Allergen sensitization associates with worse lung function parameters

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Abstract

**Aim:** To assess the association between the number of allergen sensitizations and lung function variables in individuals with airway symptoms.

**Methods:** Retrospective study with all individuals who performed lung function and skin-prick tests at CUF-Porto (01/2011-06/2016). Six allergen groups were considered. % predicted pre-bronchodilator test (BD) and % change after BD were analysed for spirometry and plethysmography parameters.

**Results:** A total of 1293 individuals were included, 54% (n=698) adults and 69% (n=891) with sensitization to ≥1 allergen group. %FEV1 was significantly higher and % change in FEV1 significantly lower in non-sensitized individuals. %Raw was higher in polysensitized (vs non-sensitized).

**Conclusions:** The presence of allergen sensitizations was significantly associated with worse key lung function parameters.

**Keywords:** allergen, sensitization, lung function, airways, skin prick test
Introduction

Sensitization to common environmental allergens is frequent: it is estimated that around 40% of the worldwide population is sensitized to at least one allergen. Allergic sensitization can be asymptomatic. However, it is a strong predictor for the future development of allergic diseases (like asthma or allergic rhinitis). The number of sensitizations has been associated with the number of allergic comorbidities, with polysensitization being a strong risk factor for the development of multimorbidity. Raciborski et al. observed that multimorbidity was rare in the case of negative skin-prick tests (SPT) to common inhalant allergens, more frequent in monosensitized subjects (one positive SPT) and very frequent in those with polysensitization (two or more positive SPT). In recent studies including allergen sensitizations in cluster analysis to classify individuals with airways disease, it was reported that presenting a larger number of allergen sensitizations was associated with classification in clusters with higher disease severity.

Considering the relation between polysensitization and multimorbidity and allergic disease severity, we hypothesized that the number of allergen sensitizations might also be associated with objective parameters of lung function.

Lung function tests (LFT) are an important tool in the assessment of patients with respiratory disease, especially with asthma, but may also be relevant in patients with AR. Only a few studies have previously reported an association between atopy and decreased lung function, mainly in individuals with asthma. To our knowledge, only one study, including children with asthma, described a significant relation between polysensitization (≥4 allergens) and lower FEV1/FVC, but the reported 95% confidence interval suggested a nonsignificant association, raising doubts about the meaning of this result. Thus, the association between the number of allergen sensitizations and lung function, irrespective of disease diagnosis, is not well studied yet.

The aim of this study was to assess the association between the number of allergen sensitizations and lung function variables in individuals with airways symptoms.
Materials and Methods

Sample and study design
This was an observational, retrospective study with all individuals who performed body plethysmography (BP) or spirometry with or without bronchodilator test (BD), and SPT at the Allergy, Inflammation and Respiration laboratory (part of an Allergy clinic) at CUF Porto, Portugal, between January 2011 and June 2016. Only the most recent assessment of each individual was included. All data were collected during routine care and the analysis was performed using an anonymised dataset with no personal identifier.

Variables and Measurements
Spirometry and plethysmography were performed following the ATS/ERS recommendations. BD test was performed, when requested, with 400µg salbutamol, delivered through holding chamber, with subsequent tests being repeated after 15 minutes. The standard centre protocol for bronchodilator medication before LFT includes a general advice to withhold inhaled medication for at least 12 hours before LFT; nevertheless, the physician requesting spirometry or BP may give a different advice according to the specific indication for testing. These recommendations are in line with the 2005 ATS guidelines for lung function testing.

A detailed list of the spirometry and BP parameters that were analysed is presented in Supplementary Table I.

Allergic sensitization was assessed by SPT, which were performed according to the guidelines of the European Academy of Allergy and Clinical Immunology. The standard allergen panel included two controls and 14 allergens that were categorized into six groups: 1) mites; 2) dog and cat epithelia; 3) tree pollens; 4) grass pollens; and 5) weed pollens, and 6) molds. Papules were measured by planimetry (Immunotek prick-film), scanned and processed using a specific reading software. The positivity criterium was the presence of an allergen wheal with >50% of the histamine wheal area (skin index >50%).

We grouped the individuals according to the number of sensitizations: not sensitized (0), monosensitized (1), polysensitized to 2 groups of allergens (2) and polysensitized to 3 or more groups of allergens (≥3).

Demographic characteristics, such as age and sex, were also analysed.
Statistical analyses

Categorical variables are presented as absolute frequencies and proportions. Continuous variables were presented using mean and standard deviation (sd). One-way ANOVA was used to compare lung function parameters among groups of allergen sensitizations (with Bonferroni post-hoc test for multiple comparisons). We stratified this analysis by age group (considering children <18 years and adults ≥18 years old). We also used ANCOVA to further explore the impact of age (included as a continuous covariate) in the relation between lung function and the number of allergen sensitizations.

The statistical analysis was performed using IBM SPSS Statistics version 25.0 (Armonk, NYIBM Corp). A p-value of <0.05 was considered statistically significant.

Results

We have included 1293 individuals aged 3 to 86 years old: 447 (35%) under 13 years, 148 (11%) with 13 to 17 years old and 698 (54%) with ≥18 years old; 688 (53%) were female. More than two thirds (n=891, 69%) were sensitized to ≥1 allergen group (Table I).

Spirometry

The description of the spirometry parameters is shown in Supplementary Table II. The comparison of spirometry parameters among groups of allergen sensitizations is shown in Figure 1 and Supplementary Table II. There were statistically significant differences between some of the groups, most when comparing non-sensitized vs. groups with at least one sensitization. These differences occurred in %FVC, %FEV1, FEV1/FVC, %MMEF, and %PEF with those in the non-sensitized group presenting higher values than at least one of the other groups. Percent changes in FEV1 and MMEF were significantly lower in the non-sensitized group compared to at least one of those with allergen sensitizations. The comparisons of FEV1 presented the most consistent results, with %FEV1 being significantly higher and the % change in FEV1 being significantly lower in non-sensitized individuals vs all groups with sensitizations.
When stratifying by age groups, in children there were no statistically significant differences in FVC between the sensitization groups. The %FEV1 and FEV1/FVC were significantly higher in non-sensitized children vs. polysensitized (>3), and FEV1/FVC was also higher in non-sensitized vs. monosensitized (Figure 1 and Supplementary Table III). The % changes in FEV1 and MMEF were significantly lower in non-sensitized vs. polysensitized to 2 allergens (Figure 1 and Supplementary Table III).

In adults, spirometry parameters showed significant differences between the groups, except for the % change in PEF. %FEV1 and % change in FEV1 were significantly higher in non-sensitized vs. monosensitized and polysensitized to ≥3 allergen groups.

FEV1/FVC and % change in MMEF were significantly higher and lower, respectively, in non-sensitized vs. polysensitized to ≥3 allergen groups (Figure 1 and Supplementary Table IV). %PEF was also higher in non-sensitized vs. monosensitized (Supplementary Table IV).

Adjusting for age with ANCOVA led to similar findings (results not shown).

Body plethysmography

Of the 287 BP analysed, 89 (31%) were performed in children (mean(sd) age 10(3) years) and 199 in adults (42(13) years; Table I). In children, 60% were male while in adults, 58% were female.

In Figure 2 and supplementary Table V are summarized the BP parameters and the stratification and comparison of BP parameters according to the number of allergen sensitizations.

A third of the participants had $sRaw > 150\%$. $sRaw$ was higher in polysensitized (2 or >3 sensitizations) vs non-sensitized and in those sensitized to 2 allergen groups vs. monosensitized. No other BP parameter presented significant differences among groups of allergen sensitization.

In children, no statistically significant differences were found in $sRaw$ or other BP parameters between the sensitization groups (Figure 2 and Supplementary Table VI). While in adults, $sRaw$ was significantly higher in adults polysensitized to 2 allergens vs. monosensitized. In adults, no other BP parameter presented significant differences
among groups of allergen sensitization (Figure 2 and Supplementary table VII). After adjusting for age with ANCOVA similar findings were obtained (data not shown).

Discussion

In this study, we observed that several spirometry parameters, including %FEV1, %FVC, FEV1/FVC, %MMEF, and %PEF were significantly higher in the non-sensitized group than in at least one of the other groups (mono- or polysensitized). While the % changes in FEV1 and MMEF were significantly lower in the non-sensitized group than in those polysensitized to 2 or ≥3 allergen groups; the % change in FEV1 was also lower in non-sensitized than in monosensitized. Regarding BP, the number of allergen sensitizations was significantly associated with %sRaw in adults, being higher in individuals polysensitized to 2 or ≥3 allergen groups vs. non-sensitized, and in those polysensitized to 2 allergens vs monosensitized.

This study is one of the first studies assessing the association between lung function parameters and the number of allergen sensitizations and demonstrating that individuals with allergen sensitization have worse lung function irrespective of the presence of an asthma diagnosis. In children, several previous studies have shown associations between the presence of allergen sensitization and decreased pulmonary function and nasal patency, and increased asthma morbidity. In adults, allergen sensitization was related to a poorer lung function, but only in individuals with asthma, which differs from our findings. Some studies reported that polysensitization is significantly associated with a poor quality of life in patients with allergic rhinitis and intermittent asthma, with higher symptom scores for dyspnoea, wheezing, and cough, and with the presence of multimorbidity. Moreover, Ciprandi et al have shown that impaired lung function occurs in polysensitized patients with allergic rhinitis; however, this study only reported on polysensitized individuals and did not clearly assess the relationship between the number of sensitizations and lung function. We could only find one study, by Nagarajan et al, specifically examining the associations between the number of aeroallergens sensitizations and lung function parameters. In this study, in patients with
highly allergic asthma (≥4 allergens), FEV1/FVC was significantly lower than in the
group sensitized to < 4 allergens. Nevertheless, these results are not completely clear as
the reported 95% confidence interval is not in agreement with a significant
association\textsuperscript{14}.

Therefore, the available evidence on the associations between allergen sensitizations,
poly-sensitization with multimorbidity, and increased disease severity are globally
aligned with the statistically significant associations we observed between the presence
of allergic sensitization and worse lung function parameters. However, compared to
monosensitized patients, we could not clearly demonstrate that spirometry or BP
parameters are lower in individuals with a higher number of allergen sensitizations.

Lung function allows an objective assessment of the effect of allergic disease in airways
function. With a more pronounced allergic drive, leading to sensitization to more
allergens, we could expect a higher impact on lung function and lower spirometric
values, as suggested by Nagarajan et al\textsuperscript{14}. Nevertheless, although theoretically sound,
the available evidence, including this study, does not consistently support such an
association. Moreover, although we found some statistically significant associations, we
could not assess the clinical relevance of the differences between groups. In fact, most
differences were small, of only a few percent points within the normal range (e.g.
%FEV1 of 106% in non-sensitized vs. 101% in polysensitized to ≥3 allergen groups,
p<0.001, corresponding to a 5% difference), which might not translate into clinical
differences. Additionally, in this study, we could not account for several factors that
might be relevant in the association between LFT parameters and the number of
allergen sensitizations, such as ongoing inhaled medication, the relevance of the
sensitizations and recent exposure to triggers, treatment with allergen immunotherapy
and even the possibility of an exacerbation at the time of LFT. Also, physician
diagnosis or clinical indication for LFT were not part of our anonymized database and
could not be included in the analysis. Nevertheless, considering the specific setting
where this study was held (an Allergy clinic), where LFT are usually performed to
patients with respiratory symptoms in the context of suspected or confirmed allergic
diseases, and that only 3% of the included LFT were requested by physicians from other
medical specialties (data not shown), we estimate that over 95% of the LFT were
performed in patients with asthma and/or rhinitis (to assess the presence of asthma).

Furthermore, this study is limited by its retrospective design and the specific setting
where it was held, that limits the generalizability of our results to other clinical contexts.
Future studies are needed to assess additional clinical parameters and the impact of possible confounding variables. Despite these limitations, this is one of the first studies showing an association between lung function parameters and the number of allergen sensitizations. The published literature is limited, and only a few studies discussed this topic. Furthermore, we analysed all the spirometry parameters and not only the main variables. Importantly, we included BP parameters that, to our knowledge, were not previously assessed in the published study that reported on the relationship between lung function and the number of allergen sensitizations.

In conclusion, in this retrospective study, the presence of allergen sensitizations was significantly associated with worse lung function and increased bronchodilator response in spirometry and increased specific resistance in body plethysmography.

Conflict of Interest

The authors declare they have no conflict of interest.

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Tables

Table I: Description of the study participants.

<table>
<thead>
<tr>
<th>Total* (n=1293)</th>
<th>Number of allergen sensitizations</th>
<th>Body plethysmography (n=287; 22%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (n=402; 31%)</td>
<td>1 (n=320; 25%)</td>
</tr>
<tr>
<td>n</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>Sex, female</td>
<td>688 53</td>
<td>267 67</td>
</tr>
<tr>
<td>Age group, ≥18 years old</td>
<td>698 54</td>
<td>252 63</td>
</tr>
<tr>
<td>Age, mean(sd)</td>
<td>25 (17)</td>
<td>30 (20)</td>
</tr>
<tr>
<td>Allergen sensitizations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mites</td>
<td>703 55</td>
<td>0</td>
</tr>
<tr>
<td>Epithelia</td>
<td>329 26</td>
<td>0</td>
</tr>
<tr>
<td>Grass pollens</td>
<td>484 38</td>
<td>0</td>
</tr>
<tr>
<td>Tree pollens</td>
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<tr>
<td>Weed pollens</td>
<td>215 17</td>
<td>0</td>
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<tr>
<td>Mold</td>
<td>82 7</td>
<td>0</td>
</tr>
<tr>
<td>At least one</td>
<td>892 70</td>
<td>0</td>
</tr>
</tbody>
</table>

* All study participants performed spirometry

Figure legends:

Figure 1: Mean with 95% confidence interval for spirometry parameters, including % predicted pre-BD (panel a) and % change with BD (panel b) stratified by age group (1, all; 2, <18 years; 3, ≥18 years). *, p<0.05; **, p<0.001.
Figure 2: Mean with 95% confidence interval for body plethysmography, including % predicted vs. BD (panel a) and % change with BD (panel b) stratified by age group (1, all; 2, <18 years; 3, ≥18 years). *, p<0.05; **, p<0.001.