaire-based variables in the study population ($n = 1452$)

	<i>n</i> =	%
Sex		
Male	764	52.6
Female	688	47.4
Atopic symptoms		
Asthma symptoms in past 12 months (Yes)	122	8.4
Doctor-diagnosed asthma symptoms in the past 12 months (Yes)	71	4.9
Allergic rhinitis symptoms in past 12 months (Yes)	579	39.8
Doctor-diagnosed allergic rhinitis symptoms in the past 12 months (Yes)	420	28.9
Eczema symptoms in past 12 months (Yes)	103	7.1
Doctor-diagnosed eczema symptoms in past 12 months (Yes)	60	4.1
Allergen sources		
Stuffed toys in bedroom (Yes)	718	49.4
Cockroach around home (Yes)	496	34.1
Visible mold patches at home (Yes)	160	11.0
Blanket on bedroom floor (Yes)	234	16.1
Passive cigarette smoke exposure (Yes)	746	51.3
Exposure to incense (Yes)	548	37.7

1566 children (97.99%). We further excluded 114 participants with missing values on the questions of atopic diseases. Hence, 1452 (90.86%) students were included in the final analysis.

3.2. Dichotomous outcome of atopic diseases

Among the eligible 1452 students, 122 (8.4%) reported symptoms of AS, 579 (39.8%) reported symptoms of AR, and 103 (7.1%) reported symptoms of EC in the 12 months before this investigation (Table 1).

Compared to the rate of self-reported symptoms, the numbers of doctor-diagnosed atopic symptoms were significantly less: 71 (4.9%) for AS, 420 (28.9%) for AR, and 60 (4.1%) for EC (Table 1).

3.3. Frequencies of IEAS

Frequencies of presence of various IEAS in the house of these students were stuffed toys, 49.4%; cockroaches, 34.1%; mold patches, 11.0%; floor blankets, 16.1%; passive cigarette smoke exposure, 51.3%; and incense exposure, 37.7% (Table 1).

3.4. Analysis of risk factors for atopic symptoms in recent 12 months (χ^2 model)

Table 2 shows the result of bivariate association analysis of atopic symptoms with IEAS, analyzed with

χ^2 model without adjustments for other risk factors. Significant IEAS associated with AS symptoms were stuffed toys (OR = 1.64, 95% CI = 1.12–2.39) and mold patches (OR = 1.66, 95% CI = 1.00–2.76), while the only IEAS significantly associated with doctor-diagnosed AS symptoms was stuffed toys (OR = 1.82, 95% CI = 1.11–2.96). Significant IEAS associated with AR symptoms were stuffed toys (OR = 1.81, 95% CI = 1.40–2.34), cockroaches (OR = 1.66, 95% CI = 1.28–2.15), mold patches (OR = 2.13, 95% CI = 1.50–3.02), and floor blankets (OR = 1.50, 95% CI = 1.09–2.06). Those IEAS associated with doctor-diagnosed AR symptoms were stuffed toys (OR = 1.80, 95% CI = 1.36–2.37), cockroaches (OR = 1.63, 95% CI = 1.24–2.15), mold patches (OR = 2.02, 95% CI = 1.40–2.93), and floor blankets (OR = 1.57, 95% CI = 1.12–2.20). IEAS significantly associated with EC symptoms were stuffed toys (OR = 1.90, 95% CI = 1.26–2.87) and cockroaches (OR = 1.16, 95% CI = 1.07–2.40). No IEAS was significantly associated with doctor-diagnosed EC symptoms.

3.5. Atopic symptoms associated environmental factors after adjustment (multivariate logistic regression model)

The association of IEAS and atopic symptoms were then analyzed with multivariate logistic regression model to adjust other potential confounding factors (Tables 3–5). Stuffed toys was the only IEAS related to AS symptoms (OR = 1.60, 95% CI = 1.80–2.37) and to the doctor-diagnosed AS symptoms (OR = 1.80, 95% CI = 1.08–3.00) (Table 2). Stuffed toys (OR = 1.65, 95% CI = 1.33–2.06) and mold patches (OR = 1.44, 95% CI = 1.02–2.05) were related to AR symptoms. Stuffed toys (OR = 1.71, 95% CI = 1.34–2.17), cockroaches (OR = 1.27, 95% CI = 1.00–1.62), and mold patches (OR = 1.48, 95% CI = 1.03–2.12) were related to doctor-diagnosed AR symptoms. Cockroach (OR = 1.90, 95% CI = 1.23–2.92) was the only significant environmental factor related to EC symptoms, and no significant environmental factor was found to relate to doctor-diagnosed EC.

3.6. Synergistic effect of presence of multiallergen sources (stuffed toys, cockroaches, and mold patches) on their relationship to atopic symptoms

The interaction of various IEAS was analyzed, while only stuffed toys, cockroaches, and mold patches had the synergistic effect of increasing the association with atopic symptoms. The interaction of stuffed toys, cockroaches, and mold patches on the appearance of various atopic symptoms was analyzed and is shown in Table 6 and Figs. 1–6. In AR (1.86 of one, 2.42 of two, to 3.41 of three IEAS), doctor-diagnosed AR (1.71, 2.47, to 2.86), and EC symptoms (1.56, 2.22, to 4.03), the

Table 2
Bivariate association of atopic disease symptoms in recent 12 months with various IEAS

	Asthma symptoms		Doctor-diagnosed asthma symptoms		Allergic rhinitis symptoms		Doctor-diagnosed allergic rhinitis symptoms		Eczema symptoms		Doctor-diagnosed eczema symptoms	
	<i>n</i> = 122	<i>P</i> -value* OR* 95% CI*	<i>n</i> = 71	<i>P</i> -value* OR* 95% CI*	<i>n</i> = 579	<i>P</i> -value* OR* 95% CI*	<i>n</i> = 420	<i>P</i> -value* OR* 95% CI*	<i>n</i> = 103	<i>P</i> -value* OR* 95% CI*	<i>n</i> = 60	<i>P</i> -value* OR* 95% CI*
Stuffed toys	0.01	1.64 1.12–2.39	0.01	1.82 1.11–2.96	0.001	1.81 1.40–2.34	0.001	1.80 1.36–2.37	0.002	1.90 1.26–2.87	0.16	1.45 0.86–2.48
Cockroaches	0.28	1.23 0.84–1.80	0.08	1.52 0.94–2.46	0.001	1.66 1.28–2.15	0.001	1.63 1.24–2.15	0.02	1.56 1.07–2.40	0.12	1.50 0.89–2.52
Mold patches	0.04	1.66 1.00–2.76	0.10	1.69 0.89–3.20	0.001	2.13 1.50–3.02	0.001	2.02 1.40–2.93	0.06	1.66 0.96–2.87	0.06	1.87 0.96–3.64
Floor blankets	0.54	1.16 0.71–1.88	0.88	0.95 0.49–1.84	0.01	1.50 1.09–2.06	0.008	1.57 1.12–2.20	0.65	0.88 0.49–1.54	0.81	0.91 0.44–1.88
Passive cigarette smoke	0.31	1.21 0.83–1.75	0.53	1.16 0.07–1.87	0.82	0.97 0.75–1.25	0.36	0.88 1.67–1.15	0.22	0.78 0.52–1.16	0.31	0.76 0.45–1.28
Exposure to incense	0.32	0.82 0.55–1.21	0.14	0.68 0.40–1.14	0.22	0.86 0.66–1.21	0.16	0.81 0.61–1.08	0.30	0.80 0.52–1.22	0.07	0.58 0.33–1.04

*Analyzed with χ^2 test; the SAS system under Microsoft Windows.

Table 3

Bivariate association of asthma and physician-confirmed asthma symptoms in recent 12 months with three major IEAS

	Asthma symptoms						Doctor-diagnosed asthma symptoms					
	Yes	No	OR ^a	95% CI	AOR ^b	95% CI	Yes	No	OR ^a	95% CI	AOR ^b	95% CI
Stuffed toys												
No (<i>n</i>)	48	686	1.00		1.00		26	708	1.00		1.00	
Yes (<i>n</i>)	74	644	1.64	1.12–2.39	1.60	1.08–2.37	45	673	1.82	1.11–2.96	1.80	1.08–3.00
Cockroaches												
No (<i>n</i>)	75	881	1.00		1.00		40	916	1.00		1.00	
Yes (<i>n</i>)	47	449	1.23	0.84–1.80	1.11	0.75–1.66	31	465	1.52	0.94–2.46	1.40	0.85–2.31
Mold patches												
No (<i>n</i>)	102	1190	1.00		1.00		59	1233	1.00		1.00	
Yes (<i>n</i>)	20	140	1.66	1.00–2.76	1.56	0.90–2.69	12	148	1.69	0.89–3.20	1.55	0.78–3.09

^a Analyzed with χ^2 test; the SAS system under Microsoft Windows.^b Adjusted OR, adjusted for sex, stuffed toys, cockroaches, mold patches, floor blankets, passive cigarette smoke, and exposure to incense. Analyzed with multivariate logistic regression model; the SAS system under Microsoft Windows.

Table 4

Association of allergic rhinitis and doctor-diagnosed allergic rhinitis symptoms in recent 12 months with three major IEAS

	Allergic rhinitis symptoms						Physician-confirmed allergic rhinitis symptoms					
	Yes	No	OR ^a	95% CI	AOR ^b	95% CI	Yes	No	OR ^a	95% CI	AOR ^b	95% CI
Stuffed toys												
No (<i>n</i>)	242	492	1.00		1.00		166	568	1.00		1.00	
Yes (<i>n</i>)	337	381	1.79	1.45–2.22	1.65	1.33–2.06	254	464	1.80	1.48–2.35	1.71	1.34–2.17
Cockroaches												
No (<i>n</i>)	357	599	1.00		1.00		252	704	1.00		1.00	
Yes (<i>n</i>)	222	274	1.35	1.09–1.69	1.22	0.97–1.53	168	328	1.43	1.13–1.80	1.27	1.00–1.62
Mold patches												
No (<i>n</i>)	495	797	1.00		1.00		354	938	1.00		1.00	
Yes (<i>n</i>)	84	76	1.78	1.28–2.46	1.44	1.02–2.05	66	94	1.862	1.33–2.59	1.48	1.03–2.12

^a Analyzed with χ^2 test; the SAS system under Microsoft Windows.^b Adjusted OR, adjusted for sex, stuffed toys, cockroaches, mold patches, floor blankets, passive cigarette smoke, and exposure to incense. Analyzed with multivariate logistic regression model; the SAS system under Microsoft Windows.

odds ratio (OR) increased stepwise as the number of IEAS increased. In AS (1.61, 1.67, to 3.13), physician-confirmed AS (1.42, 1.98, to 4.11), and doctor-diagnosed EC symptoms (1.40, 1.76, to 2.95), the OR increased stepwise and became significant only when all three IEAS were present in the environment.

4. Discussion

Our results showed that the presence of multiple allergen sources in the indoor environment might greatly increase the association of IEAS with atopic symptoms. Stuffed toys, cockroaches, and mold patches had the synergistic effect of increasing this association, while floor blankets, passive cigarette smoke, and exposure to incense did not have such an effect.

Mite allergens accumulate rapidly in stuffed toys, and because stuffed toys are often kept in close proximity to children, they form a potentially important source of mite-allergen exposure (Nagakura et al., 1996). Mites are a well-known allergen to sensitized atopic patients and induce respiratory atopic symptoms. In our study and those of others, it is the most common allergen in asthmatic children (Wang and Chen, 1992; Boner et al., 2002; Fernandez-Caldas, 2002). A recent study from Taiwan demonstrated exposure to mite allergen concentration of over 1 $\mu\text{g/g}$ of dust was associated with a higher incidence of atopic dermatitis (Huang et al., 2001). Holm et al. also found that use of polyurethane-coated cotton encasings for bedding decreased the EC severity of atopic dermatitis patients (Holm et al., 2001).

Cockroach is another common aeroallergen in Taiwan. According to Tsai et al. 39.6% and 36.4% of

Table 5

Association of eczema and doctor-diagnosed eczema symptoms in recent 12 months with three major IEAS

	Eczema symptoms						Physician-confirmed eczema symptoms					
	Yes	No	OR ^a	95% CI	AOR ^b	95% CI	Yes	No	OR ^a	95% CI	AOR ^b	95% CI
Stuffed toys												
No (<i>n</i>)	37	697			1.00		25	709	1.00		1.00	
Yes (<i>n</i>)	66	652	1.90	1.26–2.87	1.90	1.23–2.92	35	683	1.45	0.86–2.48	1.39	0.80–2.39
Cockroaches												
No (<i>n</i>)	57	899			1.00		34	922	1.00		1.00	
Yes (<i>n</i>)	46	450	1.56	1.07–2.40	1.44	0.94–2.20	26	470	1.50	0.89–2.52	1.33	0.77–2.30
Mold patches												
No (<i>n</i>)	86	1206			1.00		49	1243	1.00		1.00	
Yes (<i>n</i>)	17	143	1.66	0.96–2.87	1.45	0.81–2.62	11	149	1.87	0.96–3.64	1.70	0.82–3.50

^a Analyzed with χ^2 test; the SAS system under Microsoft Windows.^b Adjusted OR, adjusted for sex, stuffed toys, cockroaches, mold patches, floor blankets, passive cigarette smoke, and exposure to incense. Analyzed with multivariate logistic regression model; the SAS system under Microsoft Windows.

Table 6

Synergistic effect of various IEAS on their relationship to atopic symptoms within 12 months of analysis

Kinds of allergen source exposed to	Asthma symptoms	Doctor-diagnosed asthma symptoms	Allergic rhinitis symptoms	Doctor-diagnosed allergic rhinitis symptoms	Eczema symptoms	Doctor-dignosed Eczema symptoms
	Odds Ratio ^a	Odds Ratio ^a	Odds Ratio ^a	Odds Ratio ^a	Odds Ratio ^a	Odds Ratio ^a
	95% C.I. ^a	95% C.I. ^a	95% C.I. ^a	95% C.I. ^a	95% C.I. ^a	95% C.I. ^a
No allergen present in home environment	1.00	1.00	1.00	1.00	1.00	1.00
One allergen present in home environment	1.61 0.99–2.58	1.42 0.76–2.66	1.86 1.34–2.59	1.71 1.20–2.45	1.56 0.92–2.65	1.40 0.72–2.73
Two allergens present in home environment	1.67 0.94–2.95	1.98 0.97–4.02	2.62 1.79–3.84	2.47 1.64–3.70	2.22 1.22–4.03	1.76 0.82–3.80
Three allergens present in home environment	3.13 1.40–7.01	4.11 1.57–10.78	3.41 1.89–6.10	2.86 1.54–5.31	4.03 1.74–9.22	2.95 1.01–8.51

^a Adjusted OR, adjusted for sex, stuffed toys, cockroaches, mold patches, floor blankets, passive cigarette smoke, and exposure to incense. Analyzed with multivariate logistic regression model; the SAS system under Microsoft Windows.

asthmatic patients were hypersensitive to American and German cockroaches (Tsai et al., 1998). Besides respiratory atopic symptoms, our data also showed indoor cockroaches to be significantly associated with EC symptoms. This result is consistent with the studies of Wananukul et al. and Roul et al. In Wananukul's study, over 50% of atopic dermatitis patients had positive patch testing to mite, cockroach, or mold mix (Wananukul et al., 1993). In Roul's study, 41 of 146 children with atopic dermatitis had a positive reaction to cockroach allergen. This evidence showed that elimination of cockroaches from the indoor environment should be proposed for children with atopic dermatitis (Roul et al., 2001).

A significantly higher level of airborne fungi was found in our city than in the north part of Taiwan.

Airborne fungi were common in living rooms and bedrooms, and the dominant indoor fungus was *Cladosporium* (Wu et al., 2000; Li et al., 1995). Visible mold and the resulting airborne fungi might induce airway inflammatory responses when inhaled. In our study, mold patches were associated with AS symptoms (OR = 1.67), AR symptoms (OR = 2.13), and physician-confirmed AR symptoms (OR = 2.02).

The last significant indoor environmental factor was floor blankets. The floor blanket is also a major source of mite, especially in a damp environment. It is significantly associated with AR (OR = 1.50) and physician-confirmed AR-like (OR = 1.57) symptoms in our study.

The synergistic effect of stuffed toys, cockroaches, and mold patches has not been reported before. We

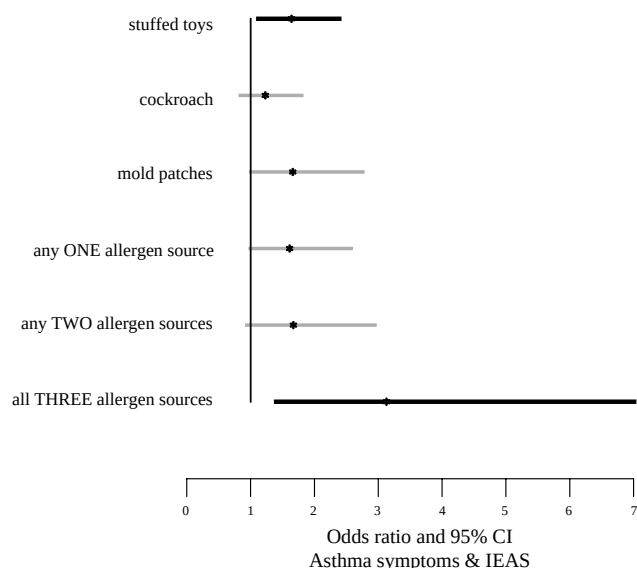


Fig. 1. Association of AS symptoms with three major IEAS separately and in combinations (shown in OR and 95% CI).

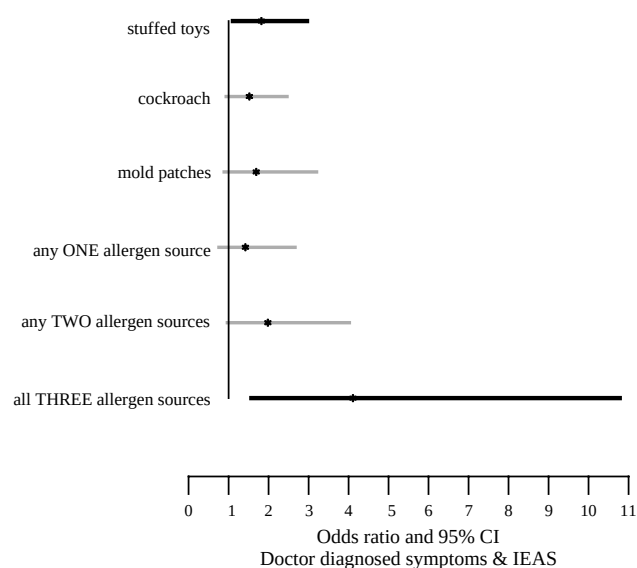


Fig. 2. Association of doctor-diagnosed AS symptoms with three major IEAS separately and in combinations (shown in OR and 95% CI).

have tried to put the floor blanket as the fourth factor in the logistic model to analyze the synergistic effect, but it did not contribute a more significant synergistic effect. Stuffed toys, cockroaches, and mold patches are allergen sources of mite, cockroach, and fungi, which are three major allergens in Taiwan. Floor blankets are also an important source of mite, but as analyzed in this study, they did not have such a synergistic effect as stuffed toys had.

It is interesting to compare our results with those of other studies in Taiwan. The most consistent environmental factor associated with atopic symptoms was a

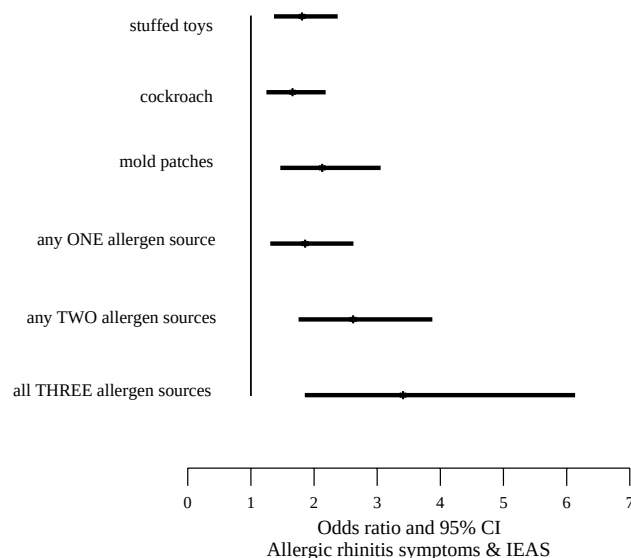


Fig. 3. Association of AR symptoms with three major IEAS separately and in combinations (shown in OR and 95% CI).

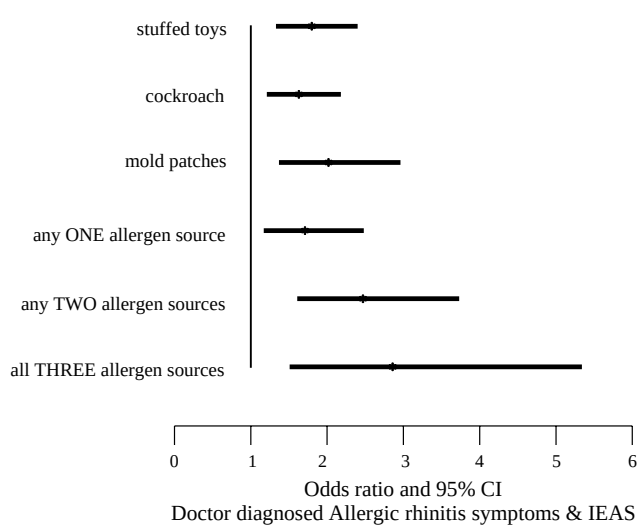


Fig. 4. Association of doctor-diagnosed AR symptoms with three major IEAS separately and in combinations (shown in OR and 95% CI).

damp environment. A case-controlled study, investigating the association between the indoor environment and childhood AS, has been performed in our city. Of the many indoor environmental factors, only home dampness showed an association with AS (OR = 2.65). Yang et al. concluded that dampness in the home is a new public health issue in subtropical areas (Yang et al., 1998). In the Taipei area, another big city 200 miles to the north of our city, the prevalence of all respiratory symptoms was consistently higher in homes with molds or dampness (Li and Hsu, 1996). Taiwan is a small island surrounded by the sea. The humidity is high, and damp houses and environments are quite common. A

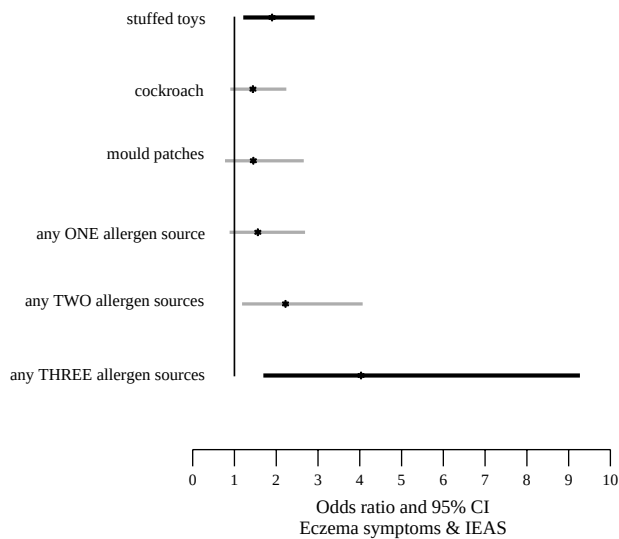


Fig. 5. Association of EC symptoms with three major IEAS separately and in combinations (shown in OR and 95% CI).

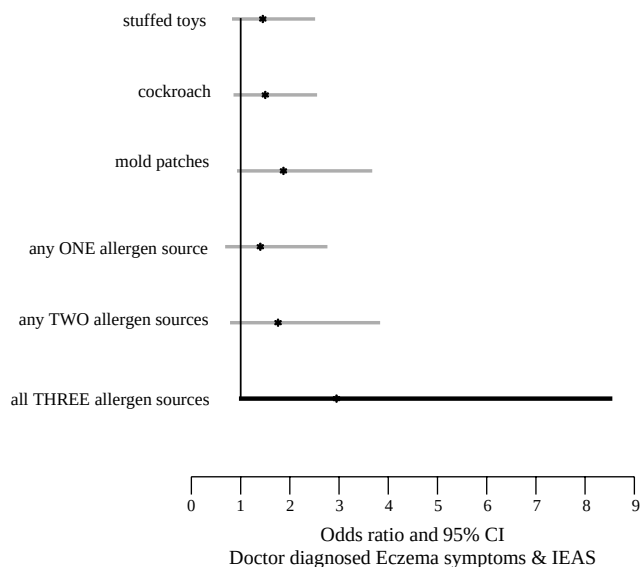


Fig. 6. Association of doctor-diagnosed EC symptoms with three major IEAS separately and in combinations (shown in OR and 95% CI).

damp environment favors overgrowth of mites, mold, and also cockroaches. The association of dampness and atopic symptoms might be due to the combined effect of these three allergen sources.

This study investigated the cross-sectional association between IEAS and atopic diseases in the past 12 months using the self-reported questionnaires. Although the temporal association should be clear that IEAS is more likely to be antecedent to atopic diseases, there could be a recall bias. These parents with children suffering from atopic disease might report in detail regarding these

IEAS. Hence, the recall bias might be differential between children with atopic diseases and without diseases. In the future, the prospective studies with more objective measurement on IEAS should be conducted to confirm our findings.

The incidence of atopic diseases in Taiwan has been increasing in recent years, and how to improve the indoor environment has become an important public health problem. It is known that genes and environment interact in the development of AS and other atopic symptoms, but the dose–response relationship between various IEAS and atopic disease has been seldom evaluated before. In this study, we showed the evidence that different allergen sources might interact to increase their association with atopic symptoms and supported a dose–response effect of the number of IEAS on atopic symptoms. This finding suggested that removal of any IEAS might help to reduce the incidence of atopic symptoms.

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