

Associations between sensitization to allergens and allergic diseases: a hospital-based case-control study in China

Supplementary Method:

1. The definition of demographic, family history, and lifestyle factors

Age was calculated as the difference between the year of birth and the year of interview. Educational status was categorized into three levels: junior high school or lower, senior high school, and university or higher. The residential region was categorized into two groups: urban and rural. Marital status was also categorized into two groups: unmarried and married. Current smokers were defined on the basis of the World Health Organization criteria, as those who self-reported smoking every day for at least 6 months⁹. Regular alcohol drinkers were defined as drinking more than twice per week for at least one year. Classification of physical exercise (PE) was defined as followed:

We estimated PE condition of study participants using three variables of a structured questionnaire, exercise intensity (EI), exercise time (ET), and exercise frequency (EF)¹⁻⁴.

EI of study participants was classified into three groups, mild, moderate and strenuous exercise according to their exercise types. Value 1, 2 and 3 were assigned to the three groups respectively⁵⁻⁸. ET was measured by the hour. EF referred to how many times a week. We defined PE as

$$PE = \sum_{i=1}^N EI \times ET$$

Where N represented EF. If $PE \geq 2$, PE was positive; PE was negative when $PE < 2$. Therefore, as for a subject jogging (moderate exercise) 15 minutes 5 times a week, his/her PE was positive because $PE \geq 2$ ($PE = 5 \times 0.25 \times 2 = 2.5$).

2. The diagnostic criteria of atopic dermatitis, allergic asthma, and allergic rhinitis

2.1 Atopic dermatitis

The following diagnostic criteria for atopic dermatitis was developed by the American

Academy of Dermatology (AAD), which is based on age-specific clinical criteria that include pruritus and chronic or relapsing spongiotic dermatitis involving the face, trunk, and/or extensor extremities in infants, flexural surfaces like the wrists/ankles and antecubital/popliteal fossae in children, or the hands in adults¹⁰.

Essential Features (both must be present):

- 1) Pruritus
- 2) Eczema (acute, subacute, chronic)
 - a. Chronic or relapsing history
 - b. Typical morphology and age-specific patterns
 - Infants: face, trunk (except “diaper area”), extensor extremities
 - Children: flexors (wrists, ankles, antecubital/popliteal fossae)
 - Adults: hands
 - All ages: sparing of the groin and axillary regions

Important Features (support the diagnosis and are observed in most cases of atopic dermatitis):

- 1) Early age of onset
- 2) Atopy
 - a. personal and/or family history; or
 - b. IgE reactivity
- 3) Xerosis

Associated Features (suggestive of atopic dermatitis, but too nonspecific to define or detect atopic dermatitis in research or epidemiologic studies):

- 1) Atypical vascular responses (eg, facial pallor, white dermatographism, delayed blanch response)
- 2) Keratosis pilaris, pityriasis alba, hyperlinear palms/ichthyosis
- 3) Ocular/periorbital changes (fissures, infraorbital folds)
- 4) Other regional findings (eg, perioral changes/periauricular lesions)
- 5) Perifollicular accentuation/lichenification/prurigo lesions

2.2 Allergic rhinitis

The diagnosis criteria for allergic rhinitis are as follows¹¹:

- 1) Clinical history

Clinical history is essential for the accurate diagnosis of allergic rhinitis and the assessment of its severity as well as its response to treatment. The most frequent symptoms include sneezing, anterior rhinorrhea, bilateral nasal obstruction, and nasal pruritus in patients with allergic rhinitis. In addition, most patients with pollen-induced rhinitis have eye symptoms. It is also important to distinguish between allergy and nonallergy symptoms. Subjective assessment of symptoms of allergic rhinitis is generally based on 4 nasal symptoms (sneezing, rhinorrhoea, nasal itching, and nasal obstruction) and 2 ocular symptoms (ocular itching/grittiness/redness and ocular tearing). In China, VAS is most commonly used to quantify the above-mentioned assessments. VAS was used to quantify the above-mentioned assessments.

2) Nasal examinations

Anterior rhinoscopy and nasal endoscopy are the widely used approaches. The nasal examination should describe: 1) the anatomical situation in the nose (e.g. the septum, the size of the inferior turbinate, and if possible the structures in the middle meatus); 2) the color of the mucosa; and 3) the amount and aspect of the mucus. Endoscopic images of nasal mucosa in patients suffering from allergic rhinitis generally demonstrate pale and edematous nasal mucosa, watery nasal discharge, and swollen inferior turbinates.

3) Skin tests

Two methods of skin testing, including intradermal skin tests and skin prick tests (SPTs), are available in China. Skin tests should be read at the peak of their reaction by measuring the wheal and the flare approximately 15 minutes after the performance of the tests. For prick tests, when the control site is completely negative, wheals of >3 mm represent a positive skin response.

4) Serum specific IgE measurements

Enzyme-labeled anti-IgE measurement has been widely used in China. Results are expressed in terms of units of IgE (IU/mL, KU/L). The IgE level above 0.35 KU/L is usually testified as a positive result.

5) Differential diagnosis

In addition, it is necessary to differentiate allergic rhinitis from other diseases, such as vasomotor rhinitis, nonallergic rhinitis with eosinophilia syndrome (NARES), infectious rhinitis, hormonal rhinitis, medicamentous rhinitis (rhinitis medicamentosa), aspirin intolerance triad, cerebrospinal fluid rhinorrhea, and so on.

2.2 Allergic asthma

The diagnosis criteria for allergic asthma are as follows¹²:

1) Clinical history

Wheezing, coughing, chest tightness

May only be present or worsened with exertion, upper respiratory infection, seasonal or perennial allergies

Nocturnal cough, particularly 2 AM to 4 AM

Need for short-acting β_2 -agonist inhaler for relief of symptoms

Personal or family history of atopy

2) Spirometry

Airway obstruction evidenced by FEV₁: FVC ratio < lower limit of normal

Demonstrated reversibility of obstruction by increase in FEV₁ \geq 200mL and \geq 12% from baseline measure after inhalation of 2-4 puffs of short-acting β_2 -agonist

Normal spirometry findings are not inconsistent with asthma

3) Bronchoprovocation with methacholine

20% or more decrease in FEV₁ with after inhalation of low concentration (< 4 mg/mL) of methacholine; used principally in patients with symptoms consistent with asthma but who exhibit normal pulmonary function tests

4) Impedance oscillometry

Elevated airway resistance at 5 HZ, elevated area of reactance, increased resonant frequency (Fres), reactance at 5 HZ more negative than predicted

5) Chest radiograph or CT scan of thorax

Usually normal but can exclude other diagnoses such as emphysema, lung cancer, infiltrative diseases, pneumonia

6) CBC

Eosinophilia, particularly > 300/ μ L; results can inform selection for mepolizumab or reslizumab therapy

7) Serum total IgE

Elevated in atopic asthma, not in nonatopic asthma; can inform selection of omalizumab therapy

8) Skin prick testing or serum-specific IgE for aeroallergens

Positive, particularly for perennial allergens, or seasonal allergens with corresponding seasonal variation in asthma symptoms; may be negative in nonatopic asthma; can inform omalizumab therapy

Positive testing can guide allergen avoidance strategies

9) Fractional excretion of nitric oxide

Intermediate level: 25-50 ppb in patients aged ≥ 12 y

High level: > 50 ppb in patients aged ≥ 12 y

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Supplementary Table:

Supplementary Table S1. Sixteen common allergens used in this study.

category	allergens			
indoor allergens	Dermatophagoides pteronyssinus	Cat and dog fur	Mould mixture ^a	
outdoor allergens	common ragweed and mugwort	German cockroach	Tree pollen mixture ^b	Hop
food allergens	Egg white/egg yolk	Blue mussel	Fish	Crab
	Mutton	Milk	Beef	Shrimp
	Wheat			

^a Mould mixture is composed of *Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus* and *Alternaria alternate*.

^b Tree pollen mixture is composed of Robur, Elm, London Plane, Willow and cottonwood.