

ORIGINAL ARTICLE

Risk factors of adverse reactions to food in German adults

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Summary

Background Allergic diseases have been increasing during the last decades. Previous studies suggest an impact of a variety of risk factors on the prevalence of food hypersensitivity.

Objective Data of a cross-sectional population-based survey were analysed to study the prevalence of food hypersensitivity in females and males adjusted for age and education.

Methods A population aged 18–79 years from a representative, randomly sampled survey studying 13 300 inhabitants from Germany (Berlin) was analysed. The Berlin study data were weighted with regard to age, sex, education and allergic diseases such as atopic dermatitis, rhinoconjunctivitis and asthma. Instruments for evaluation included mailed questionnaires, structured telephone interviews, physical examinations, detection of total IgE, skin prick tests and double-blind, placebo-controlled food challenge tests (DBPCFC).

Results Three thousand two hundred and twenty-seven questionnaires were evaluated. The data show a significantly higher risk of self-reported symptoms in the female group, among persons with higher education and in the age group of 18–39 years. Among individuals with clinical symptoms, females were at lower risk of having positive skin prick tests [aOR = 0.32; 95% CI (0.21–0.50); $P < 0.01$] and having a raised total IgE [aOR = 0.37; 95% CI (0.24–0.56); $P < 0.01$], but showed a higher risk of non-IgE and IgE-mediated food hypersensitivity [aOR = 2.27; 95% CI (1.31–3.93); $P < 0.01$] than males. Based on weighted data, the point prevalence of adverse reactions to food resulted in 3.3% [95% CI (2.4–4.5%)] for women and 1.8% [95% CI (1.2–2.7%)] for men after DBPCFC.

Conclusion From a general population survey conducted in Germany, we determined that women are at greater risk of having symptoms of food allergy and also at greater risk of having DBPCFC-confirmed symptomatic food allergy. However, among individuals with symptoms of food allergy, men have a higher prevalence of food-specific IgE-sensitization and of raised total IgE than women.

Keywords adults, DBPCFC, education, females, food allergy, food intolerance, males

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Introduction

Adverse reactions to food include both allergic and non-allergic hypersensitivity reactions [1]. The most frequent eliciting food allergens in childhood are egg, milk, peanut, soy and wheat, whereas in adults pollen-associated food allergies elicited by fruits, vegetables and nuts are most prevalent [2]. Several studies regarding the prevalence of food hypersensitivity have been published

in the past and indicate that food hypersensitivity affects approximately 2–3% of the general population. Most of the studies did not perform a risk factor-related analysis considering factors such as sex, age or education. Thereby, such data and its impact on the frequency of food hypersensitivity are almost missing [3–13].

However, a few studies have addressed this question and suggested that females might suffer from adverse reactions to food more often than males. One study has shown a higher lifetime prevalence of allergic diseases (including allergic contact eczema) in women (47%) than

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in men (33%) [14]. An extremely high prevalence rate has been reported among West German women in the age group 30–39 years (62%). In contrast, the prevalence of IgE sensitization has been reported to be unequally distributed between males and females [15].

Previous studies indicated that hormones may directly and indirectly modulate the development and outcome of the allergic immune response [16–18]. Also epidemiological studies indicate that the prevalence of atopic diseases differs between males and females [14]. Thus, the modulation of the allergic immune response by hormones aside from socio-cultural factors has been discussed [19, 20].

Previously, we determined a point prevalence of food hypersensitivity proven by double-blind, placebo-controlled food challenge (DBPCFC) of 2.6% [95% CI (2.1–3.2%)] in the general adult population at age 18–79 years [13]. The aim of this analysis was to determine the impact of risk factors such as age, sex and education on food hypersensitivity and, in particular, whether they are important for the frequency of self-reported symptoms, sensitization rates and profiles and, finally, the prevalence of clinically relevant food hypersensitivity in German adults.

Materials and methods

In 1999, the German Ministry of Health initiated a study to investigate the prevalence of food hypersensitivity in the German population and to identify the eliciting agents. The study was performed in the Berlin population. A single centre approach was chosen because a specially equipped allergy centre was required to handle severe anaphylactic reactions during provocation tests and to avoid an inter-investigator bias. It was calculated that a sample size of 4000 persons would be sufficient to report an expected prevalence rate of 2% with a 95% confidence interval (CI) smaller than 1.5–2.5.

A random sample of 15 000 German citizens of all age groups and districts was drawn from the Berlin population register, expecting a rate of reply at 30–40%. Questionnaires were sent out in eight sequential survey waves, until the number of responses exceeded 4000. For this, a total of 13 300 persons of all ages were selected cumulatively by repeated random sub sampling from the initial random sample of 15 000 [13]. On the basis of the data of the representative nation-wide German health survey from 1998 [21], which was performed 1 year before our study, it was possible to adjust the data from the Berlin survey to the German adult population aged 18–79. For this purpose, the Berlin study data were weighted with regard to age, sex, education, atopic dermatitis, rhinoconjunctivitis and asthma.

The questionnaire considered adverse reactions to food and included questions on the relation between food

ingestion and the onset of symptoms such as itching, eczema and others. In addition, questions addressed possible risk factors such as the educational status. The history of allergic diseases such as allergic rhinitis, eczema, allergic asthma and urticaria in the last 12 months was also taken. The study adhered to the guidelines of the Declaration of Helsinki and informed consent was obtained from all subjects. The study was approved by the local ethics committee and the Berlin data protection officials.

The study was performed from 1999 to 2000. Figure 1 shows a flow sheet of the study with a comparison of unweighted and weighted number of cases. 4093 questionnaires from individuals of all ages were returned. The overall response rate was 30.8%. In the adult age group, 3227 questionnaires were returned and evaluated. All responders who declared any symptoms of food hypersensitivity or the existence of allergic diseases ($n = 1798$) were followed up by a telephone interview asking questions to define food allergy/intolerance. During the telephone call, a decision was made following an algorithm as to whether food allergy/intolerance could probably be ruled out or not. Concerning this, 1528 persons had been contacted by phone. A clear decision to rule out food intolerance was made when food items had given rise to symptoms once only and were afterwards again repeatedly ingested without any complications. In cases where food hypersensitivity was not ruled out by history, individuals were selected for a personal investigation. This investigation included a detailed standardized history and a serum sample for IgE analysis (Pharmacia Cap Systems, Freiburg, Germany). A skin prick test was performed including inhalant allergens (grass pollen, birch, cat mugwort, dog, dermat. pt., alternaria, cladosporium, latex from ALK SCHERAX, Wedel and Bencard, München, Germany) and different food allergens. The food allergens (quar gum, carrageen, locust bean, pork meat, peanut, apple, potato, carrot, celery, barley flour, wheat and rye flour, oat meal, hen's egg, cow's milk, hazelnut, walnut, sesame, poppy seed, carob) were used exclusively as fresh native preparations in a prick-to-prick procedure, as described previously [22]. Only crab, mackerel, herring, mussel and soy allergen extracts were used as commercial extracts because of their limited storing properties (ALK SCHERAX, Wedel and Bencard). Prick tests were positive if a mean weal diameter of 3 mm or greater was determined.

Suspicion of food hypersensitivity was excluded by history in 403 persons. Six hundred and twenty of the remaining persons followed the invitation to the personal investigation including skin prick test and blood taking for determination of IgE antibodies.

If an adverse reaction to food was expected in the individuals according with their history and/or sensitization in the skin prick test, DBPCFC was performed. The

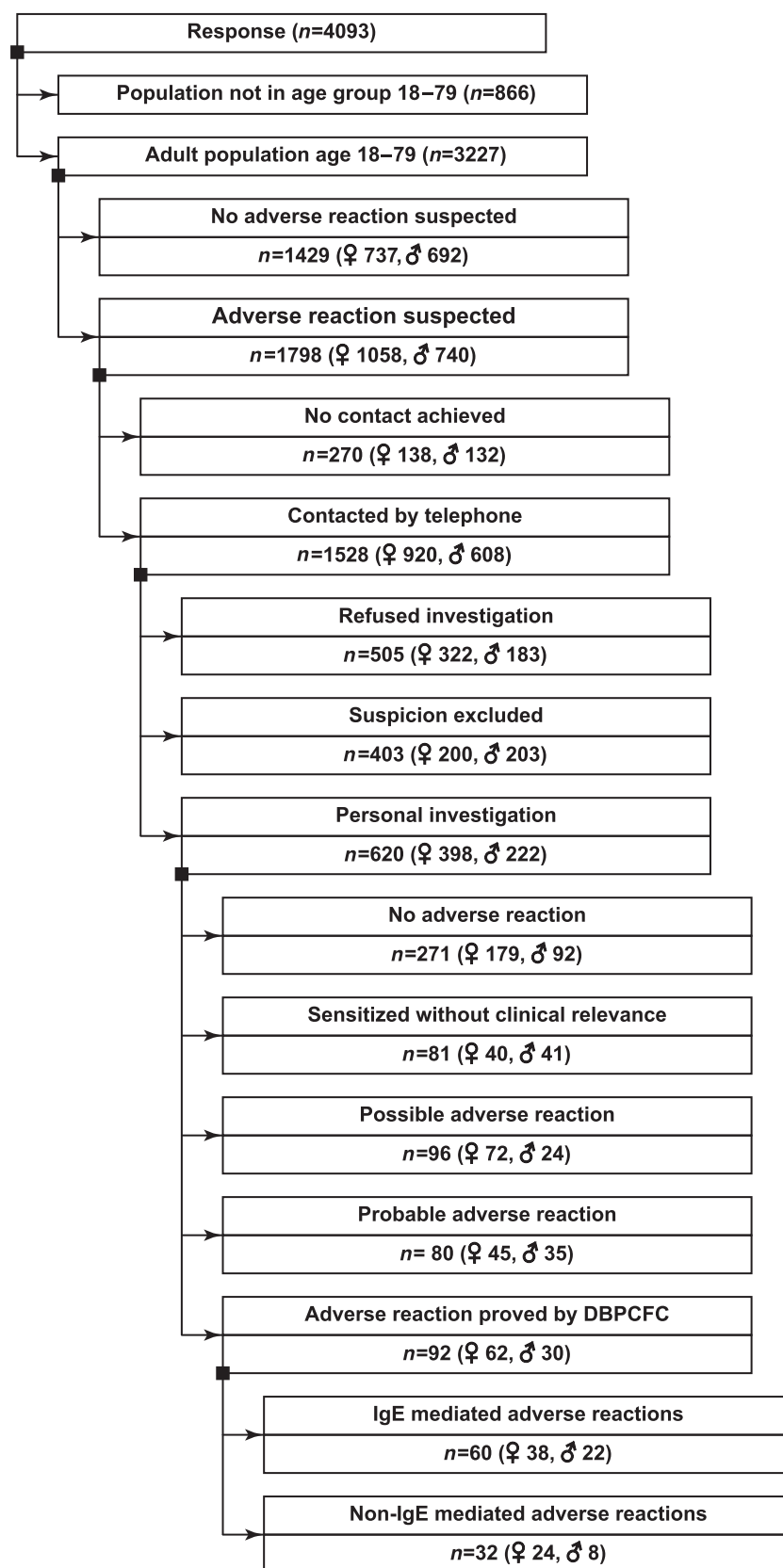


Fig. 1. Flow sheet of the study and investigations performed.

amount of food used in the provocation test considered the individual history of the patient and the level of regular consumption in the general population. In case that adverse reactions to food appeared to be unlikely by history, an open challenge test was performed. If this open challenge test was negative, food hypersensitivity was excluded. If the open challenge was positive, DBPCFC test were performed.

DBPCFC were scored positive if a single or a combination of the following clinical reactions to the challenge were noted: allergic rhinoconjunctivitis, angioedema, oral discomfort, urticaria, diarrhoea, vomiting, abdominal pain, wheezing, bronchial asthma, exacerbation of atopic eczema or cardiovascular shock.

In this study, the term IgE-mediated food allergy was used to describe clinical symptoms, which are mediated by immune system (IgE antibodies) and non-IgE-mediated food allergy to describe those which are not.

Statistical analysis

Statistical analysis was done with STATA version 9.0 (StataCorp. 2005; StataCorp LP, College Station, TX, USA). Weighted prevalence rates are reported with 95% CIs. Adjusted odds ratios (aORs) were computed with weighted multiple logistic regression. The weights were derived by comparison of the study data with the German National Health Survey from 1998 with regard to age, sex, education, atopic dermatitis, rhinoconjunctivitis and asthma. *P*-values below 0.05 are considered to be significant. Reported *P*-values are descriptive, no adjustments are made for multiple testing.

Results

Questionnaire replies were received from 3227 adults (aged 18–79 years). To analyse these data with respect to the general German population, our data were weighted according to data from the German health survey from 1998. Table 1 shows the unweighted and the weighted socio-demographic characteristics of our study group.

The weighting variables covered sex, age, education and IgE dependent diseases such as atopic dermatitis, rhinoconjunctivitis and asthma. All prevalence rates and adjusted odds ratios reported below are based on this weighted data.

Risk of self-reported symptoms depend on sex, age and education

The data show that females, individuals with a higher education and persons aged 18–39 years were at higher risk with regard to several reported symptoms (adjusted odds ratios are shown exemplarily for dysaesthesia of tongue) (Table 2). The results indicate that a further

Table 1. Socio-demographic characteristics of adult persons responding to the questionnaire

	% Unweighted	% Weighted
Questionnaires responses: adults (<i>n</i> = 3227)		
Sex		
Female	55.6	48.6
Male	44.4	51.4
Age		
18–39 years	37.0	38.0
40–59 years	36.1	34.4
60–79 years	26.9	27.6
Education		
Secondary school	18.0	23.7
Secondary modern school	34.5	47.6
Grammar school	42.6	22.0
Other	4.9	6.7

Grammar school is the highest German school degree after 13 years of school in preparation for university studies, secondary modern school requires at least 10 years, secondary school 9 years of school education.

Table 2. Association between socio-demographic risk factors and self-reported dysaesthesia of the tongue

	%Prev	aOR	<i>P</i> -value	95% CI
Sex				
Male	8.0	1		Reference
Female	12.6	1.83	0.000	1.39–2.39
Age				
18–39 years	13.2	1		Reference
40–59 years	11.8	0.92	0.561	0.70–1.22
60–79 years	4.5	0.32	0.000	0.21–0.48
Education				
Secondary school	5.6	1		Reference
Secondary modern school	11.1	1.52	0.040	1.02–2.27
Grammar school	13.6	1.92	0.001	1.19–2.85

References were male, secondary school (9 years of school education) and age between 18 and 39.

Grammar school is the highest German school degree after 13 years of school preparing for university studies, secondary modern school requires at least 10 years, secondary school 9 years of school education. Prev, prevalence rate; aOR, adjusted odds ratio; CI, confidence interval.

analysis of the impact of sex in our dataset requires the adjustment for age and education.

Increased risk of self-reported symptoms in females

Next we analysed within the study group differences between males and females regarding the frequency of self-reported symptoms. Our data show that the risk of several reported symptoms adjusted for age and education was significantly higher in the female group. Urticaria [aOR = 2.41; 95% CI (1.73–3.34); *P* < 0.01] and

Table 3. Risk (adjusted for age and education) of self-reported adverse reactions associated to food

Symptoms	%Prev	aOR	P-value	95% CI
Dysaesthesia of the tongue				
Male	8.0	1		Reference
Female	12.6	1.83	0.000	1.40–2.39
Angioedema of the lips				
Male	3.7	2.27	0.000	Reference
Female	8.0	2.27	0.000	1.60–3.24
Urticaria				
Male	4.7	1		Reference
Female	9.3	2.41	0.000	1.73–3.34
Conjunctivitis				
Male	5.0	1		Reference
Female	6.7	1.45	0.020	1.06–1.98
Dyspnoea				
Male	1.2	1		Reference
Female	2.4	2.04	0.021	1.11–3.73
Vertigo				
Male	1.1	1		Reference
Female	2.2	2.00	0.030	1.07–3.73
Gastro-intestinal symptoms				
Male	12.8	1		Reference
Female	14.0	1.18	0.177	0.93–1.51
Headache				
Male	2.5	1		Reference
Female	4.4	1.72	0.025	1.07–2.75
Other diseases				
Male	4.6	1		Reference
Female	6.1	1.41	0.052	1.00–2.00

The table shows the odds ratio in females compared with males. Significant differences were determined for all symptoms except gastro-intestinal symptoms and other diseases. Prev, prevalence rate; aOR, adjusted odds ratio; CI, confidence interval.

angioedema of the lips [aOR = 2.27; 95% CI (1.60–3.24); $P < 0.01$], but also dyspnea [aOR = 2.04; 95% CI (1.11–3.73); $P < 0.05$] and vertigo [aOR = 2.00; 95% CI (1.07–3.73); $P < 0.05$] were more frequently reported by females. Also, symptoms such as headache and conjunctivitis were reported more frequently in females. In contrast, we observed no significant differences of reported symptoms regarding symptoms such as gastrointestinal discomfort [aOR = 1.18; 95% CI (0.93–1.51)] and the category 'other symptoms' [aOR = 1.41; 95% CI (1.00–2.00)] (Table 3).

Higher risk of eczema and urticaria in females

The analysis of self-reported atopic diseases within the last 12 months revealed that females are at higher risk ($P < 0.01$), in particular, for manifestations such as eczema [aOR = 2.33; 95% CI (1.78–3.06)], urticaria [aOR = 2.28; 95% CI (1.39–3.74)] and allergic rhinitis [aOR = 1.38; 95% CI (1.14–1.67)]. In contrast, the risk of allergic asthma

Table 4. Risk (adjusted for age and education) of reported atopic diseases within the last 12 months

Allergic disease	%Prev	aOR	P-value	95% CI
Allergic rhinitis				
Male	11.6	1		Reference
Female	14.5	1.38	0.001	1.14, 1.67
Eczema				
Male	8.1	1		Reference
Female	17.0	2.33	0.000	1.78, 3.06
Urticaria				
Male	2.8	1		Reference
Female	6.4	2.28	0.001	1.39, 3.74
Allergic asthma				
Male	4.5	1		Reference
Female	5.2	1.27	0.229	0.86, 1.91

The table shows the odds ratio in females compared with males. Significant differences were determined for all symptoms except allergic asthma. Prev, prevalence rate; aOR, adjusted odds ratio; CI, confidence interval.

within the last 12 months was not significantly higher in females [aOR = 1.27; 95% CI (0.86–1.91)] (Table 4).

Decreased skin reactivity in females

Next we evaluated skin sensitivity by defining an overall positive skin prick test as having reacted positive to at least one allergen. Skin prick test were only performed in symptomatic subjects. The data show that females have a much lower risk than males [aOR = 0.32; 95% CI (0.21–0.50); $P < 0.01$] for a positive skin prick test to inhalant and/or food allergens. Risk differences were significant but less pronounced in the age groups but could not be seen in the education groups (Table 5). Considering single positive skin prick test reactions, we determined the most significant differences between males and females with regard to sensitizations towards house dust mites followed by grasses, birch and mugwort (Table 6).

These observations of a decreased risk of a positive skin prick test in females were also observed in respect of food allergens (Table 6).

Decreased immunoglobulin E reactivity in females

To test the hypothesis of an increased risk of sensitization in males, we analysed IgE in all symptomatic subjects as well. We detected a significant decreased risk of elevated total IgE levels in females [aOR = 0.37; 95% CI (0.24–0.56); $P < 0.01$]. In contrast, no differences in the age and education groups were determined (Table 5). The analysis of specific IgE (data not shown) indicates comparable results with the skin prick test.

Table 5. Increased skin prick test reactivity and total IgE reactivity in males ($n = 487$)

	Skin prick test reactivity				Total IgE reactivity			
	%Prev	aOR	P-value	95% CI	%Prev	aOR	P-value	95% CI
Sex								
Male	65.6	1		Reference		1		Reference
Female	34.7	0.32	0.000	0.21–0.50		0.37	0.000	0.24–0.56
Age								
18–39 years	55.1	1		Reference	38.4	1		Reference
40–59 years	41.3	0.57	0.025	0.38–0.94	32.1	0.87	0.547	0.54–1.38
60–79 years	32.9	0.45	0.013	0.24–0.85	27.5	0.71	0.288	0.37–1.34
Education								
Secondary school	41.3	1		Reference	28.9	1		Reference
Secondary modern school	44.4	0.77	0.418	0.40–1.46	33.5	1.04	0.920	0.52–2.05
Grammar school	57.6	1.17	0.621	0.62–2.23	37.2	1.10	0.773	0.56–2.17

References were male, secondary school (9 years of school education) and age 18–39 years.

Grammar school is the highest German school degree after 13 years of school preparing for university studies, secondary modern school requires at least 10 years, secondary school 9 years of school education. Prev, prevalence rate; aOR, adjusted odds ratio; CI, confidence interval.

Increased risk of proven food hypersensitivity in females

Restricting the analysis to patients with complete observations, females were more likely to have a positive DBFCFC than males [aOR = 2.27; 95% CI (1.31–3.93); $P < 0.01$]. Considering the other risk factors (age and education) as well, we determined an increased rate of proven food hypersensitivity in the age group of 18–39 years and for persons with higher education (data not shown) although the risk factor higher education did not reach statistical significance.

These data indicate a higher risk of IgE-mediated food allergy in the female group [aOR = 1.91; 95% CI (1.00–3.63); $P = 0.05$]. Females had also a higher risk of non-IgE-mediated food hypersensitivity [aOR = 2.82; 95% CI (1.04–7.61); $P < 0.05$], (Fig. 2). In both subgroups also significant differences were found in the different age but not in the education groups (data not shown).

Based on analysis with weighted data and considering only patients with full set analysis, a calculated point prevalence for adverse reactions to food of 3.3% [95% CI (2.4–4.5%)] in woman and 1.8% [95% CI (1.2–2.7%)] in men were determined. Because of low case numbers, these point prevalences are reported as raw prevalence rates and were not standardized with regard to age and education.

Discussion

Biologic differences between individuals, but also social and cultural factors influence the development of illness and health in males and females. Today, in affluent societies, being male is the largest demographic risk factor for early mortality with peaks of the age-specific male: female mortality ratio in young adults as high as 3:1. Compared with women, men tend to have greater height

and weight, more upper-body strength, higher metabolic rates and later sexual maturity. Some increased risks result directly from the increased vulnerability of male structural and physiological systems, especially lower resistance to infection, stress and injury [23, 24]. After adjustment for age and education, the analysis of a specific risk between males and females from our population-based study clearly indicates that females have a higher risk of self-reported allergic symptoms. In symptomatic patients that underwent physical examinations, we found that males are at higher risk with regard to sensitization determined by either skin prick test or specific IgE. Previous studies have shown that women with self-reported food hypersensitivity have been shown to exhibit greater negative affect, such as depression and neuroticism and also self-reported general ill-health, physical symptoms, as well as psychological distress were significantly higher in females compared with males [25, 26]. This may explain differences in self-assessed health in the context of perceived food allergy.

In the present study, the prevalence of proven food hypersensitivity was increased more than twofold in females in comparison with males (3.3% vs. 1.8%). These data are in line with previous data from epidemiological studies, in which differences between males and females were reported and indicated that skin reactivity to inhalant allergens is higher in young males and remains increased throughout early adult life [27]. In addition, higher serum IgE levels have been reported in young males [28]. Regarding clinically relevant allergic outcomes, e.g. allergic asthma, epidemiological studies have reported predominance of males before puberty and predominance of females after puberty [29–32]. The prevalence of reported hayfever is predominantly reported in prepubertal boys with a shift to a female predominance in

Table 6. Risk (adjusted for age and education) of positive SPT-reactions to single inhalant allergens in the skin prick test, and gender dependent prevalence of positive SPT reactions to single food allergens in the skin prick test

Allergen	% Prev	aOR	P-value	95% CI
Derm. pt.				
Male	15.1	1		Reference
Female	3.3	0.23	0.000	0.11–0.46
Grass pollen				
Male	41.6	1		Reference
Female	17.7	0.33	0.000	0.27–0.51
Birch				
Male	36.0	1		Reference
Female	18.0	0.48	0.001	0.31–0.73
Mugwort				
Male	19.9	1		Reference
Female	10.3	0.48	0.007	0.28–0.82
Cat				
Male	23.1	1		Reference
Female	12.3	0.53	0.014	0.33–0.88
Dog				
Male	12.9	1		Reference
Female	7.3	0.66	0.144	0.38–1.15
Hazelnut				
Male	24.9	1		Reference
Female	15.0	0.66	0.076	0.42–1.04
Walnut				
Male	9.7	1		Reference
Female	3.7	0.42	0.023	0.20–0.89
Apple				
Male	22.2	1		Reference
Female	13.3	0.59	0.035	0.36–0.96
Carrot				
Male	17.3	1		Reference
Female	8.7	0.53	0.016	0.31–0.89
Raw potato				
Male	20.5	1		Reference
Female	11.0	0.57	0.022	0.35–0.92
Celery				
Male	13.4	1		Reference
Female	8.3	0.62	0.081	0.37–1.06
Sesame				
Male	9.1	1		Reference
Female	3.7	0.43	0.016	0.22–0.86
Pollen				
Male	57.5	1		Reference
Female	25.3	0.33	0.000	0.22–0.50
Meal				
Male	14.0	1		Reference
Female	5.6	0.42	0.003	0.23–0.75
Positive skin prick (total)				
Male	65.6	1		Reference
Female	34.7	0.32	0.000	0.21–0.50

Prev, prevalence rate; aOR, adjusted odds ratio; CI, confidence interval.

adolescence as well [33, 34]. However, other studies have pointed out that girls have higher reported eczema prevalence during early childhood, which increases later in

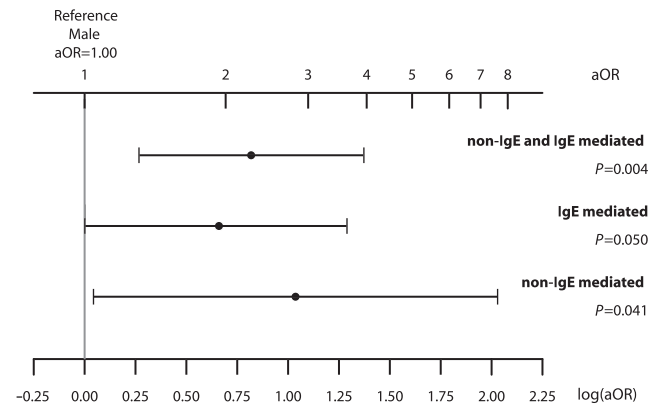


Fig. 2. IgE-mediated food allergy (weighted, $n = 37$) and non-IgE-mediated adverse reactions to food (weighted, $n = 28$) in females related to males aOR, adjusted odds ratio.

life [35]. This indicates that puberty seems to have an important impact on the prevalence of atopic diseases in general.

Furthermore, our data show an increased prevalence of self-reported symptoms in younger adults and persons with higher education. These results indicate that the analysis on the prevalence of food hypersensitivity needs adjustment for confounding factors such as education and age.

However, we need to consider that our study may be subject to a selection bias, as the response rate in the first step was only 30.8%. A low response rate by itself provides no information with regard to a selection bias but indicates that a potential selection bias should be taken into account. It may be even the case, i.e. that providing incentives for study participants increases response rates but at the same time increases selection bias. A potential selection bias was taken very seriously from the beginning of the study and the study was essentially designed in such a way that was based on a comparison with data from the National Health Survey (1998). A weighting scheme was applied making the results representative for adults aged 18–79 years. That a selection bias was present is made evident by Table 1. However, this selection bias due to a low response rate was corrected, by weighting of the data with regard to age, sex education and allergic diseases as described above. This makes the data representative for the German adult population aged 18–79 years. In any case, the main purpose of our study was to identify individuals with a history of adverse reactions to food.

Altogether, our study indicates the importance of analysing epidemiological data not only by history but also with regard to the individual sensitization pattern and provocation tests. The influence of sex hormones on the development and outcome of the allergic immune response is most probably diverse, and socio-cultural

factors need consideration and may affect the rate of sensitization and clinical disease. The observation that the increased sensitization rate in males did not necessarily led to an increased frequency of proven allergic manifestation points to the fact that the allergic effector response may be hormone dependent. Interestingly, it has been shown previously that testosterone inhibits histamine and mast cell degranulation, whereas estrogens promote mast cell degranulation [36]. Recent data have shown that estrogen- and progesterone-receptors but not testosterone-receptors are exclusively expressed on mast cells [37]. Furthermore, female hormones increase the expression of histamine receptors on several inflammatory cells and may promote eosinophilic inflammation [38].

Evidence for either beneficial or deleterious effects of female or male hormones on the immune system in general is lacking. *In vitro* studies indicated that progesterone skews the T cell differentiation towards Th2 and induces the production of IL-4 in Th1 clones [39, 40]. This suggests that progesterone may advance the manifestation of an allergic disease. However, data from clinical observations are diverse regarding this matter [41–43]. In addition, the role of oral contraceptives for the development and outcome of allergic diseases has not been finally clarified.

Altogether, we conclude that hormones have an impact on the sensitization and elicitation of the allergic immune response, but also socio-cultural factors are probably relevant. Therefore, such issues should be addressed in the assessment of epidemiological and immunological data to optimize understanding, diagnostic, treatment and prevention of food hypersensitivity.

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Conflict of interest: None.

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