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Effect-modifying impact of age on sex-based differences during oral immunotherapy

To the Editor,

Epidemiological studies have consistently reported significant sex-based disparities in the prevalence of atopic disease.^{1,2} In food allergy, the 1:1.8 female-to-male ratio observed in children was shown to be completely reversed after puberty at 1:0.53, and then to normalize after menopause.³ This likely reflects the biological effect of sex hormones on mast cells and cytokine production.⁴ The reason for male predominance during childhood is unknown but may take root in utero.⁵ There is a lack of data on how sex-based differences impact therapeutic response.⁶

Here, we sought to assess sex-based differences in therapeutic response to oral immunotherapy (OIT) in a large cohort of patients aged 7 months to 46 years (see Data S1). When considering the whole cohort, 573 of 909 patients (63.0%) were male, and the only observable difference between sex was age (Table 1). Female patients in the cohort were in average 1 year older than male patients ($p = .02$). The female-to-male ratio was 1:1.84 before the age of 13 ($n = 849$), after which it decreased to 1:1.26 ($n = 160$).

When stratifying for age, asthma was found significantly less prevalent in females (OR 0.66, $p = .03$) before 13. There was no other sex-based difference in baseline characteristics prior to treatment in the subgroups.

When assessing treatment tolerance, females under 13 were less likely to experience reactions graded CoFAR 3 and above (OR 0.46, $p = .04$) than males. In contrast, after 13, females experienced significantly more reactions graded CoFAR 2 and above (OR 2.03, $p = .03$). For both variables (CoFAR 2 vs 3), the effect of female sex was significantly different before and after the age of 13 ($p = .006$ and $p = .004$, respectively). Age was also found to modify the effect of sex on respiratory symptoms ($p = .02$), anaphylaxis ($p = .04$), or epinephrine use ($p = .02$).

In multivariate analysis, sex and age were not individually associated with severity of dose-related reactions. However, the interaction term between the two was found to be an independent predictor of dose-related reaction severity, along with baseline asthma, higher food-specific IgE and lower total IgE (Table 2).

To the best of our knowledge, this is the first study reporting sex-based differences in OIT. The observed interaction with raises a concern that sex-based differences can be missed unless analyses specifically control for it. Proper assessment of sex-based differences in OIT is critical to ensure equal quality of care for male and female patients. Small cohorts and clinical trials that lack power to assess such interactions should nevertheless stratify sex-based data by age, so that relevant trends can be observed and eventually combined to allow proper analysis.

The main limitation of our study is its retrospective design relying on patient chart review. The smaller proportion of patients older than 13 may have limited our ability to detect significant differences in this subgroup. For example, while we were able to show that female sex affects epinephrine use differently before and after the age of 13, we lacked power to conclude whether this difference is driven by a reduced risk in female children, an increased risk in females after puberty, or both. We could not separate the biologic effect of sex from the behavioral effect of gender, which could have influenced patient decisions regarding use of medication, dose observance, co-factor avoidance, and symptom reporting.

In conclusion, our data show that sex-based differences exist in OIT but depend on an interaction with patient age. To avoid missing clinically relevant sex-based differences, future studies assessing the effect of sex in OIT should be stratified for age or otherwise account for this interaction. These will help better inform decisions on whether and when to initiate OIT in female patients and could eventually lead to personalized approaches according to sex.

TABLE 1 Age and sex interaction on risk of reactions during oral immunotherapy.

	Male (n = 573)	Female (n = 336)	Effect of female sex (OR with 95% CI)			Difference in effect before vs after 13 years (p-value)
			Whole cohort	Patients <13 years	Patients ≥13 years	
Age ≥13 years old	85 (14.8%)	75 (22.3%)	1.46 (1.05–2.05)	-	-	-
Comorbidities						
Asthma	232 (40.5%)	121 (36.0%)	0.83 (0.63–1.09)	0.66 (0.48–0.91)	1.38 (0.7–2.52)	.03
Atopic dermatitis	330 (57.6%)	179 (53.3%)	0.84 (0.64–1.10)	0.86 (0.63–1.17)	0.93 (0.51–1.70)	.83
Allergic rhinitis	215 (37.5%)	123 (36.6%)	0.96 (0.73–1.27)	0.83 (0.60–1.16)	1.00 (0.54–1.88)	.60
Worst reaction pre-OIT						
CoFAR 2 and above	286 (49.9%)	155 (46.1%)	0.86 (0.66–1.12)	0.76 (0.56–1.03)	1.10 (0.59–2.04)	.29
CoFAR 3 and above	169 (29.5%)	93 (27.7%)	0.92 (0.68–1.23)	0.78 (0.55–1.13)	1.03 (0.57–1.87)	.44
CoFAR 4	36 (6.3%)	16 (4.8%)	0.75 (0.41–1.37)	0.64 (0.31–1.35)	0.94 (0.31–2.83)	.58
Allergens included in OIT						
Peanut	363 (63.4%)	212 (63.1%)	0.99 (0.75–1.31)	1.06 (0.77–1.46)	0.85 (0.46–1.55)	.52
Hen's egg	174 (30.4%)	108 (32.1%)	1.09 (0.81–1.45)	1.04 (0.75–1.44)	1.64 (0.80–3.35)	.23
Cow's milk	143 (25.0%)	72 (21.4%)	0.72 (0.59–1.13)	0.74 (0.51–1.07)	1.19 (0.59–2.39)	.26
Sesame	100 (17.5%)	70 (20.8%)	1.25 (0.89–1.75)	1.27 (0.87–1.84)	1.31 (0.57–3.01)	.94
Treenuts	186 (32.5%)	115 (34.2%)	1.08 (0.81–1.44)	1.22 (0.88–1.67)	0.71 (0.37–1.38)	.15
Others	139 (24.3%)	68 (20.2%)	0.79 (0.57–1.10)	0.73 (0.51–1.06)	1.23 (0.58–1.20)	.22
Two allergens or more	302 (52.7%)	160 (47.6%)	0.82 (0.62–1.07)	0.83 (0.61–1.12)	0.91 (0.49–1.67)	.79
Omalizumab	121 (21.1%)	68 (20.2%)	0.95 (0.68–1.32)	0.55 (0.30–1.02)	1.82 (0.82–4.03)	.09
Worst reaction during OIT						
CoFAR 1 and above	261 (45.5%)	159 (47.3%)	1.07 (0.82–1.41)	0.96 (0.71–1.31)	1.38 (0.75–2.52)	.30
CoFAR 2 and above	101 (17.6%)	61 (18.2%)	1.04 (0.73–1.47)	0.65 (0.41–1.03)	2.03 (1.08–3.83)	.004
CoFAR 3 and above	54 (9.5%)	28 (8.3%)	0.87 (0.54–1.41)	0.46 (0.23–0.90)	2.00 (0.89–4.48)	.006
CoFAR 4	0 (0%)	1 (0.3%)	-	-	-	-
Systems involved						
Skin	117 (20.4%)	73 (21.7%)	1.08 (0.78–1.50)	1.03 (0.71–1.51)	1.19 (0.59–2.39)	.73
Gastro-intestinal	184 (32.1%)	111 (33.0%)	1.04 (0.78–1.39)	0.91 (0.65–1.27)	1.29 (0.71–2.35)	.31
Respiratory	58 (10.1%)	31 (9.2%)	0.90 (0.57–1.43)	0.55 (0.30–1.02)	1.82 (0.82–4.03)	.02
Anaphylaxis	64 (11.2%)	39 (11.6%)	1.04 (0.68–1.59)	0.68 (0.39–1.20)	1.76 (0.85–3.62)	.04
Epinephrin use	44 (7.7%)	25 (7.4%)	0.97 (0.58–1.61)	0.52 (0.25–1.08)	2.10 (0.88–4.97)	.02
OIT discontinued	35 (6.1%)	27 (8.0%)	1.34 (0.80–2.26)	1.00 (0.50–1.99)	1.73 (0.73–4.06)	.33
	Male (n = 573)	Female (n = 336)	Effect of female sex (mean difference with 95% CI)			Difference in effect before vs after 13 years (p-value)
			Whole cohort	Patients <13 years	Patients ≥13 years	
Age, y (mean ± SD)	7.7 ± 6.1	8.7 ± 7.6	1.06 (0.15–1.96)	-	-	-
Highest sIgE, log ₂ kUI/L (mean, SD)	3.6 ± 2.8	3.2 ± 2.8	-0.40 (-0.83–0.29)	-0.42 (-0.91–0.06)	-0.61 (-1.50–0.28)	.60
Total IgE, log ₂ kUI/L (mean, SD)	8.2 ± 2.1	7.9 ± 2.2	-0.25 (-0.57–0.07)	-0.32 (-0.69–0.05)	-0.23 (-0.80–0.35)	.79
Updosing phase, days (mean, SD)	302 ± 242	300 ± 223	-2 (-35–31)	-8 (-44–29)	21 (-60–101)	.50

Note: Bold indicates statistically significant findings ($p < .05$).

Abbreviations: CI, confidence interval; CoFAR, consortium for food allergy research grade; OIT, oral immunotherapy; OR, Odds ratio; sIgE, specific IgE.

TABLE 2 Multivariate analysis of predictors of severity of dose-related reactions during oral immunotherapy.

	OR (95% confidence interval)	p-Value
Independent predictors for reaction CoFAR 2 or greater		
Asthma	1.60 (1.01–2.51)	.04
Interaction term: age >13 years and female sex	3.38 (1.80–6.35)	<.001
Highest sIgE, log ₂ kU/L	1.29 (1.18–1.41)	<.001
Independent predictors for reaction CoFAR 3 or greater		
Asthma	2.44 (1.29–4.62)	.006
Interaction term: age >13 years and female sex	2.78 (1.27–6.06)	.01
Total IgE, log ₂ kU/L	0.75 (0.62–0.92)	.005
Highest sIgE, log ₂ kU/L	1.47 (1.24–1.74)	<.001

Note: Logistical regression was performed using ascending conditional approach starting with all variables from Table 1, as well as an interaction term for age and sex.

Abbreviations: CoFAR, consortium for food allergy research; OR, odds ratio; sIgE, specific IgE.

KEYWORDS

age, food allergy, gender, oral immunotherapy, safety, sex, sex-based differences, tolerance

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AUTHOR CONTRIBUTIONS

CB, LP, AD, KS, RL, FG, and PB evaluated and documented patient data. CE, SL, and PB conceived the study and collected the data. CE, CB, and PB analyzed the data and drafted the manuscript. All authors critically reviewed and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Obesity increases allergic airway inflammation that can be successfully treated by oral tolerance

To the Editor,

The prevalence of obesity and allergy has increased in developed countries over the last decades,^{1,2} leading to the hypothesis that these two noncommunicable diseases might be linked. It remains unclear whether obesity, characterized by chronic low-grade inflammation that affects host immunity, contributes to the exacerbation of respiratory allergies. Additionally, the efficacy of inducing mucosal tolerance as a prophylactic intervention against allergic airway disease in obese individuals is still a subject of inquiry. The impact of obesity on immune responses has been demonstrated in vaccinated individuals, revealing diminished vaccine efficacy and impaired duration of protection.³ Our current study investigates whether obesity could impact respiratory allergy development and the induction of mucosal allergen-specific tolerance.

Male C57BL/6 mice fed with a high-fat diet (HFD) or standard chow diet (STD) for 9 weeks were immunized/sensitized and then challenged with ovalbumin (OVA) (Figure S1A). To induce allergen-specific tolerance, mice were orally treated with OVA before sensitization (Appendix S1).

We detected significant differences in body weight between STD and HFD-fed mice, whereby HFD-fed mice had twice the body weight and significantly higher serum leptin levels than STD-fed mice at the time of sacrifice (Figure 1A,B). Fourier-transform infrared spectroscopy (FTIR) of the cecal content demonstrated distinct spectra between obese and lean mice (Figure 1C-F). These findings were confirmed by 16S rRNA gene sequencing, showing that gut microbial profiles of the cecal content significantly differed between obese and lean mice, consistent with other studies.⁴ Specifically, alpha (Figure 1G) and beta (Figure 1H) diversity results revealed that (i) the obese group exhibited significantly lower diversity levels than the lean group and (ii) microbial community structure was strongly affected by diet type (Figure 1I, S2, Table S1).

Obesity exacerbates the allergic response in mice, with sensitization and challenge with OVA leading to significantly heightened manifestations compared to lean mice. This is evidenced by elevated levels of allergen-specific IgE in bronchoalveolar lavage (BAL) and serum (Figure 2A,B), as well as increased levels of IL-5 and IL-13 in the lungs (Figure 2C,D). Eosinophils, B cells, and T cells were upregulated in the lungs of allergic obese compared to allergic lean (Figure 2E,H,I), which explains the significantly higher OVA-specific IL-13 levels (Figure 2D) and exacerbated lung inflammation in the allergic obese group (Figure 2F,G). The rise in Tregs (Figure 2J) was also evident, and this increase could potentially be attributed to the overall expansion of T cells in allergic obese animals.

Interestingly, obesity did not influence the capacity to develop oral tolerance (OT), and tolerized obese mice exhibited a nonallergic phenotype similar to that observed in lean animals. Our results demonstrate an efficient downregulation of allergic parameters upon tolerization (Figure 2A-J; Allergy vs. OT groups), including IgE levels locally and systemically (Figure 2A,B), OVA-specific IL-5/IL-13 (Figure 2C,D), and decreased lung inflammation (Figure 2F,G). Although significant differences were observed in microbial compounds, microbial diversity, and community structure between obese and lean mice (Figure 1C-I), no additional changes were evident based on the treatment (Allergy, OT, PBS) approach (Figure 2K-M).

We hypothesized that a pro-inflammatory state in the gut of obese mice influenced the microenvironment in the mucus layer around the pulmonary tissue affecting different immune cells, including macrophages. We observed a shift in distributions of activated M1 and M2 macrophages in obese PBS-treated control relative to its lean counterpart. Allergic obese showed a significant reduction of M1 compared to the obese PBS control.

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