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RESEARCH LETTER

WILEY

Improvement of daily allergy control by sublingual immunotherapy: A MASK-air® study

To the Editor,

Allergen immunotherapy (AIT) is an effective treatment for allergic rhinitis and has been hypothesised as rapidly effective.[1] Rush subcutaneous AIT to pollen and mites reduces skin test reactivity to allergens within days, in a dose-dependent and time-independent manner.[2,3] Venom rush AIT is also effective within days. The tolerance of beekeepers to bee stings fades in some individuals and is also re-installed after a few stings in a dose-dependent and time-independent manner.[4] Finally, desensitisation to drug allergy is effective within hours and there is a refractory period after tolerance.[5] These short-term clinical sequences cannot be explained by an adaptive immune response (immunotherapy) but may be related to rapid and short-lasting cell downregulation responses (desensitisation).[1,6]

These considerations have prompted the hypothesis that sublingual immunotherapy (SLIT) may induce a rapid relief of allergic symptoms during the pollen season.[1] While previous studies have found that SLIT is effective in the same allergy season as when first introduced,[7] no study has ever assessed its efficacy on a daily basis. Therefore, in this study, we aimed to assess whether days of SLIT use were associated with better allergy control during the expected pollen season. Such analyses may hint at a potential short-term effect of SLIT, to be assessed by proper studies.

MASK-air® is a free mobile app available in 27 countries. The app includes a daily monitoring questionnaire which can be answered on a daily basis. The questionnaire assesses (i) the daily severity and impact of allergy symptoms (through four mandatory visual analogue scales—VASs),[8] (ii) the daily rhinitis and asthma medication used on that day by the patient and (iii) whether the patient used AIT on that day. Such information allows the computation of the combined symptom-medication score (CSMS), assessing the daily control of allergic rhinitis.[9]

We included the daily monitoring data of European MASK-air® users (i) aged between 16 years (or lower—not below 13 years—for countries with a lower age of digital consent) and 90 years, (ii) with a self-reported diagnosis of allergic rhinitis and (iii) on SLIT for grass pollen. We analysed the data provided during the months of May and June (assuming that they corresponded to the grass pollen season in Europe) from 2015 to 2021.

We performed a cross-sectional analysis, in which we studied all days reported between May and June for three different samples: (S1) all users under SLIT (of any type) for grass pollen; (S2) users taking SLIT tablets for grass pollen and (S3) users using SLIT (of any type) for grass pollen and reporting at least 1 day of AIT use during the studied period (to account for non-adherence and potential incorrect reporting of SLIT use). Sample 1 was used to assess a sufficiently-powered group. The robustness of the results of SLIT in S1 was assessed in S2 and S3, where different inclusion criteria were adopted.

We performed this cross-sectional analysis by building multivariable mixed-effects regression models to assess, for each sample, whether days of AIT use were associated with a better allergic rhinitis control (with the dependent variables being either the CSMS or the VAS quantifying the impact of global allergy symptoms—'VAS global'). In our models, we considered the clustering of observations by users, by country and by month of the year, setting these variables as random effects (i.e. we clustered observations by users, by the user's country and by the month of the year). In addition, results were further adjusted for the following independent variables which were included in our regression models: baseline domains impacted by allergic rhinitis, baseline symptoms of allergic rhinitis, patients' gender and age, self-reported diagnosis of asthma, occurrence of conjunctivitis and use of daily rhinitis or asthma medication in monotherapy or co-medication.

We also performed a longitudinal analysis, in which we analysed complete periods of 2 weeks (missing at most an average of 2 days per week) of patients using SLIT for grass pollen and reporting at least 1 day of AIT use during the same period. We performed the longitudinal study in a smaller subset of users, comparing days of AIT use versus days when AIT was not used on the CSMS and VAS global. For such comparisons, we built multivariable mixed-effects regression models similar to those applied in cross-sectional analyses.

When responding to the MASK-air® daily questionnaire, it is not possible to skip any of the questions and data are saved only after the final answer. This precludes missing data within each questionnaire. *P*-values <.05 were considered statistically significant. A Holm–Bonferroni correction was applied to account for multiple

Jean Bousquet and Bernardo Sousa-Pinto participated equally in the paper.

analyses. Additional information about study methods and findings is available in the following repository: https://github.com/BernardoSousaPinto/Improvement-of-daily-allergy-control-by-sublingual-immunotherapy-A-MASK-air-study

MASK-air® is CE1-registered and complies with the General Data Protection Regulation. All data were anonymised prior to the study. Users agreed to having their data analysed for scientific purposes in the Terms of Use. An independent review board approval was not required for this study.

In the cross-sectional analysis, we studied 3968 days from 171 patients in S1. Immunotherapy was reported in 2380 (60.0%) days.

Key messages

- mHealth-based real-world data allow rhinitis control to be monitored in patients using sublingual immunotherapy (SLIT).
- Days with SLIT use were associated with better rhinitis control than days without SLIT use.
- Our results raise the hypothesis (to be subsequently tested) that SLIT may be rapidly effective.

TABLE 1 Multivariable mixed-effects regression models assessing the association between use of immunotherapy for grass pollen and allergic rhinitis control.

	Association with the CSMS—regression coefficient (95%CI) [*p*-value]	Association with VAS global—regression coefficient (95%CI) [*p*-value]
A. Sublingual immunotherapy for grass pollen allergy		
Use of immunotherapy	−2.2 (−3.1;-1.3) [<0.001]	−3.0 (−4.5;-1.5) [<0.001]
Male sex	−7.1 (−11.3;-2.9) [0.001][a]	−9.7 (−16.2;-3.3) [0.004][a]
Age	−0.2 (−0.4;-0.1) [0.002][a]	−0.3 (−0.5;-0.1) [0.005][a]
Baseline impact[b]	0.4 (−1.3;2.1) [0.638][a]	0.9 (−1.6;3.5) [0.477][a]
Baseline symptoms	−0.8 (−2.4;0.8) [0.310][a]	−1.4 (−3.8;1.1) [0.280][a]
Asthma	−3.0 (−7.3;1.2) [0.164][a]	−8.0 (−14.6;-1.4) [0.019][a]
Conjunctivitis	5.2 (−2.7;13.2) [0.201][a]	5.0 (−7.3;17.3) [0.429][a]
Use of rhinitis medication		
No medication	-[c]	-[c]
Monotherapy	4.3 (3.5;5.1) [<0.001]	5.0 (3.8;6.3) [<0.001]
Co-medication	9.7 (8.6;10.8) [<0.001]	10.1 (8.4;11.8) [<0.001]
Use of asthma medication		
No medication	-[c]	-[c]
Monotherapy	3.2 (1.6;4.8) [<0.001]	0.9 (−1.7;3.4) [0.496][a]
Co-medication	4.9 (1.3;8.5) [0.008][a]	3.5 (−2.2;9.3) [0.229][a]
B. Sublingual immunotherapy tablets for grass pollen allergy		
Use of immunotherapy	−2.9 (−4.3;-1.5) [<0.001]	−2.9 (−5.0;-0.7) [0.010][a]
Male sex	−7.9 (−13.5;-2.3) [0.007][a]	−10.3 (−19.0;-1.6) [0.022][a]
Age	−0.3 (−0.4;-0.1) [0.014][a]	−0.3 (−0.6;0.0) [0.040][a]
Baseline impact[b]	0.3 (−1.9;2.6) [0.765][a]	0.9 (−2.6;4.4) [0.618][a]
Baseline symptoms	−1.5 (−3.5;0.6) [0.164][a]	−1.8 (−5.0;1.3) [0.264][a]
Asthma	−0.8 (−6.4;4.8) [0.771][a]	−4.5 (−13.2;4.2) [0.315][a]
Conjunctivitis	8.5 (−1.7;18.8) [0.108][a]	13.8 (−2.4;30.0) [0.099][a]
Use of rhinitis medication		
No medication	-[c]	-[c]
Monotherapy	2.9 (1.9;4.0) [<0.001]	3.9 (2.2;5.5) [<0.001]
Co-medication	10.6 (9.0;12.2) [<0.001]	12.4 (9.9;14.9) [<0.001]
Use of asthma medication		
No medication	-[c]	-[c]
Monotherapy	3.3 (1.0;5.6) [0.005][a]	0.8 (−2.8;4.4) [0.666][a]
Co-medication	3.9 (−0.4;8.2) [0.078][a]	0.9 (−5.8;7.7) [0.786][a]

(Continues)

TABLE 1 (Continued)

	Association with the CSMS—regression coefficient (95%CI) [*p*-value]	Association with VAS global—regression coefficient (95%CI) [*p*-value]
C. Sublingual immunotherapy for grass pollen users reporting AIT use for at least 1 day		
Use of immunotherapy	−2.1 (−3.0;-1.2) [<0.001]	−2.7 (−4.2;-1.2) [0.001][a]
Male sex	−6.1 (−10.7;-1.6) [0.009][a]	−9.9 (−17.1;-2.7) [0.008][a]
Age	−0.3 (−0.4;-0.1) [0.003][a]	−0.4 (−0.7;-0.1) [0.003][a]
Baseline impact[b]	−0.5 (−2.1;1.2) [0.580][a]	−0.4 (−3.1;2.2) [0.752][a]
Baseline symptoms	−0.6 (−2.2;1.0) [0.466][a]	−0.9 (−3.5;1.7) [0.490][a]
Asthma	−0.3 (−4.9;4.3) [0.899][a]	−4.3 (−11.7;3.0) [0.251][a]
Conjunctivitis	3.3 (−5.1;11.6) [0.443][a]	−0.3 (−13.7;13.0) [0.962][a]
Use of rhinitis medication		
No medication	-[c]	-[c]
Monotherapy	5.0 (4.2;5.9) [<0.001]	6.0 (4.7;7.4) [<0.001]
Co-medication	10.0 (8.9;11.1) [<0.001]	10.6 (8.7;12.4) [<0.001]
Use of asthma medication		
No medication	-[c]	-[c]
Monotherapy	3.0 (1.3;4.7) [0.001][a]	0.8 (−2.0;3.7) [0.559][a]
Co-medication	4.3 (0.6;8.0) [0.023][a]	2.9 (−3.1;8.9) [0.345][a]
MASK-air® adherence[d,e]	−0.2 (−0.3;-0.1) [0.001][a]	−0.2 (−0.4;-0.1) [0.001][a]

Note: Adherence to AIT was calculated as [*N* days when the patient reported AIT use]/[*N* days when the patient used MASK-air®].

Abbreviations: CI, Confidence interval; CSMS, Combined symptom-medication score; VAS, Visual analogue scale.

[a]Not statistically significant after Bonferroni–Holm correction.

[b]Number of domains affected by allergy.

[c]Reference category.

[d]Regression coefficients for allergen immunotherapy adherence: association with the CSMS = 2.6 (95%CI = -6.4;11.5) [*p* = .577]; association with VAS global = 5.0 (95%CI = -9.2;19.2) [*p*-value = .490].

[e]MASK-air® adherence was calculated as [*N* days when the patient answered to the MASK-air® daily monitoring questionnaire]/[*N* days between the end of 2021 and the date when the patient first answered to the MASK-air® daily monitoring questionnaire].

There were 111 users (*N* = 2311 days; S2) using SLIT tablets for grass pollen. Finally, 113 users (*N* = 3098 days; S3) indicated that they were under SLIT for grass pollen allergy and reported the use of AIT for at least 1 day.

In the longitudinal analysis, we studied 2615 days from 45 patients. Immunotherapy was reported in 2026 (77.5%) days.

The baseline characteristics of the users were not similar in all samples. The median CSMS and VAS global levels tended to be lower in days with SLIT.

In days of MASK-air® use, the average adherence to SLIT was 54.8%. Considering only users reporting at least 1 day of SLIT use, the average adherence was 83.0%.

In S1, SLIT days were associated with improved CSMS (regression coefficient = −2.2; 95%CI = −3.1; −1.3; $p < .001$) and VAS global (regression coefficient = −3.0; 95%CI = −4.5; −1.5; $p < .001$) (Table 1; Figure 1). SLIT days were also associated with decreased CSMS and VAS global in S2 and S3 (Table 1; Figure 1). Higher adherence to the MASK-air® app was found to be associated with lower CSMS and VAS global.

Ancillary analyses were performed (i) in grass pollen SLIT users reporting at least 4 days of MASK-air® use, (ii) comparing patients with high/variable median CSMS versus those with low median CSMS and (iii) considering the effect of SLIT given on the previous day. Similar results were observed in all these analyses, except when, for days without SLIT, we compared days when SLIT had been used on the previous day versus days on which this had not occurred.

Results of the longitudinal study were comparable to those of the cross-sectional study (Figure 1), with SLIT days being associated with lower CSMS (regression coefficient = −2.6; 95%CI = −3.6; −1.6) and VAS global (regression coefficient = −4.0; 95%CI = −5.6; −2.3).

This study using MASK-air® real-world data suggests that in patients under SLIT during the pollen season, AIT may have a very short-term effect. In particular, in patients under SLIT, days with AIT were associated with better allergy control than those without AIT. However, real-world data are only hypothesis-generating (considering the study design, we should be particularly careful when dealing with temporality) and such hypotheses require confirmation by future well-designed and sufficiently-powered trials.

This study has several strengths, including its multinational scope and the large volume of data analysed. In addition, the CSMS and MASK-air® VASs display medium-high validity, reliability and responsiveness.[8,9] Finally, we analysed three samples in cross-sectional analyses and performed a longitudinal analysis, observing robust results.

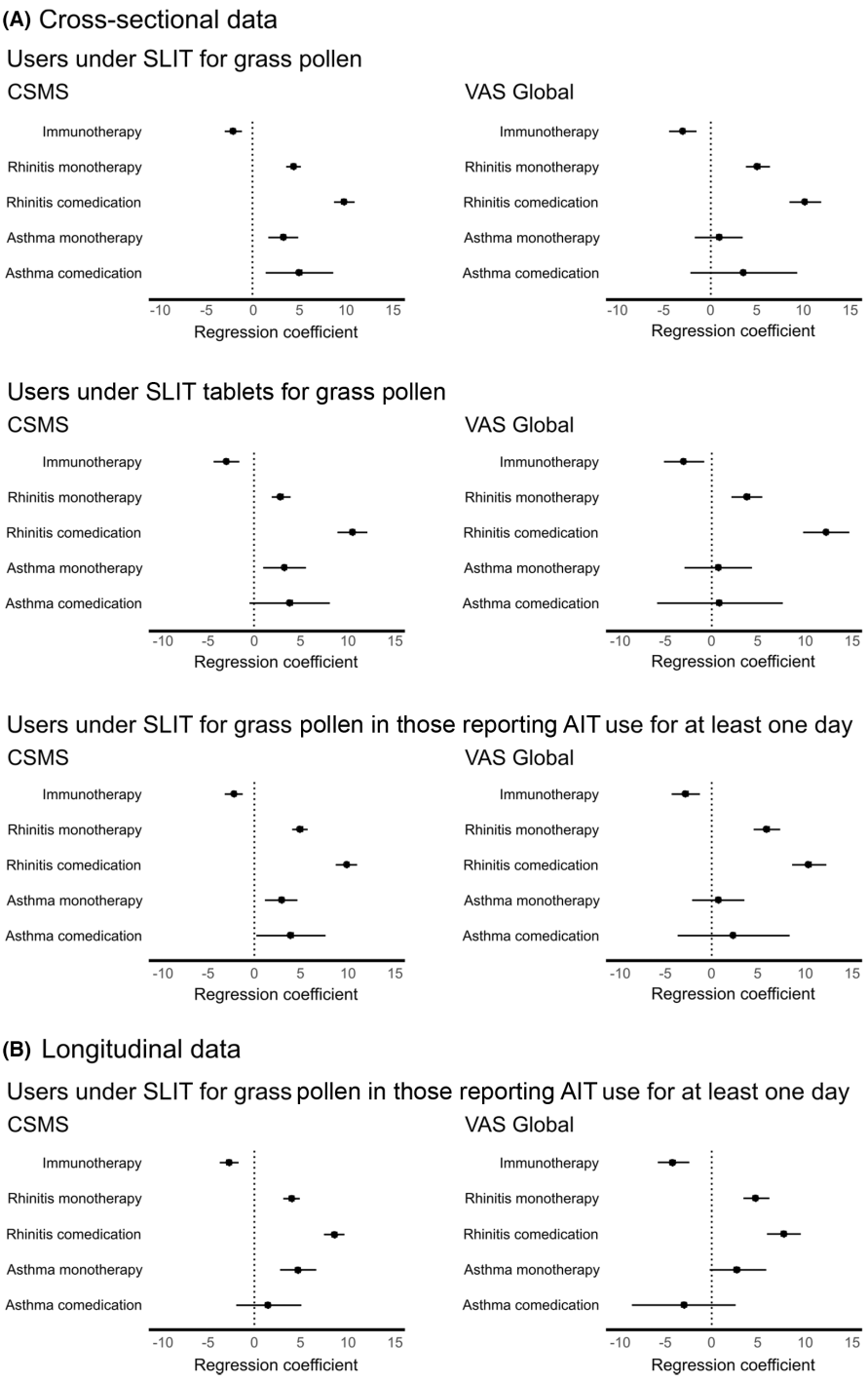

FIGURE 1 Regression coefficients for users under sublingual immunotherapy (SLIT) for grass pollen, on the association between immunotherapy or medication in the CSMS and VAS global. CSMS, Combined symptom-medication score; VAS global, Visual analogue scale on global allergy symptoms.

This study also has limitations of which some are common to other mHealth observational studies (e.g. selection biases resulting from overrepresentation of younger users and information biases related to the self-reported nature of the data).[8] In addition, there are specific limitations: (i) This is mostly a cross-sectional study, impairing the establishment of causality or of temporal relationships, and therefore being capable only of generating new hypotheses. Although we performed a longitudinal analysis, it encompassed only 45 patients. (ii) We do not have information on the date each patient started using SLIT. We are therefore unable to distinguish patients who have been on SLIT for a period long enough to allow reaching an optimal control versus those who have just started using SLIT. (iii) The grass pollen season has been roughly estimated, considering the period of May–June. (iv) We did not consider the different SLIT products in this study. These different products display highly variable standardisation, allergen content and clinical documentation of efficacy and safety. Such a limitation, however, has been partly overcome by the assessment of S2, as, in Europe, there are only a limited set of available products for grass pollen SLIT tablets.

The results of this study raise the hypothesis that SLIT may have a short-term effectiveness. If confirmed in future studies, this may provide a novel strategy in patients allergic to pollens who are

uncontrolled despite optimal pharmacotherapy. However, several limitations of the study should be considered and its results should be understood as hypothesis-generating, building the basis for future studies.

AUTHOR CONTRIBUTION

Jean Bousquet proposed the concept of the paper, analysed the results and wrote the paper. Bernardo Sousa-Pinto made the statistical plan, performed the analysis and wrote the paper. Josep M Anto, G Walter Canonica, Wienczyslawa Czarlewski, Philippe Devillier, Tari Haahtela, Daniel Laune, Joaquim Mullol, Marek Jutel, Piotr Kuna, Mohamed H Shamji, Erkka Valovirta, Torsten Zuberbier and Joao A Fonseca represented the think tank and participated in the analysis and in the writing of the paper. Ludger Klimek, Luisa Brussino, Lorenzo Cecchi, Violeta Kvedariene, Mario Morais-Almeida, Ralph Mösges, Marek Niedoszytko, Nikolaos G Papadopoulos, Vincenzo Patella, Nhân Pham-Thi, Boleslaw Samolinski, Luis Taborda-Barata[31], Sanna Toppila-Salmi, Joaquin Sastre, Arunas Valiulis and Maria Teresa Ventura proposed the MASK-air app to their patients. Oliver Pfaar participated in the concept of the study and wrote the paper. All authors have read the paper and given their final approval for submission.

CONFLICT OF INTEREST STATEMENT

JB reports personal fees from Cipla, Menarini, Mylan, Novartis, Purina, Sanofi-Aventis, Teva, Uriach, other from KYomed-Innov, other from Mask-air-SAS, outside the submitted work. LC reports personal fees from Thermofisher, personal fees from Sanofi, personal fees from Astra Zeneca, personal fees from Novartis, outside the submitted work. PD reports personal fees from ALK Abello, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Chiesi, personal fees and non-financial support from Astra Zeneca, personal fees from GlaxoSmithKline, personal fees from Menarini, personal fees from Novartis, personal fees and non-financial support from Stallergenes, personal fees from Sanofi, outside the submitted work. JAF reports being co-founder of an SME that develops mHealth technologies, such as digital biomarkers and has the copyright of the CARAT and a CARATkids PROM. TH reports personal fees from Orion Pharma, outside the submitted work. 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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Jean Bousquet[1,2,3]
Bernardo Sousa-Pinto[4,5]
Mohamed H. Shamji[6,7]
Josep M. Anto[8,9,10,11]
Ludger Klimek[12,13]
G. Walter Canonica[14,15]
Wienczyslawa Czarlewski[16]
Philippe Devillier[17]
Tari Haahtela[18]
Daniel Laune[19]
Joaquim Mullol[20,21]
Luisa Brussino[22,23]
Lorenzo Cecchi[24]
Violeta Kvedariene[25,26]
Mario Morais-Almeida[27]
Ralph Mösges[28]
Marek Niedoszytko[29]
Nikolaos G. Papadopoulos[30]
Vincenzo Patella[31,32]
Nhân Pham-Thi[33,34,35]
Boleslaw Samolinski[36]
Luis Taborda-Barata[37,38]
Sanna Toppila-Salmi[18]
Joaquin Sastre[39]
Arunas Valiulis[40,41]
Maria Teresa Ventura[42,43]
Marek Jutel[44]
Piotr Kuna[45]
Erkka Valovirta[46]
Torsten Zuberbier[1,2]
Joao A. Fonseca[4,5]
Oliver Pfaar[47]

[1]*Institute of Allergology, Charité–Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany*
[2]*Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany*
[3]*University Hospital Montpellier, Montpellier, France*
[4]*MEDCIDS—Department of Community Medicine, Information and Health Decision Sciences; Faculty of Medicine, University of Porto, Porto, Portugal*
[5]*CINTESIS@RISE–Health Research Network, Faculty of Medicine, University of Porto, Porto, Portugal*
[6]*National Heart and Lung Institute, Imperial College, London, UK*
[7]*NIHR Imperial Biomedical Research Centre, London, UK*
[8]*ISGlobal. ISGlobal, Barcelona Institute for Global Health, Barcelona, Spain*

[9]IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
[10]Universitat Pompeu Fabra (UPF), Barcelona, Spain
[11]CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain
[12]Department of Otolaryngology, Head and Neck Surgery, Universitätsmedizin Mainz, Mainz, Germany
[13]Center for Rhinology and Allergology, Wiesbaden, Germany
[14]Department of Biomedical Sciences, Humanitas University, Milan, Italy
[15]IRCCS Humanitas Research Center, Personalized medicine, Asthma and Allergy, Milan, Italy
[16]Medical Consulting Czarlewski, Levallois, France
[17]VIM Suresnes, UMR 0892, Pôle des Maladies des Voies Respiratoires, Hôpital Foch, Université Paris-Saclay, Suresnes, France
[18]Skin and Allergy Hospital, Helsinki University Hospital, and University of Helsinki, Helsinki, Finland
[19]KYomed INNOV, Montpellier, France
[20]Rhinology Unit & Smell Clinic, ENT Department, Hospital Clínic, Barcelona, Spain
[21]Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, CIBERES, University of Barcelona, Barcelona, Spain
[22]Department of Medical Sciences, University of Torino, Torino, Italy
[23]Allergy and Clinical Immunology Unit, Mauriziano Hospital, Torino, Italy
[24]SOS Allergology and Clinical Immunology, USL Toscana Centro, Prato, Italy
[25]Institute of Clinical Medicine, Clinic of Chest Diseases and Allergology, Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[26]Department of Pathology, Faculty of Medicine, Institute of Biomedical Sciences, Vilnius University, Vilnius, Lithuania
[27]Allergy Center, CUF Descobertas Hospital, Lisbon, Portugal
[28]Institute of Medical Statistics and Computational Biology, University of Cologne and ClinCompetence Cologne GmbH, Cologne, Germany
[29]Department of Allergology, Medical University of Gdańsk, Gdansk, Poland
[30]Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece
[31]Division of Allergy and Clinical Immunology, Department of Medicine, "Santa Maria della Speranza" Hospital, Agency of Health ASL, Salerno, Italy
[32]Postgraduate Program in Allergy and Clinical Immunology, University of Naples Federico II, Naples, Italy
[33]Ecole Polytechnique de Palaiseau, Palaiseau, France
[34]IRBA (Institut de Recherche Bio-Médicale des Armées), Brétigny sur Orge, France
[35]Université Paris Cité, Paris, France
[36]Department of Prevention of Environmental Hazards, Allergology and Immunology, Medical University of Warsaw, Warsaw, Poland
[37]Department of Immunoallergology, Cova da Beira University Hospital Centre, Covilhã, Portugal
[38]UBIAir—Clinical & Experimental Lung Centre and CICS-UBI Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal
[39]Allergy Service, Fundacion Jimenez Diaz, Autonoma University of Madrid, CIBERES-ISCIII, Madrid, Spain
[40]Institute of Clinical Medicine and Institute of Health Sciences, Vilnius, Lithuania
[41]Medical Faculty of Vilnius University, Vilnius, Lithuania
[42]Unit of Geriatric Immunoallergology, University of Bari Medical School, Bari, Italy
[43]Institute of Sciences of Food Production, National Research Council (ISPA-CNR), Bari, Italy
[44]Department of Clinical Immunology, Wrocław Medical University, ALL-MED Medical Research Institute, Wroclaw, Poland
[45]Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical University of Lodz, Lodz, Poland
[46]Department of Lung Diseases and Clinical Allergology, University of Turku, Turku, Finland
[47]Section of Rhinology and Allergy, Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Marburg, Philipps-Universität Marburg, Marburg, Germany

Correspondence
Jean Bousquet, Institute of Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany.
Email: jean.bousquet@orange.fr

ORCID

Mohamed H. Shamji https://orcid.org/0000-0003-3425-3463
Joaquin Sastre https://orcid.org/0000-0003-4689-6837
Oliver Pfaar https://orcid.org/0000-0003-4374-9639

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