Contribution of MASK-air® as a mHealth tool for digitally-enabled person-centred care in rhinitis and asthma

Brief running title: MASK-air in rhinitis and asthma

Sousa-Pinto B[1,2], Fonseca JA[1,2], Bousquet J[3-5]

[1]MEDCIDS, Department of Community Medicine, Information and Health Decision Sciences, Faculty of Medicine, University of Porto, Porto, Portugal
[2]CINTESIS@RISE, Health Research Network, MEDCIDS, Faculty of Medicine, University of Porto, Porto, Portugal
[3]Institute of Allergology, Charité, Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt, Universität zu Berlin, Berlin, Germany
[4]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany
[5]MASK-air, Montpellier, France

Corresponding author:

Bernardo Sousa-Pinto
MEDCIDS, Department of Community Medicine, Information and Health Decision Sciences, Faculty of Medicine, University of Porto.
Porto, Portugal.
E-mail: bernardo@med.up.pt

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0994

Abstract

In chronic diseases, mobile health apps may help to (i) improve clinical management and (ii) provide valuable real-world scientific evidence. In allergic rhinitis, a market research study has only identified four mHealth apps which were multilingual, resulted in scientific publications and displayed a comprehensive list of medications. Ot those, MASK-air® was the app with the highest number of scientific publications. MASK-air® has been launched in 2015 and is currently available in 30 countries, having collected data from more than 30,000 users. It comprises a daily monitoring questionnaire, allowing patients to register (i) their daily allergy symptoms by means of visual analogue scales, and (ii) their medication use. The achievements of MASK-air® include the development of two digital biomarkers for daily monitoring of rhinitis and asthma (combined symptom-medication score and electronic daily asthma control score). In addition, MASK-air® data have allowed to assess patients' behaviours, suggesting that patients do not follow guideline recommendations, but rather treat themselves (and often use co-medication) whenever feeling worse. Using MASK-air® data, it has also been possible to quantify the impact of allergic diseases in quality-of-life, school and work productivity. MASK-air® real-world data is being used as a source of evidence for the Allergic Rhinitis and its Impact on Asthma 2024 guidelines, in an innovative process of incorporation of mobile health data into guidelines. This review discusses the clinical and scientific contributions of MASK-air® for person-centred care of rhinitis and asthma, providing an illustrative example on the use of mobile health in chronic diseases.

Key words: Allergic rhinitis. Asthma. Mobile health. Patient-reported outcome measures.

Resumen

En las enfermedades crónicas, las aplicaciones de salud móviles pueden ayudar a (i) mejorar la gestión clínica y (ii) proporcionar evidencia científica valiosa del mundo real. En el caso de la rinitis alérgica, un estudio de mercado solo identificó cuatro aplicaciones mHealth que eran multilingües, habían dado lugar a publicaciones científicas y mostraban una lista completa de medicamentos. De estos, MASK-air® fue la app con mayor número de publicaciones científicas. MASK-air® se lanzó en 2015 y actualmente está disponible en 30 países, habiendo recopilado datos de más de 30.000 usuarios. Consta de un cuestionario de seguimiento diario que permite a los pacientes registrar (i) sus síntomas de alergia diarios mediante escalas visuales analógicas y (ii) su uso de medicación. Los logros de MASK-air® incluyen el desarrollo de dos biomarcadores digitales para el seguimiento diario de la rinitis y el asma (puntuación combinada de síntomas y medicación, y puntuación electrónica diaria de control del asma). Además, los datos de MASK-air® han permitido evaluar el comportamiento de los pacientes, lo que sugiere que los pacientes no siguen las recomendaciones de las guías, sino que se tratan ellos mismos (y a menudo usan comedicación) cuando se sienten peor. Utilizando los datos de MASK-air®, también ha sido posible cuantificar el impacto de las enfermedades alérgicas en la calidad de vida, la productividad escolar y laboral. Los datos del mundo real de MASK-air® se están utilizando como fuente de evidencia para las guías sobre la rinitis alérgica y su impacto en el asma 2024, en un proceso innovador de incorporación de datos móviles de salud en las guías. Esta revisión analiza las contribuciones clínicas y científicas de MASK-air® para la atención de la rinitis y el asma centrada en la persona, proporcionando un ejemplo ilustrativo sobre el uso de la salud móvil en enfermedades crónicas.

Palabras clave: Rinitis alérgica. Asma. Salud móvil. Resultados informados por los pacientes.

doi: 10.18176/jiaci.0994

INTRODUCTION

mHealth apps may help to address some unmet needs in chronic diseases, including in respiratory allergy diseases such as rhinitis and asthma [1]. In fact, they have the potential of supporting the provision of high-quality care and the satisfaction of patients and health care professionals, with a reduction in health care utilization and costs. However, these tools need to be tested firstly for privacy rules, validity, acceptability, usability and cost-effectiveness. In addition, they should be evaluated in the frame of the digital transformation of health, their impact on healthcare delivery and health outcomes.

Randomised controlled trials (RCTs) are considered to provide evidence of the highest level for the assessment of the efficacy and safety of interventions. However, RCTs also have important limitations. Firstly, on account of the strict eligibility criteria that are frequently adopted, enrolled patients are usually not representative of those seen in daily clinical practice (a study performed in the general practice has reported that only 7% of their patients would be eligible to participate in RCTs) [2,3], limiting the capacity of RCTs to assess real-world patients' behaviours. In addition, given the fact that they are so resource-consuming, RCTs typically have a limited geographical and temporal scope. Therefore, there is an increasing need for evidence from RCTs to be complemented from that obtained using real-world data [3,4]. Among the different sources of real-world data, mHealth stands out for its potential of generating large volumes of data, advancing knowledge and contributing to improved clinical practice [4,5]. This is particularly so considering the ubiquitous ownership of smartphones and the possibility for patients to directly provide data using apps [5].

Rhinitis and asthma are two conditions for which mHealth has already resulted in relevant scientific findings that can be translated into a more patient-centred clinical practice. These findings were mostly based on the MASK-air® mHealth app. In fact, having collected data from more than 30,000 users, MASK-air® has resulted in more than 25 original scientific publications on rhinitis and/or asthma [6]. The underlying scientific evidence may then support the development of clinical recommendations, as

doi: 10.18176/jiaci.0994

already occurring with the Allergic Rhinitis and its Impact on Asthma (ARIA) 2024 guidelines. This renders MASK-air® a particularly interesting case study of translation of digitally-enabled direct patient data into the clinical practice (Figure 1).

In this review, we will discuss the scientific and clinical contributes of the MASK-air® app in rhinitis and asthma. We will start by presenting the available mHealth tools in rhinitis and asthma and by describing the characteristics of the MASK-air® app. Then, we will discuss the contributions of MASK-air® for patient monitoring, assessment of patients' behaviours, characterisation of allergy phenotypes, quantification of the impact of rhinitis and asthma, and assessment of the impact of rhinitis and asthma interventions. Finally, we will discuss how data from the MASK-air® app is being incorporated in the ARIA 2024 guidelines, as well as provide some indications on future steps.

mHealth tools in rhinitis and asthma

Searching for "allergic rhinitis" or "asthma" in app stores returns a large number of results. However, not all mHealth apps addressing rhinitis or asthma are adequate for patient monitoring or have associated published scientific evidence. In this context, a market research of mobile health apps for allergic rhinitis has been conducted in the Google Play and Apple App stores, using both a manual and an automatic process [7]. While more than 1500 apps were identified by querying the app stores on rhinitis-related terms, only 21 were found to be potentially relevant for allergic rhinitis. However, only four were multilingual, resulted in scientific publications and displayed a list of all medications – AllergyMonitor, Galenus, MASK-air® and Pollen (Austria). Of these apps, MASK-air® was the one available in the largest number of countries and with the highest number of scientific publications (including publications of methodological validation and of new scientific findings). A similar market research study is being conducted for asthma apps. However, it is expected that – as with rhinitis – only a minority of available results consist of apps which are adequate for the daily monitoring of patients.

The MASK-air® app

The MASK-air® app has been developed by the Allergic Rhinitis and its Impact on Asthma (ARIA) group [8]. This mobile health app has been launched in 2015, being currently available in 30 countries (Figure 2) [6]. It is freely available in GooglePlay and Apple App Store, and it fully complies with the General Data Protection Regulation (GDPR) [9].

MASK-air® has been classified as a Good Practice of Directorate General Health and Food Safety (European Commission) for digitally enabled, patient-centred care in rhinitis and asthma multimorbidity [10]. In addition, it is one of the 13 Organisation of Economic Cooperation and Development (OECD) Best Practices in integrated care for chronic diseases [11]. In its assessment of MASK-air®, the OECD pointed it to be "an equity-enhancing digital health intervention, which has improved the knowledge base in on [allergic rhinitis] and asthma" [12].

The MASK-air app® includes a daily monitoring questionnaire, allowing patients to report their daily symptoms and medication use. Daily symptoms are reported through four visual analogue scales (VASs), whose scale ranges between 0-100 (Table 1). In addition, there are VASs assessing the impact of allergy symptoms on work and school productivity (which are only meant to be answered if the user reports to be working or attending classes on that day). The VASs of the daily monitoring questionnaire have been assessed on their validity, reliability, responsiveness and minimal important difference [13,14]; in addition, cut-offs have been defined [15].

MASK-air® users can report their daily medication use through a scroll list that includes all prescribed and over-the-counter medications available in the respective country of the user. When patients report medication use, they are asked to rate their treatment satisfaction. Daily immunotherapy use is also possible to be reported [16]. Should patients allow it, results of the daily monitoring questionnaire can be immediately shared with clinicians in the clinical practice by scanning a QR code (allowing such data to be easily pasted into the patients' electronic health records).

doi: 10.18176/jiaci.0994

In addition to the daily monitoring questionnaire, MASK-air® includes some non-mandatory validated questionnaires, including the Control of Allergic Rhinitis and Asthma Test (CARAT), the EQ-5D-5L and the Work Productivity and Activity Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI+CIQ:AS) questionnaires. The CARAT questionnaire assesses both allergic rhinitis and asthma control over the previous four weeks; its measurement properties have been systematically reviewed and indicated good consistency, reliability, construct validity and responsiveness [17-18]. The EQ-5D-5L is a generic health-related quality-of-life instrument [19], including (i) five items assessing the domains of mobility, self-care, activities, pain/discomfort, and anxiety/depression; and (ii) a VAS assessing the overall health status. The WPAI+CIQ:AS questionnaire allows to quantify work and academic productivity losses (both in terms of absenteeism and presenteeism) due to allergies, as well as the impact of allergies in daily activities [20-22].

Contributions of MASK-air® in rhinitis and asthma

Patient monitoring: Patient reported outcome measures

Patient-reported outcomes measures (PROMs) are increasingly used. Validated PROMs are essential for patient monitoring. They can improve shared-decision making, clinician awareness of symptoms, symptom management, patient satisfaction and quality of life. PROMs must be carefully defined to capture important information from patients. Validated PROMs in MASK-air® the VASs included in the daily monitoring questionnaire [23]. In addition, MASK-air® has allowed for the development of two electronic scores which combine information on daily symptoms and medication use to inform on the daily control of allergic rhinitis and asthma. These daily monitoring scores (also termed “digital biomarkers”) are the combined symptom medication score (CSMS) and the electronic daily asthma control score (e-DASTHMA), which respectively concern allergic rhinitis and asthma [24,25].

Both the CSMS and the e-DASTHMA have been developed and validated using data-driven approaches applied to MASK-air® data [24,25]. In detail, different data-driven approaches were tested, resulting in the derivation of several candidate scores. Of those, the ones found to display the best concurrent

doi: 10.18176/jiaci.0994

validity, test-retest reliability, responsiveness and accuracy were selected as the CSMS and e-DASTHMA. The e-DASTHMA was further externally validated in a cohort of patients who had had their diagnosis and control of asthma ascertained by a physician [25].

The values of the CSMS and the e-DASTHMA range between 0 and 100, with 0 indicating perfect control and 100 indicating the worst possible control. Table 2 summarises the formulae, cut-off values and minimal important difference for these two scores.

Patient monitoring: Digital biomarkers in rhinitis and asthma

Non-invasive easily-applied biomarkers can be particularly relevant for the diagnosis, treatment and follow-up of asthma or rhinitis. Although some biologic biomarkers exist in specialist care for asthma (e.g. sputum eosinophils or FeNO), they cannot be largely used in primary care. Considering the potential of mHealth for patient monitoring, ARIA and the European Academy of Allergy and Clinical Immunology (EAACI) developed a taskforce aimed at proposing digital biomarkers that can be easily used for different purposes in rhinitis and asthma and make a bridge between clinical practice, RCTs and allergen challenges [26]. Such taskforce has resulted in the development and validation – based on the MASK-air® app – of the CSMS and the e-DASTHMA.

The development of the CSMS and of the e-DASTHMA has allowed for the proposal of a new approach for monitoring the control of rhinitis and asthma [27]. This new approach involves the combined assessment of allergic diseases both on their long-term control (using tools such as the CARAT, which has a recall period of four weeks) and on their daily control (using the CSMS and/or the e-DASTHMA). The use of daily control scores is particularly relevant, as it allows for short-term fluctuations to be captured, thus resulting in a subsequent improved disease monitoring and shared management. This approach is analogous to the one used in diabetes, whose monitoring encompasses the combined assessment of a long-term and of a daily biomarker (respectively, glycated haemoglobin and glycaemia).

Currently, studies assessing the use of MASK-air® to longitudinally monitor patients with asthma are being performed. The concurrent daily assessment of symptoms and medication use may have implications for shared decision-making, allowing physicians and patients to understand – among others – whether (i) medication adherence should be improved, (ii) further medication should be added, or (iii) biologics should be started or stopped.

Assessment of patients' behaviours and adherence

Being a source of direct patient data, and having allowed the collection of over 500,000 days (reported by over 30,000 users), MASK-air® can provide relevant information on patients' behaviours in regard to their disease and treatments. In fact, assessing MASK-air® data on rhinitis medication patterns, we observed that (i) oral antihistamines are the most commonly used medications in monotherapy, (ii) co-medication is common, with almost three-quarters of the MASK-air® users reporting at least one day of co-medication [14], and (iii) the use of different medications of the same or of different groups by the same patient throughout the year is common (being observed in more than three-quarters of MASK-air® patients) [28]. These findings were complemented by subsequent cross-sectional and longitudinal studies, which found that co-medication tended to be more frequently reported in days when patients were more poorly controlled (by contrast, using no medication was more common in days in which patients had well-controlled symptoms) [14,29]. Overall, these results suggest that most patients do not follow guideline recommendations. In fact, instead of using rhinitis medication on a daily basis, patients tend to treat themselves when feeling worse (Figure 3) (curiously, this pattern has also been observed among allergists who suffer from allergic rhinitis [30]). These findings are particularly relevant for guideline development – person-centred guidelines may consider discussing whether to recommend, particularly for patients with mild rhinitis, medication on a *pro re nata versus* on a chronic basis [31].

Complementing these assessments on patients' behaviours, there have been studies specifically evaluating adherence to rhinitis and asthma medication. In fact, when assessing rhinitis medication, we observed an overall high adherence, suggesting that patients more adherent to the app may also be more

doi: 10.18176/jiaci.0994

adherent to medication (future studies may assess whether adherence to MASK-air® may promote medication adherence) (Sousa-Pinto et al. Under review). That same study did not find relevant adherence differences when comparing medication classes. On the other hand, regarding asthma medication, lower adherence was observed for inhaled corticosteroids (ICS) + formoterol than for ICS + other long-acting β-agonists (LABA), despite these two groups being associated with similar levels of asthma control [32]. That same study reported that increased adherence to ICS-LABA was associated with lower use of short-acting β-agonists. These studies have an important limitation, as they have been performed based on data from users who are adherent to the MASK-air® app (who are not representative of all patients).

Classification of allergy patients and assessment of phenotypes

Two studies have applied clustering methods to MASK-air® data, in order to obtain a non-supervised classification of allergy patients or trajectories [29,33]. One of such studies was performed in order to improve the identification of patients with asthma, as well as to assess the extent of potential asthma underreporting and undertreatment [33]. In brief, based on (i) whether they self-reported asthma, (ii) asthma symptoms, and (iii) reported use of asthma medications, MASK-air® users were classified into seven clusters and three major groups ("no evidence of asthma", "possible asthma" or "probable asthma"). As an example, there was one cluster consisting of patients with no self-reported asthma but with poor symptom control (suggesting asthma underdiagnosis). Another cluster included patients with uncontrolled symptoms despite treatment. This study, therefore, presents an example on how MASK-air® data can be used to identify patients who would benefit from further clinical assessment for diagnostic or therapeutic reasons (including potentially underdiagnosed or undertreated patients).

The other study used clustering methods to classify weekly trajectories of rhinitis symptom control in 16,177 weeks [29]. A total of 16 clusters were identified, corresponding to weeks with different levels of rhinitis control. The assessment of cluster trajectories indicated that patients having a week with good rhinitis control would be expected to display another week with good rhinitis control. By contrast, for

doi: 10.18176/jiaci.0994

a patient displaying a week with poor or variable rhinitis control, more unstable trajectories were expected.

There has been a growing body of evidence suggesting that rhinitis alone and rhinitis + asthma may be two different entities [34,35]. Indeed, these two conditions seem to display different genomic and sensitisation patterns (polysensitisation is more common in rhinitis + asthma than in rhinitis alone) [34,35]. In addition, a general population epidemiological study has reported that patients with rhinitis + asthma tend to display more severe rhinitis symptoms than patients with rhinitis alone [36]. This finding has also been observed using MASK-air® data [37]. In fact, among MASK-air® users, patients with rhinitis + asthma displayed higher CSMS values and higher VAS levels on nasal or ocular symptoms. MASK-air® data have also shown that rhinitis + asthma was associated with an increased use of rhinitis medications compared to rhinitis alone. This provides an elegant example on how mHealth data from MASK-air® can complement other sources of evidence.

Assessment of the impact of rhinitis and asthma

MASK-air® includes the EQ-5D-5L and the WPAI+CIQ:AS questionnaires, respectively assessing health-related quality-of-life and work and academic productivity due to allergies. Analysis of data from these questionnaires, alongside that of the daily monitoring questionnaire has allowed for a quantification of the impact of allergic rhinitis and asthma in the quality-of-life as well as in work and school productivity.

Regarding the impact of allergy disease in the quality-of-life, a cross-sectional study using MASK-air® data assessed the association between (i) allergy control (assessed using VASs or the CSMS) and (ii) the levels of each EQ-5D domain [38]. Using multivariable models, this study identified that a poorer control of allergic rhinitis and asthma was associated with a worse health-related quality-of-life, particularly with more severe pain/discomfort and more impairments in the performance of daily activities. In addition, a poor rhinitis control tended to be associated with worse levels of anxiety/depression, while a poorer asthma control tended to be associated with more impairments of

doi: 10.18176/jiaci.0994

mobility ("walking around"). The MASK-air® EQ-5D-5L data have also allowed for the estimation of the utilities associated with good, partial and poor control of rhinitis and asthma in several European countries (Vieira et al. Under review). The use of multilevel regression models with post-stratification has allowed for the computation of national estimates accounting for biases in sex and age distributions of MASK-air® users.

MASK-air® data have been used to compute the impact of allergic rhinitis in academic productivity (measured through a VAS and using the WPAI+CIQ:AS questionnaire) [39]. That cross-sectional study has found that a poorer control of allergic rhinitis (especially of nasal symptoms) was associated with worse academic productivity. On the other hand, immunotherapy was associated with improved academic productivity. Of those users who answered to the WPAI+CIQ:AS questionnaire, 35% had indicated the loss of at least some education hours due to allergies.

Studies are being conducted using MASK-air® data to quantify productivity losses associated with allergic rhinitis and asthma. Productivity losses are being assessed using the WPAI+CIQ:AS questionnaire in terms of absenteeism and presenteeism. Preliminary results indicate that (i) the impact of rhinitis and asthma on work productivity is mainly driven by presenteeism, (ii) a poorer allergy control is associated with worse work productivity, and (iii) for the same level of control, the percentage of hours with work impairment is worse for patients with rhinitis + asthma than for patients with rhinitis alone (Vieira et al. In preparation). MASK-air® can also be used to assess the impact of allergic diseases in daily activities (a variable which has been demonstrated to be correlated with work impairment [40]).

Assessment of the impact of allergy interventions: The example of allergen immunotherapy

Given that MASK-air® data are not collected on an experimental data, it cannot straightforwardly inform on the effectiveness of interventions. However, it can provide some information on the levels of allergy control associated with different treatments. For instance, on allergen immunotherapy, there have been three studies using MASK-air® data [16,41,42]. Two of these studies have found that (i) days

doi: 10.18176/jiaci.0994

of users treated with immunotherapy were found to display better overall symptom control and lower impact of symptoms on work productivity, and (ii) patients treated with sublingual immunotherapy displayed better rhinitis control (measured using VASs and the CSMS) than those treated with subcutaneous immunotherapy or than those not receiving immunotherapy [16,41]. The third study – using cross-sectional and longitudinal methods – assessed MASK-air® users under treatment with sublingual immunotherapy [42]. Days in which sublingual immunotherapy was used were found to be associated with better rhinitis control than those in which such treatment was not used. These findings raise the hypothesis of a potential short-term effect of sublingual immunotherapy, which may be explored by future studies.

Incorporation of direct patient data from MASK-air in the ARIA 2024 guidelines

The ARIA guidelines had their first edition in 2001 [43], having been subsequently revised in 2008 [44], 2010 [45] and 2016 [46]. The 2024 edition of the ARIA guidelines is currently being prepared and, as with previous editions, it will follow the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [47]. However, differently from other editions, in the ARIA 2024 guidelines, contributes from MASK-air® data will be paramount. In particular, they will be considered in the following steps:

- Question generation: Evidence obtained from MASK-air® data has allowed for several hypotheses to be raised. Such hypotheses, as well as MASK-air®-based findings, will allow the formulation of several guideline questions that may possibly result in recommendations for clinical practice;
- Outcome identification: In the context of guideline development, there is identification of a list of potentially relevant outcomes (such outcomes then undergo prioritization, so that those considered more relevant by the guideline panel members are assessed [48]) – MASK-air® studies will allow for the identification of some of these allergic rhinitis outcomes.

- Formulation of recommendations: In the GRADE approach, incorporation of the best available evidence for the formulation of recommendations involves the use of the Evidence-to-Decision framework. This framework comprises 12 criteria, including, among others, desirable effects, undesirable effects, values and preferences, costs, equity, acceptability, and feasibility [49]. MASK-air® data can provide evidence for several of these criteria (including values and preferences, costs and acceptability), complementing more traditional sources of evidence.

Next steps

The analysis of MASK-air® data has resulted in relevant scientific findings and in the generation of new hypotheses to be explored by studies with different designs. A summary of its potential impact is summarised in Supplementary Table 1. There are, however, several fields yet to be explored using MASK-air®. In particular, its role in improving the management of patients with rhinitis and asthma in everyday clinical practice needs to be further established. In this context, the following steps are envisioned:

1. Conduction of clinical studies assessing the impact of MASK-air® in the individual monitoring of patients with rhinitis and asthma: While some studies in allergy clinics have already been conducted [50-52], there are several questions that still need to be addressed, such as whether the use of MASK-air® promotes adherence to rhinitis or asthma medication, better disease self-care and less need for healthcare visits. Assessing the impact of using MASK-air® to monitor patients with severe asthma may be particularly relevant both from a clinical and from a health services point of view (so that future studies are planned with this goal). In fact, such an assessment may allow to a better identification of patients who would benefit from treatment with biologics as well to a better definition of stopping rules.
2. Developing of early warning systems for rhinitis and impact on planetary health: For users with activated geolocation, MASK-air® provides information on pollen and air quality data. This information is made available from the Finnish Meteorological Institute through SILAM (System

doi: 10.18176/jiaci.0994

for Integrated modeLling of AtMospheric composition). Based on pollen and air quality predictions, as well as on previous symptoms reported by MASK-air® users, personalised early warning systems are being developed for MASK-air® [53]. It is projected that such systems would generate personalised alerts to patients whenever their allergy symptoms are expected to worsen [53]. Of note, these early warning systems are being developed in the context of the Horizon Europe grant CATALYSE (Climate Action to Advance HeaLthY Societies in Europe [53]) and follow the participation of MASK-air in events on Planetary Health during the Finnish presidency of the European Union [54,55], in line with the Helsinki declaration [54,55].

3. Assessment of the role of MASK-air® as a tool to improve care by overcoming language barriers: Following the war in Ukraine, the UCRAID project has been developed to support provision of allergy care to Ukrainian refugees [56]. This project involved the launch of MASK-air® in Ukrainian, allowing refugees to fill in the daily monitoring questionnaire in Ukrainian, but with physicians receiving results in their native language. This model can be extended to improve care to other migrants (including refugees from other wars) and to foreign travellers, as MASK-air® is available in several languages.
4. Use of MASK-air® as a tool in allergy RCTs: In RCTs, MASK-air® can be used as a tool allowing participants to directly introduce their data. This app has allowed for the development of two validated digital biomarkers that can potentially be used as endpoints in RCTs [24,25]. In addition, pre-enrolment adherence to the MASK-air® app may help identifying the most adequate candidates for RCTs (e.g., it may help to stratify patients according to their allergy severity as well as to identify those patients who have the highest probability of completing the RCTs). While there have been single-arm trials using MASK-air® (Bousquet et al. Under review), the feasibility of using this app in RCTs is yet to be established.

In addition to the aforementioned projects, it is expected that MASK-air® data will continue to bring new findings on allergy patients' behaviours, on the impact of rhinitis and asthma, and on the satisfaction associated with the different medication classes.

doi: 10.18176/jiaci.0994

CONCLUSION

MASK-air® provides and elegant example on how mHealth can advance scientific knowledge and improve clinical knowledge in chronic diseases. Its data have allowed for (i) the development of two digital biomarkers for daily monitoring of rhinitis and asthma, (ii) a better understanding on how patients behave in relation to their diseases, (iii) increased knowledge on allergy phenotypes, and (iv) a quantification of the impact on rhinitis and asthma in the quality-of-life and in productivity. Evidence obtained using the MASK-air® app will be supporting the recommendations of the ARIA 2024 guidelines, therefore contributing to a more patient-centred care in respiratory allergic disease.

Conflict of interests

MASK-air® has been supported by EU grants (POLLAR, EIT Health; Structural and Development Funds, Twinning, EIP on AHA and H2020), and educational grants from Mylan-Viatris, ALK, GSK, Novartis and Uriach. JB reports personal fees from Cipla, Menarini, Mylan, Novartis, Purina, Sanofi-Aventis, Teva, Uriach and is a Shareholder of KYomed Innov and MASK-air-SAS.

References

1. Bousquet J, Chavannes NH, Guldemond N, Haahtela T, Hellings PW, Sheikh A. Realising the potential of mHealth to improve asthma and allergy care: how to shape the future. *Eur Respir J*. 2017;49(5) doi:10.1183/13993003.00447-2017
2. Costa DJ, Amouyal M, Lambert P, Ryan D, Schunemann HJ, Daures JP, et al. How representative are clinical study patients with allergic rhinitis in primary care? *J Allergy Clin Immunol*. 2011;127(4):920-6 e1. doi:10.1016/j.jaci.2010.10.058
3. Kim HS, Lee S, Kim JH. Real-world Evidence versus Randomized Controlled Trial: Clinical Research Based on Electronic Medical Records. *J Korean Med Sci*. 2018;33(34):e213. doi:10.3346/jkms.2018.33.e213

4. Liu F, Panagiotakos D. Real-world data: a brief review of the methods, applications, challenges and opportunities. *BMC Med Res Methodol*. 2022;22(1):287. doi:10.1186/s12874-022-01768-6

5. Sim I. Mobile Devices and Health. *N Engl J Med*. 2019;381(10):956-968. doi:10.1056/NEJMra1806949

6. Bousquet J, Anto JM, Sousa-Pinto B, Czarlewski W, Bedbrook A, Haahtela T, et al. Digitally-enabled, patient-centred care in rhinitis and asthma multimorbidity: The ARIA-MASK-air((R)) approach. *Clin Transl Allergy*. 2023;13(1):e12215. doi:10.1002/clt2.12215

7. Anto A, Sousa-Pinto B, Czarlewski W, Pfaar O, Bosnic-Anticevich S, Klimek L, et al. Automatic market research of mobile health apps for the self-management of allergic rhinitis. *Clin Exp Allergy*. 2022;52(10):1195-1207. doi:10.1111/cea.14135

8. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy*. 2008;63 Suppl 86:8-160. doi:ALL1620 [pii] 10.1111/j.1398-9995.2007.01620.x

9. Laune D, Arnavielhe S, Viart F, Bedbrook A, Mercier J, Lun San Luk G, et al. [Adaptation of the General Data Protection Regulation (GDPR) to a smartphone app for rhinitis and asthma (MASK-air(R))]. *Rev Mal Respir*. 2019;36(9):1019-1031. doi:10.1016/j.rmr.2019.08.003

10. Bousquet J, Bedbrook A, Czarlewski W, Onorato GL, Arnavielhe S, Laune D, et al. Guidance to 2018 good practice: ARIA digitally enabled, integrated, person-centred care for rhinitis and asthma. *Clin Transl Allergy*. 2019;9:16. doi:10.1186/s13601-019-0252-0

11. Integrating Care to Prevent and Manage Chronic Diseases: Best Practices in Public Health, OECD. Éditions OCDE, Paris, https://doiorg/101787/9acc1b1d-en. 2023;

12. OECD. Integrating Care to Prevent and Manage Chronic Diseases. 2023.

13. Sousa-Pinto B, Eklund P, Pfaar O, Klimek L, Zuberbier T, Czarlewski, W, et al. Validity, reliability, and responsiveness of daily monitoring visual analog scales in MASK-air(R). *Clin Transl Allergy*. 2021;11(7):e12062. doi:10.1002/clt2.12062

14. Sousa-Pinto B, Schunemann HJ, Sa-Sousa A, Vieira RJ, Amaral R, Anto JM, et al. Comparison of rhinitis treatments using MASK-air(R) data and considering the minimal important difference. *Allergy*. 2022;77(10):3002-3014. doi:10.1111/all.15371

15. Sousa-Pinto B, Sa-Sousa A, Vieira RJ, Amaral R, Pereira AM, Anto JM, et al. Cutoff Values of MASK-air Patient-Reported Outcome Measures. *J Allergy Clin Immunol Pract*. 2023;11(4):1281-1289 e5. doi:10.1016/j.jaip.2022.12.005

16. Pfaar O, Sousa-Pinto B, Devillier P, Canonica GW, Klimek L, Zuberbier T, et al. Effects of allergen immunotherapy in the MASK-air study: a proof-of-concept analysis. *Allergy*. 2021;76(10):3212-3214. doi:10.1111/all.14955

17. Vieira RJ, Sousa-Pinto B, Cardoso-Fernandes A, Jacome C, Portela D, Amaral R, et al. Control of Allergic Rhinitis and Asthma Test: A systematic review of measurement properties and COSMIN analysis. *Clin Transl Allergy*. 2022;12(9):e12194. doi:10.1002/clt2.12194

18. Jacome C, Pereira R, Almeida R, Amaral R, Correia MA, Mendes S, et al. Validation of App and Phone Versions of the Control of Allergic Rhinitis and Asthma Test (CARAT). *J Investig Allergol Clin Immunol*. 2021;31(3):270-273. doi:10.18176/jiaci.0640

19. Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: Past, Present and Future. *Appl Health Econ Health Policy*. 2017;15(2):127-137. doi:10.1007/s40258-017-0310-5

20. Reilly MC, Tanner A, Meltzer EO. Work, classroom and activity impairment instruments: validation studies in allergic rhinitis. *Clinical drug investigation*. 1996;11:278-288.

21. Reilly MC, Tanner A, Meltzer EO. Allergy impairment questionnaires: validation studies. *J Allergy Clin Immunol*. 1996;97:989.

22. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993;4:353-365.

23. Sousa-Pinto B, Fonseca JA, Gemicioglu B, Regateiro FS, Scichilone N, Ventura MT et al. Patient-reported outcome measures (PROMs) using the MASK-air(R) app in severe asthma. *Allergy*. 2022;77(5):1600-1602. doi:10.1111/all.15248

24. Sousa-Pinto B, Azevedo LF, Jutel M, Agache I, Canonica GW, Czarlewski W, et al. Development and validation of combined symptom-medication scores for allergic rhinitis. *Allergy*. 2022;77(7):2147-2162. doi:10.1111/all.15199

25. Sousa-Pinto B, Jacome C, Pereira AM, Regateiro FS, Almeida R, Czarlewski W, et al. Development and validation of an electronic daily control score for asthma (e-DASTHMA): a real-world direct patient data study. *Lancet Digit Health*. 2023;5(4):e227-e238. doi:10.1016/S2589-7500(23)00020-1

26. Bousquet J, Shamji MH, Anto JM, Schunemann HJ, Canonica GW, Jutel M, et al. Patient-centred digital biomarkers for allergic respiratory diseases and asthma: the ARIA-EAACI approach. *Allergy*. 2023; doi:10.1111/all.15740

27. Bousquet J, Shamji MH, Anto JM, Schunemann HJ, Canonica GW, Jutel M, et al. Patient-centered digital biomarkers for allergic respiratory diseases and asthma: The ARIA-EAACI approach - ARIA-EAACI Task Force Report. *Allergy*. 2023;78(7):1758-1776. doi:10.1111/all.15740

28. Sousa-Pinto B, Sa-Sousa A, Vieira RJ, Amaral R, Klimek L, Czarlewski W, et al. Behavioural patterns in allergic rhinitis medication in Europe: A study using MASK-air((R)) real-world data. *Allergy*. 2022;77(9):2699-2711. doi:10.1111/all.15275

29. Sousa-Pinto B, Schunemann HJ, Sa-Sousa A, Vieira RJ, Amaral R, Anto JM, et al. Consistent trajectories of rhinitis control and treatment in 16,177 weeks: The MASK-air(R) longitudinal study. *Allergy*. 2023;78(4):968-983. doi:10.1111/all.15574

30. Bousquet J, Murray R, Price D, Somekh D, Munter L, Phillips, et al. The allergic allergist behaves like a patient. *Ann Allergy Asthma Immunol*. 2018;121(6):741-742. doi:10.1016/j.anai.2018.07.034

31. Bousquet J, Toumi M, Sousa-Pinto B, Anto JM, Bedbrook A, Czarlewski W, et al. The Allergic Rhinitis and Its Impact on Asthma (ARIA) Approach of Value-Added Medicines: As-Needed Treatment in Allergic Rhinitis. *J Allergy Clin Immunol Pract*. 2022;10(11):2878-2888. doi:10.1016/j.jaip.2022.07.020

32. Sousa-Pinto B, Louis R, Anto JM, Amaral R, Sa-Sousa A, Czarlewski W, et al. Adherence to inhaled corticosteroids and long-acting beta2-agonists in asthma: A MASK-air study. *Pulmonology*. 2023;doi:10.1016/j.pulmoe.2023.07.004

33. Bousquet J, Sousa-Pinto B, Anto JM, Amaral R, Brussino L, Canonica GW, et al. Identification by cluster analysis of patients with asthma and nasal symptoms using the MASK-air(R) mHealth app. *Pulmonology*. 2023;29(4):292-305. doi:10.1016/j.pulmoe. 2022.10.005

34. Bousquet J, Melen E, Haahtela T, Koppelman GH, Togias A, Valenta R, et al. Rhinitis associated with asthma is distinct from rhinitis alone: The ARIA-MeDALL hypothesis. *Allergy*. 2023;78(5):1169-1203. doi:10.1111/all.15679

35. Aguilar D, Lemonnier N, Melen E, Bustamante M, Gruzieva O, Guerra S, et al. Distinction between rhinitis alone and rhinitis with asthma using interactomics. *Sci Rep*. 2023;13(1):13125. doi:10.1038/s41598-023-39987-6

36. Savoure M, Bousquet J, Leynaert B, Renuy A, Siroux V, Goldberg M, et al. Rhinitis phenotypes and multimorbidities in the general population: the CONSTANCES cohort. *Eur Respir J*. 2023;61(2)doi:10.1183/13993003.00943-2022

37. Bousquet J, Sousa-Pinto B, Regateiro FS, Pereira AM, Brussino L, Kvedariene V, et al. MASK-air(R) direct patient data support the ARIA-MeDALL hypothesis on allergic phenotypes. *Allergy*. 2023;78(10):2790-2794. doi:10.1111/all.15842

38. Sousa-Pinto B, Louis G, Rodrigues J, Giuliano AFM, Baiardini I, Braido F, et al. Impairment of EQ-5D-5L Domains According to Allergic Rhinitis and Asthma Control: A MASK-air Real-World Study. *J Allergy Clin Immunol Pract*. 2023;11(12):3742-3751 e9. doi:10.1016/j.jaip.2023.08.006

39. Vieira RJ, Pham-Thi N, Anto JM, Czarlewski W, Sa-Sousa A, Amaral R, et al. Academic Productivity of Young People With Allergic Rhinitis: A MASK-air Study. *J Allergy Clin Immunol Pract*. 2022;10(11):3008-3017 e4. doi:10.1016/j.jaip.2022.08.015

40. Bousquet J, VandenPlas O, Bewick M, Arnavielhe S, Bedbrook A, Murray R, et al. The Work Productivity and Activity Impairment Allergic Specific (WPAI-AS) Questionnaire Using Mobile Technology: The MASK Study. *J Investig Allergol Clin Immunol*. 2018;28(1):42-44. doi:10.18176/jiaci.0197

41. Sousa-Pinto B, Azevedo LF, Sa-Sousa A, Vieira RJ, Amaral R, Klimek L, et al. Allergen immunotherapy in MASK-air users in real-life: Results of a Bayesian mixed-effects model. *Clin Transl Allergy*. 2022;12(3):e12128. doi:10.1002/clt2.12128

42. Bousquet J, Sousa-Pinto B, Shamji MH, Anto JM, Klimek L, Canonica GW, et al. Improvement of daily allergy control by sublingual immunotherapy: A MASK-air(R) study. *Clin Exp Allergy*. 2023;53(8):854-861. doi:10.1111/cea.14318

43. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G, World Health O. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108(5 Suppl):S147-334. doi:10.1067/mai.2001.118891

44. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization,

GA(2)LEN and AllerGen). *Allergy*. 2008;63 Suppl 86:8-160. doi:10.1111/j.1398-9995.2007.01620.x

45. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126(3):466-76. doi:10.1016/j.jaci.2010.06.047

46. Brozek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol*. 2017;140(4):950-958. doi:10.1016/j.jaci.2017.03.050

47. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy*. 2009;64(5):669-77. doi:10.1111/j.13989995.2009.01973.x

48. Baldeh T, Saz-Parkinson Z, Muti P, Santesso N, Morgano GP, Wiercioch W, et al. Development and use of health outcome descriptors: a guideline development case study. *Health Qual Life Outcomes*. 5 2020;18(1):167. doi:10.1186/s12955-020-01338-8

49. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ*. 2016;353:i2089. doi:10.1136/bmj.i2089

50. Kvedariene V, Biliute G, Didziokaite G, Kavaliukaite L, Savonyte A, Rudzikaite-Fergize G, et al. Mobile health app for monitoring allergic rhinitis and asthma in real life in Lithuanian MASK-air users. *Clin Transl Allergy*. 2022;12(9):e12192. doi:10.1002/clt2.12192

51. Vardaloglu I, Sousa-Pinto B, Bousquet J, Dodek P, Bedbrook A, Karatas M, et al. In symptomatic patients on as-needed inhaled corticosteroids-formoterol, VAS asthma is associated with small airways resistance. *J Asthma*. 2023:1-8. doi:10.1080/02770903.2023.2248485

52. Ventura MT, Giuliano AFM, Buquicchio R, Bedbrook A, Czarlewski W, Laune D, et al. Implementation of the MASK-Air(R) App for Rhinitis and Asthma in Older Adults: MASK@Puglia Pilot Study. *Int Arch Allergy Immunol*. 2022;183(1):45-50. doi:10.1159/000518032

53. Sousa-Pinto B, Palamarchuk Y, Leemann L, Jankin S, Basagana X, Ballester J, et al. From MASK-air(R) and SILAM to CATALYSE (Climate Action to Advance HeaLthY Societies in Europe). *J Investig Allergol Clin Immunol*. 2023:0. doi:10.18176/jiaci.0923

54. Halonen JI, Erhola M, Furman E, Haahtela T, Jousilahti P, Barouki R, et al. A call for urgent action to safeguard our planet and our health in line with the helsinki declaration. *Environ Res*. 2021;193:110600. doi:10.1016/j.envres.2020.110600

55. Halonen JI, Erhola M, Furman E, Haahtela T, Jousilahti P, Barouki R, et al. The Helsinki Declaration 2020: Europe that protects. *Lancet Planet Health*. 2020;4(11):e503-e505. doi:10.1016/S2542-5196(20)30242-4

56. Bousquet J, Samolinski B, Kaidashev I, Maurer M, Roche N, Sousa-Pinto B, et al. UCRAID (Ukrainian Citizen and refugee electronic support in Respiratory diseases, Allergy, Immunology and Dermatology) action plan. *Allergy*. 2023;78(10):2581-2595. doi:10.1111/all.15855

Table 1. List of the visual analogue scales (VAS) available in the daily monitoring questionnaire of MASK-air®.

Scale	Question
VAS Global allergy symptoms	"Overall, how much are your allergic symptoms bothering you today?"
VAS Nose	"How much are your nose symptoms bothering you today?"
VAS Eyes	"How much are your eye symptoms bothering you today?"
VAS Asthma	"How much are your asthma symptoms bothering you today?"
VAS Work	"Today, how much did allergies affect your work activities?"
VAS School	"Today, how much did allergies affect your productivity while in school or attending classes in an academic setting?"

Table 2. Formulae, cut-offs and minimal important differences (MID) for the CSMS and the e-DASTHMA.

Score	Formula	Cut-offs	MID
CSMS	[(0.037 × VAS Global Symptoms) + (0.033 × VAS Eyes) + (0.020 × VAS Nose) + (0.027 × VAS Asthma) + (0.450 if AzeFlu is used) + (0.424 if intranasal corticosteroids are used) + (0.243 if asthma medication is used) + (0.380 if other rhinitis relief medication is used)] × 7.577)	• Good control: <15.8 • Partial control: 15.8-35.3 • Poor control: >35.3	10
e-DASTHMA	[(0.086 × VAS asthma) + (1.756 if ICS are used) + (0.859 if ICS-LABA except formoterol are used) + (1.238 if ICS-Formoterol are used) + (0.559 if SABA or SAMA are used) + (4.022 if biologicals or LAMA are used)] × 6.695	• Good control: <16.4 • Partial control: 16.4-28.9 • Poor control: >28.9	8

CSMS: Combined symptom-medication score; e-DASTHMA: electronic daily asthma combined score; ICS: Inhaled Corticosteroids; LABA: Long-acting beta2-agonists; LAMA: Long-acting muscarinic antagonists; SABA: Short-acting beta2-agonists; SAMA: Short-acting muscarinic antagonists; VAS: Visual analogue scale

Figure 1. Illustration on how MASK-air® can provide contribution for research and for clinical practice.

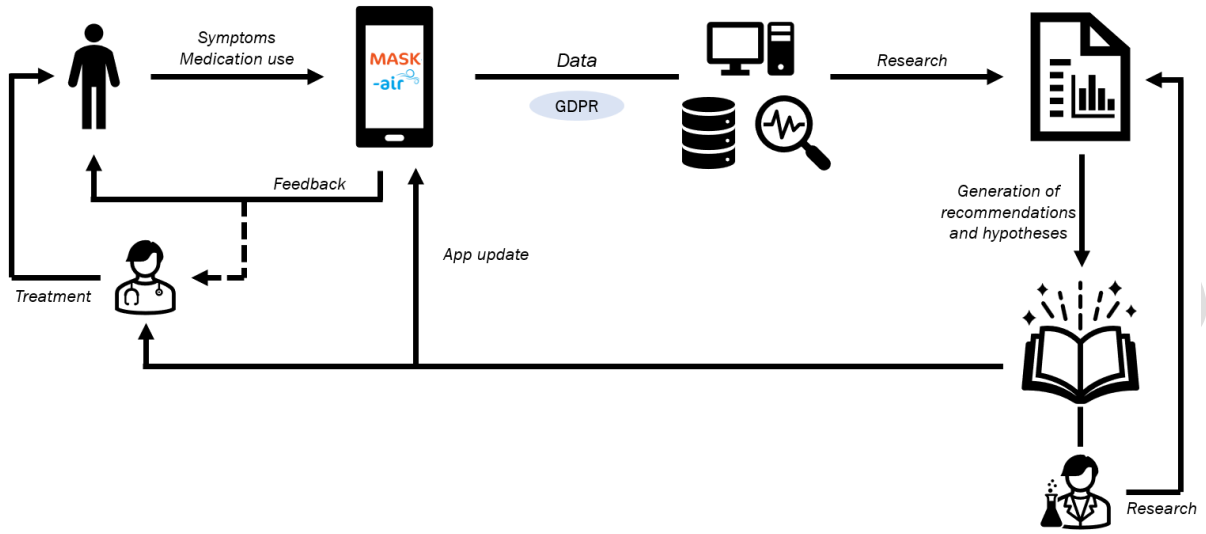

Figure 2. Map indicating the countries in which the MASK-air® is available as of January 2024.

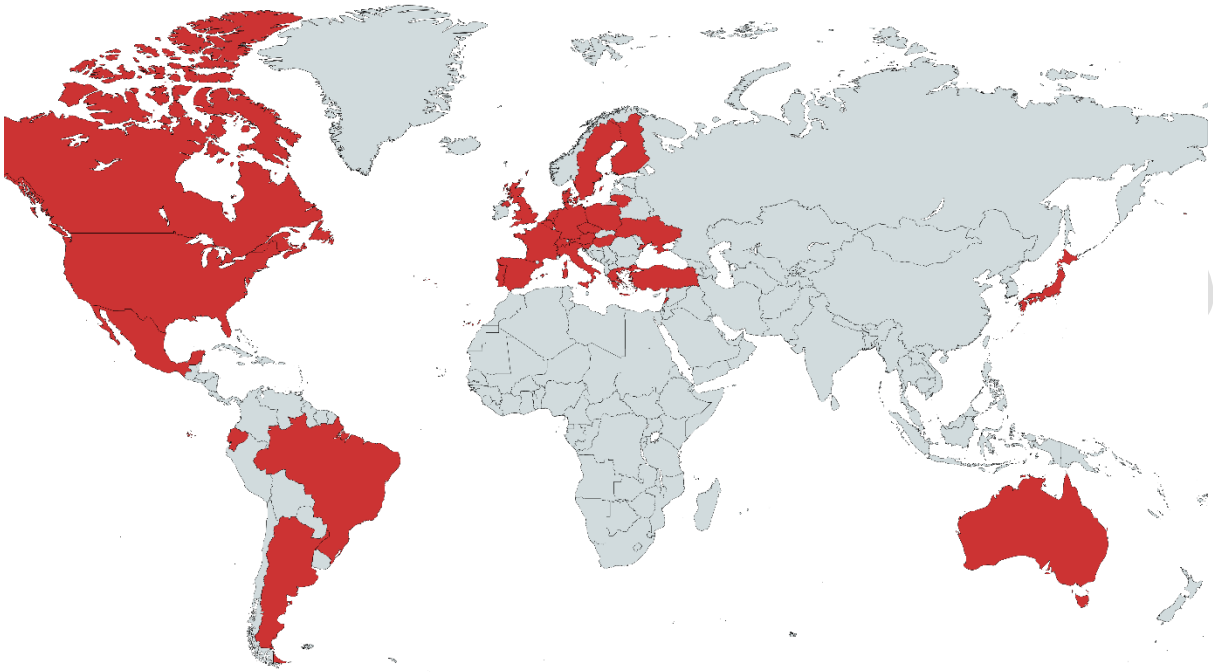

Figure 3. Median visual analogue scale (VAS) on global allergy symptoms according to the number of medications used per day.