

# Sensitization to contact allergens and bronchial hyper-responsiveness

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**Background:** Exposure to contact allergens and specific allergic sensitization to them are common, but possible related health effects have been rarely studied.

**Objectives:** We aimed to analyse possible associations between contact sensitization to nickel sulfate and fragrance mix I and lung function parameters or bronchial hyper-responsiveness.

**Methods:** Within a population-based study in Augsburg, 1052 adults performed lung function tests, including forced expiratory volume in 1 second (FEV<sub>1</sub>), forced vital capacity (FVC) and bronchial hyper-responsiveness (BHR). Patch tests were performed, and information was assessed by medical examinations and interviews. Logistic regression models were applied to study associations between contact allergies and lung function parameters.

**Results:** Women were sensitized significantly more often than men to nickel [odds ratio (OR) 3.97, 95% confidence interval (CI) 2.50–6.29] and fragrance mix I (OR 2.28, 95% CI 1.50–3.46). Patch test results for nickel and fragrance mix I did not influence mean FEV<sub>1</sub> and FVC % predicted values. However, in women, a higher rate of BHR was associated with positive patch test reactions to fragrance mix I (OR 2.24, 95% CI 1.11–4.52).

**Conclusions:** Contact sensitization to fragrance mix I is associated with a higher rate of BHR in women. Thus, in women with contact allergy to fragrances, airway obstruction should be considered as a possible co-morbidity.

**Key words:** allergic contact dermatitis; bronchial hyper-responsiveness; fragrance; lung function; nickel.  
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## Background

Sensitization to contact allergens is common, and overall sensitization rates for a panel of the 25 most common allergens reach 15–20% of the general adult population (1, 2); in some studies, these rates

even reach up to 40–50% (3, 4). Hitherto, any associations between allergic contact sensitization and potential health effects have been rarely studied. Skin exposure to fragrances, jewellery or cosmetics may result in eczema. Known acute symptoms caused by inhalation of volatiles from cosmetics or fragrances are mainly eye irritation or airway symptoms such cough or dyspnoea (5, 6). However, these latter complaints are not strictly associated with a contact allergy—they may indicate hyper-reactivity (7). Several studies have indicated that

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some people have an overall increased propensity to develop contact sensitization, which is expressed in multiple sensitizations and strong allergic patch test reactions (1, 8). Furthermore, people with a defined contact allergy and those with a history of hand eczema or active lung diseases may have more frequent and more severe symptoms after exposure to fragrances or nickel salts (6, 5, 9). The mechanisms from sensitization to contact allergens to clinical symptoms are complex. Several occupational studies and animal experiments have indicated that there might be an association between contact allergy and the onset of respiratory diseases (10, 11). However, this possible association has never been analysed in a population-based setting.

We aimed to analyse, within a population-based study, whether sensitization to the most common contact allergens (nickel sulfate and fragrance mix I) affect lung function parameters, including forced expiratory volume in 1 second (FEV<sub>1</sub>) and forced vital capacity (FVC), as well as bronchial hyper-responsiveness (BHR).

## Methods

### *Study population*

We report the results of the KORA C study. The subjects were recruited from the third MONICA survey, which was performed in Augsburg, Germany, during the years 1994 and 1995. The objective and protocol of the MONICA surveys in Augsburg have been published previously (12). The third MONICA survey consisted of a random sample of 4178 individuals stratified for age and sex, drawn from all registered residents aged 25–74 years of the city of Augsburg. The KORA C study was performed between September 1997 and December 1998. KORA C is a subset of the third MONICA survey, enriched with subjects with positive test results for specific IgEs against common aeroallergens (grass and birch pollen, house-dust mite, cat, and *Cladosporium herbarum*). Details of the cross-sectional KORA C study design have been reported elsewhere (13). Finally, 1537 subjects participated (60.5%), of whom 50.2% had at least one positive radioallergosorbent test (RAST) result. Besides questionnaire evaluations, detailed dermatological examinations, patch tests and lung function tests were performed. Lung function tests were only performed among those younger than 60 years (1090 participants). After exclusion of those with invalid results for the lung function testing, 1052 valid tests were included in the final analysis (Table 1). A written, informed consent form was received from all participants, and ethical approval for the study was obtained from the local ethics committees.

### *Outcome assessment*

**Lung function.** For all participants aged 59 years or younger who did not smoke or use inhalers 1 hr before the test FEV<sub>1</sub> and FVC were determined by spirometry. All spirometric tests were performed with strict adherence to the European Community Respiratory Health Survey protocol, the most common method for lung function tests in epidemiological studies in cohorts at the international level (14), and have been previously published (15). Tests were considered valid if three valid measures could be obtained throughout a maximum of five trials. When there were no contraindications (acute heart disease during the past 3 months, taking  $\beta$ -blockers, taking drugs for heart diseases or epilepsy, pregnancy, lactation, an initial FEV<sub>1</sub> value of less than 70% as compared with the index value, or an FEV<sub>1</sub> value of less than 1.5 l), BHR was also tested for by methacholine provocation. The methacholine challenge has been described in detail elsewhere (15, 16). After inhalation of saline as a diluent, increasing doses of methacholine were given. The provocation was stopped when the FEV<sub>1</sub> value fell by more than 20% as compared with the post-saline FEV<sub>1</sub> check value or at a cumulative dose of 2 mg of methacholine. For analysis, the concentration of methacholine causing a 20% decline in FEV<sub>1</sub> as compared with the post-diluent value was weighted by the number of inhalations, and the results were added to a cumulative dose of methacholine (PD<sub>20</sub>). A cumulative dose of  $\leq 2$  mg of methacholine (PD<sub>20</sub>  $\leq 2$  mg) was defined as an increased BHR, according to Abramson et al. (17).

**Dermatological examination and patch tests.** All subjects received a full dermatological examination. Individuals with atopic eczema and psoriasis were identified on a clinical basis. Patch tests were performed as recommended by the International Contact Dermatitis Research Group (18). The actual baseline panel of the time, which includes 25 allergens, was tested (Hermal, Reinbek, Germany). As compared with the most recent European baseline series of 2005, a total of 19 allergens, including nickel sulfate 5% and fragrance mix I 8%, are identical. Finn Chambers® were used. The tests were applied for 2 days on the upper back, and the participants were asked to remove the patches after that time and to return for a reading by the investigating physicians on D3. For the final analysis, only definitive positive (+ to +++) and negative (0) results were considered, irritative and questionable (+?) results being excluded.

**Questionnaire.** As part of the study, a computer-assisted standardized interview was performed. Besides data on age and sex, information on sociodemographic parameters and medical history

was assessed. The subjects were additionally asked whether they had experienced adverse skin reactions (such as itch, redness or dermatitis) to certain products, and, if so, whether they could link these to specific things such as costume jewellery or fragrances. In addition, all participants were asked whether they had ever undergone a patch test and whether contact allergy was diagnosed on the basis of positive reactions.

### Statistical analyses

A secondary statistical analysis was performed for the KORA C study to investigate whether sensitization to the most common contact allergens affects lung function parameters. Descriptive statistical analysis was performed for the study population, lung function parameters, BHR and patch test results with SAS, version 9.13. For the two most common contact allergens, nickel sulfate and fragrance mix I, detailed analyses were performed. Trend testing based on *T*-tests was used to describe trends for the prevalence of contact sensitization. Chi-square tests and multivariate logistic regression models were applied for the association between lung function parameters or BHR and sensitization to contact allergens. The final model were adjusted for age, sex, smoking, atopic family history, atopic diseases and positive sensitization to at least one inhalation allergen (RAST). Stratified and total calculations were performed for males and females.

### Results

A total of 1052 valid lung function tests were analysed. FEV<sub>1</sub> and FVC values were significantly lower for women than for men, and women showed a higher rate of BHR (Table 1). The highest prevalences of positive patch test reactions were seen for nickel (14.7%) and fragrance mix I (14.8%). Women were sensitized significantly more often to any of the 25 allergens than men [37.9% versus 19.0%; odds ratio (OR) 3.22, 95% confidence interval (CI) 2.29–4.52]. There was a decreasing trend for the prevalence of sensitization to nickel with older age (*P*-trend < 0.01). However, the sensitization to fragrance mix I increased with age (*P*-trend < 0.01) (Table 2).

The association between the lung function parameters, FEV<sub>1</sub> % predicted and FVC % predicted (according to Quanjer) and patch tests for nickel or fragrance mix I was not statistically significant, except for certain FVC values (Table 3). Here, the mean FVC % predicted value was higher for those with a positive patch test result for fragrance than for those with a negative patch test result (mean ± standard deviation 112.11 ± 15.03 versus

Table 1. Characteristics of the study population

|                                                              | Total (N = 1052) |
|--------------------------------------------------------------|------------------|
| Males <sup>a</sup>                                           | 509/1052 (48.4)  |
| Age (years) <sup>b</sup>                                     | 44.4 ± 8.9       |
| Higher education <sup>a</sup>                                | 529/1051 (50.3)  |
| Smoking <sup>a</sup>                                         | 553/957 (57.8)   |
| BMI <sup>b</sup>                                             | 25.4 ± 4.1       |
| Family history of atopic diseases <sup>a</sup>               | 159/1052 (15.1)  |
| Asthma <sup>a</sup>                                          | 83/1052 (7.9)    |
| Hay fever <sup>a</sup>                                       | 300/1052 (28.5)  |
| Atopic dermatitis <sup>a</sup>                               | 44/1051 (4.2)    |
| RAST-positive <sup>a</sup>                                   | 558/1052 (53.0)  |
| Lung function <sup>b</sup>                                   |                  |
| FEV <sub>1</sub> (l)                                         | 3.59 ± 0.84      |
| Males                                                        | 4.16 ± 0.73      |
| Females                                                      | 3.05 ± 0.53      |
| FVC (l)                                                      | 4.31 ± 1.05      |
| Males                                                        | 5.07 ± 0.86      |
| Females                                                      | 3.60 ± 0.62      |
| BHR <sup>a</sup>                                             | 122/617 (19.8)   |
| Males                                                        | 49/338 (14.5)    |
| Females                                                      | 73/279 (26.2)    |
| Contact allergen (positive patch test results <sup>a</sup> ) |                  |
| Nickel sulfate                                               | 118/801 (14.7)   |
| Males                                                        | 26/387 (6.7)     |
| Females                                                      | 92/414 (22.2)    |
| Fragrance mix                                                | 117/793 (14.8)   |
| Males                                                        | 37/384 (9.6)     |
| Females                                                      | 80/409 (19.6)    |

BHR, bronchial hyper-responsiveness; BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; RAST, radioallergosorbent test.

<sup>a</sup>n/N (%).

<sup>b</sup>Mean ± standard deviation.

109.02 ± 14.33; *P* = 0.03). Further sensitivity analyses, including the relationship between FEV<sub>1</sub> and FVC, and the stratification for asthma and for sensitization to at least one of the common inhalation allergens, did not show any association between the lung function parameters FEV<sub>1</sub> and FVC and the patch test results. However, sensitization to nickel (OR 1.59, 95% CI 0.91–2.77) or fragrance mix I (OR 1.68, 95% CI 0.94–3.01) increased the risk of BHR (Table 4), but only after stratification for sex could a statistically significant association between sensitization to fragrance mix and BHR be observed in females (OR 2.24, 95% CI 1.11–4.52). Similar results were obtained after adjusting for age (OR 2.14, 95% CI 1.05–4.35) and after adjusting for age, smoking, atopic family history, atopic diseases and positive sensitization based on RAST (OR 2.29, 95% CI 1.00–5.25). An additional sensitivity analysis showed that the association between sensitization to fragrance mix I and BHR in women was only seen in women with allergic sensitization to at least one of the common inhalant allergens (OR 2.61, 95% CI 1.11–6.12), and not in non-sensitized women (OR 1.04, 95% CI 0.21–5.22). Men showed no relationship between sensitization

Table 2. Lung function, bronchial hyper-responsiveness and positive patch test result by age categories

|                                                             | <i>P</i> -trend | 25–34 years    | 35–44 years    | 45–54 years    | 55–59 years    |
|-------------------------------------------------------------|-----------------|----------------|----------------|----------------|----------------|
| Total no. of participants with lung function data           |                 | 181            | 369            | 306            | 196            |
| Lung function <sup>a</sup>                                  |                 |                |                |                |                |
| FEV <sub>1</sub> (l)                                        |                 | 4.04 ± 0.77    | 3.77 ± 0.85    | 3.34 ± 0.75    | 3.20 ± 0.71    |
| FEV <sub>1</sub> % predicted                                |                 | 107.12 ± 11.33 | 107.97 ± 15.04 | 108.66 ± 14.54 | 110.79 ± 16.86 |
| FVC (l)                                                     |                 | 4.74 ± 1.01    | 4.55 ± 1.07    | 4.04 ± 0.96    | 3.89 ± 0.89    |
| FVC % predicted                                             |                 | 106.91 ± 11.89 | 110.07 ± 15.04 | 109.87 ± 14.38 | 110.90 ± 16.82 |
| BHR <sup>b</sup>                                            |                 | 15/119 (12.6)  | 51/228 (22.4)  | 43/180 (23.9)  | 13/90 (14.4)   |
| Contact allergen (positive patch test results) <sup>b</sup> |                 |                |                |                |                |
| Nickel sulfate                                              | <0.01           | 30/126 (23.8)  | 49/274 (17.9)  | 30/241 (12.5)  | 9/160 (5.6)    |
| Fragrance mix                                               | <0.01           | 13/128 (10.2)  | 30/270 (11.1)  | 42/238 (17.7)  | 32/157 (20.4)  |
| Males                                                       |                 | 92             | 182            | 136            | 99             |
| Lung function <sup>a</sup>                                  |                 |                |                |                |                |
| FEV <sub>1</sub> (l)                                        |                 | 4.62 ± 0.58    | 4.36 ± 0.72    | 3.93 ± 0.58    | 3.67 ± 0.63    |
| FEV <sub>1</sub> % predicted                                |                 | 106.56 ± 11.33 | 107.01 ± 15.62 | 107.12 ± 13.89 | 109.61 ± 16.79 |
| FVC (l)                                                     |                 | 5.51 ± 0.72    | 5.34 ± 0.84    | 4.82 ± 0.75    | 4.52 ± 0.71    |
| FVC % predicted                                             |                 | 106.07 ± 11.42 | 108.27 ± 14.34 | 106.30 ± 13.65 | 107.68 ± 15.25 |
| BHR <sup>b</sup>                                            |                 | 7/66 (10.6)    | 21/123 (17.1)  | 16/93 (17.2)   | 5/56 (8.9)     |
| Contact allergen (positive patch test results) <sup>b</sup> |                 |                |                |                |                |
| Nickel sulfate                                              |                 | 9/63 (14.3)    | 5/138 (3.6)    | 7/108 (6.5)    | 5/78 (6.4)     |
| Fragrance mix                                               |                 | 2/63 (3.2)     | 9/136 (6.6)    | 15/108 (13.9)  | 11/77 (14.3)   |
| Females                                                     |                 | 89             | 187            | 170            | 97             |
| Lung function <sup>a</sup>                                  |                 |                |                |                |                |
| FEV <sub>1</sub> (l)                                        |                 | 3.45 ± 0.41    | 3.20 ± 0.49    | 2.86 ± 0.48    | 2.72 ± 0.41    |
| FEV <sub>1</sub> % predicted                                |                 | 107.69 ± 11.36 | 108.90 ± 14.44 | 109.90 ± 14.97 | 112.00 ± 16.93 |
| FVC (l)                                                     |                 | 3.95 ± 0.53    | 3.78 ± 0.60    | 3.41 ± 0.56    | 3.24 ± 0.53    |
| FVC % predicted                                             |                 | 107.77 ± 12.36 | 111.82 ± 15.53 | 112.73 ± 14.33 | 114.18 ± 17.77 |
| BHR <sup>b</sup>                                            |                 | 8/53 (15.1)    | 30/105 (28.6)  | 27/87 (31.0)   | 8/34 (23.5)    |
| Contact allergen (positive patch test results) <sup>b</sup> |                 |                |                |                |                |
| Nickel sulfate                                              |                 | 21/63 (33.3)   | 44/136 (32.4)  | 23/133 (17.3)  | 4/28 (4.9)     |
| Fragrance mix                                               |                 | 11/65 (16.9)   | 21/134 (15.7)  | 27/130 (20.8)  | 21/80 (26.3)   |

BHR, bronchial hyper-responsiveness; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity.

<sup>a</sup>Mean ± standard deviation; % predicted according to Quanjer.

<sup>b</sup>n/N (%).

to contact allergens and BHR, either for sensitized or for non-sensitized subjects.

## Discussion

Our results indicate that contact sensitization to fragrance mix I is associated with an increased risk for BHR in women but not in men. The higher exposure to perfumes in women might explain this observation (19, 20). Additionally, women may show stronger adverse reactions to contact allergens than men (21, 22). Furthermore, several studies have indicated that there might be an association between skin exposure to occupational agents and the development of certain occupational lung diseases (10, 11, 23, 24). For example, isocyanate skin exposure might contribute to the development of isocyanate asthma, presumably by the induction of systemic sensitization. However, all data supporting the hypothesis that skin may induce systemic sensitization to certain occupational allergens in human beings are mainly indirect. It has been demonstrated in different mouse and rat models that skin exposure to chemical sensitizers induces systemic

sensitization, with subsequent inhalation challenge resulting in asthmatic-like responses (25, 26). However, to our knowledge, this is the first population-based study to investigate the association between patch test results and BHR.

A historical study indicated that numerous chemical factors, such as tobacco smoke and perfumes, can induce airway symptoms through BHR in sensitive individuals (27). It could be speculated that the olfactory sensory system plays a considerable role in causing these symptoms, and strong-smelling perfumes are important trigger factors for these airway symptoms. Furthermore, an association between fragrance contact allergy and eye and airway symptoms elicited by fragrance products has been shown (6). Interactions between skin inflammation and airway sensitivity may be one of the mechanisms, as well as a common endogenous predisposition. It was shown that BHR was linked to mucosal symptoms elicited by fragrance exposure, but no association between low FEV<sub>1</sub> and these symptoms was found (28). This indicates that such mucosal symptoms related to fragrance products are more prevalent in asthmatics, but not in individuals with

Table 3. Lung function as compared with positive patch test results

|                                         | FEV <sub>1</sub> % predicted <sup>a</sup> |                | <i>P</i> -value | FVC % predicted <sup>a</sup> |                | <i>P</i> -value |
|-----------------------------------------|-------------------------------------------|----------------|-----------------|------------------------------|----------------|-----------------|
|                                         | Patch+                                    | Patch–         |                 | Patch+                       | Patch–         |                 |
| Total participants with patch test data |                                           |                |                 |                              |                |                 |
| Nickel sulfate                          | 109.68 ± 13.20                            | 108.08 ± 14.81 | 0.27            | 111.65 ± 13.42               | 109.29 ± 14.88 | 0.11            |
| Fragrance mix                           | 110.18 ± 14.69                            | 107.79 ± 14.26 | 0.10            | 112.11 ± 15.03               | 109.02 ± 14.33 | 0.03            |
| Male                                    |                                           |                |                 |                              |                |                 |
| Nickel sulfate                          | 108.95 ± 14.18                            | 107.21 ± 14.68 | 0.56            | 107.02 ± 15.91               | 107.29 ± 13.71 | 0.93            |
| Fragrance mix                           | 109.25 ± 16.87                            | 107.14 ± 14.18 | 0.40            | 108.42 ± 16.27               | 107.20 ± 13.46 | 0.61            |
| Female                                  |                                           |                |                 |                              |                |                 |
| Nickel sulfate                          | 109.88 ± 12.98                            | 109.06 ± 14.92 | 0.63            | 112.96 ± 12.41               | 111.55 ± 15.81 | 0.37            |
| Fragrance mix                           | 110.61 ± 13.65                            | 108.48 ± 14.34 | 0.23            | 113.82 ± 14.20               | 110.94 ± 14.97 | 0.12            |

Patch+, sensitized to contact allergen; Patch–, not sensitized to contact allergen.

<sup>a</sup>Mean ± standard deviation; % predicted according to Quanjer.

Table 4. Logistic regression models for sensitization to contact allergens and bronchial hyper-responsiveness (BHR)

| BHR            | Crude |           | Adjusted model 1 <sup>a</sup> |           | Adjusted model 2 <sup>b</sup> |           |
|----------------|-------|-----------|-------------------------------|-----------|-------------------------------|-----------|
|                | OR    | 95% CI    | OR                            | 95% CI    | OR                            | 95% CI    |
| Total          |       |           |                               |           |                               |           |
| Nickel sulfate | 1.59  | 0.91–2.77 | 1.41                          | 0.78–2.54 | 1.55                          | 0.80–2.99 |
| Fragrance mix  | 1.68  | 0.94–3.01 | 1.45                          | 0.79–2.63 | 1.48                          | 0.76–2.91 |
| Males          |       |           |                               |           |                               |           |
| Nickel sulfate | 0.60  | 0.13–2.71 | 0.61                          | 0.13–2.74 | 0.81                          | 0.17–3.80 |
| Fragrance mix  | 0.46  | 0.11–2.05 | 0.45                          | 0.10–2.01 | 0.53                          | 0.11–2.60 |
| Females        |       |           |                               |           |                               |           |
| Nickel sulfate | 1.62  | 0.84–3.11 | 1.84                          | 0.93–3.64 | 2.16                          | 0.97–4.82 |
| Fragrance mix  | 2.24  | 1.11–4.52 | 2.14                          | 1.05–4.35 | 2.29                          | 1.00–5.25 |

<sup>a</sup>Adjusted for age, and additionally for sex in 'Total'.<sup>b</sup>Adjusted for age, smoking, atopic family history, atopic diseases and positive sensitization to at least one of the common inhalation allergens (radioallergosorbent test), and additionally for sex in 'Total'.

chronic obstructive pulmonary diseases. Additionally, the lack of association with atopy suggests that non-IgE-mediated immunological mechanisms play a major role. This is in line with our results, indicating that contact sensitization to fragrances, which is a type IV allergy, is related to asthma. A similar result was shown for respiratory symptoms elicited by airborne chemicals other than fragrances that were related to allergic contact dermatitis but not to IgE-mediated allergy (29). Here, too, female sex showed a positive association with respiratory symptoms. Thus, exposure to chemicals including fragrances could be considered to be a trigger factor for asthma and bronchospasm (30).

However, nickel has a lower impact on respiratory parameters. This is not surprising, as inhalation is only one of the exposure pathways of nickel, but not the most common. Skin contact is much more important, as nickel is present in the workplace, objects of daily use, tools, toys, fashion, food and urban air (31). Nickel exposure is therefore varied, and it is one of the most frequent contact allergens (31). Furthermore, nickel salts induce occupational asthma (32). The underlying mechanisms have not been fully explained yet. There may be non-immunological and immunological

mechanisms, and the latter could be either IgE-dependent or non-IgE-mediated (9). Delayed hypersensitivity might be involved in asthma caused by nickel, which could explain the association between skin reactions to nickel and BHR.

In the interpretation of the results, possible limitations of the study also have to be considered. Because of the study design, it has to be taken into account that we analysed an allergy-enriched population in which half of the subjects exhibited type I sensitization. This was considered in the statistical analysis, in which we also adjusted for positive sensitization on the basis of RAST. Furthermore, a stratified analysis showed that the association between contact sensitization to fragrance mix I and BHR was mostly seen in women with allergic sensitization. Additionally, a previous detailed analysis of contact allergies in our study found no differences in contact sensitization depending on associated type I sensitization (13). This makes an ascertainment bias unlikely. Although the rate of fragrance sensitivity in our study population (14.8%) seems to be relatively high, comparison with other studies shows that our results are well within the expected range. Thus, the Information Network of Departments of Dermatology, which collected data from 42 centres

of a Central European Network from 1993 to 2003, showed an average fragrance sensitization rate of 11.2%, with a maximum of 13.1% in 1999 (8, 33). Nevertheless, it has to be taken into account that our study population, including only residents of the city of Augsburg, may differ in several aspects not recognized in this study.

Concerning the association that we demonstrated between contact sensitization to fragrance mix I and BHR, it has to be considered that epidemiological studies investigate associations, but it is hard to interpret these associations as causal. Therefore, we cannot confirm whether the association is causal or common-grounded. There might be a genetic tendency for hyper-responsiveness in the airways and the skin, which would predict a strong response to fragrance in both organs. This hypothesis is supported by the fact that we could not observe an association for nickel. As both fragrance and nickel induce T-cell-driven type IV contact allergy, one might expect both to be associated with BHR. One possible mechanism for such an interaction between skin inflammation and airway sensitivity might be a recirculating, systemic T-cell-driven response in the lungs, which has been observed in cat-allergic subjects (34). These authors showed a T-cell-derived late asthmatic reaction, without the requirement for an early IgE cell-dependent response, after an intradermal injection of cat peptides. Also, the main exposure pathway of nickel is skin contact and not inhalation, which might explain why we could not find an association between nickel contact sensitization and BHR. However, it has to be considered that the association between contact sensitization to fragrance mix I and BHR could be demonstrated only in women. This female predominance might indicate a causal association, as women are more frequently exposed to perfumes and cosmetics than are men.

To determine the kind of association, further studies are necessary. For example, a prospective study would provide a more valid study design to evaluate whether a temporal sequence and causality exist between contact sensitization and BHR. Additionally, it would be helpful for the interpretation to have more information about personal exposure patterns for certain contact allergens, and to monitor real-time lung function and BHR before and after patch testing. Furthermore, experimental studies are needed to investigate the mechanisms of exposure to fragrances and the development of BHR and finally asthma.

The main strengths of our study are the population-based setting, the considerably high sample size, covering adults from a large age range, and the broad performance of patch tests and lung function tests including methacholine challenge tests.

## Conclusions

Our results indicate that sensitization to fragrance mix I is associated with BHR in women. Thus, in women with contact allergy to scents, an airway obstruction should be considered as a possible co-morbidity. In this context, positive patch test results might be associated with respiratory diseases, especially with asthma.

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