Pilot study of mobile phone technology in allergic rhinitis in European countries

the MASK-rhinitis study

PROF. PHILIPPE DEVILLIER (Orcid ID : 0000-0003-4107-8317)

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J Bousquet, MD (1, 2), DP Caimmi, MD (3, 4), A Bedbrook, MSc (1), M Bewick, MD (5), PW Hellings, MD (6), P Devillier, MD (7), S Arnavielhe, PhD (8), C Bachert, MD (9), KC Bergmann, MD (10), GW Canonica, MD (11), N Chavannes, MD s (12), AA Cruz, MD (13), R Dahl, MD (13), P Demoly, MD (3,4), G De Vries, PhD (14), E Mathieu-Dupas, PhD (8), A Finkwagner (15), J Fonseca, MD (16), N Guldemond, MD (17), T Haahtela, MD (18), B Hellqvist-Dahl, PhD (19), J Just, MD (20), T Keil, MD (21), L Klimek, MD (22), ML Kowalski, MD (23), M Kuitunen, MD (24), P Kuna, MD (25), V Kvedariene, MD (26), D Laune, PhD (8), AM Pereira, MD (16), P Carreiro-Martins, MD (28), E Melén, MD (29), M Morais-Almeida, MD (46), J Mullol, MD (30), A Muraro, MD (31), R Murray, PhD (32), L Nogueira-Silva, MD (33), NG Papadopoulos, MD (34), G Passalacqua, MD (11), F Portejoie (1), D Price, MD (35), D Ryan, MD (36), B Samolinski, MD (37), A Sheikh, MD (38), V Siroux, PhD (39), O Spranger (15), A Todo Bom, MD (40), PV Tomazic, MD (41), A Valero, MD (45), E Valovirta, MD (27), A Valiulis, MD (44), O VandenPlas, MD (43), S van der Meulen (42), M van Eerd (14), M Wickman, MD (29), T Zuberbier, MD (10)

1. MACVIA-LR, Contre les MAladies Chroniques pour un VIeillissement Actif en Languedoc-Roussillon, European Innovation Partnership on Active and Healthy Ageing Reference Site, France
2. INSERM, VIMA : Ageing and chronic diseases Epidemiological and public health approaches, U1168, Paris, and UVSQ, UMR-S 1168, Université Versailles St-Quentin-en-Yvelines, France
3. CHRU de Montpellier, Sorbonne Universités, UPMC Paris 06, UMR-S 1136, IPLESP, Equipe EPAR, F-75013 Paris, France
4. Department of Respiratory Diseases, Montpellier University Hospital, France
5. iQ4U Consultants Ltd, London, UK
6. Laboratory of Clinical Immunology, Department of Microbiology and Immunology, KU Leuven, Leuven, Belgium

7. Laboratoire de Pharmacologie Respiratoire UPRES EA220, Pôle des Maladies Respiratoires, Hôpital Foch, Suresnes Université Versailles Saint-Quentin, France

8. Kyomed , Montpellier France

9. Upper Airways Research Laboratory, ENT Dept, Ghent University Hospital, Ghent, Belgium

10. Comprehensive Allergy-Centre-Charité, Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Berlin, Germany; Global Allergy and Asthma European Network (GA^2LEN), Germany

11. Allergy and Respiratory Diseases Clinic, DIMI, University of Genoa, IRCCS AOU San Martino-IST, Genoa, Italy

12. Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands

13. ProAR – Nucleo de Excelencia em Asma, Federal University of Bahia, Brasil and GARD Executive Committee

14. Peercode BV, The Netherlands

15. Global Allergy and Asthma Platform GAAPP, Altgasse 8-10, 1130 Vienna, Austria

16. Center for Health Technology and Services Research- CINTESIS, Faculdade de Medicina, Universidade do Porto; and Allergy Unit, CUF Porto Instituto & Hospital, Porto, Portugal

17. Institute of Health Policy and Management iBMG - Erasmus Universit, Rotterdam,The Netherlands

18. Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland

19. Department of Respiratory Diseases, Odense University Hospital, Denmark

20. Allergology department, Centre de l'Asthme et des Allergies Hôpital d'Enfants Armand-Trousseau (APHP); Sorbonne Universités, UPMC Univ Paris 06, UMR_S 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Equipe EPAR, F-75013, Paris, France

21. Institute of Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Berlin, and Institute for Clinical Epidemiology and Biometry, University of Wuerzburg, Germany

22. Center for Rhinology and Allergology, Wiesbaden, Germany

23. Department of Immunology, Rheumatology and Allergy, Medical University of Lodz, and HARC, Poland

24. Children's Hospital, University of Helsinki and University Hospital of Helsinki, Finland

25. Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical University of Lodz, Poland

26. Clinic of infectious, chest diseases, dermatology and allergology, Vilnius University, Vilnius, Lithuania

27. Department of Lung Diseases and Clinical Allergology, Univ of Turku, and Allergy Clinic, Terveystalo, Turku, Finland

28. CEDOC, Respiratory Research Group, Nova Medical School, Campo dos Martires da Patria, Lisbon, and Serviço de Imunoalergologia, Hospital de Dona Estefânia, Centro Hospitalar de Lisboa Central, EPE, Lisbon, Portugal 29. Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm and Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

30. ENT Department, Hospital Clinic; Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, CIBERES, Universitat de Barcelona, Barcelona, Catalonia, Spain

31. Food Allergy Referral Centre Veneto Region, Department of Women and Child Health, Padua General University Hospital, Padua, Italy

32. Medical Communications Consultant, MedScript Ltd, Dundalk, Co Louth, Ireland

33. Center for Health Technology and Services Research - CINTESIS and Department of Internal Medicine, Centro Hospitalar Sao Joao, Porto, Portugal

34. Center for Pediatrics and Child Health, Institute of Human Development, Royal Manchester Children's Hospital, University of Manchester, Manchester M13 9WL, UK Allergy Department, 2nd Pediatric Clinic, Athens General Children's Hospital "P&A Kyriakou," University of Athens, Athens 11527, Greece

35. Observational and Pragmatic Research Institute, Singapore and Academic Centre of Primary Care, University of Aberdeen, Aberdeen, UK

36. Honorary Clinical Research Fellow, Allergy and Respiratory Research Group, The University of Edinburgh, Edinburgh, UK

37. Department of Prevention of Envinronmental Hazards and Allergology, Medical University of Warsaw, Poland

38. Centre of Medical Informatics, Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, Scotland, UK

39. INSERM, Université Grenoble Alpes, IAB, U 1209, Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, Université Joseph Fourier, Grenoble, France

40. Imunoalergologia, Centro Hospitalar Universitario de Coimbra and Faculty of Medicine, University of Coimbra, Portugal

41. Medical University of Graz, ENT University Hospital Graz, Austria

42. Attorney at law, Axon Lawyers, the Netherlands

43. Department of Chest Medicine, Centre Hospitalier Universitaire UCL Namur, Université Catholique de Louvain, Yvoir, Belgium

44. Vilnius University Clinic of Children's Diseases and Public Health Institute, Vilnius, Lithuania, European Academy of Paediatrics (EAP/UEMS-SP), Brussels, Belgium

45. Pneumology and Allergy Department. CIBERES and Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, Universitat de Barcelona, Spain

46. Allergy and Clinical Immunology Department, Hospital CUF-Descobertas, Lisboa, Portugal

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Address for correspondence:

Professor Jean Bousquet

CHRU Arnaud de Villeneuve, 371 Avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, France Tel +33 611 42 88 47 jean.bousquet@orange.fr

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Abstract

Background

The use of Apps running on smartphones and tablets profoundly affects medicine. The MASK-rhinitis (MACVIA-ARIA Sentinel NetworK for allergic rhinitis) App (*Allergy Diary*) assesses allergic rhinitis symptoms, disease control and impact on patients' lives. It is freely available in 20 countries (iOS and Android platforms).

Aims

To assess in a pilot study whether (i) *Allergy Diary* users were able to properly provide baseline characteristics (ii) simple phenotypic characteristics based upon data captured by the *Allergy Diary* could be identified and (iii) information gathered by this study could suggest novel research questions.

Methods

The *Allergy Diary* users were classified into 6 groups according to the baseline data that they entered into the App: (1) asymptomatic; (2) nasal symptoms excluding rhinorrhea; (3) rhinorrhea; (4) rhinorrhea plus 1-2 nasal/ocular symptoms; (5) rhinorrhea plus ≥3 nasal /ocular symptoms and (6) rhinorrhea plus all nasal/ocular symptoms.

Results

By June 1, 2016, 3,260 users had registered with the *Allergy Diary* and 2,710 had completed the baseline questionnaire. Troublesome symptoms were found mainly in the users with the most symptoms. Around 50% of users with troublesome rhinitis and/or ocular symptoms suffered work impairment. Sleep was impaired by troublesome symptoms and nasal obstruction.

Conclusions

This is the first App (iOS and Android) to have tested for allergic rhinitis and conjunctivitis. A simple questionnaire administered by cell phones enables the identification of phenotypic differences between *a priori* defined rhinitis groups. The results suggest novel concepts and research questions in allergic rhinitis that may not be identified using classical methods.

Abbreviations

AHA: Active and Healthy Ageing

AR: allergic rhinitis

ARIA: Allergic Rhinitis and its Impact on Asthma

EIP: European Innovation Partnership

HIT: Health information technology

ICT: information and communications technology

MACVIA: Contre les MAladies Chroniques pour un VIellissement Actif

MASK: MACVIA-ARIA Sentinel NetworK

NAR: non allergic rhinitis

AIT: specific immunotherapy

VAS: visual analogue scale

Key words: rhinitis, mobile technology, MASK-rhinitis, EIP on AHA, allergen immunotherapy (AIT), *Allergy Diary*

Introduction

Survey questionnaires are important tools in clinical practice and epidemiology. The use of information and communications technology (ICT) or health information technology (HIT), such as apps running on consumer smart devices (i.e., smartphones and tablets), is becoming increasingly popular and has the potential to profoundly affect healthcare (1). Novel app-based collaborative systems can have an important role in gathering information quickly and improving coverage and accessibility of prevention and treatment (2). Classical tools are being replaced by newer smartphone technologies, providing individual measures across larger populations. However, variation in the mode of delivering a survey questionnaire may affect the quality of the responses collected, and data equivalence between survey questionnaires and apps is lacking (3). There are potential biases when using apps, since the information gathered is usually simple and less complete than when using lengthy questionnaires. Furthermore, the interpretation of studies on health effects is hindered by uncertainties in the exposure assessment (4). Implementing ICT innovations may also have disruptive consequences, so it is important to test applicability in each individual situation. In most instances, studies using ICT tools may have a selection bias since the phenotypic characteristics of the population are poorly known and the study may not be representative of the general population. Thus, the information provided by questionnaires and apps is almost certainly not identical, but may provide complementary information for understanding unmet needs of diseases. Moreover, ICT tools may allow the proposal of novel concepts and research questions.

Several unmet needs have been identified in allergic rhinitis (AR). These include optimal AR control, multi-morbidities, stratification of patients, promotion of multidisciplinary teams within integrated care pathways, endorsing innovation in clinical trials and encouraging patient empowerment (5, 6). Similar unmet needs have also been found in non-allergic rhinitis (NAR) (7, 8). In addition, NAR endotypes and phenotypes (9) need to be further evaluated to better understand pathophysiology, diagnosis and management (7).

Smart devices and internet-based applications are already used in rhinitis and may help to meet some of the unmet needs (10-16). MASK-rhinitis (MACVIA-ARIA Sentinel NetworK for allergic rhinitis), an ICT system centred around the patient (5, 17), is one of the implementation tools of the B3 Action Plan of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA) (18, 19). A mobile phone app (*Allergy Diary)* central to MASK-rhinitis belongs to the Région Occitanie (France). App users are asked to complete a short demographic questionnaire, thus providing baseline characteristics of their disease, and to use the touch screen to provide a daily visual analogue scale (VAS) score-based assessment of AR control. The *Allergy Diary* has been launched in 20 countries (5, 17).

Aims

At the onset of the project, it was proposed that a first analysis would be carried out after the enrolment of 3,000 users. On June 1, 2016, information on baseline characteristics was made available for the first 3,260 users of the MASK-rhinitis survey in Europe. The aims of this cross-sectional pilot study were to assess whether (i) *Allergy Diary* users were able to provide baseline characteristics, (ii) simple phenotypic characteristics based upon data captured by the *Allergy Diary* could be identified and (iii) information gathered by this pilot study might generate novel concepts and research questions.

Methods

Users

All consecutive users from August 1, 2015 to June 1, 2016 were included in the study. Some of the demographic characteristics (age, sex, country and language) were recorded. The App was used by those who found it via the internet, Apple store, Google Play or elsewhere. A few of the users were clinic patients who were asked by their physicians to use it. However, due to anonymisation of data that was requested in some of the countries, no specific information was gathered. None of the users were enrolled in a clinical study as we aimed to have a real life assessment. There was no pan-European promotional campaign. Several approaches were proposed in the different countries such as (i) an e-mail to members of the University Hospital of Montpellier during the pollen season informing them of MASK, (ii) an observational study in Spain, (iii) the involvement of the Allergy societies in Germany, Portugal and Italy and (iv) press releases and information to allergists during the EAACI meeting

Allergy Diary

The app collects the following data: (i) information on the AR symptoms experienced (nasal and ocular), (ii) disease type (intermittent/persistent), (iii) how symptoms impact users' lives, and (iv) type(s) of AR treatment used (Table 1 and Annex). Geolocalized users assess their daily symptom control using the touchscreen functionality on their smart phone to click on 3 consecutive VAS (i.e. general, nasal and ocular symptoms). Mobile phone messaging facilitates the management of AR, providing prompts to assess disease control, to take medication, and to visit a health care provider, if appropriate. The system was initially deployed in 15 countries and in 15 languages (translated and back-translated, culturally adapted and legally compliant). It is now also available in Australia, Brazil, Canada, Mexico and Switzerland.

Ethics

The Terms of Use, translated into all languages and customized according to the country's legislation, allow the use of the results for research purposes. The example of the UK terms of use is given in online supplement 1.

The data are anonymised except for the geolocalized data which are never totally anonymous. The European Commission's Article 29 Working Party stated that geolocation information is personal data (http://ec.europa.eu/newsroom/just/item-detail.cfm?item_id=50083) and that information can only be collected, shared, or stored with people's express consent. This is the case for MASK since users agree to geolocation in the terms of use of the App. Moreover, geolocation is optional given that the user can allow it or not on his/her cell phone and that it can be removed at any time. The problem of privacy due to geolocation was examined by the lawyers of each of the countries in which MASK has been launched and it was found to be in accordance with the existing laws. Moreover, geolocation is not used in the data mining process, nor is the phone IP.

An IRB approval was not required.

Outcomes

In this study, VAS measurements were not considered. Only the type and number of nasal/ocular symptoms were assessed to classify the users (Table 1 and online supplement 2).

Classification of users

The clinical differentiation between AR and NAR may be difficult. Symptoms may differ depending on allergen sensitivity and exposure, as well as ethnicity, cultural differences, age, sex and other environmental risk factors. In the ARIA report, the major symptom differentiating AR and NAR was proposed to be rhinorrhea (20), although this may also exist in NAR (7, 8). Rhinorrhea is thought to be more severe in patients with pollen allergy than in those with mite allergy. However, it appears that the vast majority of mite allergic patients present rhinorrhea during nasal challenge (21) (Bergman, personal communication) or during clinical trials (22, 23). Thus, in general, "sneezers" and "runners" may be ascribed to AR whereas "blockers" may be ascribed to NAR (24, 25). Patients suffering from AR usually present with all four of the cardinal nasal symptoms at a variable level (i.e. nasal obstruction, rhinorrhea, sneezing and pruritus) (26-29) and often also suffer from conjunctivitis (30, 31).

As a working hypothesis, we proposed to classify symptomatic participants according to rhinorrhea as an entry criterion (Figure 1 online).

We then used the MeDALL results, which indicated that multi-morbidity is associated with more severe disease (32, 33). We hypothesized that users with many nasal and ocular symptoms have a more severe disease (34). Moreover, ocular symptoms are associated with severe AR (34, 35).

Users were classified into 6 groups: (1) asymptomatic; (2) nasal symptoms excluding rhinorrhea; (3) rhinorrhea; (4) rhinorrhea plus 1-2 nasal/ocular symptoms; (5) rhinorrhea plus 3-5 nasal /ocular symptoms and (6) rhinorrhea plus all 6 nasal/ocular symptoms (Figure 1).

The pharmacologic treatment received by the users was not considered due to the large diversity in this relatively small sample and also because VAS scores for a given level of AR severity are not impacted by medications (36). On the other hand, since there was no information on the effect of allergen-specific immunotherapy (AIT) on work, daily activity or sleep, we compared users who reported AIT with those who reported no AIT.

Biases

There are potential measurement biases when using apps since the information collected is usually restricted and less complete than when using lengthy paper or web-based questionnaires. Furthermore, the interpretation of studies on health effects is hindered by uncertainties in the exposure assessment of pollutants or allergens (4). However, this study was not designed to compare questionnaires with apps. A bias might be introduced given that the app users might be a selected subset of all patients which is not representative. Higher education or specific age ranges might apply. The study was not meant to be representative of the general population.

Size of the study

In this exploratory pilot study, all registered users were included to obtain the best possible estimates for the specified time window.

Statistical methods.

The proportion of patients experiencing troublesome symptoms and impairment (i.e. work/school, daily activities and sleep) was described for each of the 6 symptom groups of the full data set. This aspect was further explored for subgroups suffering from particular symptoms potentially associated with impairment, i.e. ocular symptoms or nasal obstruction.

The effect of AIT was also analysed. Users were classified into two groups according to AIT status: (i) No AIT (i.e. 'No' to Q6) and (ii) AIT (i.e. 'Yes' to Q6 and responses to Q7 and Q8). Users with a 'Yes' to Q6 and no response to Q7 and/or Q8 were excluded from the AIT analysis.

The statistical analysis used chi-square analysis.

Results

Users

Among the 3,260 registered users, 550 did not complete the questionnaire. 2,710 files were analysable with reported symptoms and treatments in 20 countries (Table 1 online). Users included 1,165 women (43%) and 1,545 men (57%), with a mean age of 33 ± 6.6 years. Eight countries had more than 100 users and, in some countries, numbers were low. The percentage of users who provided data ranged from 68.4% (UK) to 95.2% (The Netherlands).

AIT use (Q6) was reported by 264 users. 15 of them did not respond to Q7 and/or Q8 and were excluded from further analyses (Figure 2 online). The number of AIT users was too low to allow complete analyses. However, in group 3 (rhinorrhea with no other symptom), there was a greater number of users with AIT than without AIT (Figure 3 online).

Main results

Users who did not report " rhinitis" (Q1) did not report any nasal symptom (Q3) and only 5% of them reported ocular symptoms. The impact of the disease (troublesome symptoms, sleep, work or school, daily activities) in the different groups was estimated in the full data set (Table 2). Users with no reported nasal and ocular symptoms (Group 1) rarely had any troublesome symptoms or impairment. Those with symptoms but without rhinorrhea (Group 2) often had troublesome symptoms (76%) but few experienced impairment of work or school and daily activities. In general, the proportion of patients reporting troublesome symptoms and impairment increased as the number of symptoms in addition to rhinorrhea increased.

The impact of the disease on each of the 6 symptom groups in those who did not report AIT was similar to that in the full data set and is shown in the online supplement (Table 2 online).

Asthma

Table 3 presents results for asthma reporting. More users without rhinitis did not respond to the asthma question. There was no significant difference between the different groups in reported asthma.

Impact of individual symptoms on impairment

In subjects with rhinorrhea, the impact of individual symptoms on impairment is shown in Table 4. Impairment at work/school and of daily activities is associated with troublesome symptoms, nasal obstruction and ocular symptoms. On the other hand, sleep is similar and is high in all groups.

Discussion

In this pilot study, it is suggested that (i) the *Allergy Diary* users were able to complete the baseline characteristics in 20 countries using 20 languages, (ii) a simple questionnaire administered by cell phones on either iOS or Android platforms allows identification of phenotypic differences between *a priori* defined rhinitis groups, (iii) a simplistic approach using 6 categories can be used and (iv) although the sample size is relatively limited, information gathered suggested novel concepts and research questions on AIT or the impact of AR symptoms on work.

Strengths and limitations

The strengths of the mobile technology are obvious. However, there is a need to use appropriate questions, and results should be confirmed by pilot studies. The mobile technology of MASK-rhinitis uses epidemiological methodology stating a hypothesis, collects and analyses data to test the hypothesis, and reaches conclusions about the hypothesis. Moreover, it can also be applied to an unbiased exploratory hypothesis generating investigation purposes.

Smart devices and internet-based applications are already used in rhinitis (10-15) but the hypotheses raised in the present study have never been assessed.

There are potential biases when using apps since there is necessarily a selection bias: those who use these instruments are likely to be young and well educated. Also, the information gathered is usually restricted and phenotypes less characterized than when using questionnaires. In the present study, we collected country, language, age, sex and date of entry of information. The response rate was high and most baseline questions were answered by users, suggesting that the *Allergy Diary* is simple and user friendly. However, we did not apply satisfaction or usability questionnaires. Moreover, we did not

check accuracy or the time taken to complete the self-administered survey. None of the studies included in a recent meta-analysis assessed how elements of user interaction design, survey questionnaire design and intervention design might influence mode effects (3). Our observations cannot offer any insights into these important questions. Larger scale studies in the future will permit assessments to address these elements and their interactions.

Additional biases may be introduced by the countries with high versus low numbers of participants but we shall test this further to the enrolment of more users.

Interpretation of the results and generalisability

Users of the *Allergy Diary* were apparently able to complete the baseline characteristics. It was found that a few questions should be added (current and/or past asthma, current and/or past AIT). The question on asthma did not appear to be discriminative among the asymptomatic and symptomatic groups and should be re-evaluated.

The period of study was winter and spring suggesting that the relevant allergens were indoor allergens (e.g. house dust mites, animal dander) and pollens.

For the classification of rhinitis, simple phenotypic characteristics based on the information collected by the App could be identified. Rhinorrhea was used as the first discriminating symptom of the algorithm. It appears that users with rhinorrhea had increasing work or daily impairment associated with the increasing number of concomitant symptoms. This finding has not been previously reported and needs to be confirmed in other studies. However, it is in line with the MeDALL results proposing that multi-morbidity is associated with severity of allergic diseases (33). The impact of asthma on the severity of AR needs more investigations as it is likely that the questionnaire was not informative enough. A refined version is currently being tested.

In the present study, nasal obstruction and ocular symptoms were associated with impaired work productivity. Although ocular symptoms are the most bothersome symptoms of AR (34, 35), their relationship with work has not been fully understood. These findings need to be confirmed using appropriate tests such as the Work Productivity and Activity questionnaire (WPAI-AS (37)) and EuroQuol (38), both of which are now embedded in the App.

The severity of symptoms (troublesome symptoms) was associated with an impairment of work productivity, daily activities and sleep. However, ocular symptoms were not associated with sleep impairment.

Interesting findings have been observed for AIT. A higher AIT ratio for Group 3 only suggests a positive impact of AIT on AR management with a reduction in occurrence of other nasal symptoms, although causation cannot be implied in the current study. The number of subjects is low and does not allow any firm conclusion. However, as for pharmacotherapy, treatment does not affect the reporting of impairment by symptomatic subjects.

The mobile technology is available in 16 European countries as well as in Australia, Brazil, Canada and Mexico.

This study shows how data collected via mobile technologies can provide different insights compared to the traditional conduct of research. Information gathered by this pilot study may suggest novel

concepts and research questions enabling large studies that collect real-time data on people's location, environment, health and stratification (39).

- The following authors participated to the translation, cultural adaptation and country dissemination of the App : J Bousquet, MD (1, 2), D Caimmi, MD (3, 4), A Bedbrook, BSc (1), M Bewick, MD (5), P Hellings, MD (6), P Devillier, MD (7), S Arnavielhe, PhD (8), C Bachert, MD (9), KC Bergmann, MD (10), GW Canonica, MD (11), N Chavannes, MD s (12), AA Cruz, MD (13), R Dahl, MD (13), P Demoly, MD (3,4), A Finkwagner (15), J Fonseca, MD (16), N Guldemond, MD (17), T Haahtela, MD (18), B Hellqvist-Dahl, PhD (19), J Just, MD (20), T Keil, MD (21), L Klimek, MD (22), ML Kowalski, MD (23), M Kuitunen, MD (24), P Kuna, MD (25), V Kvedariene, MD (26), D Laune, PhD (8), AM Pereira, MD (16), P Carreiro-Martins, MD (28), E Melén, MD (29), M Morais Almeida, MD (46), J Mullol, MD (30), A Muraro, MD (31), R Murray, PhD (32), L Nogueira-Silva, MD (33), N Papadopoulos, MD (34), G Passalacqua, MD (11), F Portejoie (1), D Price, MD (35), D Ryan, MD (36), B Samolinski, MD (37), A Sheikh, MD (38), V Siroux, PhD (39), O Spranger (15), A Todo Bom, MD (40), PV Tomazic, MD (41), A Valero, MD (45), E Valovirta, MD (27), A Valiulis, MD (44), O VandenPlas, MD (43), M Wickman, MD (29), T Zuberbier, MD (10)

- G De Vries, PhD (14), and M van Eerd (14) developed the App
- E Mathieu-Dupas, PhD (8) analysed the results
- S van der Meulen (42) was the lawyer

Upon submission of a manuscript all co-authors should also be registered with correct e-mail addresses.

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Table 1: Questions on symptoms and impact of symptoms

Q1: I have rhinitis: Yes/No
Q2: I have asthma: Yes/No
Q3: My symptoms (tick)
• Runny nose
• Itchy nose
• Sneezing
• Congestion (blocked nose)
• Red eyes
• Itchy eyes
• Watery eyes
Q4: How they affect me: My symptoms (tick)
• Affect my sleep
• Restrict my daily activities

- Restrict my participation in school or work
- Are troublesome

Q5: Medications

Q6: Are you currently receiving immunotherapy (a small dose of the thing you are allergic to, usually taken as an injection or placed under your tongue)? Yes/No

If YES to Q6 (Q7 and Q8)

Q7: What allergy is this?

- Grass pollen
- Parietaria pollen
- Birch pollen
- Other pollen
- Dust mite
- Animal
- Cypress tree pollen
- Don't know
- Add allergy

Q8: How do you receive your treatment?

- Injection
- Tablet under the tongue
- Drops under the tongue
- Spray under the tongue
- Other

Table 2: Impairment in users of the full data set (N=2,710)

Group	Symptom		N	Troublesome symptoms	Impairment			
	Rhinorrhea	Any other symptom			Work or school	Daily activities	Sleep	Any
1	NO	NO	283	20 (7%)	5 (2%)	11 (4%)	11 (4%)	18 (6%)
1*	NO	Yes	39	23 (59%)	6 (15%)	5 (13%)	8 (21%)	15 (38%)
2	NO	Yes	614	467 (76%)	118 (19%)	170 (28%)	210 (34%)	319 (52%)
3	YES	None	87	23 (26%)	8 (9%)	17 (20%)	36 (41%)	55 (63%)
4	YES	1 or 2	366	258 (70%) *	68 (19%)*	100 (27%)	95 (26%)	188 (51%)
5	YES	3, 4 or 5	870	728 (84%) **	256 (29%)**	394 (45%)*	342 (39%)**	585 (67%)
6	YES	ALL (6)	451	398 (88%)	220 (49%)***	284 (63%)***	233 (52%)***	365 (81%)

Chi2 test : P<0.01 group 4 vs 3*; group 5 vs 4**; group 6 vs 5***

*: subjects who answered “no rhinitis” Q1

Table 3: Reporting of asthma

Population with informed symptoms (n=2710)				
Group	**N**	**Asthma (Yes)**	**No Asthma**	**NA**
1	322	107 (33.2%)	135 (41.9%)	74 (22.9%)
2	614	202 (32.9%)	339 (55.2%)	60 (10%)
3	87	62 (71.3%)	17 (19.5%)	7 (8.0%)
4	366	105 (28.7%)	208 56.8%)	47 (12.8%)
5	870	259 (29.8%)	521 60.0%)	72 (8.3%)
6	451	157 34.8%)	244 (54.1%)	42 (9.3%)

Table 4: Impact of individual symptoms on impairment in subjects with rhinorrhea

Subjects with rhinorrhea (N=1774)			Impairment		
			Work or school	Daily activities	Sleep
Troublesome symptoms	Yes	N=1407	483 (34%) **	659 (47%) **	603 (43%) **
	No	N=367	69 (19%)	136 (37%)	103 (28%)
Nasal obstruction	Yes	N=1274	467 (37%) ***	635 (50%) ***	591 (46%) **
	No	N=500	85 (17%)	160 (32%)	115 (23%)
Ocular symptoms	Yes	N=1324	461 (35%) ***	659 (50%) ***	541 (41%) NS
	No	N=450	91 (20%)	136 (30%)	165 (37%)

Chi2 test : ** P<0.01; *** P<0.001, NS: not significant

Figure 1: Classification of users

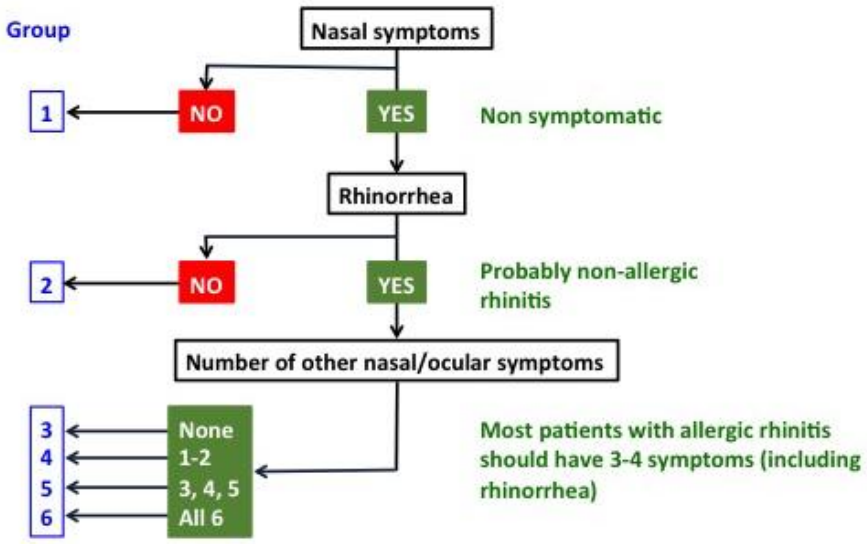

Figure 2: Distribution of the users