

Mobile Airways Sentinel network (MASK-air®)

Person-centred, digitally enabled, artificial intelligence-assisted care

06-2026 (new)

Abbreviations

ACT: Asthma control test
AIRWAYS-ICPs: Integrated care pathways for airway diseases (EIP on AHA)
AIT: Allergen Immunotherapy
API: Application programming interface
AR: Allergic Rhinitis
ARIA: Allergic Rhinitis and its Impact on Asthma
Aze-Flu: Azelastine-Fluticasone fixed combination
CARAT: Control of Allergic Rhinitis and Asthma Test
CHRODIS: EU Joint Action on Chronic Diseases
CM: Change management
COSMIN: Consensus-based standards for the selection of health measurement instruments
CSMS: Combined symptom-medication score
EAACI: European Academy of Allergy and Clinical Immunology
e-DASTHMA: Electronic daily control medication score for asthma
EIP on AHA: European Innovation Partnership on Active and Healthy Ageing (DG Santé & DG Connect)
EQ-5D: Euro-QOL (European Quality of Life 5 Dimension)
GDPR: General Data Protection Regulation
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
HCP: Healthcare professional
INAH: Intranasal H₁-Antihistamine
INCS: Intranasal corticosteroid
MASK: Mobile Airways Sentinel network
MeDALL: Mechanisms of the Development of Allergy
mHealth: Mobile Health
MID: Minimal important difference
MPR: Medication Possession Ratio
MDR: Medical Device Regulation
OAH: Oral H₁-Antihistamines
OCS: Oral Corticosteroids
OECD: Organisation for Economic Co-operation and Development
OR: Odds Ratio
OTC: Over-the-Counter
PDC: Proportion of days covered
POLLAR: Impact of air Pollution on Asthma and Rhinitis
PPP: Purchase Power Parity
PRN: Pro Re Nata (as needed)
PROM: Patient-reported outcome measure
RCT: Randomised Controlled Trial
SCIT: Subcutaneous immunotherapy
SCUAD: Severe Chronic Upper Airway Disease
SLIT: Sublingual immunotherapy
VAS: Visual Analogue Scale
WPAI-AS: Work Productivity and Activity Impairment
p: Rho, Spearman rank test

The MASK-air® app 2015-2024: Executive summary

MASK-air® is a large observational implementation study in which an mHealth app is used by over 90,000 people with allergic rhinitis and/or asthma in 35 countries. It can help to address unmet patient needs in rhinitis and asthma care, in particular severe asthma, and generate innovative hypotheses on the understanding and management of these diseases.

MASK-air® is a validated mHealth app and a Medical Device regulation Class IIa.

MASK-air® is a Good Practice of DG Santé on digitally enabled, person-centred care and of OECD (Organisation for Economic Co-operation and Development).

1- The MASK-air® app

The MASK-air® app includes a daily questionnaire (visual analogue scales (VAS) for global allergy symptoms, nose, eye, asthma, work or education and EQ-5D), daily medications using a scroll list questionnaire, digital symptom-medication scores for allergy (CSMS) or asthma (e-DASTHMA) and additive questionnaires (Control of Allergic Rhinitis and Asthma Test: CARAT, a PROM that assesses the level of control of both asthma and AR using a single tool over a period of 4 weeks; EQ-5D and WPAI-AS). Pollen counts and air pollution are available daily on a 5 km radius in Europe. MASK-air® can be used in adolescents and the elderly.

The MASK-air® Technology Readiness Level (TRL) ranges from 8 to 9 (rhinitis) and 3 to 9 (asthma).

The MASK-air® methodologic evaluation has been published in 25 peer-reviewed original articles carried out in up to 397,000 users in 27 countries.

Limitations and strengths are those of mHealth studies in cross-sectional or longitudinal studies.

Patient-reported outcome measures (PROMs) have been carefully designed in MASK-air®. VAS have been studied in pencil and paper or electronically before their inclusion in the app in up to over 50,000 patients globally. Validated questions for asthma, conjunctivitis and rhinitis have been digitalised in the app. They have been tested in around 40,000 users.

With the development of MASK-air® in 2015, the previously validated VAS PROMs were adapted to the digital format and further methodologic evaluations were performed to validate PROMs, e-CSMS and e-DASTHMA.

Additional questionnaires are included in MASK-air®: WPAI-AS and EQ-5D. However, other control or QOL tests can also be included.

Acceptability of MASK-air® by allergic patients has been carried out and the app has been modified according to patients' views.

Electronic shared-decision making is available daily using a very simple tool using GDPR requirements and QR code. The results of the users VAS scores are visually displayed on a web-based system (e.g. computer) which facilitates discussion with an HCP.

A transfer of innovation was carried out building an Interoperable platform with MASK. Twenty-five Reference Sites of the European Innovation Partnership on Active and Healthy Ageing (EIP on AHA)

participated as well as Argentina, Australia, Brazil, Canada and Mexico. The MASK transfer of innovation was considered as the most mature of the EIP on AHA. Moreover, several studies in MASK-air® found that PROMs can be used in all countries of MASK-air®.

MASK-air® is associated with WHO (GARD demonstration projects), EU grants and ARIA-EAACI Task Forces.

2- Major results

2-1- Novel multimorbid phenotype discovery based on MASK-air®

- i. **Discovery of “extreme” allergy phenotype** including multimorbidity and lack of control assessed both in cross-sectional and longitudinal studies
- ii. **Confirmation of this phenotype** by canonical epidemiologic and genetic studies
- iii. **Discovery of an “extreme” asthma phenotype** including multimorbidity, lack of control and resistance to treatment in cross-sectional studies.

2-2- MASK-air® innovative results in rhinitis

(i) When the full database is analysed, most patients:

1. are not adherent and do not follow guidelines,
2. use as-needed treatment,
3. often use OTC medications,
4. do not take medication when they are well,
5. increase their treatment based on symptoms similarly in all European countries irrespective of the culture and the treatments bought in the pharmacies,
6. do not use the recommended treatment,
7. and control (symptoms, work productivity, educational performance) is not necessarily improved by increasing medications including co-medication.
8. Co-medication of an intra-nasal and an oral medication is usually associated with worse control than single medication (cross-sectional and longitudinal analyses).
9. Overall, patients treat themselves when they are not well, self-medicate and increase their medications when they are not controlled showing that they do not follow guidelines and physicians' prescriptions.

(ii) When patients adherent to the app are analysed:

1. They are also often adherent to medications, and adherence to the app appears to be associated with adherence to medications.
2. However, except for intra-nasal corticosteroids, increased adherence is not associated with an increased level of control.
3. Switching of medications is common (longitudinal analyses).

(iii) Clinical trials

1. A cluster-randomised RCT showed that pollen allergic rhinitis patients using a MASK-air®-based strategy were better improved than when using best practice.
2. In a quasi-experimental study in Greece, CARAT and MASK-air® provided complementary information on AR symptom control.

3. A Proof-of-concept open-labelled study showed that a cat food containing antibodies against Fel d 1 significantly improved all symptoms and CSMS in cat-allergic subjects.

iv- A combined symptom-medication score (CSMS) has been validated under the auspices of EAACI and ARIA.

2-3- MASK-air® innovative results in allergen immunotherapy (AIT)

When the full database is analysed:

- 1- AIT is effective in a real-world setting.
- 2- AIT provides an add-on efficacy over medications in the combined symptom-medication score (CSMS) and work.
- 3- AIT is effective for mild and more severe symptoms (CSMS below or over 20/100).
- 4- Using a Bayesian model, SLIT was more effective than SCIT on VAS symptoms, VAS work and CSMS.
- 5- AIT is likely to have a disease-modifying effect in contradistinction to pharmacotherapy as shown by the effects on education.
- 6- SLIT might induce a rapid improvement over medications and reduce daily symptoms.

2-4- MASK-air® innovative results in asthma

- i. **Evaluation of the diagnosis and control of asthma:** Comparing CARAT and MASK-air® VAS, it was found that wheezing is highly specific of asthma whereas dyspnea is associated with control. In general practice, a patient with rhinitis and wheezing has a 94% chance of being asthmatic.
- ii. **Phenotypes of asthma using clusters based on control and medications**
 - 1- An observational cross-sectional MASK-air® analysis defined 6 asthma (probable and possible asthma) and one rhinitis clusters that were confirmed in asthmatic patients enrolled by specialists. The clusters were confirmed in asthmatic patients diagnosed by physicians.
 - 2- In 253 patients who filled at least 26 days a month and reported at least one ICS ($\pm$ LABA), a cluster analysis in the first month of app use discovered 6 different phenotypes based on control, SABA use and adherence to ICS. The demonstration study validated the clusters in 2539 days.
- iii. **When patients adherent to the app are analysed (longitudinal studies):**
 - 1- Adherence to ICS or ICS-LABA was high (56.3-81.2% days).
 - 2- Adherence was higher for ICS+other LABA than for ICS+formoterol (ICS+F). However, control was similar in both groups, ICS+F was associated with a meaningful lower SABA use and similar VAS asthma, e-DASTHMA or VAS work.
- iv. **Severe asthma**
 - 1- Applicability of the MASK-air® app was explored in severe asthmatic patients in a longitudinal (observational) study. Highly variable trends were found for VAS asthma, and asthma remission can be assessed using daily e-DASTHMA and VAS asthma.
 - 2- In a Portuguese registry of severe asthma, adherence to the MASK-air app was able to determine whether uncontrolled asthma is associated with lack of adherence and to predict adherence in the next 6 months. Moreover, an adherence over 50% in one month was associated with improvement of control. The results were confirmed in the MASK-air database.

- 3- In The same Portuguese registry and in 2 Turkish ones, oral corticosteroids are mainly administered in patients with very low adherence to the app both in the previous year after MASK-air® introduction and in the year after.

v. A combined symptom-medication score (e-DASTHMA) has been validated under the auspices of EAACI and ARIA.

vi. Info-epidemiology studies have been carried out to assess risk factors for asthma exacerbations (e.g. rhinovirus).

3- Impact of MASK-air®

3-1- Impact on quality-of-life, work and economic evaluation

i. VAS work, VAS education and WPAI-AS:

Rhinitis, asthma and ocular symptoms have a significant impact on work productivity or education. Patients with the rhinitis and asthma phenotype have significantly more impairment on work than those with rhinitis alone.

ii. EQ-5D-5L

- 1- Worse control of rhinitis, conjunctivitis or asthma (median VAS and CSMS) were associated with an impairment of EQ-5D domains. Mobility was particularly associated with VAS asthma.
- 2- Poor control of rhinitis or asthma or conjunctivitis was associated with decreased QoL assessed by either EQ-5D-5L utility values or EQ-5D VAS. The largest differences in QoL concerned comparisons between poor *versus* other levels of control for all symptoms, particularly for the EQ-5D VAS.

iii. Economic evaluation

- 1- The monetary impact (indirect costs) of AR was assessed on work productivity for all OECD countries and countries where MASK-air® is available by using the human-capital method (PPP). In poorly controlled weeks, presenteeism was associated with indirect costs ranging from 65.7 US\$ PPPs in Brazil to 693.6 US\$ PPP in Iceland. Patients with rhinitis + asthma showed higher overall work impairment than patients with AR alone, particularly in poorly controlled weeks.
- 2- Another paper assessed the monetary value of 1 point of the CMSS and e-DASTHMA and of the control of rhinitis and asthma. This study will allow us to estimate the indirect beneficial cost of interventions.

3-2- Digital biomarkers

Biomarkers for the diagnosis, treatment and follow-up of patients with rhinitis and asthma are urgently needed. Although some biologic biomarkers exist in specialist care for asthma or rhinitis, they cannot be largely used in primary care. Digital biomarkers may prove to be quite effective.

3-2-1- Allergic rhinitis

Potential benefits of digital biomarkers in allergic rhinitis include (i) optimisation of shared-decision making, (ii) observational studies with real-world data, (iii) the triangulation of RCTs and (iv) epidemiologic studies.

3-2-2- Allergen immunotherapy

MASK-air® can be used in clinical trials. Proposed benefits of apps include the ability to longitudinally collect symptoms and medication usage data, allowing the detection of changes during treatment. Data from external sources, including weather, allergen load and air quality reports are integrated. The placebo effect may be minimised.

The clinical course of patients undergoing AIT can be monitored more precisely than with current methods, in particular, daily allergen exposure in a 5 km radius.

3-2-3- Asthma

Using the MASK-air® app as a model, a daily electronic combined symptom-medication score for allergic diseases (CSMS) and for asthma (e-DASTHMA) was reported and embedded in a strategy similar to the diabetes approach for disease control.

In biologics, patient stratification for indication, follow-up and cessation of treatment can be easily assessed.

In severe asthma, asthma remission can be studied daily.

3-3- Impact on guideline development (ARIA 2024)

The ARIA 2024 guidelines will use real-world data from MASK-air® for the development of PICO questions and the assessment of real-world data using a novel GRADE approach.

3-4- Impact on policies

The OECD has made a detailed assessment of MASK-air® and concluded that “MASK is an equity enhancing digital health intervention which has improved the knowledge base on AR and asthma. Subsequent evaluations of MASK using adherence, productivity and quality of life as outcomes, should be of key interest to policy makers and therefore strongly supported.” These conclusions were based on 2022 data and adherence, productivity and quality-of-life have now been obtained, strengthening the OECD recommendations.

MASK-air® has been accredited by the Ministries of Health from Ukraine (March 2023) and Poland (May 2024).

Introduction

In 2014, MASK (Mobile Airways Sentinel network) was launched by the European Innovation Partnership on Active and Healthy Ageing (EIP-on-AHA, DG Health and Food Safety and DG CONNECT).^{1,2} It is the ARIA (Allergic Rhinitis and its Impact on Asthma)^{3,4} Phase 3 initiative. MASK is a flexible e-platform for rhinitis (R) and asthma (A) and includes the MASK-air® app.⁵ It is freely operational in 35 countries and 23 languages. Over 80,000 users have been registered. It has already been extended to urticaria,⁶ senior vigilance⁷ and falls.⁸

MASK-air® is a validated mHealth app. It is a well-being app and a Medical Device regulation Class IIa (in the process of being transferred from NL to France) centred around the patient.⁹ It is a Good Practice of DG Santé on digitally enabled, person-centred care.¹⁰ It is also a Good Practice of OECD (Organisation for Economic Co-operation and Development).¹¹ It has been accredited by the Polish Government (April 2024).

The strategic objectives of MASK-air® are listed in Box 1.

Box 1: Strategic objectives of MASK-air®

The mission of MASK-air® is to support the digital transformation of the healthcare system into integrated care with organisational health literacy centred around the person, in order to (i) fill some of the unmet needs in the real-life assessment of patients' treatment choices in rhinitis and/or asthma (and multi-morbidities) control and, ultimately, (ii) propose person-centred care for these diseases as a model of non-communicable disease.

The vision is to provide a novel cost-effective strategy developing a person-centred, digitally enabled and artificial intelligence-assisted care pathway.

The overarching objective of MASK-air® is (i) to propose a multisectoral care pathway to transform - in a cost-effective manner - health and care systems in rhinitis and asthma (including severe asthma) using mHealth tools acceptable for the patient and the health careworker and (ii) to strengthen planetary health.

MASK-air® is a Good Practice of DG Santé on digitally enabled, patient-centred care. It is also a Best Practice of OECD (Organisation for Economic Co-operation and Development) for policy makers.

1. MASK-air®

1.1. The MASK-air® app

1.1.1. Customer needs

Using daily visual analogue scales (VAS), users can track their symptoms for AR (global allergy impact, nose, eyes) and asthma (VAS asthma). We have also added to MASK-air® daily monitoring the impact of the diseases on work¹² or education¹³ as well as a generic VAS QOL questionnaire (EQ-5D-5L VAS).^{14,15} One question, VAS “dyspnea”, was added temporarily to MASK-air® but the results showed a highly significant correlation with VAS “asthma” in patients with severe asthma ($\rho = 0.93$ and 0.90).^{16,17} The question was therefore subsequently deleted.

Users record their medications for R, conjunctivitis and asthma daily using a regularly updated treatment scroll list which includes all medications customised for each country (Table 1 and Figures 1 & 2).

Table 1: Daily visual analogue scales (VAS) available in MASK-air®

Scale	Question
Daily monitoring VAS Global allergy symptoms VAS Nose VAS Eyes VAS Asthma Impact VAS work VAS education* EQ-5D-5L VAS	“Overall, how much are your allergic symptoms bothering you today?” “How much are your nose symptoms bothering you today?” “How much are your eye symptoms bothering you today?” “How much are your asthma symptoms bothering you today?” “How much are your allergic symptoms affecting your work today?” “Today, how much did allergies affect your productivity while in school or attending classes in an academic setting?” EQ-5D-5L VAS ¹⁴

*Question derived from WPAI-AS (¹⁸⁻²⁰)

Figure 1: The MASK-air® app

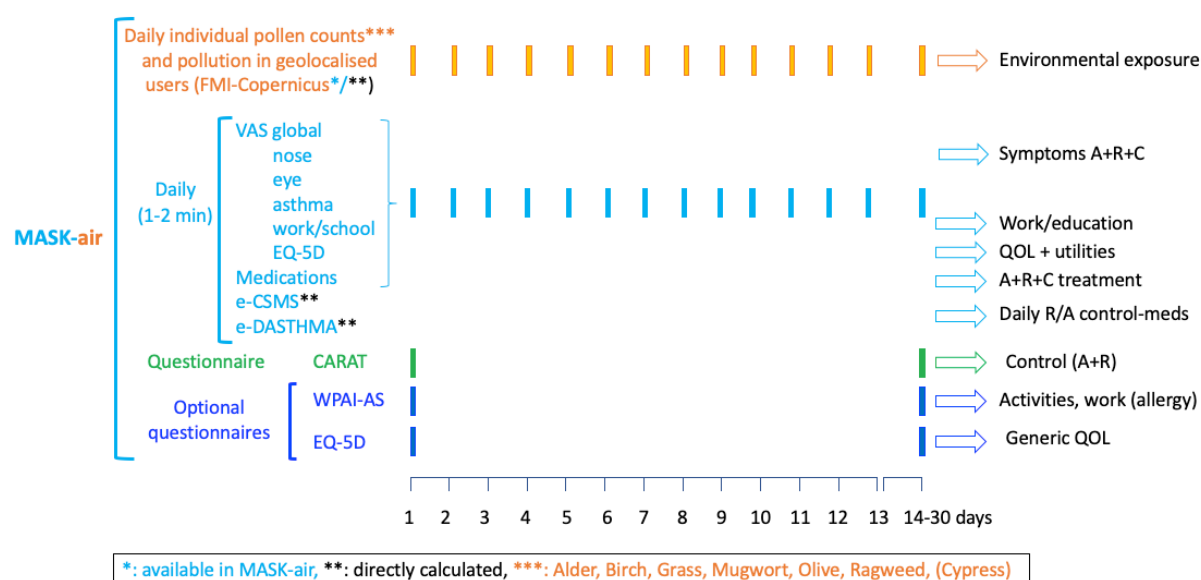
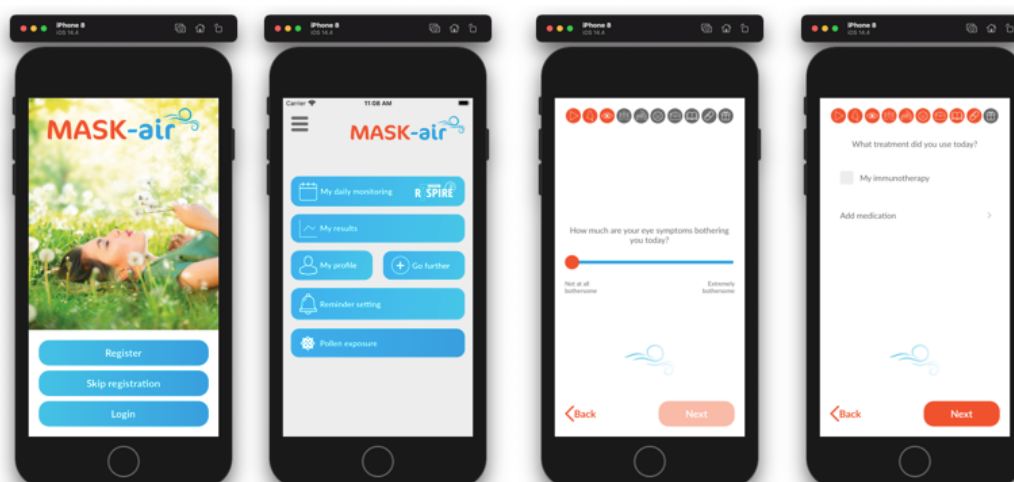


Figure 2: MASK-air® screens



MASK-air® is combined with prediction on allergen exposure and air quality (POLLAR: Impact of air POLLution on Asthma and Rhinitis, EIT Health-funded project) using COPERNICUS data provided by the Finnish Meteorological Institute (Figure 3).²¹

Figure 3: MASK-air® screens on pollen and pollution on two consecutive days during the 2024 grass pollen season in Montpellier



The MASK-air® app has been designed to avoid any missing data in the secure database.

We are conducting a Horizon Europe grant (CATALYSE) to investigate how we can include pollen and pollution alerts in the app.²² Three countries are participating: Germany, Italy and Lithuania.

1.1.2. Intended use

To help patients with AR and/or asthma monitor their symptoms and inform them on their control. The app does not suggest any specific treatment decisions and is a supportive tool. However, since the app is a medical device regulation (MDR) class IIa, these features can be activated at a later stage.

1.1.3. Intended users

Patients affected by AR and/or asthma. The app is not intended for minors (children under 16 or internet majority depending on the country). However, after ethical agreement and parents' approval, the app can be used in minors.

1.1.4. Software (SW) operation, functionality and technical description

MASK-air® is a mobile phone app freely available for Android and iOS. The MASK-air website (<https://www.mask-air.org/data>) shares data collected on the user's phone with the healthcare provider

during an appointment. The app consists of (i) VAS and medication scroll list, (ii) a QR code reader module, (iii) my profile, (iv) reminders and (v) additional questionnaires: EQ-5D,¹⁵ WPAI-AS (Work Productivity and Activity²³) and CARAT (Control of Rhinitis and Asthma Test).²⁴

1.1.5. Labelling information app

The software (SW) MASK-air[®] was initially marketed as the “Allergy App”.²⁵ The SW application itself identifies the legal manufacturer (Peercode, <https://www.peercode.nl/nl/welkom/>) and provides screens with contact details. It includes an integrated Terms of Use (ToU)/Privacy Policy section that covers all applicable regulatory required labelling content, such as specific operating instructions prior to use and any potential use-related advice.²⁶ No specific warnings, separate non-digital labelling documentation or Instructions for Use are provided to the user.

The ToU information contains the instructions relevant prior and during use and is available at all times in the App Stores as well as in the app and exchange-website itself.²⁶ The ToU were revised by a lawyer in February 2026 to comply with EU rules.

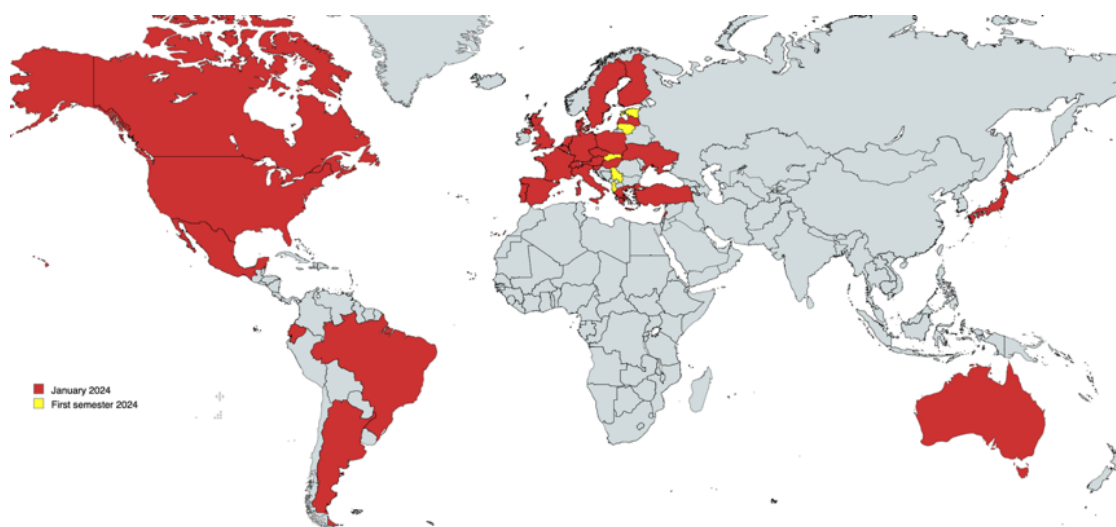
After downloading the app and prior to use, the user has to accept the ToU containing the privacy policy. With acceptance of the ToU, the information is considered understood and accepted.

1.1.6. Data Privacy Officer (DPO)

Maître Claire Lauria, Cabinet d’avocats Ydès, Lyon, France.

1.1.7. MASK-air[®] is available in country relevant languages (Figure 4)

Figure 4: Geographical distribution of MASK-air[®]



1.1.8. Labelling information on the physician’s exchange website

On the bottom banner, a link to Privacy Policy and Terms of Use is shown. The CE mark with notified body number is shown when applicable. Clicking on the CE symbol opens the additional information such as legal manufacturer and contact details.

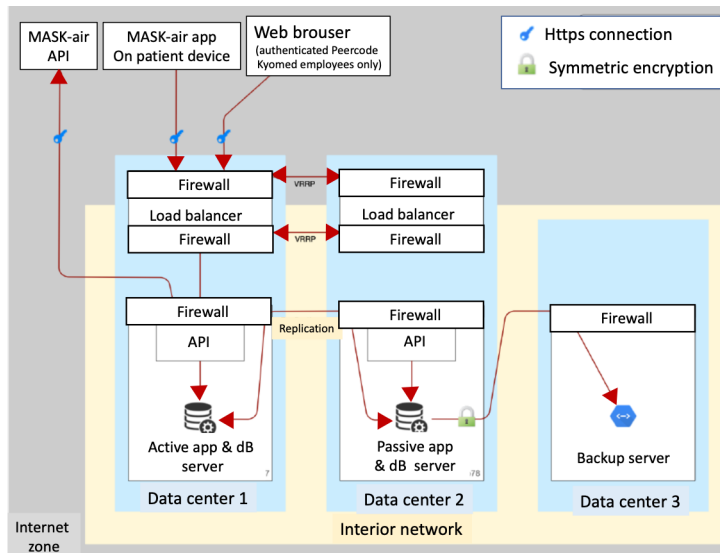
1.1.9. Labelling information peercode.nl website

A link is provided to the ToU/ Privacy Policy and to the Labelling as provided on the mask-air.org website. Over 93,000 users have been registered.

1.2. Secure database

The secure database is shown in Figure 5.

Figure 5: Secure database



1.2.1. Hosting architecture

- ISO 27001 certified
- No single point of failure: everything is redundant
- 24×7 monitoring of multiple performance indicators
- Extensive data protection
- Realtime replication to save database
- Daily dump to disk
- Daily backup to separate data centre
- All hard disks in RAID configuration
- Double firewall
- Exterior firewall which filters both inbound and outbound traffic
- Interior firewall on every server
- No Access to the application except via HTTP(S) (so no ssh either)
- Only standard tools are used which are updated with authorised security patches on a daily basis
- Geo-redundancy of complete hosting architecture
- Guarded security
- 24h/24h – 7d/week on-site support service
- Full system administration, including system installation, configuration, fine-tuning
- System updates and security management
- Automated real-time monitoring of availability of services

1.1.2. API -Transfer

This is a REST API (Application programming interface) with which the MASK-air App communicates to provide and retain data. It is also responsible for authorising users within the MASK-air App.

The API also communicates with the other sub-systems:

- The API accepts study codes from <https://www.asa-sas.com/>. A study code is created on the ASA platform and then ASA sends the created study code to the MASK-air API.
- The MASK-air[®] API stores this study code in the database.

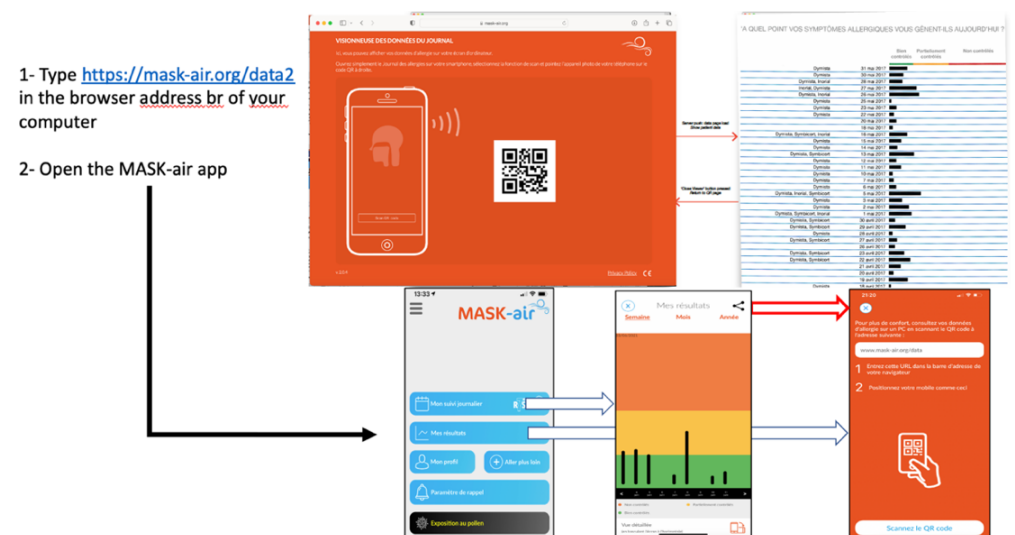
Future external actors could also be connected to the API to improve the MASK-air Mobile App. This application will be deployed to servers managed by Peercode. The MASK-air[®] API has been built.

1.3. Electronic shared decision making

In MASK-air[®], a very simple tool was devised for SDM using GDPR requirements (Figure 6).^{9,27}

A QR code reader facilitates the sharing of data. The results of the users' VAS scores are visually displayed on a web-based system (e.g. computer) which facilitates discussion with a HCP. QR-CODE scanning requires internet connection via <https://www.mask-air.org/data>.

Figure 6: Electronic shared decision making



1.4. Transfer of innovation

A transfer of innovation was carried out. The rhinitis Twinning made it possible to build an Interoperable platform with MASK. Twenty-five Reference Sites of the EIP on AHA participated as well as Argentina, Australia, Brazil, Canada and Mexico.²⁷ The MASK transfer of innovation was considered as the most mature of the EIP on AHA.²⁸

2. Strategic overview

The MASK-air[®] vision based on ARIA led to a strategic objective (Table 2).

Table 2: Strategic overview (adapted from ²⁹⁾)

	Acronym & ref	Name	Dates
WHO-associated projects			
	GARD ³⁰	Global Alliance against Chronic Respiratory Diseases, demonstration project	2003-23
	WHO-ITU ³¹	“Be He@lthy, Be Mobile” handbook on asthma and COPD	2017
EU grants and projects			
	EIP on AHA ²⁸	European Innovation Partnership on Active and Healthy Ageing (DG Santé & CONNECT)	2012-20
	Joint Research Center (JRC) Scientific and Policy Reports on Strategic Intelligence Monitor on Personal Health Systems Phase 3 (SIMPHS3) ³²		2015
	MACVIA ³³	European Regional Development Fund (ERDF-Région Languedoc-Roussillon)	2016-7
	Twinning ²⁷	Transfer of Innovation (DG Santé & CONNECT)	2017-9
	DHE Twinning ³⁴	Transfer of innovation in severe asthma (H2020)	2019-20
	POLLAR ^{21,35}	Impact of air Pollution on Asthma and Rhinitis (EIT Health)	2018-9
	CATALYSE ²²	Climate change (Horizon Europe)	2022-6
	MASK@PACA	European Regional Development Fund (ERDF-Région PACA)	2021-2
	CAMBAS	Horizon Europe	2026-
	ClimAir	Horizon Europe	2026-
	Good Practice DG Santé on digital health (DG Santé) ¹⁰		2018
	Best Practice OECD-DG Santé ^{11,36}		2023
	Accreditation by Polish Government		2024-6
ARIA-EAACI Task Forces and Position Papers			
	Electronic daily symptom-control score in allergy (CSMS) ^{18,37,38}		2022
	Electronic daily symptom-control score in asthma (e-DASTHMA) ^{37,38}		2023
	Digital biomarkers in asthma ³⁹		2024
	Digital biomarkers in allergen immunotherapy ⁴⁰		2024
	UCRAID ⁴¹		2023

ARIA: Allergic Rhinitis and its Impact on Asthma, CARAT: Control of Allergic Rhinitis and Asthma Test, EAACI: European Academy of Allergy and Clinical Immunology, e-CDSS: electronic clinical decision support system, GA²LEN: Global Allergy and Asthma European Network, GARD: Global Alliance against Chronic Respiratory Diseases, OECD: Organisation for Economic Co-operation and Development, POLLAR: Impact of air Pollution on Asthma and Rhinitis, CATALYSE: Climate Action to Advance HeaLthY Societies in Europe, WHO: World Health Organization. ITU: International Telecommunication Union, UCRAID/ Ukrainian Citizen and refugee electronic support in Respiratory diseases, Allergy, Immunology and Dermatology

3. General Data Protection Regulation (GDPR) and Medical Device Regulation (MDR)

The download and usage of the app are free of charge and there are no adverts. It falls under the French jurisdiction. It follows the General Data Protection Regulation (GDPR) which regulates the processing of personal data in the European Union (EU). ²⁶ Geolocation also follows the GDPR. ⁴²

The Privacy Impact Assessment (PIA) has been performed and there is an external Data Protection Manager (DPO).

Two different ethics co-exist.

- i. The app is available in the app stores to anyone who wishes to assess asthma and/or rhinitis control. It is intended for personal and individual use. The data collected in the framework of the use of the

app are however relevant for scientific research purposes in order to improve management. In this respect, the data are processed for a secondary scientific purpose provided with the consent of the user. Consequently, an ethics review board is not required with regard to the data protection regulation.

- ii. However, when a clinical trial or an EU project were performed, an IRB approval was requested and obtained in France, Germany, Italy, Lithuania, Poland, Portugal and Turkey.

4. Maturity levels

The Technology Readiness Level (TRL) ⁴⁵ has been assessed (Table 3).

Table 3: Maturity level of MASK-air® (adapted from ²⁹)

Rhinitis platform	TRL		Asthma platform	TRL	
App for rhinitis and multimorbidity (MASK-air®): 28 countries, 17 languages	9	9,46,47	Adaptation of the MASK-air app for SA tested by the DHE SA-TWINNING	8	34
PROMs for rhinitis	9		PROMs for asthma	9	16
CARAT questionnaire for screening and control of rhinitis and asthma, 20 countries	9	24,48-50	The same questionnaire will be used	9	24,48,49
e-physician questionnaire for rhinitis (available on the MASK-air website) deployed in 28 countries and 20 languages	9	27	Adaptation of the MASK questionnaire for SA developed by the DHE SA-TWINNING	6	34,35
Electronic CDSS in English for rhinitis	8	51			
Embedding air quality (outdoor air pollution) and pollen data in MASK-air® (POLLAR)	9	21	Alerts for air pollution and pollens predicting asthma exacerbations	5	
			Alerts for rhinovirus predicting asthma exacerbations	4	52,53
EAACI-ARIACARE-digital network (28 countries, 20 languages)	9		The same network will be used	9	
Symptom-medication score for rhinitis	9	12	Daily control-medication score for asthma	5	
	NA		Sensors for pulmonary function	3	
Embedding artificial intelligence in MASK-air®	2		Embedding artificial intelligence	2	

5. Methodologic validation

COSMIN (Consensus-based standards for the selection of health measurement instruments) guidelines ⁵⁴ were used for the VAS scales (Table 4). There was an excellent internal consistency (Cronbach's test >0.84, test-retest >0.7), reliability (>0.9) and acceptability. In addition, VAS had a good sensitivity when users (n=521) answered them twice in less than three hours. In a second study in 17,780 users, ⁵⁵ intra-rater reliability (intraclass correlation coefficients, ICCs) ranged from 0.870 to 0.937. Test-retest reliability in clinically stable users ranged from 0.604 to 0.878. Responsiveness (Cohen's effect size and standardised response mean) was assessed in users with two consecutive measurements of EQ-5D VAS or VAS Work indicating clinical change. Moderate/large effect sizes were observed (highest responsiveness for VAS global allergy and lowest responsiveness for VAS sleep).

Quality of data was checked ¹² using insufficient effort responding (IER) to assess the intra-individual response variability (IRV) index. ⁵⁶ The independency of VAS questions assessed using the Bland and Altman regression analysis ⁵⁷ showed that all VAS measurements were independent. ⁵⁸

Table 4: Methodologic validation of MASK-air® (updated from ⁵)

	Study name	Ref	Study type	N users	N days	N countries
Methodology	COSMIN guidelines	54	Obs, CS-L	2,497	14,612*	15
	Test-retest, intra-class coefficient	55	Obs, CS-L	17,780	317,176	25
	Quality of data (intra-individual response variability)	12	Obs, CS	14,189	205,904	23
	Independence of data	55	Obs, CS	1,136	5,889	18
	VAS work	12,23,33,58	Obs, CS	14,189	205,904	18
	EQ-5D VAS	23,33	Obs, CS	1,288	NA	18
Impact	EQ-5D domains	23,33,58,59	Obs, CS			26
	Work Productivity and Activity Impairment Allergic Specific (WPAI:AS)	23,33,58,59	Obs, CS	1,288	NA	18
	CARAT	50	Obs, CS	1,086	2,042	22
	CARAT*	60	Systematic review			
PROMs	Validation of PROMs	61				
	PROMs in adolescents and young adults	62	Obs, CS			
	PROMs in severe asthma		Obs, CS	86	2,349	12
	Asthma and small airways	63	Obs, CS			Turkey
	MASK-air in old age adults	64	Obs, CS	19,888	349,045	27
	Combined symptom-medication scores for allergic rhinitis (ARIA-EAACI CSMS)	18	Obs, CS	17,780	317,176	25
	Electronic daily control-medication score in asthma (e-DASTHMA)	37	Obs, CS	1662	135,635	25
	Cut-off levels	65	Obs, CS-L	23,201	395,223	27
	Mobile health app for monitoring AR and asthma in real life in Lithuanian MASK-air users	66	Obs, CS-L	149	NA	Lithuania
	Implementation of the MASK-air® app for rhinitis and asthma in old age adults. MASK@Puglia	67	Obs, CS	174	NA	Italy
Patient's perception	Impact of MASK-air on patients	68	Obs, CS	131	NA	Poland
	Factors Affecting Usage of a MASK-air® by Old-Age Asthmatics Living in Inner Central Portugal	69	Obs, CS	72		Portugal
	Comparison of anti-histamine reporting by MASK-air, Google Trends and sales in Europe	70	Obs, CS			
	CDSS (Clinical Decision Support System)	71		NA	NA	NA
	CHRODIS guidelines	72		NA	NA	NA
	Patient's satisfaction	73,74	Obs, CS	1691	28,177	Europe
Privacy	Geolocation (GDPR)	42	Obs, CS	8535	93,116	22
	GDPR	26		NA	NA	NA

ARIA: Allergic Rhinitis and its Impact on Asthma, CARAT: Control of Rhinitis and Asthma test, CHRODIS: Joint Action on Chronic Diseases, COSMIN: COnsensus-based Standards for the selection of health Measurement INstruments, EAACI: European Academy of Allergy and Clinical Immunology, EQ-5D: EuroQol, GDPR: General Data Protection Regulation, PROMs: Patient-reported outcome measure, VAS: visual analogue scale. Obs: Observational study, CS: Cross-sectional study, L: Longitudinal study, NA: not applicable*: Systematic review carried out for MASK-air

6. Limitations and strengths

Limitations and strengths are those of mHealth studies in cross-sectional or longitudinal studies. However, observational studies using mHealth are mainly hypothesis-driven and very often need confirmation using appropriate studies.

6.1. Limitations (Table 5)

i. Selection bias

- Users who download and regularly use the app may not represent the general population.
- Participants are often younger, more digitally literate, or have higher education levels than average.

ii. Self-reported data

- Symptoms, medication use, and diagnoses are entered by patients without independent verification.
- This introduces the possibility of inaccurate reporting or recall bias.
- Mitigation: Many studies compared self-reported data and physician's diagnosed asthma and results of self-reported asthma were almost identical with

iii. No physician-confirmed diagnosis

- The app cannot confirm whether users truly have allergic rhinitis, asthma, or conjunctivitis.
- Although questionnaires (such as CARAT) improve diagnostic confidence, clinical confirmation is lacking.
- Mitigation:
 - In some studies physician-confirmed diagnosis was available and the diagnosis was confirmed.
 - Moreover, VASs were carefully selected and validated in “paper and pencil” studies in up to 37,000 patients.
 - We have assessed a combination of VAS to better assess diagnosis.

iv. Limited clinical information

- Compared with clinical studies, the app collects fewer variables.
- Important information such as allergy test results, lung function, comorbidities, or physical examination findings is generally unavailable.
- Mitigation: This appears to be a strength as no clinical study could enrol 93,000 users in 35 countries and real-world MASK-air® studies complement clinical trials.

v. Medication reporting bias

- Users may forget to record medications or enter them inconsistently.
- Underreporting of medication use is a recognized limitation.

vi. Unsupervised data entry

- Data are entered without researcher or clinician oversight.
- Missing entries, inconsistent reporting, or misunderstanding of questions can affect data quality.
- Mitigation: The 75 published studies show that these comments may not apply to MASK-air®. Moreover, we bring another concept: the person-centered approach.

vii. Observational design

- MASK-air® provides real-world evidence but cannot establish cause-and-effect relationships.
- Associations observed in the data cannot prove that a treatment caused an improvement or worsening of symptoms.

viii. **Variable adherence**

- Many users discontinue using health apps over time.
- Long-term follow-up data may therefore be incomplete, potentially introducing attrition bias.
- Mitigation: Of extreme interest is that adherence to the app informs clinicians on patient behaviour.

Table 5: Limitations of MASK-air® (derived from ⁵)

Limitations	Mitigation
mHealth limitations	
Different from general population (selection bias)	ARIA classes in epidemiologic studies and MASK-air® Except when patients are enrolled by physicians
Diagnosis of patient usually unknown	
Possible under-reporting of medications	
Unsupervised input of data	
Adherence to the app may be low	
Observational studies are only hypothesis-generating and should be confirmed	
Many MASK-air® studies are cross-sectional	Longitudinal studies
Causal inference	>44,000 weeks with 6-7 day-reporting
• Cannot provide definite information about temporality	>8000 months with >26 day-reporting
• Let alone cause-and-effect relationships	

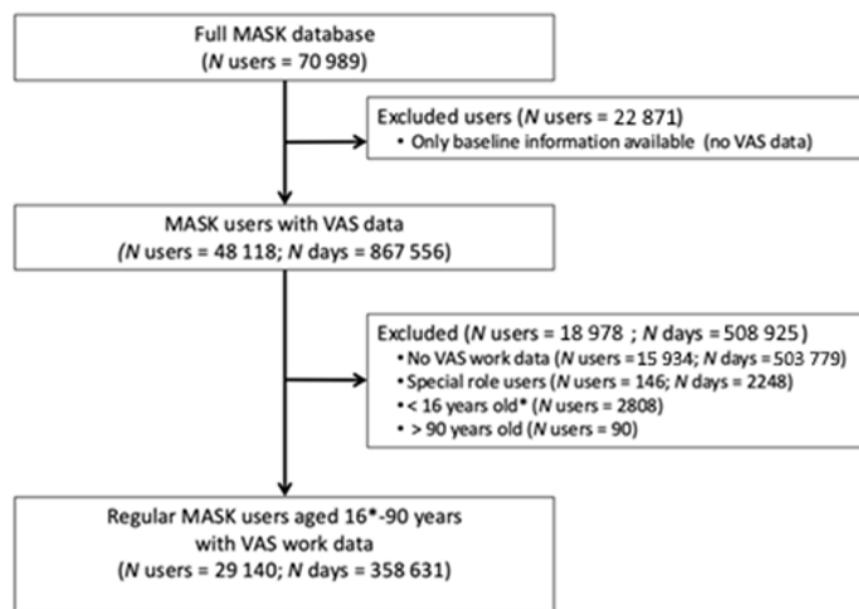
6.2. Strengths

Freely available and quickly available data, large samples, reproducibility of results between countries (generalisability), individual reports to guide management and shared decision making (SDM), patient and physician education for a proactive role, assessment of new interventions or consequences of climate change. There are 58,000 weeks with 6 or 7 days of reporting and 9500 months with over 26 days of reporting (Figure 7).

- The MASK-air® app available in 35 countries (23 languages) is inter-operable with a web-based physician's questionnaire,²⁷ an electronic combined symptom-medication score for AR (e-CDSS)⁵¹ and A (e-DASTHMA).⁷⁵
- MASK-air has accumulated data from tens of thousands of users across multiple countries and its findings have been highly consistent across studies,
- The MASK-air database does not have any missing values due to the structure of the app.
- MASK-air PRO: MDR Class IIa (currently on hold for transfer in France).
- Includes pollen data and pollution (daily and predictive) based on geolocation using the FMI and Copernicus freely available data.^{35,76}
- Good Practice of DG Santé for digitally-enabled, patient-centred care¹⁰ and Best Practice of OECD for the management of chronic diseases.¹¹
- Accredited by the Polish Ministry of Health (2024-2026).

viii. In asthma, all categories of patients are included and the database can be used to compare asthmatics of different severity grade.

Figure 7: Repartition of MASK-air® users (December 2025)



7. MASK-air® patient-reported outcome measures (PROMs)

7.1. Daily visual analogue scales (VAS)

7.1.1. Strengths and weaknesses of VAS (Table 6)

Table 6: Strengths and weaknesses of the VAS

Strengths

- The VAS is more sensitive to small changes than simple descriptive ordinal scales on which symptoms are rated, for example, as mild, moderate or severe.
- The VAS takes less than one minute to complete.
- It is easy to use with routine treatment.
- Training is not usually required to fill in a VAS, but some training may be needed when it is administered digitally.
- It is acceptable for the patients.
- It is inexpensive.

Weaknesses

- The assessment is clearly highly subjective.
- The VAS may be less valuable when comparing across a group of patients at a one-time point.
- The VAS is administered either as a paper-and-pencil measure or digitally. As a result, it cannot be administered verbally or by phone.⁷⁷
- Test-retest reliability is good, but is higher among literate compared to illiterate patients⁷⁸ and among younger compared to older adults.
- Drawbacks with paper-filled VAS do not exist when administered digitally.
- In some diseases, in the absence of a gold standard, criterion validity cannot be evaluated.

7.1.2. Validation of PROMs before inclusion in MASK-air®

Several studies were carried out to validate VAS that were further used in the app (Table 7).

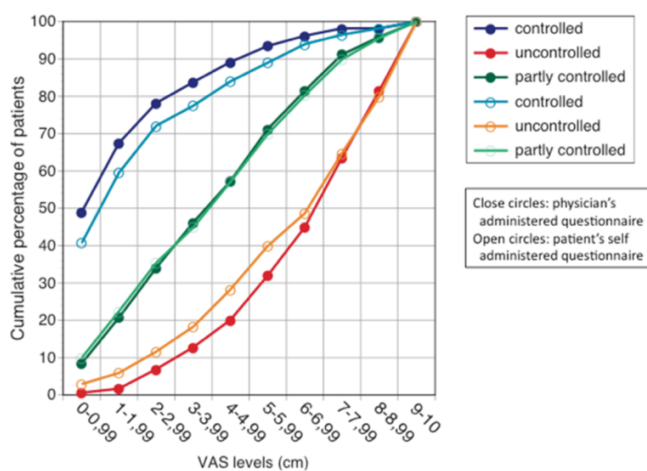
Table 7: Studies performed to validate the VAS that were later included in MASK-air®

Study		Country	N patients	VAS	Type of study	Comparator		
						RQLQ	TNSS/TSS	Other
1	Paper ⁷⁹	France	3052	Global, asthma*	Observational	X		ARIA
2	Paper ⁸⁰⁻⁸²	France	586	Global, nose, asthma*	Cluster RCT	X	X	
3	Paper ⁸³⁻⁸⁵	France	990	Global	Observational	X	X	ARIA
4	Paper ^{19,86}	France	806	Global	Observational	X	X	work
5	Paper ⁸⁷⁻⁸⁹	Japan	29,518	Nose Asthma	Observational			GINA ACT
6	e-diary ⁹⁰	Europe-CDN	547	Global	DB-PC-RCT	X	X	
7	e-diary ⁹¹	Europe-CDN	716	Global	DB-PC-RCT	X	X	
8	e-diary ⁹²	Europe	482	Rhino-conjunctivitis	DB-PC-RCT	X	X	

*: unpublished, ACT: asthma control test, RCT: randomised controlled trial, DB-PC: double-blind, placebo-controlled, CDN: Canada

A study in Japan included 1910 physicians who enrolled 29,518 patients with diagnosed and treated asthma. ⁸⁷ Self- (49%) and physician-administered questionnaires produced similar results. An *a priori* sub-analysis found that VAS asthma was a strong predictor of GINA-defined asthma. ⁸⁸ Median VAS rhinitis levels were of 5.49 (2.51-7.90) in the self-administered questionnaire *versus* 5.60 (2.75-7.85) in the physician-administered questionnaire. An *a priori* sub-analysis found that the VAS was a strong predictor of GINA-defined asthma. ⁸⁸ VAS asthma predicted levels of GINA-defined control categories (the area under the ROC curve ranged from 0.704 to 0.837), particularly with the VAS cut-offs of 1.50, 4.79 and 7.19. Similar results have been obtained with self- and physician-administered questionnaires showing the consistency of the results (Figure 8).

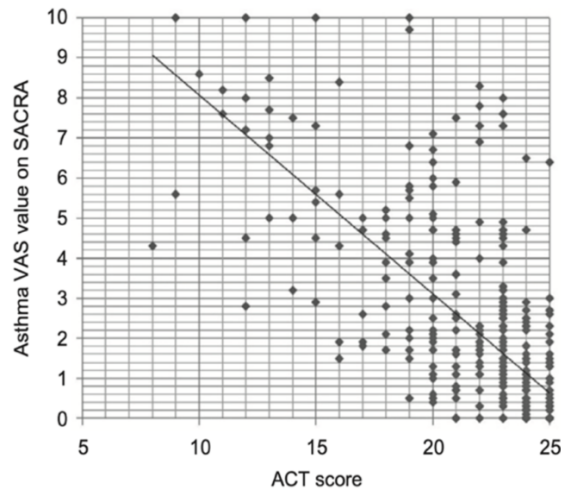
Figure 8: Distribution of GINA control categories relative to VAS levels in Japan (N=29,518 patients)



An *a posteriori* sub-analysis of the Japanese study was carried out in 420 asthma patients using self-administered questionnaires, ⁸⁹ VAS asthma and the Asthma Control Test (ACT) score. It showed a strong correlation ($\rho = -0.70$, $p < 0.001$) (Figure 9). For an ACT < 19 (cut-off for asthma control), most

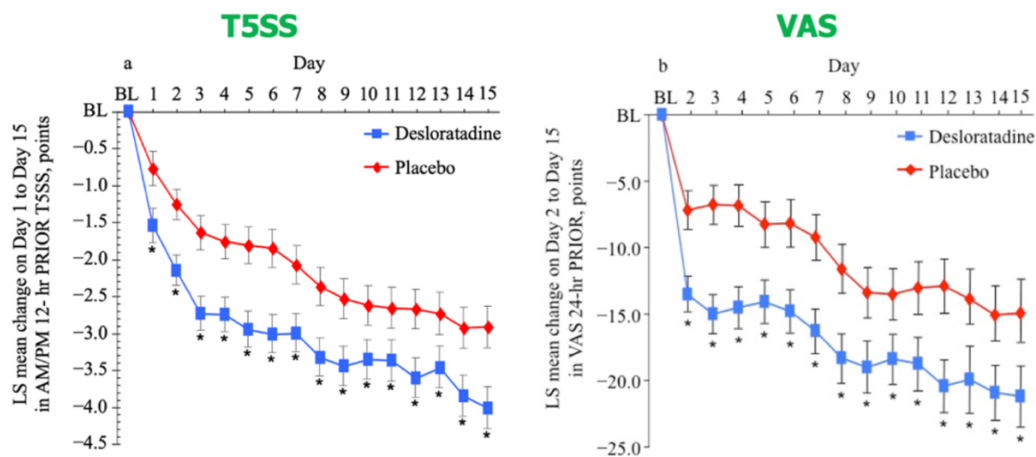
of the VAS asthma levels were over 20/100. However, for an ACT>19, many patients had high VAS asthma levels.

Figure 9: Correlation between ACT and VAS asthma (SACRA) (from ⁸⁹)



Two double-blind, placebo-controlled, randomised-controlled trials (DB-PC-RCTs) were conducted to assess whether desloratadine was effective in intermittent or persistent AR against placebo. ^{90,91,93,94} VAS global allergy symptoms were similar to RTSS 5 (nasal + ocular symptoms) results (Figure 10).

Figure 10: Evolution of TSSS and VAS global allergy symptoms in patients with intermittent allergic rhinitis treated by desloratadine or placebo



7.1.3. Patient's satisfaction with the treatment

Patients' satisfaction with their treatment (medication satisfaction) is an important PROM to consider for the successful AR management as it may influence treatment adherence and medication use patterns. ^{95,96} In fact, if patients are not satisfied with their treatment, they may tend to switch or increase their medications ^{97,98}. In MASK-air[®], while symptom control and treatment satisfaction are two different outcomes, they are interrelated with symptom control. ⁷⁴

7.1.4. Validation of MASK-air® PROMs

With the development of MASK-air® in 2015, the previously validated VAS PROMs were adapted to the digital format and further methodologic evaluations were performed.

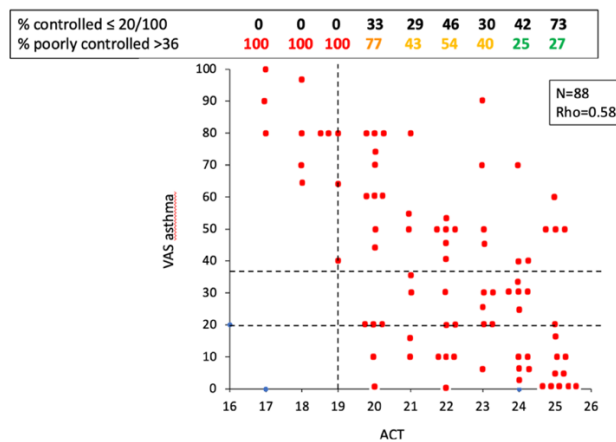
VAS asthma was studied using MASK-air® data. Correlations between VAS asthma and other MASK-air® daily reported PROMs were studied in severe asthmatic patients with nasal symptoms. Strong correlations were found between VAS asthma and other measures (Table 8).^{16,17}

Table 8: Correlation coefficients between different PROMs in severe asthma (from ¹⁶)

	N observations	Spearman correlation coefficient (95%CI)	Repeated measures correlation coefficient (95%CI) ⁹⁹
VAS asthma vs VAS dyspnea	1862	0.898 (0.879;0.915)	0.713 (0.690;0.735)
VAS asthma vs VAS global	4822	0.767 (0.750;0.784)	0.544 (0.524;0.564)
VAS asthma vs VAS nose	4822	0.755 (0.738;0.771)	0.465 (0.443;0.487)
VAS asthma vs VAS work	1840	0.768 (0.739;0.793)	0.658 (0.631;0.683)

Small airways represent an important feature of asthma and, in Turkey, VAS asthma has been correlated with impulse oscillometry (IOS) in symptomatic patients.¹⁰⁰ In a follow-up analysis of this study, ACT and VAS asthma were correlated (Figure 11). No patient with uncontrolled ACT had controlled VAS levels. On the other hand, several patients with controlled ACT had uncontrolled VAS confirming the paper and pencil study in Japan.

Figure 11: Correlation between ACT and VAS asthma (derived from ¹⁰⁰)



In MASK-air, cut-offs were calculated using two approaches in 395,223 days from 23,201 users: one based on the VAS percentiles and another based on VAS work and EQ-5D levels (Table 9).¹⁰¹

Table 9: MASK-air cut-off levels (/100) (from ¹⁰¹)

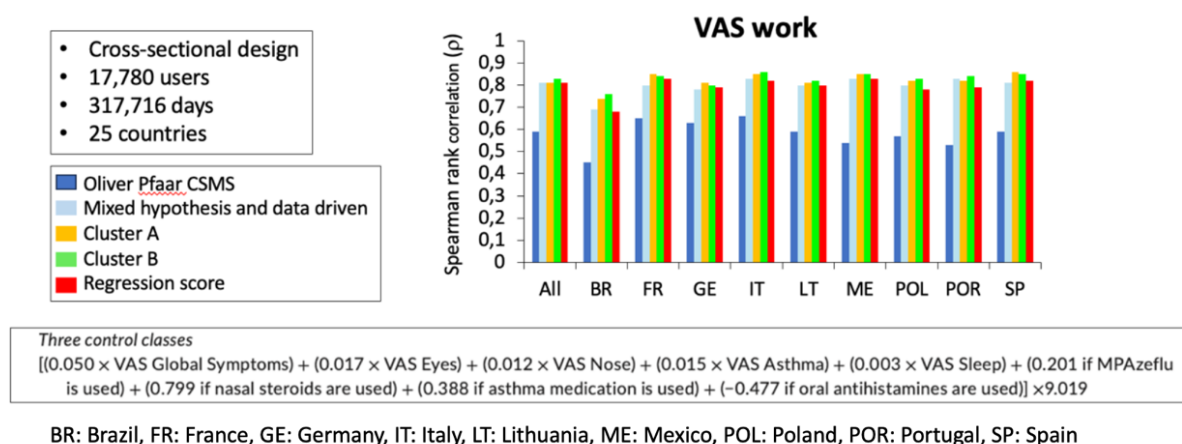
	Arbitrary ³	Outcome-oriented ¹⁰¹	
		VAS global, nose, asthma	VAS eye
Full control	0	0	0
Control	1-19	1-19	1-12
Partial control	20-49	20-35	13-35
No control	≥50	≥35	≥35

7.2. Daily electronic symptom-medication scores

7.2.1. Allergy e-CSMS

In 317,176 days of MASK-air[®] use from 17,780 users aged 16-90 years, in 25 countries, allergy e-CSMS was computed following cluster analysis, regression models or factor analysis (Figure 12). ¹⁸ The selected CSMS displayed high accuracy (capacity of discriminating different levels of rhinitis control), medium-high validity, reliability and accuracy, rendering it as a candidate for primary endpoints in future rhinitis trials. Results were similar in different countries showing the transferability and cultural adaptation of the CSMS. e-CSMS has been used in several MASK-air[®] studies. ^{18,98,102-106}

Figure 12: Allergy e-CSMS compared to VAS work (from ¹⁸)

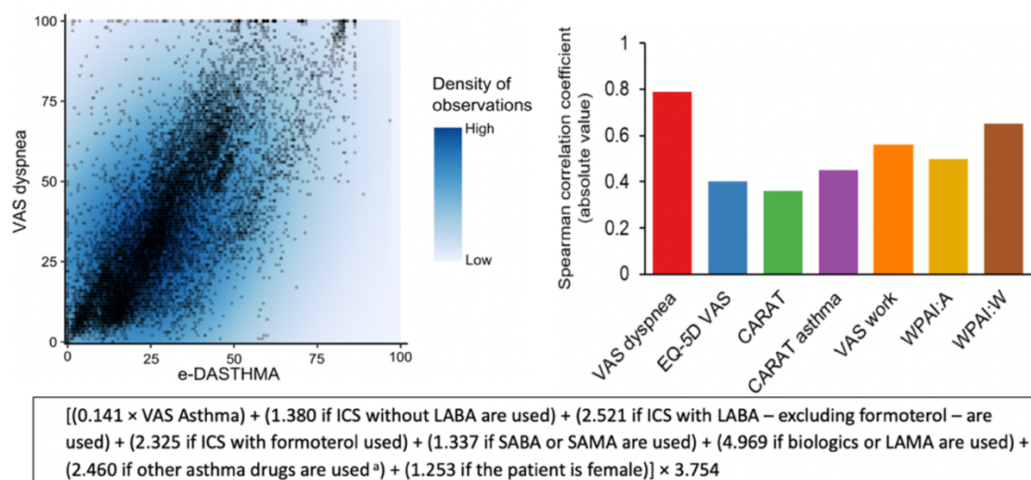


7.2.2. e-DASTHMA

An electronic daily asthma control score, e-DASTHMA, ⁷⁵ has been developed in a cross-sectional study (35,635 days of MASK-air[®] data, 1662 users). The developed score was strongly correlated with VAS dyspnea and moderately correlated with other outcomes. It displayed high test-retest reliability and moderate-to-high responsiveness (Figure 13).

An external validation of e-DASTHMA was performed using an independent cohort of patients with physician-diagnosed asthma (INSPIRERS). ¹⁰⁸ e-DASTHMA was strongly correlated with the GINA classification of control. e-DASTHMA has been used in MASK-air[®] studies. ¹⁰⁹

Figure 13: Results between the best performing e-DASTHMA and comparators (from ¹⁰⁷)



Limitations of the control symptom scores: Lack of a gold-standard for the daily control of asthma; AR may not be generalisable for children; overrepresentation of young adults.

7.3. Impact of age on MASK-air® PROMs

MASK-air® studies have included users from 16 to over 90 years. Seniors can easily use the MASK-air® app, sometimes after a short training period.⁶⁷ We assessed 19,369 users <65 years (333,395 days) and 519 users ≥65 (15,650 days) from 24 countries.¹⁰⁶ Users under and over 65 years had overall similar clinical characteristics, A, R and medication patterns. However over ≥75 years, small to moderate effect size measures were found for in some variables, particularly in VAS eye and VAS asthma.

In allergic rhinitis and asthma, adolescents and young adult patients may differ from older patients. In a cross-sectional study (2015-2022), we assessed European users of three age groups: 965 adolescents (15,252 days), 4595 young adults (18-26 years, 58,161 days) and 15,154 adults (>26 years 258,796 days).⁶² In multivariable models, age groups did not significantly differ in their adherence to rhinitis or asthma medication. These models also found that adolescents reported lower VAS on global allergy, ocular and asthma symptoms (as well as lower CSMS) than young adults and adults.

7.4. Transferability and cultural acceptability of daily PROMs

MASK-air® data are derived from up to 27 countries. The transfer of MASK-air was tested in a specific study.²⁷ Moreover, when results were provided for each of the countries, there was a high correlation between them including Brazil and Mexico. It can be concluded that MASK-air® can be used in many countries and that results are similar. However, for every new country, transferability would need to be confirmed since some questions may not be fully relevant in all countries.

7.5. Methodologic assessment of daily PROMs

7.5.1. Intra-rater reliability (ICC)

Between 2412 (“VAS work”) and 5827 (“VAS nose” and “VAS eyes”) days with more than one daily VAS input provided by the same user were recorded.⁵⁵ For all VAS, over 50% days had no differences in the first and second values provided within the same day. Differences between the first and second daily values differing by over 10% ranged between 11.2% (“VAS asthma”) and 24.4% (“VAS nose”). The ICCs were over 0.87 (“VAS global allergy symptoms”). Similar results were observed when analysing data from MASK-air® European users only, or when taking into account the first and last daily measurements. Overall, MASK-air® VAS display a high intra-rater reliability.

7.5.2. Test-retest reliability

Using clinical stability, the test-retest reliability of daily monitoring VAS was assessed based on data from 102 (“VAS work”) to 270 (“VAS global allergy symptoms,” “VAS nose,” “VAS eyes” and “VAS asthma”) patients.⁵⁵ Overall, MASK-air® VAS display a high test-retest reliability, with ICC being always above 0.74. That is, VAS levels tend to display no or small changes in clinically stable patients.

7.5.3. Ability to change

Using clinical change, defined according to several outcomes, the responsiveness of monitoring VAS daily was assessed based on data from 27 to 108 users. Meaningful low-moderate effect size measures were observed for all analyses, indicating that MASK-air® VAS may have moderate responsiveness (i.e., meaningful change in clinically unstable patients).

7.6. Impact of daily PROMs

7.6.1. Pre-MASK-air® studies

For construct validity, in patients with rhinitis and/or asthma, the different VAS used have been shown to be highly correlated to RQLQ and total symptom scores for rhinitis and asthma control scores or the GINA classification of control. Cut-off VAS values have been identified. Ability to detect a change was also found, and correlated with TNSS or TSS and RQLQ.

7.6.2. MASK-air® studies

Similar findings have been observed with MASK-air® for daily PROMs. More data are needed for ability to change. Importantly, similar results were found in different countries, indicating the transferability and cultural acceptability of MASK-air® PROMs across countries.

7.6.3. Clinical relevance of MASK-air® PROMs and future studies

Simple PROMs, easily translated in several languages, do not need cultural adaptation, and are available in an electronic form in MASK-air®. They are based on clinical relevance. The daily e-CSMS and e-DASTHMA represent an improvement over VAS as they represent both PROMs and medications.

However, these tools need to be tested to find their relevance in the stratification of severe patients and the cost-effective management of rhinitis and/or asthma to provide recommendations for policy makers.

7.7. Additional questionnaires for airways control

Additional questionnaires are included in MASK-air®: Control of Allergic Rhinitis and Asthma Test (CARAT, a PROM that assesses the level of control of both asthma and AR using a single tool over a period of 4 weeks)⁶⁰, WPAI-AS^{110,111} and EQ-5D. However, other tests can be included in MASK-air®.

CARAT is a monthly control questionnaire including both A and R (Figure 14). The methodological quality of studies on CARAT measurement properties was thoroughly reviewed (Figure 15).

Figure 14: The CARAT questionnaire

5- CARAT Questionnaire <i>Question 5- A) should be read to the patient with the patient choosing the answer. There should be no "interpretation": the physician should not fill in the questionnaire on behalf of the patient.</i>				
A) Due to your allergic respiratory diseases (asthma, rhinitis, allergies) in the last four weeks, on average, how many times did you have:				
	Never	Up to 2 days per week	More than 2 days per week	Almost every day
Blocked nose?	●	●	●	●
Sneezing?	●	●	●	●
Itchy nose?	●	●	●	●
Runny nose?	●	●	●	●
Shortness of breath/dyspnoea?	●	●	●	●
Wheezing in the chest?	●	●	●	●
Chest tightness during physical exercise?	●	●	●	●
Tiredness/limitations in doing daily tasks?	●	●	●	●
Waking up in the night?	●	●	●	●

Figure 15: Methodological properties of CARAT (from ⁶⁰).

	Structural validity	Internal consistency	Reliability	Measurement error	Construct validity Convergent validity	Discriminative validity	Responsiveness
Fonseca 2010 ³³	A	V	-	-	V	-	-
Fonseca 2012 ¹⁵	-	V	V	-	-	-	A
Lourenço 2014 ^{34,35}	-	-	-	-	A	A	-
Sá-Sousa 2015 ³⁶	-	-	-	-	A	-	-
van der Leeuw 2015 ^{16,19}	-	V	V	V	A	-	A
Domingues 2016 ^{17,37}	-	-	-	-	A	A	-
Oudkerk 2016 ³⁸	-	-	-	-	A	-	-
Werner 2018 ²⁰	V	V	-	-	A	A	-
Gani 2019 ³⁹	-	-	-	-	A	-	-
Pereira Martins 2019 ⁴⁰	-	-	-	-	A	-	-
Kosse 2020 ^{41,42}	-	-	-	-	A	-	-
Tosca 2020 ⁴³	-	-	-	-	D	-	-
Guedes 2021 ⁴⁴	-	V	-	-	A	-	-
Harbyeli 2021 ¹⁸	V	V	V	-	A	-	A
Jácóme 2021 ⁴⁵	-	V	-	-	-	-	-
Sousa-Pinto 2021 ⁴⁶⁻⁴⁸	-	-	-	-	A	V	-
Overall risk of bias	Low	Low	Low	Low	Low	Low	Low

V = Very good; A = Adequate; D = Doubtful; I = Inadequate; - = not assessed (not applicable).

8. Acceptability of MASK-air® by patients

Many patients do not understand the needs and benefits of mHealth and may worry about data privacy. A qualitative study was carried out by MADOPA in 2016 for MASK-air® to better understand the patients' needs and expectations. The app was modified accordingly.²⁹ (Table 10)

Table 10: Patients' expectations (adapted from ²⁹)

Patients' expectations	Existing items when the study was performed	Added items	
		Item	Expected
Advice to modify the treatment	Simple advice exists in line with the GDPR		Available
Pollen and pollution		POLLAR: pollen and pollution in the app ^{21,35} CATALYSE: alerts on peak of pollen and pollution exposure ²²	Available 2027
Visualisation of control and medications	Existing but poorly found by patients and physicians	More user friendly and better information	Available
Shared-decision making	Existing		Available
Help science to better understand the disease in order to get future benefits	Existing		Available

In Lithuania, the satisfaction of patients was assessed after app usage (Figure 16). ⁶⁶ Similar results have been found in Poland ⁶⁸ (Figure 17) and in France (MASK@PACA).

Figure 16: Satisfaction of the app in Lithuania (N=149) (from ⁶⁶)

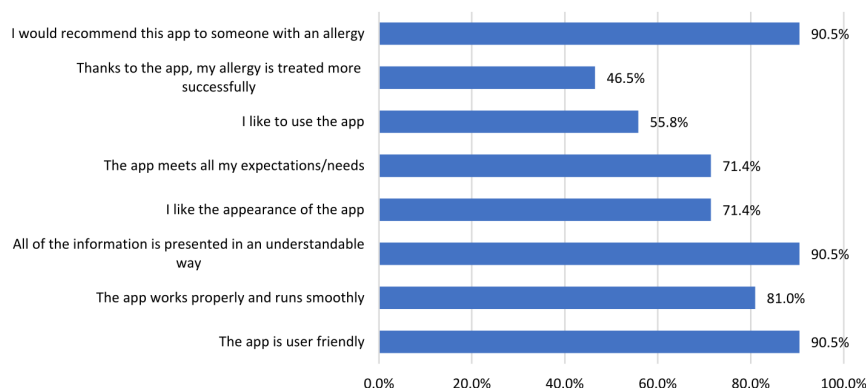
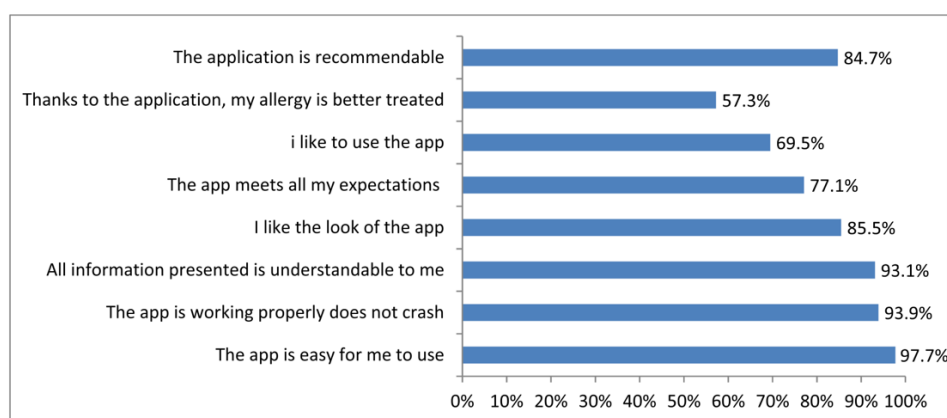


Figure 17: Satisfaction of the app in Poland (N=131) (from ⁶⁸)



In older adults, the app can be used up until the age of 85 years, but some outcomes may differ after 75 years. ^{64,67,112}

9. Major studies of MASK-air®

Major studies are reported in Table 11.

Table 11: Major achievements (updated from ⁵)

Study name	Ref	Study type	N users	N days	N countries
1- Baseline characteristics					
Pilot study of mobile phone technology in AR in European countries. The MASK-rhinitis study	25	Obs, CS	3,260	NA	20
Treatment of AR during and outside the pollen season using mobile technology. A MASK study	113	Obs, CS	9,035	70,286	Europe 18
2- Symptoms in the diagnosis and control of asthma					
Impact of asthma symptoms on QOL**	114	Obs, CS	171	171	Belgium
Impact of CARAT questions on the diagnosis and control of asthma	115	Obs, CS	951	2,153	25
Under-reporting of rhinitis in asthma	116	Obs, CS	35,251	529,751	25
3- Phenotype of allergic diseases and asthma					
Daily allergic multimorbidities	46	Obs, CS	4,210	32,585	19
Clusters of asthma and rhinitis	117	Obs, CS	8,075	297,169	26
Trajectories of allergic rhinitis	118	Obs, L	2,590	113,239 16,177 wks ⁺	26
Rhinitis associated with asthma is distinct from Rhinitis alone	104	Obs, L	3,797	256,839	27
ARIA classes in MASK-air®	119	Obs, L	2,273	180,796	25
4- Adherence to treatment of AR using mobile technology					
Adherence to treatment of AR using mobile technology	120	Obs, L	6,949	NA	21
Adherence to treatment in AR during the pollen season in Europe	121	Obs, L	1,361	8,212 wk ⁺	
5- Real-world data in allergic rhinitis					
Treatment of AR using mobile technology with real-world data: The MASK observational pilot study	122	Obs, CS	2,871	39,634	25
Mobile technology offers novel insights on control and treatment of AR. The MASK study	47	Obs, CS	9,122	112,054	23
Treatment of AR during and outside the pollen season using mobile technology. A MASK study	113	Obs, CS	9,035	70,286	Europe 18
Comparison of rhinitis treatments using MASK-air® data considering the Minimal Important Difference	123	Obs, CS	10,860	269,837	28
Differences in behavioural patterns in AR medication in Europe: A study using MASK-air® real-world data	124	Obs, CS	13,122	222,024	Europe 18
Effectiveness, target emulation trial	125	Obs, CS	648		
Satisfaction	73,74	Obs, CS	1691	28,177	18
On demand or continuous treatment	In press	Obs, CS	1042	18,830 2690 wks ⁺	17
6- Real-world data in asthma					
Longitudinal severe asthma pilot study	126	Obs, CS	13	1,250	Italy
Treatment of asthma using mHealth real-world data: The MASK-air observational study	127	Obs, CS	3,229	70,270	27
Adherence to ICS/LABAs in asthma	109	Obs, L	866	26,396 6,444 wks ⁺	27
7- Impact of allergic diseases					

Work productivity	12,23,33,58 128	Obs, CS	Up to 20,754	Up to 260,378	18
EQ-5D	12,23,33,58	Obs, CS			18
EQ-5D	12,23,33,58	Obs, CS			18
WPAI-AS	12,23,33,58	Obs, CS			18
VAS work and symptoms	128	Obs, CS			18
Weekly indirect costs		Obs, CS			18
Effectiveness, target emulation trial	125	Obs, CS			18
Daily costs induced by work	In press	Obs, CS			18
8- Clinical trials					
Validation of the MASK-air App for assessment of AR	129	RCT	267	7,500	Spain
Effect of nasal irrigation on AR control in children; complementarity between CARAT and MASK	130	RCT	76	NA	Greece
Pilot study with Fel d1 food for cat allergy	131	POC, open			France
9- Allergen immunotherapy					
Effect of AIT in the MASK-air® study: proof-of-concept analysis	132	Obs, CS	17,780	317,176	25
Allergen AIT in MASK-air users in real-life: results of a Bayesian mixed-effects model	133	Obs, CS	1,093	42,756	25
Daily improvement of allergy control by sublingual AIT: A MASK-air® cross-sectional study	134	Obs, L	217	4,726	14
10- Aerobiology and air pollution					
POLLAR	76	Obs, CS	3,323	36,440	15
POLLAR*	35	Review of methods used in POLLAR and embedded in MASK-air			
CATALYSE	22	Climate change**			
11- Planetary Health					
Finnish Presidency of the EU	135	MASK-air in Planetary Health**			

Obs: Observational, RCT: randomised controlled trial, CS: cross-sectional, L: longitudinal, NA: not available

AIT: Allergen immunotherapy, AR: Allergic Rhinitis, CARAT: Control of Rhinitis and Asthma Test, LABA: Long-acting β_2 agonist, ICS: Inhaled corticosteroids, POC: proof-of-concept, POLLAR: Impact of air POLLution on Asthma and Rhinitis.

*: Review carried out for MASK-air®, **: Paper related to MASK-air®

+: Weeks with 6-7 days reporting

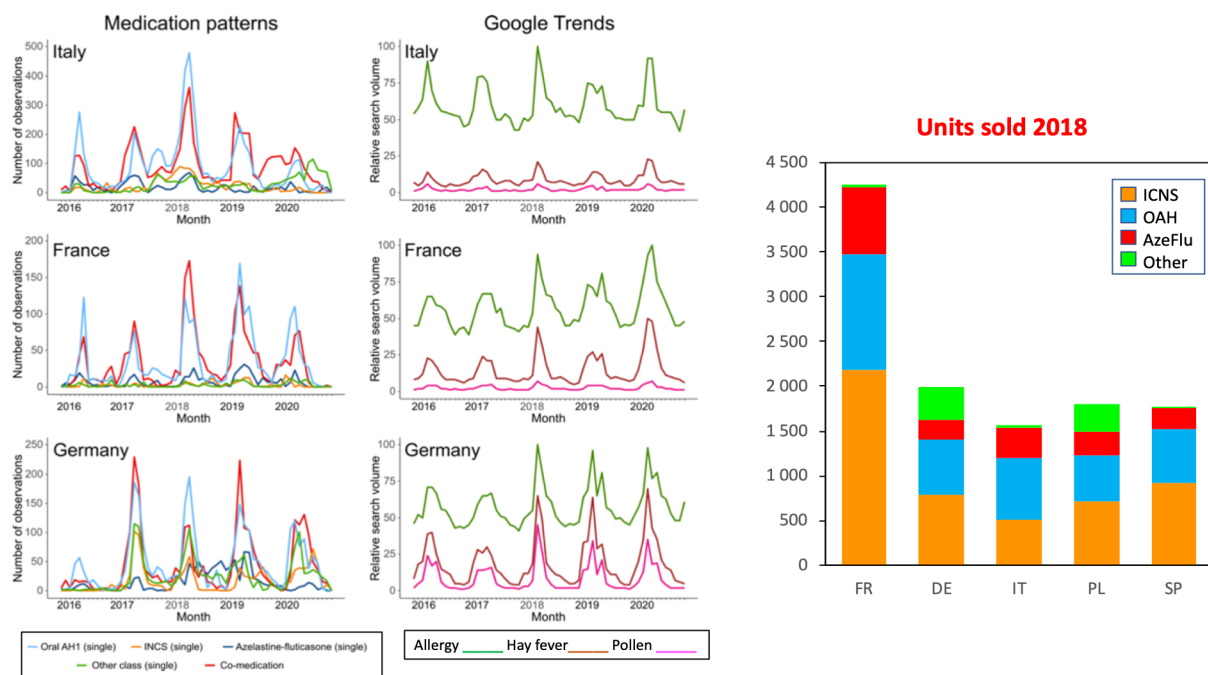
10. Rhinitis

Observational MASK-air[®] data made it possible to assess real-life use of medications to better understand how medications are used and to propose a novel person-centred approach for the ARIA guidelines.

10.1. Across Europe, patients treat themselves when they are not well

In a cross-over study in the entire dataset, medication use peaked during the pollen season in all of the investigated European countries ⁵⁹ (Figure 18) whereas cultural behaviour - assessed using Google Trends - ¹³⁶ differs. Oral antihistamines (OAH) were the most common medications reported in monotherapy and comedication (OAH and intra-nasal corticosteroids: INCS). This is against guideline recommendations ^{137,138} and does not accord with the dispensing of medications (OTC and prescribed) in the pharmacy. ¹³⁹ These studies suggest that patients treat themselves when they have symptoms and do not follow guidelines.

Figure 18: Behavioural patterns of medication usage in MASK-air[®] (from ^{124,136,140})



Limitations of the study: European MASK-air[®] users are not fully representative of European patients with AR, posing generalisability concerns.

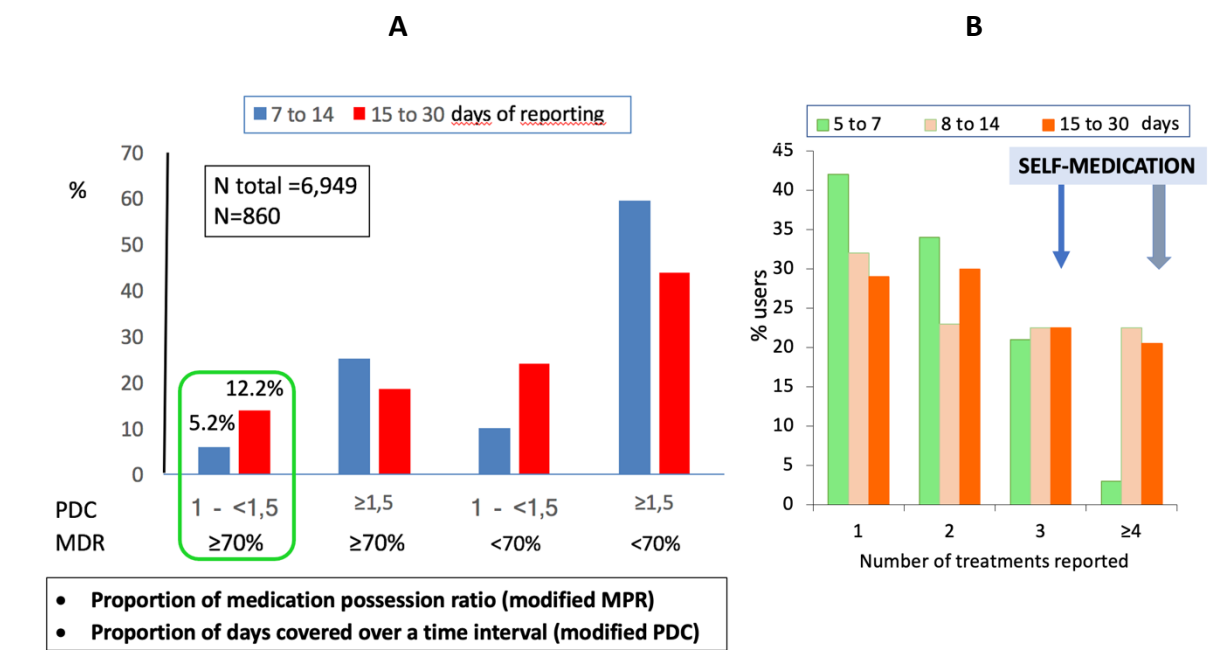
10.2. Adherence to rhinitis treatment

10.2.1. Adherence is poor in unselected patients

An observational cross-sectional study has assessed the adherence to treatment in AR patients using MASK-air. ¹²⁰ Patients were selected as using 7 or 15 days of MASK-air[®] data any time (continuous or in sequence). Secondary adherence was assessed by using the modified Medication Possession Ratio (MPR) and the Proportion of Days Covered (PDC) approach. 1,887 users reported ≥ 7 days of VAS data. 11.3% of users were adherent ($\text{MPR} \geq 70\%$ and $\text{PDC} \leq 1.25$), 4.2% were partly adherent ($\text{MPR} \geq 70\%$

and PDC = 1.50) and 14.6% were switchers. When physicians are allergic, they behave like patients,¹⁴¹ suggesting the need for behavioural science to improve adherence (Figure 19A)

Figures 19A: Adherence to treatment in unselected patients and 19B: Self-medication in the same study (from ¹²⁰)



Limitations of the study: We only considered the users who reported over 6 days of MASK-air® use. We did not analyse the type of treatment due to its great variability. We did not include a questionnaire on medication adherence.

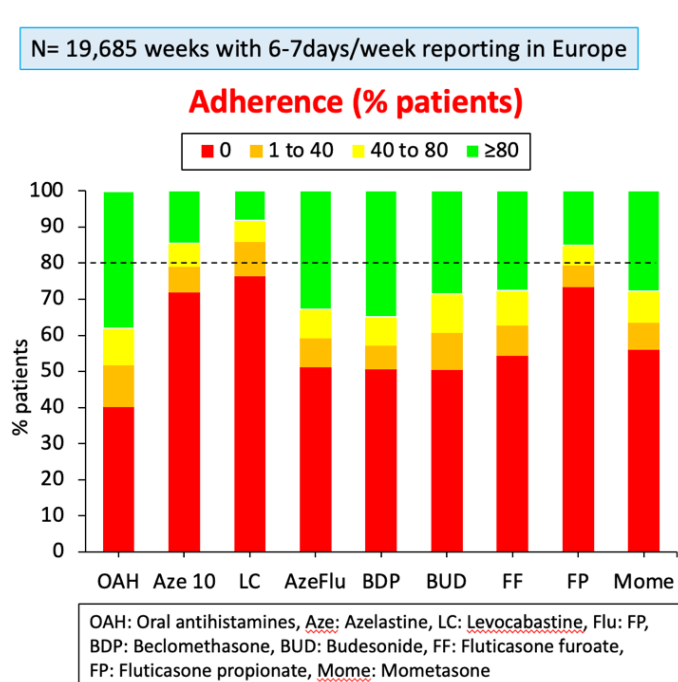
10.2.2. Adherence is higher in adherent users to the MASK-air® app

We studied a subsample of the MASK-air® database, assessing weeks during which patients answered the MASK-air® questionnaire on all days. We analysed symptoms using VAS and CSMS, performing stratified analyses by weekly adherence levels. Medication adherence was computed as the proportion of days on which patients reported rhinitis medication use. Sensitivity analyses were performed considering all weeks with at most one day of missing data and all months with at most four days of missing data.¹²¹

We assessed 8212 complete weeks (1361 users). Adherence (use of medication >80% days) to specific drug classes ranged from 31.7% weeks for azelastine-fluticasone to 38.5% weeks for OAH.¹²¹ Similar adherence to rhinitis medication was found in users with or without self-reported asthma, except for INCS (better adherence in asthma patients). VAS and CSMS levels increased from no adherence to full adherence, except for INCS. A higher proportion of days with uncontrolled symptoms was observed in weeks with higher adherence. In full adherence weeks, 41.2% days reported rhinitis co-medication. The sensitivity analyses displayed similar results (Figure 20).

High adherence was found in patients reporting regular use of MASK-air®. Adherence is not associated with better control except for INCS. Comparing the two studies on adherence,^{120,121} it is indirectly suggested that MASK-air® adherence is associated with medication adherence.

Figure 20: Adherence to treatment in users adherent to MASK-air® (from ¹²¹)



Different adherence patterns were found for intranasal corticosteroids (INCS) compared to oral antihistamines (OAH) or Aze-Flu.

10.3. Real-life medications reported

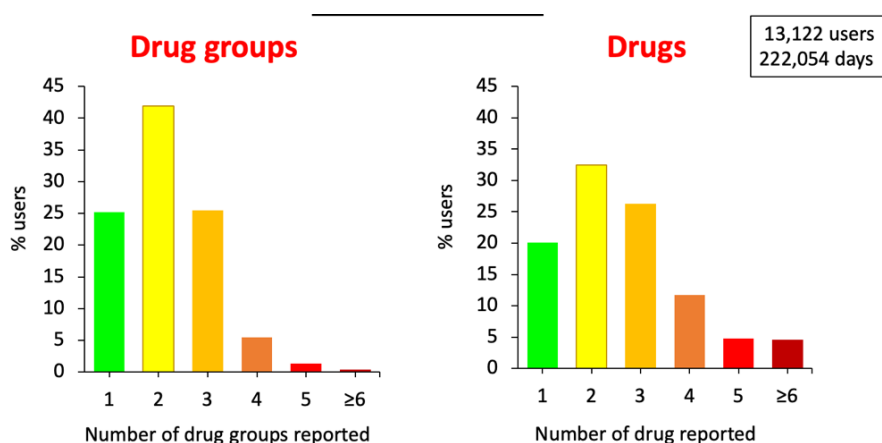
10.3.1. Many patients use OTC medications and self-medicate

A large number of patients use OTC medications and self-medicate. In Europe, users reported an annual average of 2.7 drugs, with 80% reporting two or more drugs (Figure 19B).¹²⁰

10.3.2. Many patients use multiple medications

In a cross-sectional study, it was found that many patients use many groups of drugs and that within a group of drugs, they use many medications (Figure 21).

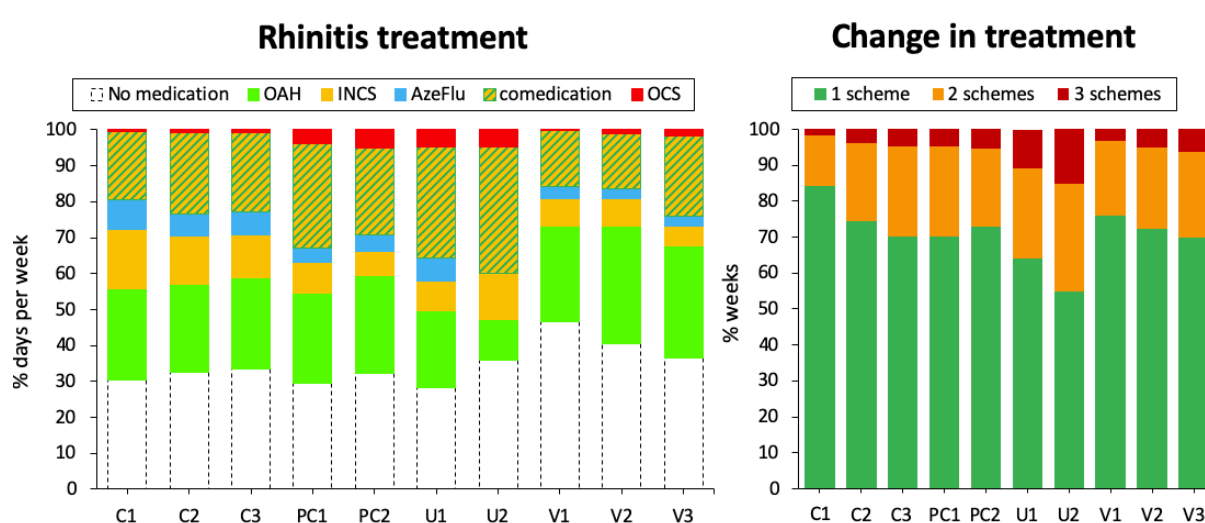
Figure 21: Number of drugs reported in a cross-sectional study (from ⁵⁹)



10.3.3. Switching of treatments is common (longitudinal analysis)

A longitudinal analysis of MASK-air[®] data assessed 16,177 weeks of patients answering to the daily monitoring questionnaire on all 7 days (Figure 22).⁹⁸ K-means cluster analysis methods were applied in order to group weeks according to their daily AR control. Ten clusters of users receiving a treatment were identified: 3 controlled (C1-C3), 2 partly controlled (PC1-PC2), 2 uncontrolled (U1-U2) and 3 with variable control (V1-V3) (Figure 22). In these users, no medication was reported in 30 to 40% of days. Moreover, comedication (INCS/AzeFlu + Other oral medication(s)) was reported in 19-32%. Except for the most severe cluster (U2), OAH were reported in around 20-25% of days. Change of treatment within a week was reported in 15% (C1) to 42% (U2) of days, and change of two treatments from 2 to 12% of days.

Figure 22: Rhinitis treatment and change of treatment in users reporting app data 7 days a week (from⁹⁸)



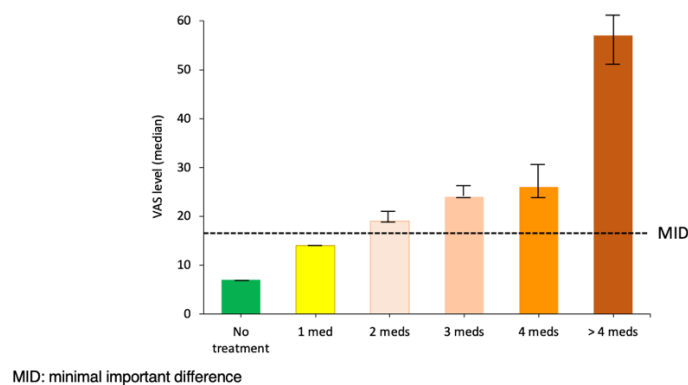
C1, C2, C3: Controlled patients, PC1, PC2: Partly controlled patients, U1, U2: Uncontrolled patients, V1, V2, V3: Patients with variable control

10.3.4. Increasing the number of medications is usually associated with impairment of control

Control worsens when medication number increases (Figure 23). This finding does not accord with guidelines proposing that medications should be stepped-up to achieve control. However, this accord with the concept of SCUAD (Severe Chronic Upper Airway Disease)¹⁴², and the severity of some chronic diseases including asthma is associated with multiple medications.

Limitations of the study: European MASK-air[®] users are not fully representative of European patients with AR, posing generalisability concerns.

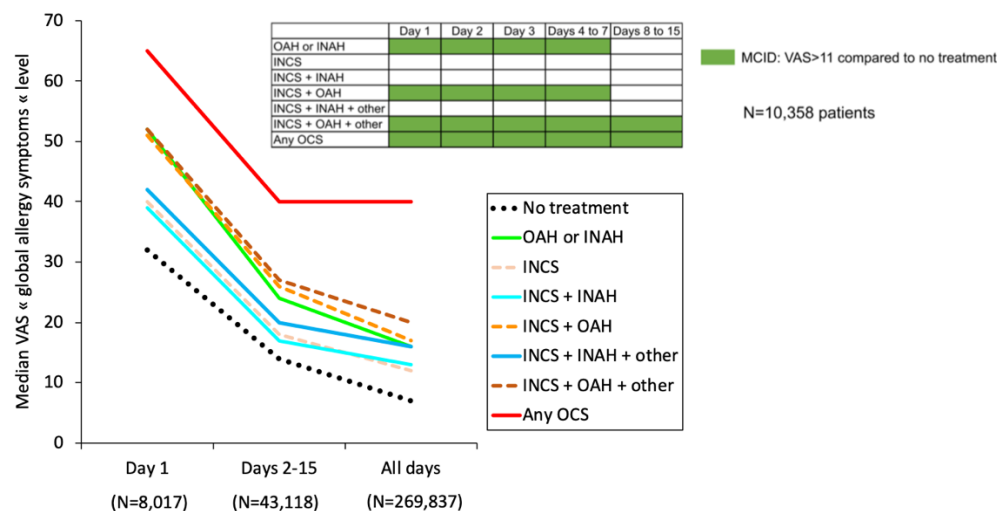
Figure 23: Daily VAS for global allergy symptoms depending on the number of medications reported



10.3.5. Co-medication is associated with impaired control by comparison to monotherapy

In several papers, the same results were observed: comedication is associated with worse control by comparison to monotherapy.^{47,113,122,143} Days with the best control were those with no medication. The same results were observed during and outside the pollen season. In all four studies, the trends between medications were similar from the first day of reporting to long-term reporting. However, the levels of VAS global allergy symptoms decreased largely with time in treated and untreated days (Figure 24).

Figure 24: Daily VAS global allergy symptoms depending on the day of the treatment reporting in a cross-sectional study¹²³



Limitations of the study: Overall limitations.

10.3.6. Patient satisfaction decreases with co-medication and partly explains why unsatisfied patients increase their medications

Satisfaction with treatments may affect medication adherence and use patterns, including co-medication. We compared different AR medications on (i) patients' satisfaction and (ii) co-medication use frequency.

In the first study,⁷⁴ we assessed 28,177 days reported by 1691 MASK-air users. In monotherapy, satisfaction was lower for INAH than for other classes (Table 12). For all classes but INAH, co-

medication was associated with decreased satisfaction. VAS satisfaction levels were moderately correlated with a change in VAS global (-0.44 (-0.66;-0.14) [p=0.005]), without significant correlations in relation to changes in VAS nose (-0.28 (-0.55;0.04) [p=0.087]) or VAS eye (-0.32 (-0.58;-0.01). A reduction of satisfaction appears to partly explain why unsatisfied patients increase their medications.

Table 12. VAS levels on treatment satisfaction and global allergy symptoms for each medication class in monotherapy *versus* co-medication (from ⁷⁴)

Medication	Treatment satisfaction			Maximum VAS global		
	Monotherapy - Median (IQR) [n]	Co-medication - Median (IQR) [n]	Cohen's <i>d</i>	Monotherapy - Median (IQR) [n]	Co-medication - Median (IQR) [n]	Cohen's <i>d</i>
INAH	52 (52)	75 (41)	0.68	47 (40)	57 (49)	0.33
INCS	85 (29)	81 (31)	0.23	35 (45)	57 (44)	0.69
INAH+INCS	81 (28)	74 (53)	0.30	41 (40)	54 (43)	0.43
OAH	82 (35)	79 (39)	0.14	50 (47)	58 (42)	0.25

IQR – Interquartile range; INAH – Intranasal antihistamines; INCS – Intranasal corticosteroids; INAH+INCS – Intranasal antihistamines and intranasal corticosteroids fixed combination; OAH – Oral antihistamines

In the second study, ⁷³ when comparing individual intranasal medications, fluticasone furoate and fluticasone propionate tended to be more frequently used in co-medication. Among individual OAH, desloratadine and rupatadine were associated with higher satisfaction, while fexofenadine was more frequently used in co-medication. Moreover, control assessed by CSMS levels on the previous day was associated with patients' satisfaction ranging from 91 (good control) to 76 (medium control) and 44 (poor control).

Table 13. Treatment satisfaction and frequency of days using co-medication and medications for each class according to (i) CSMS levels of the previous day and (ii) categories of the ARIA score (from ⁷³)

A. CSMS levels of the previous day			
Variable	Good control – CSMS <15.8 (N days=14,237)	Medium control – 15.8≤CSMS≤35.3 (N days=9109)	Poor control – CSMS>35.3 (N days=4831)
VAS satisfaction levels – median (P25-P75)	91 (85-96)	76 (62-84)	44 (17-58)
Days using co-medication - N (%)	4747 (33.3)	4051 (44.5)	2611 (54.0)
Days using medication from each class – N (%)			
INAH	179 (1.3)	102 (1.1)	99 (2.0)
INCS	6554 (46.0)	4662 (51.2)	1745 (36.1)
INAH+INCS	2429 (17.1)	2059 (22.6)	1700 (35.2)
OAH	8905 (62.5)	5533 (60.7)	3489 (72.2)

Conclusion: Using patient-reported data, we evaluated different medication classes and treatments in terms of satisfaction and co-medication frequency. These results provide key insights into the acceptability of AR treatments and will contribute to future treatment guidelines.

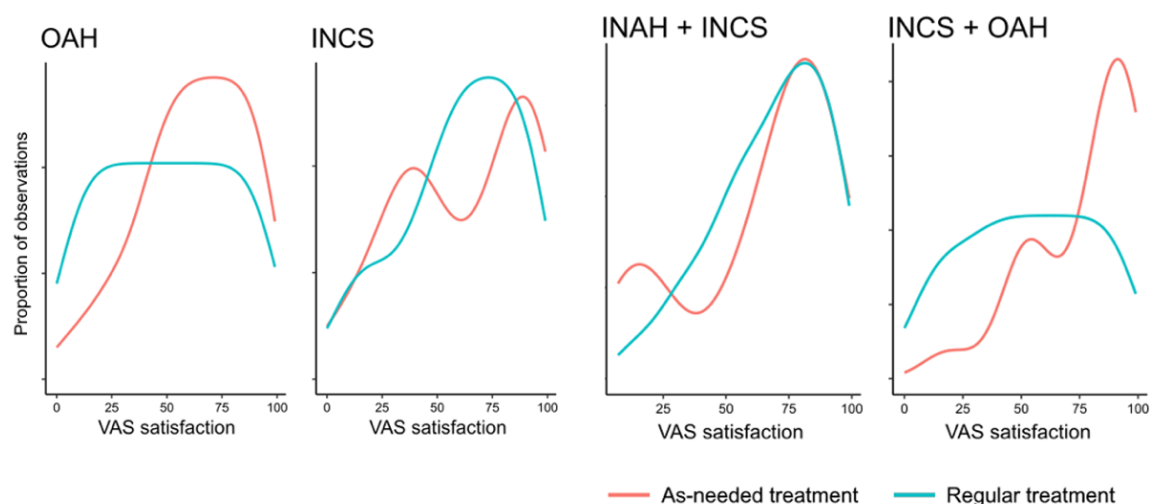
10.3.7. Differences between regular and PRN (Pro Re Nata) use of medications

Patients with AR often use medications on an as-needed instead of on a regular basis. We compared weeks when medication was used on a PRN versus regular basis in terms of treatment satisfaction and symptom control. We assessed 2690 weeks (18,830 days) reported by 1042 users. For INCS and fixed combinations of INAH + INCS, there were no significant differences between PRN versus regular

treatment on satisfaction. By contrast, for OAH and INCS+OAH, results tended to favour PRN strategies. For symptom control, we observed either no significant differences between PRN and regular strategies or significant differences favouring PRN medication use (Figure 25).

Patients opting for an PRN strategy can potentially achieve levels of symptom control and treatment satisfaction that are comparable to that achieved by patients taking regular treatment.

Figure 25. Distribution of the values of the visual analogue scale assessing patient satisfaction with rhinitis treatment (VAS satisfaction)



10.4. Assessment of AR medication effectiveness using a target trial emulation approach

Randomised controlled trials (RCTs) are the gold standard for evaluating treatment efficacy, but their generalisability is often limited. Advances in the assessment of observational data aim to overcome some RCT limitations while accounting for confounding. This study aimed to use a target trial emulation framework to compare the effectiveness of allergic rhinitis (AR) treatments using mHealth data.¹²⁵

This study analysed data with self-reported AR before and after medication use within a 24-hour period. We compared OAH, INCS, INAH + INCS in improving VAS AR symptoms. Treatment effects were estimated using a Bayesian approach through regression models with inverse probability of treatment weighting. Separate treatment effects were estimated for patients with and without asthma.

A total of 648 days of MASK-air[®] data were analysed. Overall, INCS and INAH+INCS were more effective than OAH, and differential effects in relation to asthma status were observed (Table 14).

Table 14. Changes in VAS Eye and Nose levels (from ¹²⁵).

Comparison	Difference in VAS [95% Credible Interval], probability of intervention being more effective than comparison	
	Participants with asthma	Participants without asthma
VAS Eye		
INCS vs. OAH	-5.29 [-8.61, -0.21], 97.8	-4.32 [-8.76, -0.82], 99.0
INAH + INCS vs. INCS	-0.25 [-7.23, 9.20], 60.0	0.01 [-8.58, 6.88], 55.6
INAH + INCS vs. OAH	-1.74 [-7.93, 5.11], 72.8	-6.93 [-9.13, -3.75], >99.9
VAS Nose		
INCS vs. OAH	-6.86 [-10.0, -3.07], >99.9	-6.69 [-9.51, -3.94], 99.9
INAH + INCS vs. INCS	-0.10 [-10.8, 10.6], 54.5	0.05 [-11.2, 6.64], 38.7
INAH + INCS vs. OAH	10.9, [1.74, 18.5], 0.02	-9.13 [-13.3, -6.09], 99.9

10.5. Impact of MASK-air® in understanding the bilateral interactions between asthma and rhinitis

10.5. 1. Rhinitis alone and rhinitis and asthma

Atopic dermatitis (AD), A, R, C and are interrelated clinical phenotypes that partly overlap in the human interactome. ^{144,145} Complex genetic and epigenetic mechanisms interact with the environment to determine disease expression and lead to distinct and frequently co-existing phenotypes (multimorbidity). ¹⁴⁵ The concept of “one-airway-one-disease” ¹⁴⁶ led 25 years ago to the development of ARIA ¹⁴⁷ is an over-simplification of the links between R and A. Two distinct AR phenotypes were identified 20 years ago across countries: (i) R alone, affecting around 70-80% of patients and (ii) R+A multimorbidity, affecting 20-30%. ¹⁴⁸ On the other hand, most A patients have allergic or non-allergic R. ¹⁴⁹⁻¹⁵¹ A recent review confirmed common pathways in R+A and R-specific pathways from genomic data to mHealth and epidemiologic studies suggesting that AR and AR+A represent two distinct phenotypes. ¹⁵²

It is however important to re-assess the links between A, R and other allergic multimorbidity (C and AD) to complement the recent review ¹⁵² (i) with new data from a literature search, (ii) data obtained in real life, in particular from MASK-air® (Table 14), (iii) to confirm the distinction between single diseases and multimorbidity, (iv) identify the clinical relevance of these findings and (v) propose research needs.

Table 14: MASK-air® data on rhinitis alone and rhinitis and asthma

Ref	study	diseases	
46	CS	A, R, C	Extreme allergy phenotype assessed in days including A+C+R with increased severity by comparison to A, R, A+R or R+C
98	L	A, R, C	Extreme allergy phenotype assessed in patients including A+C+R with increased severity by comparison to A, R, A+R or R+C
104	CS	A, R	Patients with A+R required more R medications, they had more severe VAS levels for nasal and ocular symptoms and work than R patients. Robust results were obtained when assessing data from individual countries or in the sub-analysis of 282 patients enrolled by physicians.
153	L	A, R	K-means cluster analysis methods identified 7 groups of A patterns. Patients with treated A needed more OAH with ICNS or AzeFlu (12.3% to 21.9%) than those with untreated A (9.3%) and those with R alone (7.9%)
154	CS	A, R, C	VAS nose and VAS eye were increased in patients with R+A by comparison with those with R alone in most ARIA classes
6	CS	A, R	EQ-5D-5L utilities and VAS were compared with the control of the disease with differences between R and R+A

155	CS	A, R	Using WPAI-AS of AR was measured in work productivity (presenteeism and absenteeism) depending on the disease control. Large differences were found between R alone and R+A
156	CS	A, R	Weekly indirect costs per country: Patients with R+A showed higher overall work impairment than patients with R alone, particularly in poorly-controlled weeks

A: asthma, C: conjunctivitis, R: rhinitis, CS: cross sectional study, L: longitudinal study, AzeFlu: Intranasal azelastine fluticasone

10.5.2 Diagnosis of asthma in patients with rhinitis

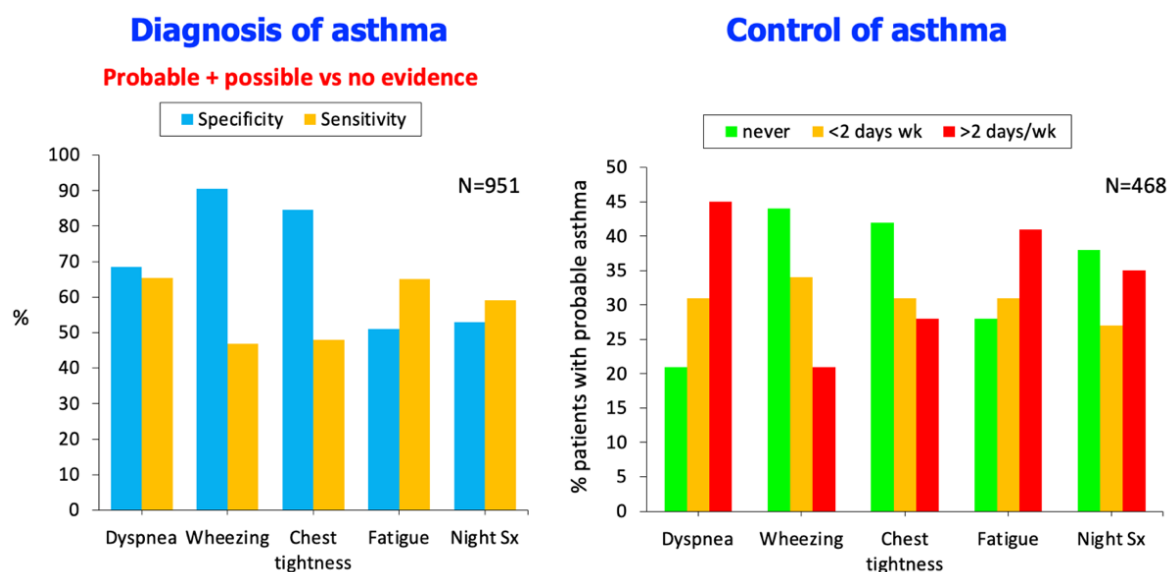
Although pulmonary function tests with reversibility represent the gold standard for A diagnosis they are rarely performed in primary care because (i) many GPs do not have the equipment, in particular in developing countries, (ii) it is not reimbursed in many countries and there is no incentive to perform the test, (iii) it is time consuming, especially if the reversibility is performed and (iv) the interpretation of the test may be difficult. In some studies, as few as 5% of GPs use pulmonary function, even if they are trained and the test is reimbursed (Belgium, Louis, personal communication).

The relevance of individual bronchial symptoms for A diagnosis and control was carried out in R patients with rhinitis using MASK-air[®].¹¹⁵

We compared the frequency of occurrence of five A symptoms (dyspnea, wheezing, chest tightness, fatigue and night symptoms, as assessed by the CARAT questionnaire) in 951 patients with probable, possible or no current A defined according to Bousquet et al.¹¹⁷ assessed the association between each symptom and asthma control (measured using the e-DASTHMA score). Results were validated in a sample of patients with a physician-established diagnosis of asthma.

Wheezing displayed the highest specificity (90.5%) and positive predictive value (90.8%) for A (Figure 26). In patients with probable A, dyspnoea and chest tightness were more strongly associated with A control than other symptoms. In this study, over 95% of patients with R and wheezing had A. On the other hand, for A control, dyspnoea was the most relevant symptom. Consistent results were observed when assessing patients with a physician-made diagnosis of asthma.

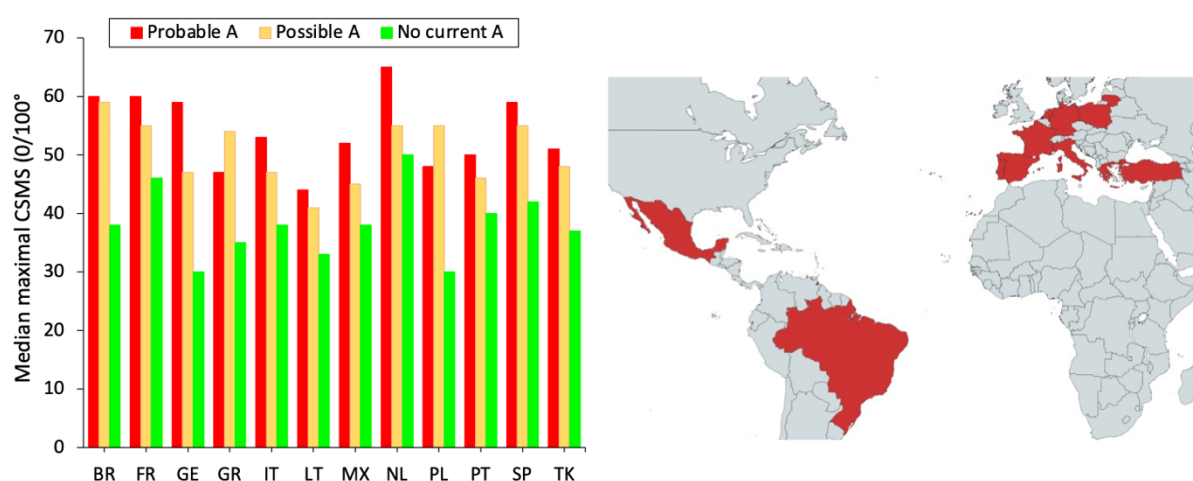
Figure 26: Sensitivity, specificity of the ever occurrence of specific asthma symptoms, as assessed by the Control of Allergic Rhinitis and Asthma Test (CARAT) (from ¹¹⁵)



10.5.3. Control of rhinitis depends on rhinitis phenotype (AR or AR+A) and results are similar in 12 countries

The ARIA-MeDALL hypothesis had not been tested using direct patient real-world data. compared reported symptoms and medication in R *versus* A+R using direct patient data from the MASK-air® mHealth app. We analysed data from 3,797 patients (256,839 days). Patients with A+R required more rhinitis medications and had more severe VAS levels for ocular symptoms and work than R patients. The allergy-CSMS was also higher in A+R patients than in R patients. Robust results were obtained when assessing data from individual countries (Figure 27) or in the sub-analysis of 282 patients enrolled by physicians. In all analyses, R and A+R were distinct in terms of allergy-CSMS and reported symptoms. This study supports the ARIA-MeDALL hypothesis.

Figure 27: Median maximal CSMS in different countries for probable asthma, possible asthma and no current asthma (from)



10.5.4. Rhinitis medications depend on rhinitis phenotype

Research needed

10.5.5. Overall conclusion

Rhinitis and R+A represent two distinct diseases that need to be considered independently in the management of AR. This information should be reflected in ARIA-EAACI guidelines. (i) If A diagnosis is not established, it can be made using MASK-air® (rhinitis VAS and “self-reported” asthma or wheezing in CARAT). (ii) Then, for the management, the higher medication strategy is preferable in AR+A.

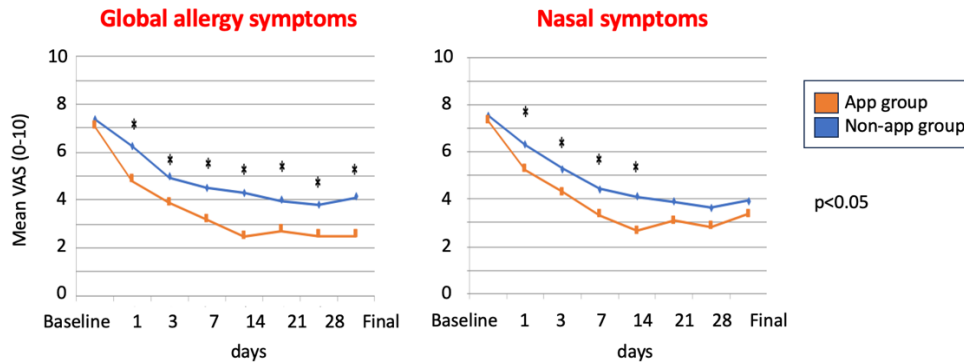
10.6. Clinical trials

10.6.1. RCT comparing a MASK-air® strategy with best practice in pollen allergy

A cluster-randomised trial was performed in 267 patients with AR. The patients were randomly assigned into 2 groups (i) those who were invited to use the Spanish version of the Allergy Diary App at the baseline visit and (ii) those who were not invited to use the App (non-App group).¹²⁹ After one month, both groups had a controlled disease and there was no significant difference between them. However, a relevant improvement of all parameters was observed over baseline at the end of the study ($p < 0.001$).

In nasal, ocular and global VAS, improvement was reached sooner in the App group than in the non-App group (Figure 26). Moreover, there was a significant correlation between VAS asthma and ACT score (Pearson -0.79132, $p < 0.0001$).

Figure 26: Speed of onset between the App and the non-App groups (from ¹²⁹)



Limitation of the study: None.

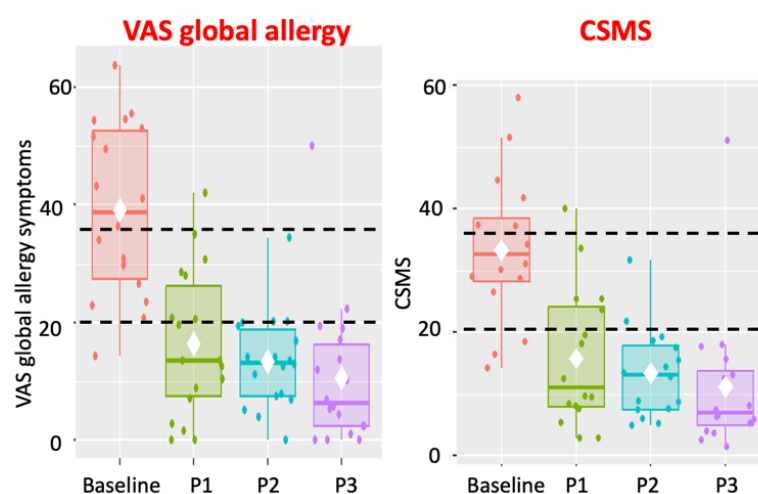
10.6.2. RCT comparing MASK-air® and CARAT in children with pollen allergy

In a quasi-experimental study in Greece, CARAT and MASK-air® provided complementary information on AR symptom control, possibly mirroring differences in time periods assessed by these two tools (4 weeks versus daily assessment).¹³⁰

10.6.3. Proof-of-concept for a cat food containing antibodies against Fel d 1

An innovation to better manage cat-allergic patients utilises anti-Fel d 1 IgY antibodies to neutralise Fel d 1 after its production by the cat. A longitudinal, open-label, proof-of-concept study was carried out to approach clinical efficacy of the cat food in cat-allergic patients. Of the 49 patients screened, 42 were followed-up and 33 (78.5%) reported MASK-air data at all 3 evaluation periods. The primary end point (VAS global allergy symptoms) was highly significantly improved ($p < 0.0001$). All symptoms (VAS nose, eye, asthma), VAS work and CSMS were significantly improved after one month. The percentage of uncontrolled days (VAS > 20/100) decreased from 64% at baseline to 35% at one month ($p < 0.0001$) and 14% at 3 months. A sensitivity analysis in patients with uncontrolled disease at baseline found similar results (Figure 27).

Figure 27: Median levels of symptoms or CSMS in patients whose cats are being given a special food for 3 months (P1-P3): sensitivity analysis in uncontrolled disease at baseline



Dashed lines: cut-off values¹⁰¹

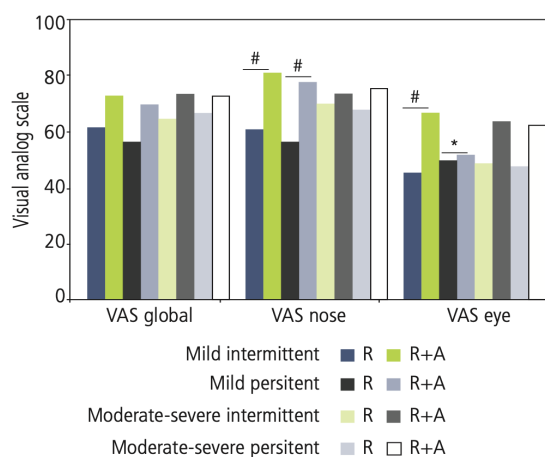
Limitation of the studies: This is a pilot study without a control group.

10.7. ARIA classes in MASK-air® users

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines classify rhinitis as "intermittent" or "persistent" and "mild" or "moderate-severe". We assessed ARIA classes using MASK-air®.

A total of 2273 users (180 796 days) were assessed. Most users had moderate-severe rhinitis (n=2003; 88.1%) and persistent rhinitis (n=1144; 50.3%).¹¹⁹ The frequency of patients with probable asthma was 35.7% (95%CI, 34.5%-37.0%) for intermittent rhinitis and 48.5% (95%CI, 47.1%-49.9%) for persistent rhinitis. The maximum VAS values for R symptoms and the combined CSMS were lower in patients with mild R than in those with moderate-severe R (irrespective of whether they had persistent or intermittent R). In most ARIA classes, VAS nose, VAS eye and R comedication were more frequent in patients with R+A than in those with rhinitis alone (Figure 28).

Figure 28: VAS global score (MASK-air® data) in ARIA classes (from¹¹⁹)



This study suggests that (i) A is more closely related to R persistence than to severity and (ii) comorbid A may be associated with poorer R control across the different ARIA classes.

10.8. Impact of MASK-air® data on person-centred, digitally enabled, AI-assisted ARIA guidelines (2024-2026)

The Allergic Rhinitis and its Impact on Asthma (ARIA) initiative first proposed guidelines for AR and asthma multimorbidity in 1999¹⁵⁷ and 2008⁴. Four innovative iterations have been produced (2010,¹⁵⁸ 2016,¹³⁸ 2020¹⁵⁹ and 2024-2025^{160,161}).

ARIA has evolved from the first multimorbidity guideline in respiratory diseases using the Shekelle evidence-based model¹⁵⁷ to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) framework for evidence-based guidelines^{138,162}. ARIA 2016 was used as the clinical scenario on how to interpret and use a guideline in a review published in the Journal of the American Medical Association¹⁶³. ARIA 2010 and 2016 devised a medication algorithm^{138,162}. However, digitalisation was not implemented. In 2019, next-generation guidelines using an expert consensus on real-life MASK-air® data and allergen exposure chamber studies proposed digitally enabled person-centred care for the first time¹⁵⁹. The next iteration, ARIA 2024-2025, endorsed by the European Academy of Allergy and Clinical Immunology (EAACI), has resulted in a person-centred, digitally enabled, artificial intelligence (AI)-assisted guideline.^{160,161} It is now evolving towards a living guideline using real-world data (Figure 29 and Table 15).

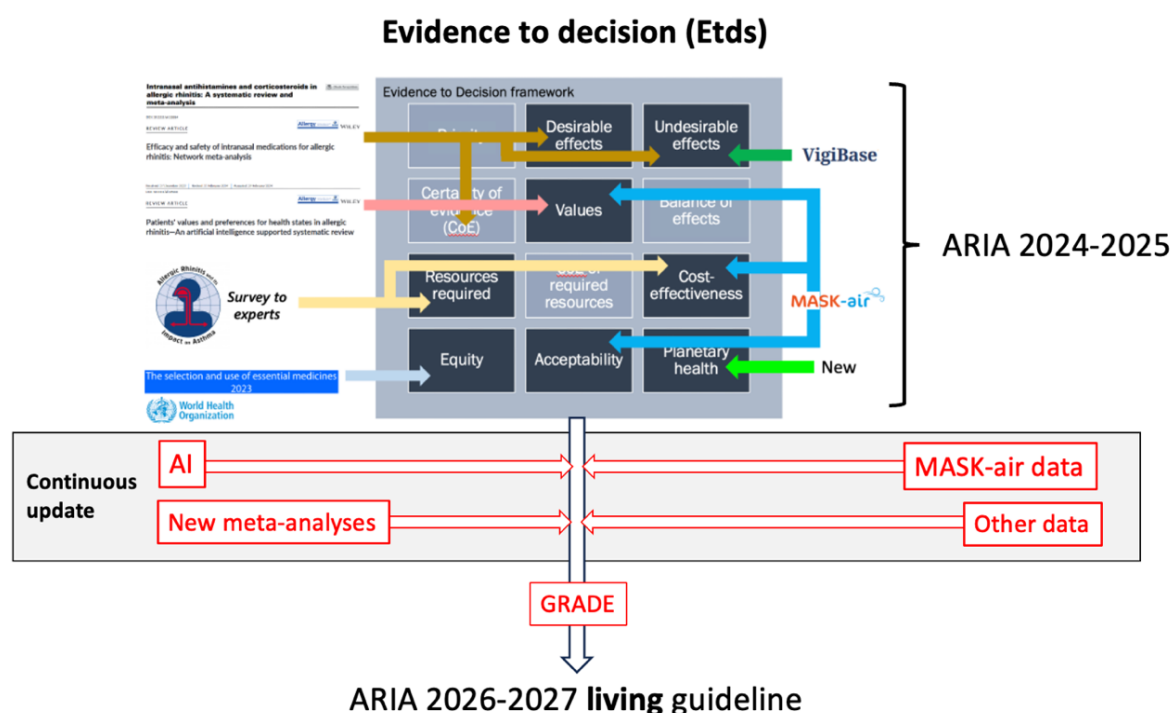
Table 15: Methods used for the development of ARIA 2024-2025

Steps		Person-centred	Digitally enabled	AI assisted	Ref
Selection of PICO question	Review				160,161
	ARIA-driven				164,165
	KOL-driven				166-168
	MASK-air®	X	X		5,11,39,98,122,169,170
	Patient's view	X		LLM, Google Trends	171
	Individual meds vs classes	X			
Value and preferences	Review				172
	V & P: ARIA survey				173
	V&P			Meta-analysis	174
EtDs	Guidelines				154
	Meta-analyses: INCS, INAH, OAH, oral vs intranasal medications, Children				170,175-180
	Safety				
	Satisfaction	X	MASK-air®		73,74
	Adherence	X	MASK-air®		120,121
	Co-medication	X	MASK-air®		123,124,143
	Impact	X	MASK-air®		12,13,23,33,58,59,103,128,156,181-183
	Efficacy	X	MASK-air®		125,129,184

	Costs	X	MASK-air®		In press, JACI Pract
	Planetary health-Climate change				21,22,76,135,185

Overall, the EtDs were derived from more data than simply meta-analyses (Figure 28).

Figure 29: Novel approach to perform Evidence to Decision (EtD) framework in ARIA 2024-2025 and its evolution towards the ARIA 2026-2027 living guideline (from ^{161,186,187})



10.9. Potential implications of digital biomarkers in allergic rhinitis

Table 16: Potential implications of the CSMS (from ³⁹)

1- Clinical practice

- Indication of a treatment in stratified patients
- Follow-up of a treatment and early stopping rule
- Follow-up of a treatment and regular review of efficacy
- Follow-up of the patient when the treatment is stopped
- Re-introduction and follow-up of the treatment in patients who relapse

2- Randomised Controlled Trials (RCTs): mHealth biomarkers are currently exploratory end points but may become primary end points mimicking real-life after validation

3- Observational studies can triangulate RCTs and make a link with clinical practice

4- Real-world data are the *data* relating to patient health status and/or the delivery of health care routinely collected from a variety of sources including apps. They allow large simple trials and pragmatic clinical trials to be performed

5- Epidemiologic studies will use the same approach to better relate RCTs and clinical practice

6- Allergen challenge can triangulate RCTs and make a link with clinical practice

11. Allergen immunotherapy (AIT)

11.1. AIT is effective using real-world data

Evidence regarding AIT efficacy on AR has been provided mostly by RCTs. A MASK-air[®] pilot study showed that AIT improved symptoms and work productivity (Table 17).¹³²

Table 17: Impact of AIT on real-world data using MASK-air[®] (from ¹³²)

Medication scheme	N observations (%)		Symptoms VAS – median [95%CI] (IQR)		P value
	AIT	No AIT	AIT	No AIT	
All observations	36,229 (11.4)	280,947 (88.6)	9 [9-9] (24)	12 [12-12] (28)	<0.0001
No medication	21,613 (12.1)	157,259 (87.9)	7 [6-7] (19)	8 [8-8] (24)	<0.0001
Single medication	8712 (10.4)	75,291 (89.6)	11 [11-12] (24)	14 [14-15] (28)	<0.0001
Comedication	5904 (10.9)	48,397 (88.1)	17 [16-18] (31)	20 [19-20] (35)	<0.0001

CI=Confidence interval; IQR=Interquartile range; Symptoms VAS = MASK-air[®] visual analogue scale assessing the severity of overall allergic symptoms on that day; Work VAS = MASK-air[®] visual analogue scale assessing the work impact of allergic symptoms on that day

In a second study in 10,860 users,¹²³ AIT was more effective on days with oral antihistamines (OAH) than on those with intranasal corticosteroids (INCS, monotherapy or comedication) (Table 18).

Table 18. VAS on global allergy symptoms by medication scheme for days under treatment with allergen immunotherapy (AIT) and days with no AIT (from ¹²³)

	Days under treatment with AIT			Days with no AIT			Difference in AIT use – Average difference in VAS (95%CI) [p-value]
	N days	Median VAS (P25-P75)	Average difference in VAS ^a (95%CI) [p-value]	N days	Median VAS (P25-P75)	Average difference in VAS ^a (95%CI)	
No treatment	43,499	5 (0-16)	-	84,078	8 (0-23)	-	-2.2 (-3.4;-1.0) [<0.001]
OAH or INAH	9921	13 (3-29)	7.8 (7.4;8.1) [<0.001]	29,816	18 (6-41)	8.0 (7.7;8.2) [<0.001]	-1.8 (-3.4;-0.1) [0.041]
INCS	6360	10 (4-24)	3.1 (2.6;3.5) [<0.001]	16,218	13 (4-28)	1.8 (1.4;2.2) [<0.001]	-2.6 (-4.8;-0.4) [0.021]
AzeFlu	3058	12 (3-22)	1.5 (0.9;2.2) [<0.001]	9698	13 (4-31)	1.5 (1.0;1.9) [<0.001]	-1.4 (-4.9;2.0) [0.415]
INCS + OAH	6732	13 (4-31)	7.3 (6.7;7.8) [<0.001]	16,869	19 (7-41)	8.9 (8.5;9.4) [<0.001]	-1.2 (-3.6;1.1) [0.298]
AzeFlu + other	5652	16 (6-27)	4.3 (3.8;4.9) [<0.001]	16,553	16 (5-34)	3.1 (2.7;3.5) [<0.001]	-0.7 (-3.7;2.2) [0.614]
INCS + OAH + other	4825	20 (9-33)	8.5 (7.9;9.0) [<0.001]	13,287	20 (9-39)	7.9 (7.4;8.4) [<0.001]	-2.4 (-5.3;0.5) [0.110]
Any OCS	395	27 (11-45)	^{-b}	2063	43 (25-62)	21.2 (19.3;23.1) [<0.001] ^c	^{-b}

AzeFlu=Azelastine-Fluticasone intranasal formulation; CI=Confidence interval; INAH=Intranasal antihistamines; INCS=Intranasal corticosteroids; OAH=Oral antihistamines; OCS=Oral corticosteroids; ^a Comparisons between each medication scheme *versus* no treatment; ^b Insufficient sample size for analysis to be performed; ^c Difference higher than the minimal important difference (MID).

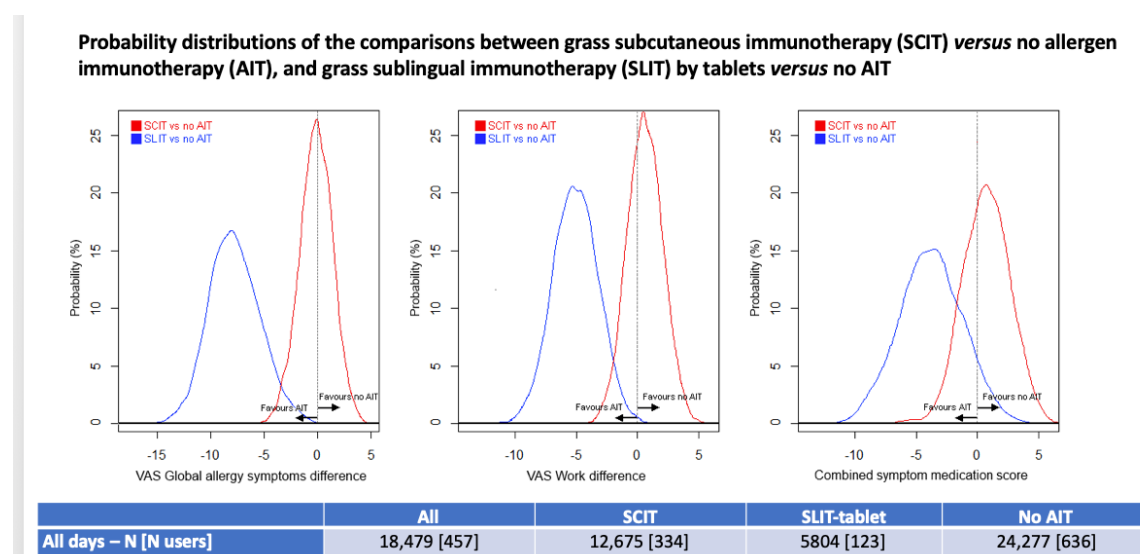
Limitations of the studies: There was no differentiation between SCIT and SLIT, and between different vaccines.

11.2. SLIT is more effective than SCIT

VAS global allergy symptoms and work as well as e-CSMS were studied in users receiving sublingual AIT (SLIT) or subcutaneous AIT (SCIT), and in those with no AIT in European users with self-reported AR. In grass pollen allergic patients, Bayesian mixed-effects models - with clustering by patient, country and pollen season - were analysed (Figure 30).¹⁰²

Limitations of the studies: There was no differentiation between different SLIT or SCIT vaccines. This was not possible due to the number of patients.

Figure 30: Probability distribution between SLIT, SCIT and no AIT (from¹⁰²)



11.3. AIT improves educational activities in young people and its effects differ from pharmacotherapy

Several studies have suggested an impact of AR on academic productivity. However, large studies with direct patient data were not available. We assessed variables measuring the impact of allergies on academic performance (VAS school, WPAI+CIQ:AS impact of allergy symptoms on academic performance and percentage of hours of school lost due to allergies). Factors associated with the impact of allergic symptoms on academic productivity were assessed using multivariable mixed models.

In 1970 users (13-26 years) and 13,454 days, AIT improved school productivity whereas rhinitis medications had no effect (Table 19).¹³

Table 19. Main model of the association between VAS school and other independent variables using multi-level mixed effects linear regression (from¹³)

	Association with VAS school		
	Regression coefficient	95% CI	p-value
Baseline impact	1.40	0.91;1.89	<0.001
Baseline symptoms	-0.63	-0.95;-0.30	<0.001
AIT	-2.70	-4.41;-0.98	0.002
Oral antihistamines	0.06	-0.67;0.79	0.119
Topical antihistamines	1.71	-0.52;3.94	0.132
Nasal steroids	-0.85	-1.79;0.10	0.081
Azelastine + Fluticasone	-1.36	-4.15;1.44	0.342

Systemic steroids	5.19	1.06;9.33	0.014 ^a
Asthma medications	-0.14	-1.53;1.25	0.842
VAS eyes	0.19	0.17;0.2	<0.001
VAS nose	0.37	0.36;0.38	<0.001
VAS asthma	0.18	0.16;0.2	<0.001

CI = Confidence Interval; VAS = Visual Analogue Scale.

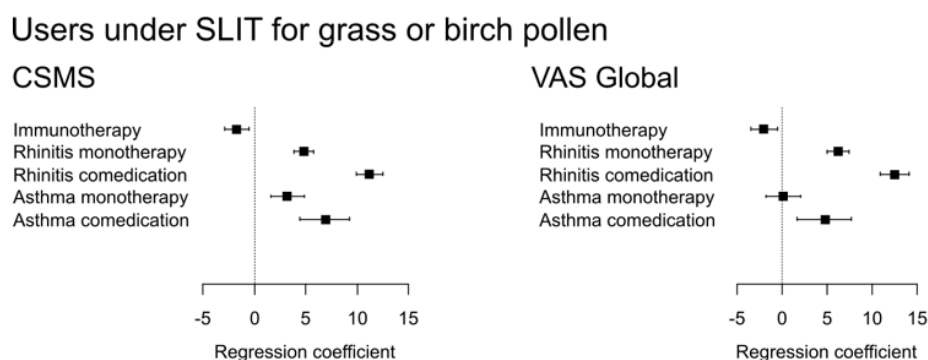
^a — not statistically significant after Bonferroni correction.

Limitations of the studies: There was no differentiation between SCIT and SLIT, and different vaccines.

11.4. Rapid relief of symptoms by SLIT

AIT was suggested to be possibly rapidly effective in AR.¹³⁴ In Europe, in patients reporting grass pollen AIT, days with AIT were compared against days without AIT. 2296 days from 80 patients using SCIT and 3098 days from 113 patients using SLIT were analysed. In users under SLIT, days with AIT were associated with better AR control than days without AIT (Figure 31). Use of AIT was not associated with improved AR control in patients under SCIT.

Figure 31: Daily improvement of allergy control by SLIT (regression coefficients) (from¹³⁴)



These rapid clinical effects cannot be explained by an adaptive immune response (immunotherapy), but may be related to rapid and short-lasting cell downregulation (desensitisation), particularly in basophils and mast cells.^{134,188} SLIT might induce a rapid relief of allergic symptoms during the pollen season. However, this hypothesis requires confirmation by appropriate studies.

Limitations of the study: Low number of users but highly consistent results.

11.5. Potential benefits of digital biomarkers in AIT

11.5.1. AIT trials

Proposed benefits of apps include the ability to longitudinally collect symptoms and medication usage data, allowing the detection of changes during treatment. Data from external sources, including weather, allergen load and air quality reports are integrated.⁴⁰

Overall, mHealth data are important as:

- Observational studies can triangulate RCTs.
- The real-life approach allows us to study a large number of patients in several studies.

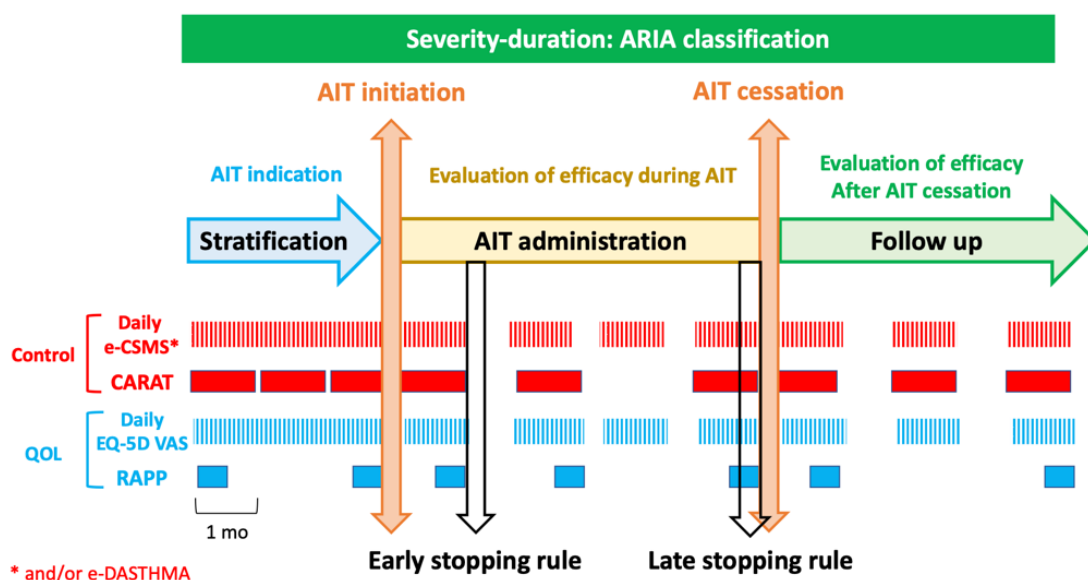
- Most patients using AIT need a pharmacologic treatment. In RCTs, there is a standardisation of medication use. Real-life data enable the assessment of all medications with an impact on efficacy and costs.
- Rare allergens can be studied.
- The placebo effect can be reduced by comparing exposed and non-exposed days. In patients who voluntarily accept to be geolocalised, daily pollen and air pollution indexes are available with a radius of 5 km. Pollen exposure can be monitored when they travel or during rainy days (Figure 3) allowing to *pre-hoc* discard data during days when pollens are low. The exact level of pollen is currently monitored in CATALYSE (Horizon Europe grant) comparing MASK-air[®].²²
- Cost-effectiveness in real life can be available.

11.5.2. Clinical course of patients selected for and followed using AIT

Following the ARIA care pathways, the ARIA-EAACI Position Paper on digital biomarkers in AIT proposed^{40,189} that digital biomarkers associated with clinical decision support systems (CDSS)⁵¹ may change the scope of the clinical impact of AIT to enable:

- Patient stratification,
- Monitoring of AIT efficacy and safety,
- Development and implementation of guidance for the continuation or cessation of treatment after a short (early stopping rule) or long (late stopping rule) period and
- Assessment of AIT efficacy after its cessation. Clinical stopping rules should be developed for AIT (Figure 32).

Figure 32: Digital biomarkers in AIT (adapted from the ARI-EAACI Position Paper on digital biomarkers in AIT^{39,40}).



Limitations and future needs:

Few patients are highly adherent to the app and most will not fill the app daily. However, it appears that patients fill the app more commonly when they are unwell. Thus, instead of using median values, maximal values on the worst days may be used. Moreover, patients who will not be adherent to the app

during stratification are unlikely to be adherent to SLIT during treatment and this may be considered in prescribing SLIT. These hypotheses should be tested. It is possible to define the number of days needed to appreciate the pollen season.

12. Asthma

12.1. Phenotypes of asthma and multimorbidity

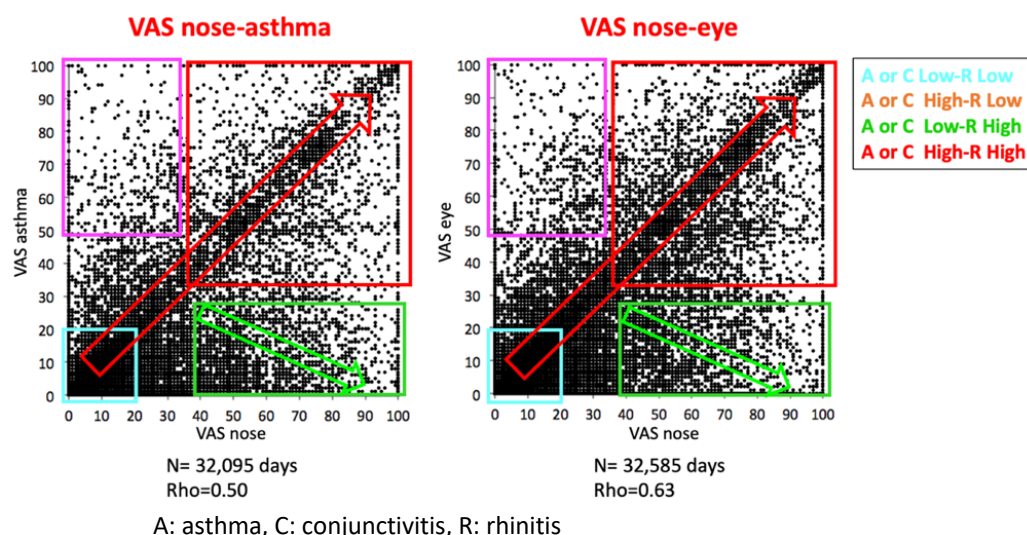
12.1.1. Rhinitis without asthma

Rhinitis is a common comorbidity in A patients. However, underreported R in A is not clear. We assessed the characteristics of patients with self-reported A and no self-reported R, and the extent of R underreporting.¹¹⁶ A cross-sectional study of all MASK-air® users (2015-2022, 27 countries), compared reported symptoms and medication use in patients with (i) self-reported A without R ("asthma alone"), (ii) self-reported R+A and (iii) self-reported R without A ("R alone"). A cluster analysis was performed to identify groups of patients under-reporting R and/or undertreated for R. We assessed 35,251 users (529,751 days): 671 (1.9%) A alone, 25,882 (73.4%) R alone and 8698 (24.7%) R+A. Overall, 27% of patients reporting A alone were treated with R medications, but these patients displayed a lower frequency of days under R medication and less severe nasal symptoms than those reporting R+A. Among patients reporting A alone, 3 clusters were identified: (A; 22.2%) severe R symptoms and low frequency of R medication use, (B, 41.0%) moderate R symptoms and high frequency of R medication use (41.0%), and (C, 36.8%) mild or no R symptoms and almost no R medication use. This study suggests that, among patients with self-reported A, R underreporting or undertreatment may be common.

12.1.2. Multimorbidity

Daily multimorbidity was assessed in a cross-sectional analysis (4,210 users, 19 countries).⁴⁶ A specific group ("extreme" allergy phenotype) combined R "High" (VAS>50/100) patterns - A "High" - C "High" and was identified in 2.9% of the days. This previously unknown extreme pattern of multimorbidity had the greatest impact on uncontrolled symptoms and work productivity (Figure 33). Differences in control were found in R alone and R+multimorbidity.

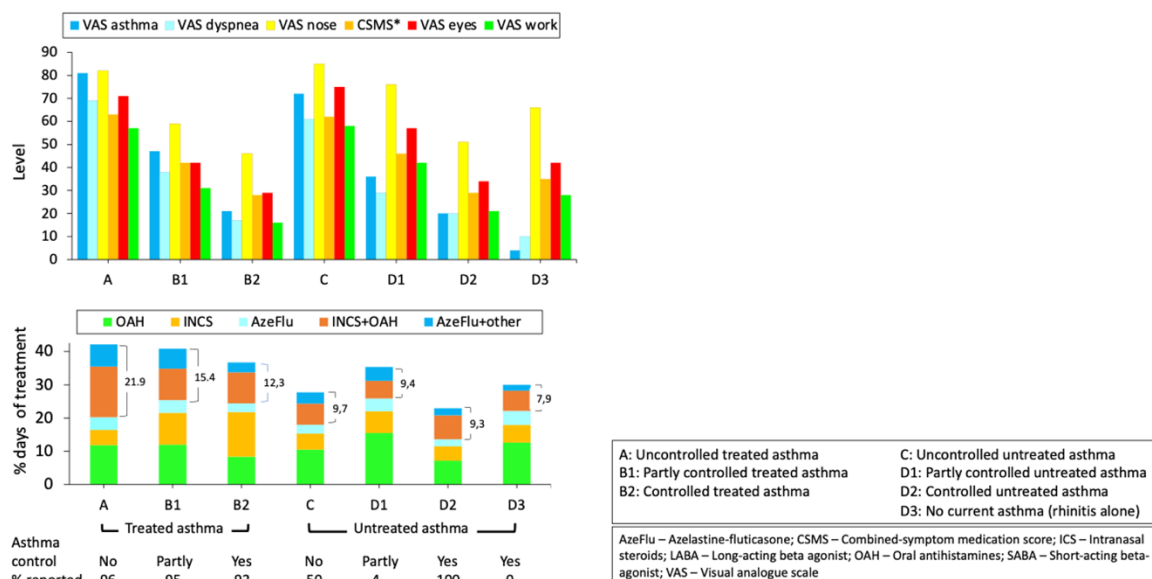
Figure 33: Patterns of multimorbidity in days reported in MASK-air® (from ⁴⁶)



This study was followed by two cluster analyses - a cross-sectional analysis based on A patterns (over 8000 patients and 267,000 days)¹⁵³ and a longitudinal one based on R patterns (over 2500 patients, 297,000 days and 16,000 weeks with 7 day-reporting).⁹⁸ The extreme "A", "R" and "C" phenotypes were confirmed in days (cross-sectional analysis) and patients (longitudinal) (Figure 34). Patients with

A+R required more rhinitis medication and had worse ocular and rhinitis control than patients with R alone.¹¹⁸

Figure 34: K-means cluster analysis using asthma patterns (from ¹⁵³)



Limitations of the studies: In the MASK-air[®] studies, AD was not considered. However, the results of mHealth apps are hypothesis generating and need to be confirmed in classical epidemiologic studies.

Canonical epidemiologic studies showed that (i) the risk of adult-onset A increases with the number of allergic multimorbidities,¹⁹⁰ (ii) severe A is associated with multimorbidity,¹⁹¹ (iii) age of onset and parental allergy suggest that multimorbidity behaves differently to R or A alone^{192,193} and (iv) the role of sex hormones at puberty appears to be influenced by multimorbidity.^{194,195}

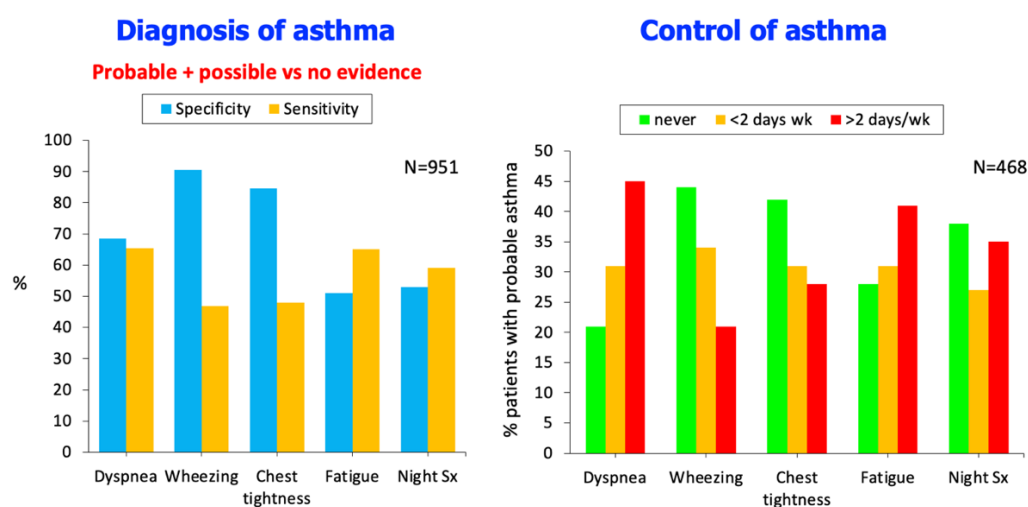
12.2. MASK-air[®] and CARAT in the diagnosis or control of asthma

The five main asthma symptoms (wheezing, dyspnea, chest tightness, cough and airway secretion) may have a different association with the diagnosis or control of asthma. A cross-sectional study assessed the frequency of individual symptoms (wheezing, dyspnea, chest tightness) in the diagnosis and control of asthma. The frequency of individual symptoms was based on the CARAT lower airways questions.¹⁹⁶ Asthma in MASK-air[®] users was classified according to a previous study as “probable asthma”, “possible asthma” or “no evidence of asthma”.¹¹⁷ Asthma control was assessed by e-DASTHMA.¹⁰⁷

In 951 patients, we assessed 2153 CARAT questionnaires. Although all symptoms were associated with asthma diagnosis, wheezing and shortness of breath were the most specific. On the other hand, dyspnoea was the most sensitive and the most consistent symptom associated with e-DASTHMA (Figure 35).

This study was reinforced by a prospective cross-sectional study in 171 untreated asthmatic adults in Liège. Multiple linear regression analysis showed that dyspnea and chest tightness were the two leading symptoms associated with asthma-related QOL.¹⁹⁷

Figure 35. Sensitivity and specificity of CARAT asthma symptoms in the diagnosis of asthma



12.3. Asthma treatment

Using the MASK-air[®] app and the methods used to assess adherence in rhinitis,¹²⁰ we studied adherence to inhaled steroid (ICS)-containing medications.

12.3.1 Overall adherence

We analysed MASK-air[®] users who used the app in at least three different months to limit “false-positives”.¹¹⁷

There were:

- 578 SABA-only users (reporting 12,705 days; average of 22 days per user);
- 1217 ICS+LABA-only users (26,291 days; average of 22 days per user);
- 2227 ICS+LABA-co-medication users (77,827 days; average of 35 days per user);
- 868 ICS-only users (34,693 days; average of 40 days per user).

The outcomes included (Table 20):

- Total adherence to MASK-air[®]: Proportion of days with MASK-air[®] use among the total number of days since MASK-air[®] installing.
- One-month adherence to MASK-air[®]: Proportion of days with MASK-air[®] use within the first 30 days after MASK-air[®] installing.
- Proportion of days using each medication class among days of MASK-air[®] use.

Table 20: Adherence to asthma medications (from¹¹⁷)

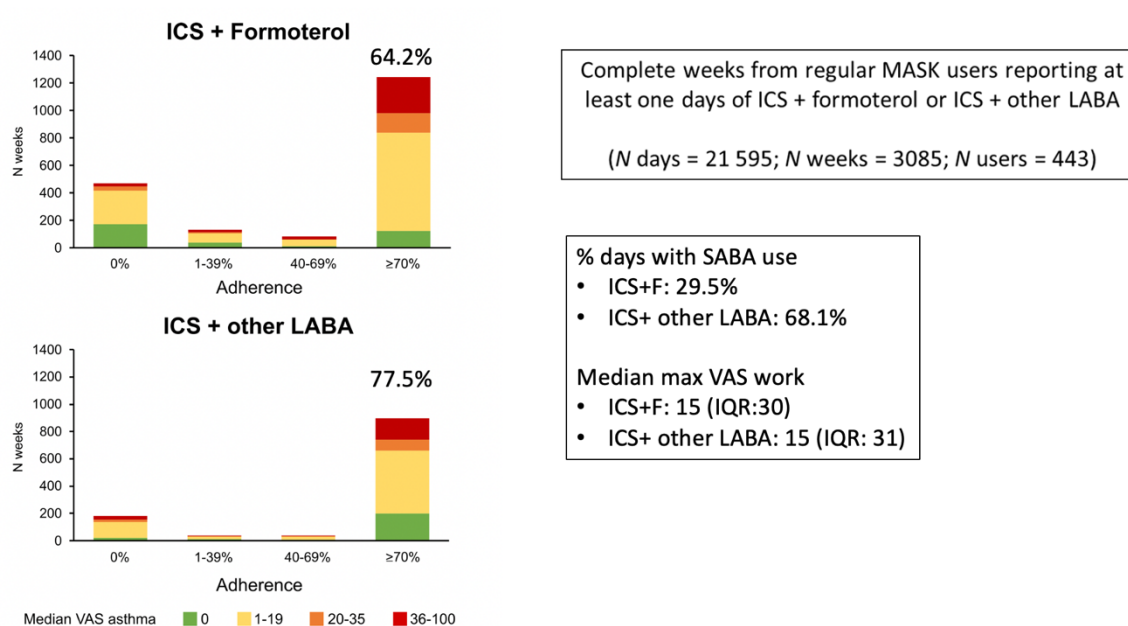
	SABA	ICS/LABA		ICS
		Only	All	
<i>N</i> users reporting VAS asthma in 3 months (%)	183 (31.7)	348 (28.6)	826 (37.1)	360 (41.5)
<i>N</i> days (average <i>N</i> days per user)	10 903 (60)	22 108 (121)	70 688 (86)	32 206 (89)
Total adherence to MASK-air [®]	3.1 (7.7)	3.5 (8.0)	4.5 (11.0)	4.3 (8.0)
One-month adherence to MASK-air [®]	38.7 (48.4)	41.9 (58.1)	48.4 (58.1)	58.1 (58.1)
Proportion of days using medication	14.3 (27.4)	80.0 (62.2)	81.2 (58.3)	56.3 (71.5)

12.3.2. Adherence to ICS+LABAs

In a second study, we compared adherence levels in MASK-air® data, assessing complete weeks (with a reporting of 6 or 7 days) from patients with self-reported asthma and at least one day of ICS + formoterol (F) or ICS + other LABAs). (Figure 36).

In 2598 users reporting the use of ICS+LABAs, 621 (23.9%) reported 4824 complete weeks, and 866 (34%) reported weeks with at most one missing day. Adherence was higher for ICS+other LABA (use of medication $\geq 80\%$ of weekly days) than for ICS+F (59.3%). However, control was similar in both groups and ICS+F was associated with a meaningful lower SABA use and similar VAS asthma, e-DASTHMA or VAS work. Overall, increased adherence to either ICS+F or ICS+other LABA was associated with decreased SABA use.

Figure 36: Adherence to inhaled corticosteroids (ICS) + long-acting β -agonists (LABA)

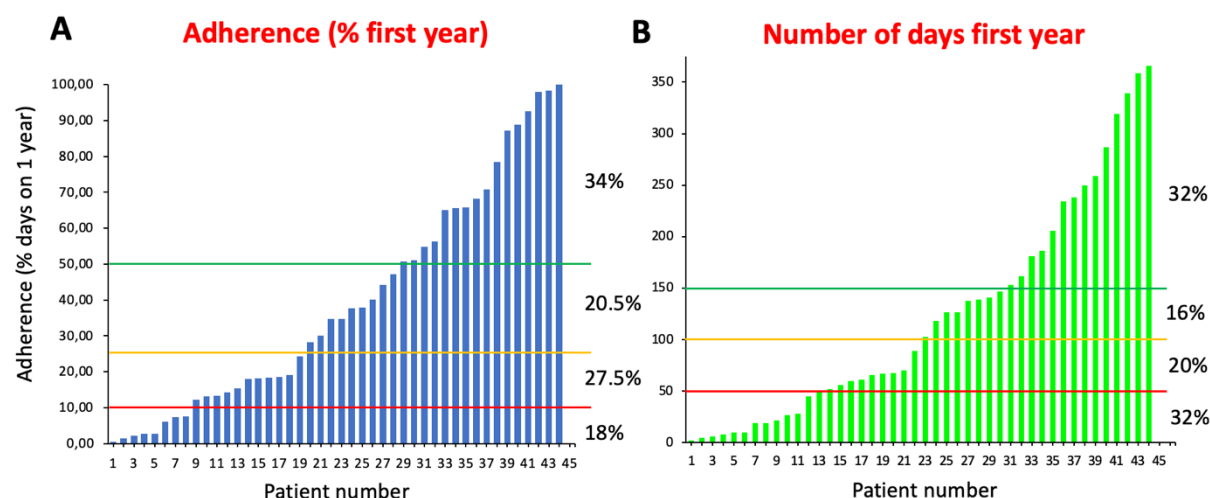


Limitations of the study: Doses

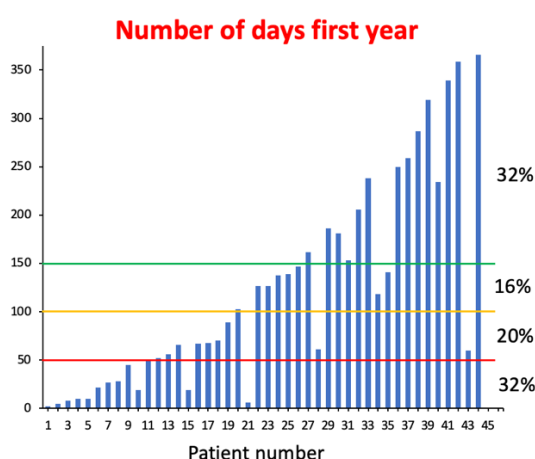
12.3.3. Adherence of patients treated by biologics

In Italy, Lithuania, Portugal and Turkey, 44 patients were treated by biologics. They were not all enrolled by physicians. Adherence to the app for the first year of follow up was examined (Figure 37 A-B). However, some patients recruited in 2023 did not have the full year's data and the number of days of reporting was lower (N°21, 28, 34, 35 and 43, Figure 37C).

Figure 37: Adherence to the app of patients receiving biologics



To be noted that the numbers do not correspond to the same patients in the 2 graphs. In the left graph (A), patients have been selected by their adherence level and in the right one (B), by the number of days.



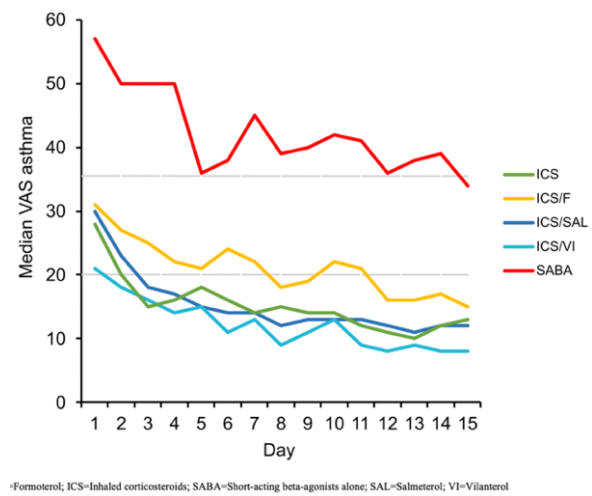
In this graph, patients were selected by their adherence level (equivalent to graph A of the upper figure). Patients 15, 21, 28 and 43 were recently enrolled.

12.3.4. Comparison of treatments used in asthma

A cross-sectional study used MASK-air[®] real-world data to compare reported asthma control on days with several treatments used alone or in co-medication.¹⁹⁸ In 70,271 days (3229 users, mean age=43.3±13.7 years), VAS asthma was higher for SABA (always uncontrolled median days). No treatment days had the lowest VAS asthma. ICS F days were less controlled than other ICS alone or ICS+LABA (Figure 38).

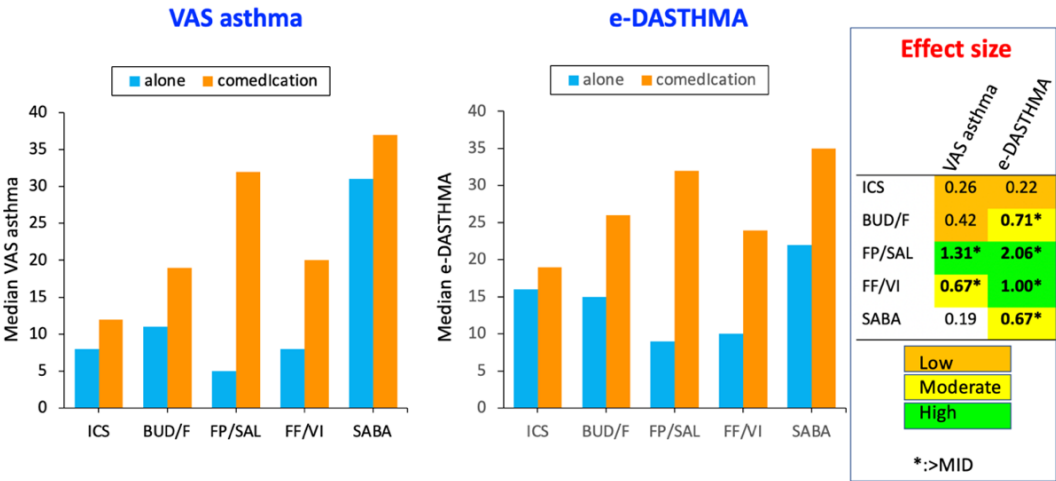
Limitations of the study: Doses and strengths of medications were not included. The study shown in the graph is cross-sectional.

Figure 38: Median VAS asthma according to medication schemes for asthma and the day of MASK-air® use (cross-sectional study)



In single medication days, ICS/F associated with worse reported asthma control than ICS/SAL or ICS/VI, but all differences were lower than the MID. Days of SABA use were associated with worse control than days under any ICS or ICS/long-acting beta-agonist (LABA). The differences were higher than the MID. For a drug or a drug class, co-medication days were less well controlled than days with single medication (fixed dose combination therapy considered as single medication) (Figure 39).

Figure 39: Comparison of treatments used in asthma



Effect size by Cohen's d test

12.3.5. Follow up of asthmatic patients reporting over 26 days a month and at least one day of ICS

A longitudinal observational study was carried out on asthmatic patients who filled at least 26 days during the first month of reporting the MASK-air® app and who received a treatment with inhaled corticosteroid with or without long-acting β_2 agonist (ICS $\pm$ LABA).¹²⁷ Validated daily Patient-Reported Outcome Measures (PROMs: visual analogue scale (VAS) asthma and an electronic symptom-control score (e-DASTHMA)) were compared during the first month of survey between patients using the same ICS $\pm$ LABA (non-switchers) and patients switching ICS $\pm$ LABA (switchers). Every day, MASK-air®

PROMs as well as all medications used were reported. Cluster analysis (k means) was used to differentiate patients' phenotypes.

Results: 192 (78.7%) patients were non-switchers and 52 were switchers. 75.6% of non-switchers were well-controlled versus 42% of switchers. Moreover, around two-thirds of the patients were adherent to treatment irrespective of the switch strategy. Based on control, adherence to ICS±LABA, short-acting β -agonist use and biologics as well as long-acting anti-muscarinics, six distinct groups of different clinical relevance were retrieved in non-switchers (Table 21 and Figure 40). Switchers displayed two extra groups.

Table 21: Distinct groups of clinical relevance

Asthma control	Adherence	SABA use	LAMA and/or biologics use	Cluster [entire sample] (%)	Cluster [non-switchers] (%)	Cluster [switchers] (%)
Poor	High	High	Low	A (6.2%)	A' (4.7%)	A'' (18.0%)
		Low	High	B (4.1%)	-	-
	Low	Medium	Low	C (12.3%)	C' (14.5%)	-
Volatile			High	D (9.5%)	D' (5.2%)	-
Good	High	Low	Low	-	-	G'' (12.0%)
	Low			E (40.7%)	E' (43.0%)	E'' (18.0%)
				F (27.2%)	F' (32.6%)	F'' (52.0%)

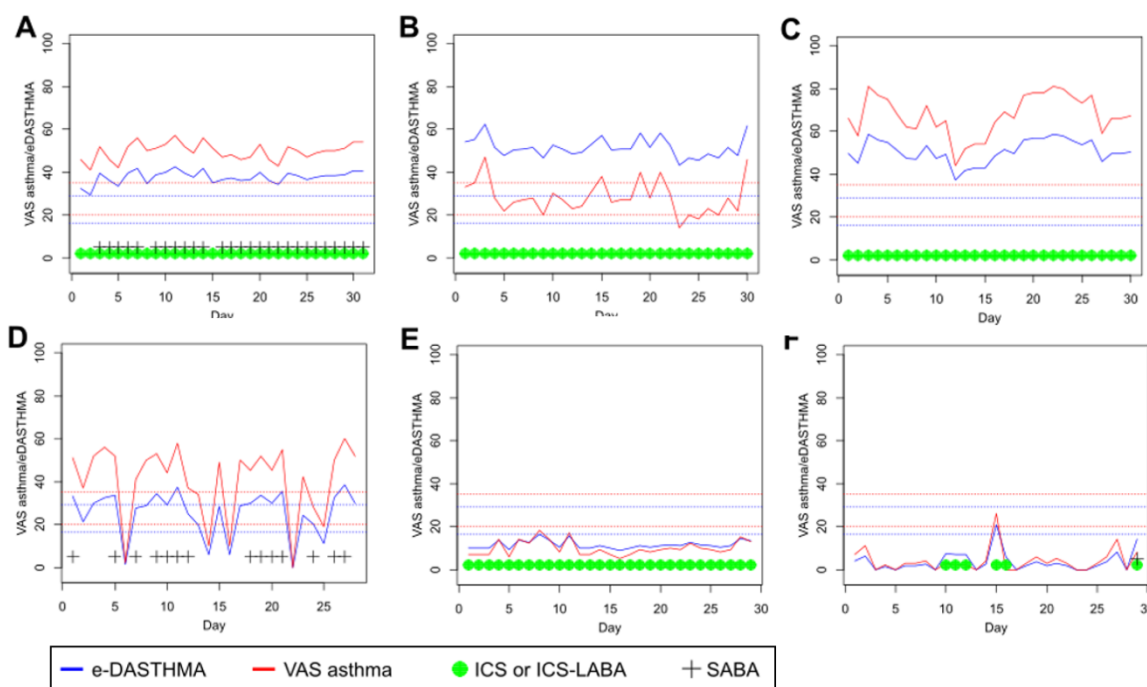
VAS: VAS asthma, poor: median >36/100, Good: VAS <20/100, volatile: highly variable

Adherence to ICS±LABA: High >80%, Low <80%,

SABA use: High >80% days, medium 25%, Low <20%

LAMA=Long-acting muscarinic antagonists; SABA=Short-acting beta-agonist

Figure 40: Examples of representative months for each of the clusters



Two samples were studied. The discovery analysis in 253 months in 253 patients (Table 16) was completed by a validation study the entire database (2,539 months) and similar clusters were found.

Conclusion: Switchers and non-switchers have different phenotypes and their management should be considered differently. Patients adherent to the app are also highly adherent to treatment.

Limitations of the study:

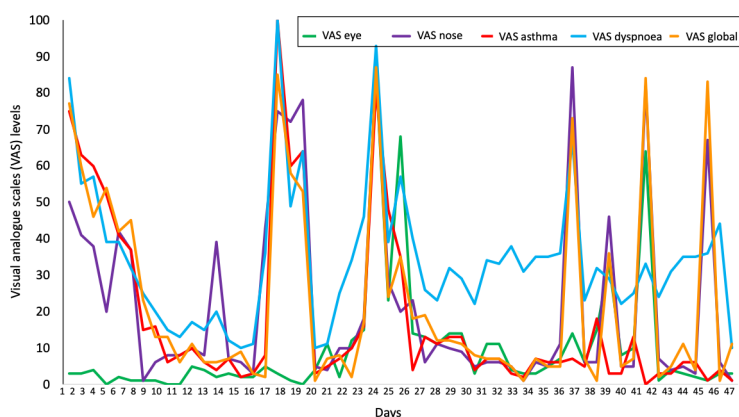
12.4. Severe asthma

12.4.1. Longitudinal pilot study in severe asthma

Applicability of the MASK-air[®] app was explored in severe asthmatic patients in a longitudinal (observational) study. Patients with a diagnosis of severe asthma were proposed to use the MASK-air[®] app for 6 months along with best practice treatment. VAS for asthma, shortness of breath, rhinitis, conjunctivitis, work and sleep were monitored. Adherence to MASK-air[®] and to asthma treatment was also checked.¹²⁶

Thirteen patients (11 on biologics) reported 1229 days of MASK-air[®] use. The average app adherence was of 51.8% (range: 19.7-98.9%) suggesting that patients with severe asthma under biologics may not be more adherent than the regular asthmatic patients receiving ICS. There was no correlation between app and medication adherence. Highly variable trends were found for VAS asthma. Five patients had over 90% of well-controlled days, four had well- or moderately controlled asthma (up to 20% of uncontrolled days), one patient had moderately controlled asthma with around 20% of uncontrolled days, and one patient had 80% of uncontrolled days. Highly significant correlations were found for VAS asthma and other patient-reported VASs (including work, dyspnea, sleep and rhinitis) (Figure 41).

Figure 41: Evolution of PROMs in a patient with severe asthma (from ¹²⁶)



12.4.2. Longitudinal study in a Portuguese severe asthma registry: Impact of the introduction of MASK-air[®] for the follow-up of patients with severe asthma

In this study, we assessed (i) the adherence of SA patients to an mHealth tool (MASK-air[®] app) with an asthma daily monitoring questionnaire, and (ii) whether using such a tool would be associated with an improvement in asthma patient-reported outcomes (PROMs) over a 6-month study. To conduct this study, we recruited a sample of SA patients in a single centre (“main cohort”: 56 patients) and evaluated users registered in the MASK-air[®] database with self-reported asthma who reported the use of biologics (“sensitivity analysis cohort”: 116 patients). The results of the main cohort with well-characterised patients were similar to a sensitivity analysis using the MASK-air[®] database.

The following points were observed: (i) adherence to MASK-air® during the first month can predict adherence in subsequent months (Figures 42 & 43); (ii) the introduction and regular use of the app was associated with a marked improvement of asthma symptoms (with a trend to higher improvement in patients with high adherence) (Figure 44); and (iii) no major differences in terms of app adherence were observed in patients receiving or not receiving biologics.

Figure 42: Scatter plots displaying the correlations between adherence to MASK-air® in the first month and adherence in the subsequent months (main cohort)

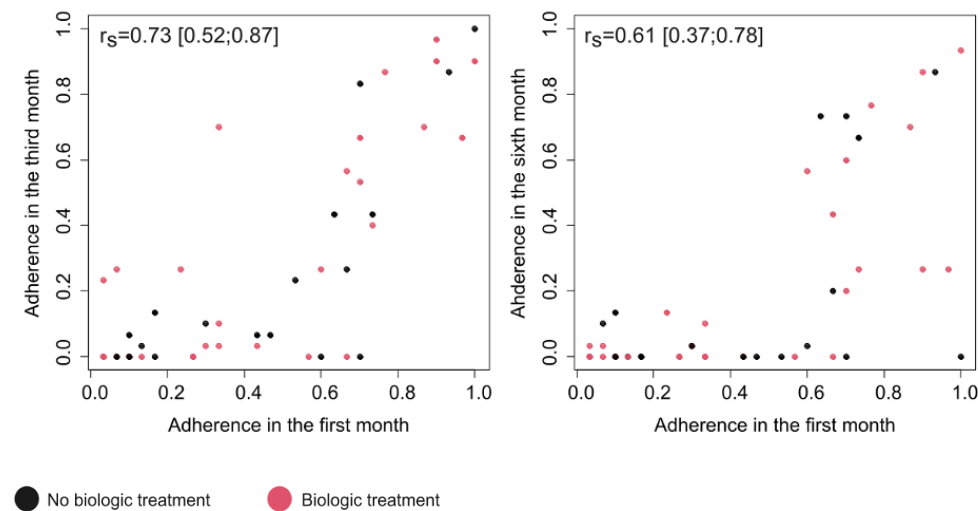


Figure 43: Scatter plots displaying the correlations between adherence to MASK-air® in the first month and adherence in the subsequent months (sensitivity analysis cohort)

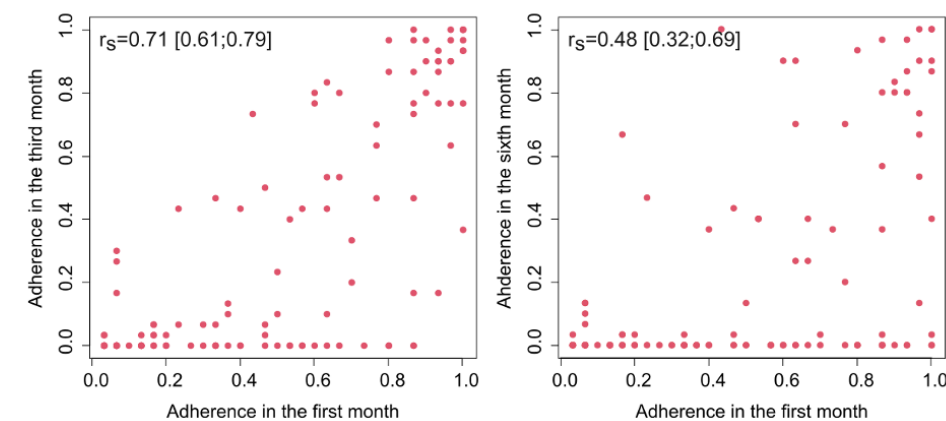
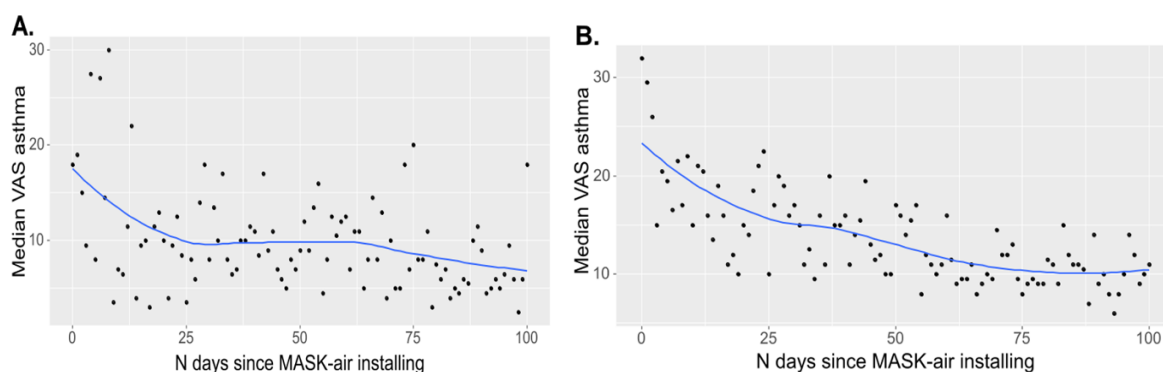


Figure 44: Median levels of the visual analogue scale of asthma symptoms (“VAS asthma”) per day since MASK-air® installing in patients with an adherence ≥50% in first month.

Each dot corresponds to a specific day since MASK-air® installing. A: Main cohort; B: Sensitivity analysis cohort



This study suggests that one month of MASK-air[®] use in patients with severe asthma may predict long-term adherence and that adherence is associated with improvement in control. The same effect is seen in clinical trials in which placebo-treated patients improve.¹⁹⁹

12.5 Potential benefits of digital biomarkers in person-centred care in asthma

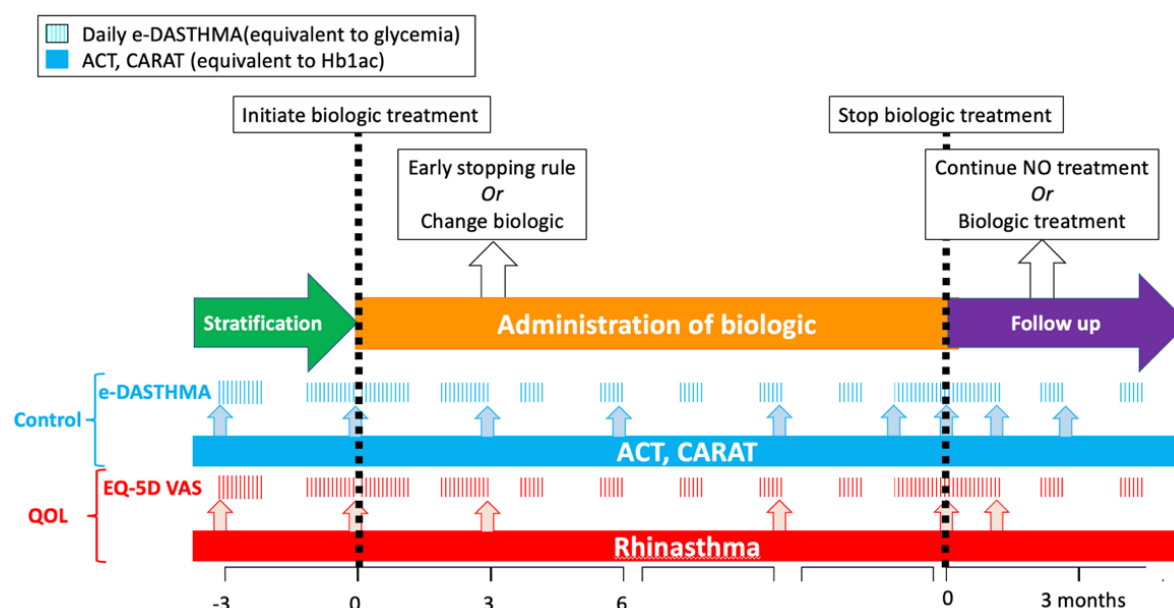
12.5.1. Potential implications of MASK-air combined symptom-medication scores: The diabetes approach adapted to asthma

Biomarkers for the diagnosis, treatment and follow-up of patients with rhinitis and asthma are urgently needed. Although some biologic biomarkers exist in specialist care for asthma, they cannot be largely used in primary care. There are no validated biomarkers in R or AIT that can be used in primary care. MASK-air[®] has defined mHealth biomarkers that should make a bridge between clinical practice, randomised controlled trials, observational real-life studies and allergen challenges. Using the MASK-air app as a model, a daily electronic combined symptom-medication score for allergic diseases (CSMS) and for asthma (e-DASTHMA) was reported and embedded in a strategy similar to the diabetes approach for disease control.

12.5.2. Application to biologic treatment in severe asthma

Currently, a major criterion to initiate or stop a biologic in asthma is the frequency of exacerbations. In MASK-air[®], exacerbations can be defined by the occurrence of uncontrolled VAS using the cut-offs calculated ($VAS \geq 36/100$) and/or the use of oral corticosteroids. With the available data on file, MASK-air[®] researchers are assessing whether the change in e-DASTHMA could be associated with an exacerbation. Moreover, in future studies, with the new development of MASK-air[®] (MDR Class IIa), e-DASTHMA values will be refined (Figure 45).

Figure 45: Applicability of digital biomarkers in severe asthma using the diabetes approach (ARIA-EAACI Taks Force on patient-centered digital biomarkers). ³⁹

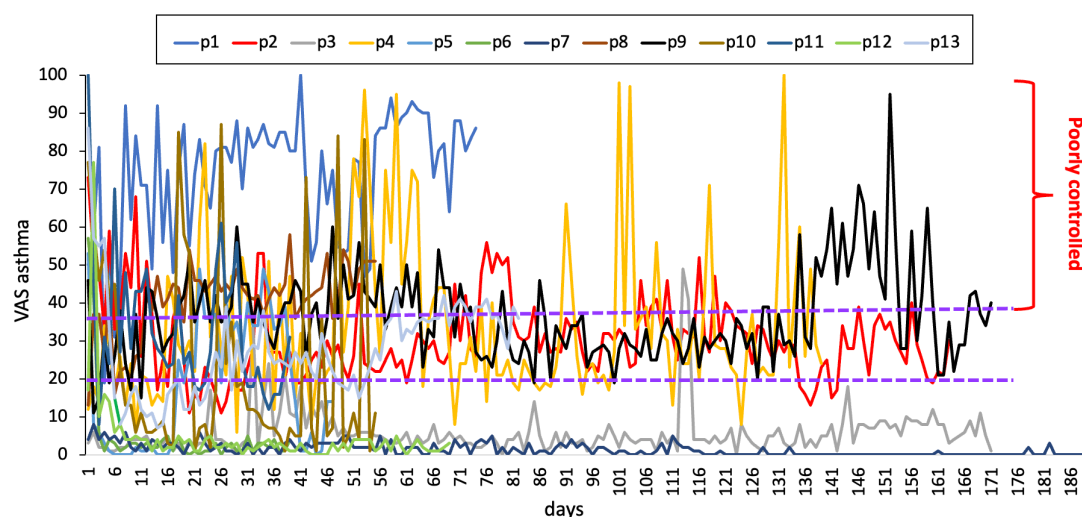


There is therefore a potential of the MASK-air[®] app with regards to public health care, defining lack of compliance, adherence, lack of control with huge potential of optimisation of healthcare costs. Finally, MASK-air[®] may be introduced into public payer systems in severe asthma.

12.5.3. Assessment of asthma remission in patients under biologics

Remission is an important issue in the management of asthma treated by biologics. Several definitions and criteria referring to clinical or pathophysiological remission have been proposed but none assess the daily control of the disease.²⁰⁰ Although assessing control may not be sufficient,²⁰⁰ daily control does however appear to be a very important criterion. In MASK-air[®], a study in 13 asthmatic patients treated by biologics showed that most patients did not achieve remission.¹²⁶ However, in two patients, remission was obtained although, in one of them, one exacerbation was observed (Figure 46).

Figure 46: Remission of asthma in patients treated by biologics (from ¹²⁶)



12.6. Assessment of risk factors for asthma exacerbations

Combining MASK-air® data with other tools may help to define risk factors for exacerbations. Embedding these results with other tools may also provide information for the exacerbations reported by the app.

12.6.1. Pollen and pollution exposure

In patients who are voluntarily geolocalised, daily pollen and pollution exposure is available (FMI and Copernicus, Figure 3).²¹

12.6.2. Prediction of asthma hospitalisations using Google Trends for common cold

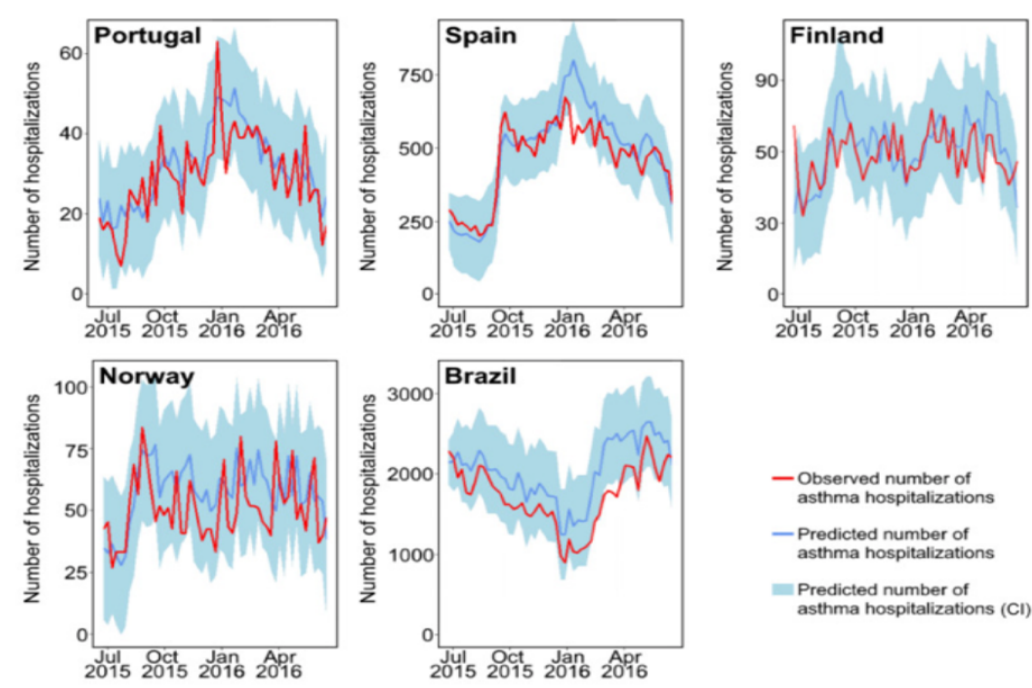
In contrast to air pollution and pollen exposure, data on the occurrence of the common cold are difficult to incorporate in models predicting asthma hospitalisations from data derived from an app.

A study assessed whether web-based searches on *common cold* would correlate with and help to predict asthma hospitalisations (Figure 47).

We analysed all hospitalisations with a main diagnosis of asthma occurring in 5 different countries (Portugal, Spain, Finland, Norway and Brazil) for a period of approximately 5 years (January 1, 2012-December 17, 2016). Data on web-based searches on *common cold* were retrieved from Google Trends (GT) using the *pseudo-influenza syndrome* topic and local language search terms for *common cold* for the same countries and periods. We applied time series analysis methods to estimate the correlation between GT and hospitalisation data. In addition, we built autoregressive models to forecast the weekly number of asthma hospitalisations for a period of 1 year (June 2015-June 2016) based on admissions and GT data from the 3 previous years.

In time series analyses, GT data on *common cold* displayed strong correlations with asthma hospitalisations occurring in Portugal (correlation coefficients ranging from 0.63 to 0.73), Spain ($\rho=0.82-0.84$) and Brazil ($\rho=0.77-0.83$), and moderate correlations with those occurring in Norway ($\rho=0.32-0.35$) and Finland ($\rho=0.44-0.47$) (Figure 44). Similar patterns were observed in the correlation between forecasted and observed asthma hospitalisations from June 2015 to June 2016, with the number of forecasted hospitalisations differing on average between 12% (Spain) and 33% (Norway).

Figure 47: Predicted and observed numbers of asthma hospitalisations for one year



Predicted values were obtained using GTs for common cold

observed hospitalisations.

Common cold-related web-based searches display moderate-to-strong correlations with asthma hospitalisations and may be useful in forecasting them.

13. Impact on work-education and economic evaluation

Allergic rhinitis may display a relevant impact on work productivity and result in substantial economic costs. MASK-air[®] data have been used to assess the impact of rhinitis/conjunctivitis and asthma using quality-of-life and activities, work productivity and education.

The economic evaluation is currently being assessed and several MASK-air[®] tools can be compared. They include (i) the cost of medications effectively used, (ii) the cost of absenteeism and presenteeism (VAS Work, WPAI-AS-work), (iii) costs of health resource utilisation (EQ-5D VAS) and (iv) potential benefits of expensive treatments such as AIT or biologics.

13.1. Work productivity: daily VAS work and Work Productivity and Activity Questionnaire for Allergic Symptoms (WPAI-AS) data

13.1.1. VAS work

In subsequent concurrent validity studies, it was found that rhinitis, conjunctivitis and asthma have a significant impact on work productivity (Figure 48 and Table 22).²⁰¹ A significant correlation has been found between VAS work and WPAI-AS.

Figure 48: Correlation of VAS work with VAS global allergy symptoms in 16,925 days (from ⁹)

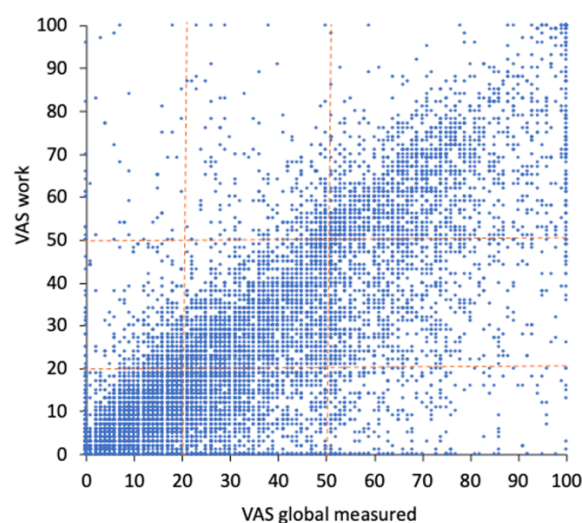


Table 22: Correlations using Spearman ρ test between VAS work and other VAS

	N days (study)	VAS global	VAS nose	VAS asthma	VAS eye
Bousquet ⁵⁸	6120 (CS)	0.83	0.80	0.57*	0.70
Bousquet ⁹	16,925 (CS)	0.82	0.77	0.60*	0.69
Bedard ¹²	98,303 (CS)	0.73	0.68	0.45*	0.56
Sousa-Pinto ⁵⁵	149,732 (CS)	0.81	0.78		
Sousa-Pinto ¹⁶	1840 (L)			0.79**	
Benfante ²⁷	1222 (L)			0.85***	

Entire population of MASK-air® patients *, only asthmatic patients **, only severe asthmatic patients ***
CS: cross-sectional, L: longitudinal

Limitations of the studies: Possibility of selection biases. Several of the correlations have not taken into account repeated measures by the same user.

13.1.2. Correlation with disease control (Table 23)

Table 23: Correlations using Spearman ρ test between VAS work and other VAS

	N days (study)	VAS global	VAS nose	VAS asthma	VAS eye
Bousquet ⁵⁸	6120 (CS)	0.83	0.80	0.57*	0.70
Bousquet ⁹	16,925 (CS)	0.82	0.77	0.60*	0.69
Bedard ¹²	98,303 (CS)	0.73	0.68	0.45*	0.56
Sousa-Pinto ⁵⁵	149,732 (CS)	0.81	0.78		
Sousa-Pinto ¹⁶	1840 (L)			0.79**	
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Entire population of MASK-air® patients *, only asthmatic patients **, only severe asthmatic patients ***
CS: cross-sectional, L: longitudinal

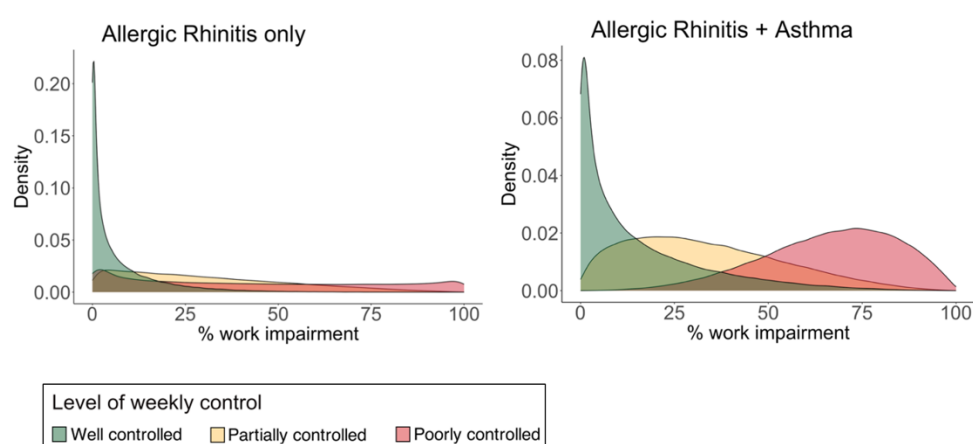
13.1.3. WPAI-AS

A cross-sectional study using WPAI-AS measured the impact of AR in work productivity (presenteeism and absenteeism) depending on the disease control and considering patients with and without asthma.

A multiparameter approach was based on Bayesian methods to model work impairment.¹⁵⁵ The study included 364 patients reporting 677 full weeks of data. Presenteeism contributed more to these costs than absenteeism. Regarding presenteeism, the median impact of AR in weeks of good rhinitis control was 4.4% (P25-75=0.8-12.9%), while partial and poor disease control were respectively associated with an impact of 25.0% (P25-P75=12.1-42.4%) and 60.7% (P25-P75=24.9-74.2%). Large differences were found between rhinitis alone and rhinitis + asthma (Figure 49).

Limitations of the studies: Possibility of selection biases which could affect the generalisability of the findings. The WPAI-AS questionnaire has been validated for allergies but is not specific for AR or asthma.

Figure 49: Total percent work impairment in patients with allergic rhinitis per level of rhinitis control.



13.2. Academic productivity: daily VAS education and WPAI-AS data

13.2.1. VAS education and WPAI-AS

Allergic diseases have a significant impact on academic performance, and a MASK-air[®] study compared VAS on allergy symptoms with VAS education.¹³ In XX patients (13,454 days), there was a significant correlation between VAS education and VAS global ($p=0.70$) and VAS nose ($p=0.66$). The WPAI-AS provided data on the impact of allergies on school performance in 125 weeks with 6-7 days of reporting. There was a significant correlation between WPAI-AS and VAS education ($p=0.80$). Similar results were obtained when correlations using repeated measures correlation coefficients (Table 24).

Table 24. Spearman and repeated measures correlation coefficients for outcome variables and relevant independent variables (from ¹³).

	VAS education	VAS eyes	VAS nose	VAS asthma	VAS global	CSMS	% hours missed
Spearman correlation - correlation coefficient (95% CI)							
VAS education	—	0.39 (0.38;0.40)	0.66 (0.65;0.68)	0.15 (0.13;0.17) ^a	0.70 (0.68;0.71)	0.70 (0.69;0.71)	—
Impact of allergy symptoms on academic productivity	0.71 (0.58;0.80)	0.40 (0.26;0.54)	0.43 (0.27;0.58)	0.37 (0.21;0.52)	0.51 (0.35;0.64)	0.56 (0.39;0.68)	0.50 (0.34;0.63)
Education hours missed	0.38 (0.23;0.52)	0.43 (0.26;0.56)	0.22 (0.05;0.38)	0.39 (0.21;0.55)	0.27 (0.11;0.42)	0.41 (0.24;0.55)	—

Repeated measures correlation – correlation coefficient (95% CI)

VAS education	—	0.41 (0.40;0.43)	0.58 (0.57;0.59)	0.27 (0.26;0.29) ^b	0.63 (0.62;0.64)	0.65 (0.64;0.66)	—
Impact of allergy symptoms on academic productivity	0.86 (0.65;0.95)	0.71 (0.34;0.89)	0.70 (0.32;0.88)	0.01 (-0.47;0.49)	0.62 (0.20;0.85)	0.74 (0.34;0.91)	0.30 (-0.21;0.68)
Education hours missed	0.04 (-0.44;0.51)	0.09 (-0.41;0.54)	0.03 (-0.46;0.50)	-0.11 (-0.56;0.39)	-0.17 (-0.60;0.34)	-0.10 (-0.60;0.46)	—

CI = Confidence Interval; CSMS = Combined Symptom-Medication Score; VAS = Visual Analog Scale

^a With self-reported asthma: 0.363 (95%CI=0.334;0.394) Without self-reported asthma: 0.079 (95%CI=0.060;0.100); ^b With self-reported asthma: 0.371 (95%CI=0.341;0.400) Without self-reported asthma: 0.233 (95%CI=0.211;0.254)

Limitations of the studies: Possibility of selection biases; sample mostly comprised of young adults; no access to patient-independent measures of academic performance.

13.2.2. WPAI-AS

A cross-sectional study using WPAI-AS allowed us to study academic absenteeism (hours of school or classes missed in the previous seven days due to allergies), presenteeism (perceived impact of allergy symptoms on academic productivity), and total time of school missed (absenteeism + presenteeism). These items were correlated with the control of the disease and multimorbidities using Bayesian methods, modelling the probability of losing one academic hour (Table 25). There was a highly significant difference depending on the control of the disease but no differences in rhinitis alone or rhinitis + asthma.

Table 25- Percentage of hours with academic impairment in allergic rhinitis (AR) according to weekly disease control (A) or comorbid status (B).

	Absenteeism	Presenteeism % — Median (P25-P75)	Total
A. Allergic disease control			
Well controlled	0.1 (0.0-1.7)	8.7 (1.8-24.0)	8.9 (1.7-25.6)
Uncontrolled	1.1 (0.0-13.5)	32.8 (15.4-55.4)	37.2 (14.7-63.9)
B. Comorbid status			
AR alone	0.1 (0.0-6.8)	26.5 (8.0-55.1)	30.0 (8.4-62.2)
AR + Asthma	0.1 (0.0-7.4)	26.7 (9.1-52.3)	31.3 (10.1-61.7)

P = Percentile of the posterior predictive distribution.

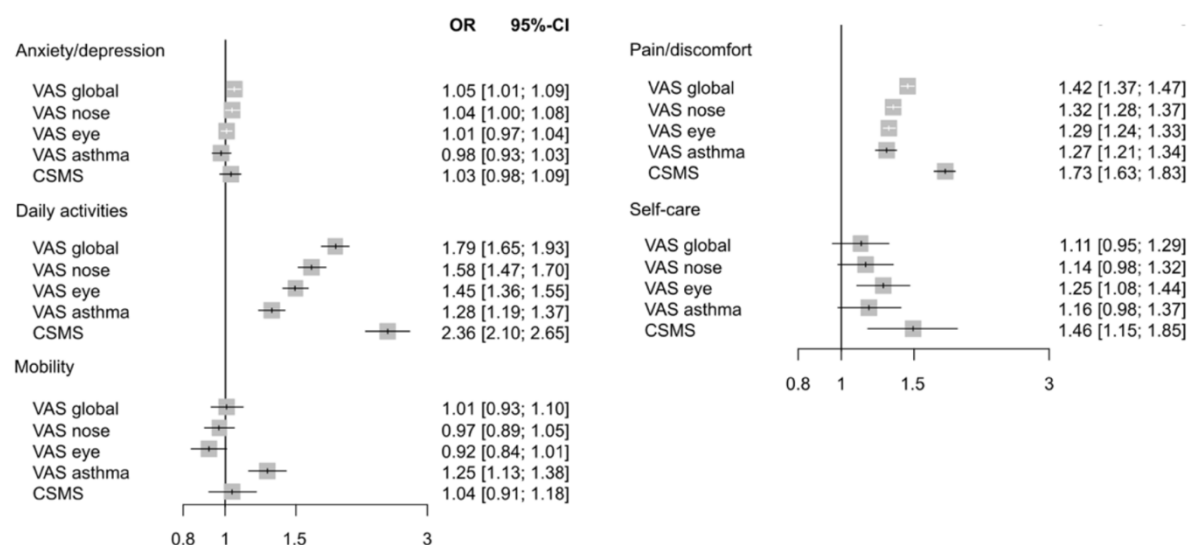
Limitations of the studies: Possibility of selection biases; small sample size; sample mostly comprised of young adults.

13.3. Generic quality-of-life and activity: EQ-5D and WPAI-AS

13.3.1. EQ-5D-5L domains

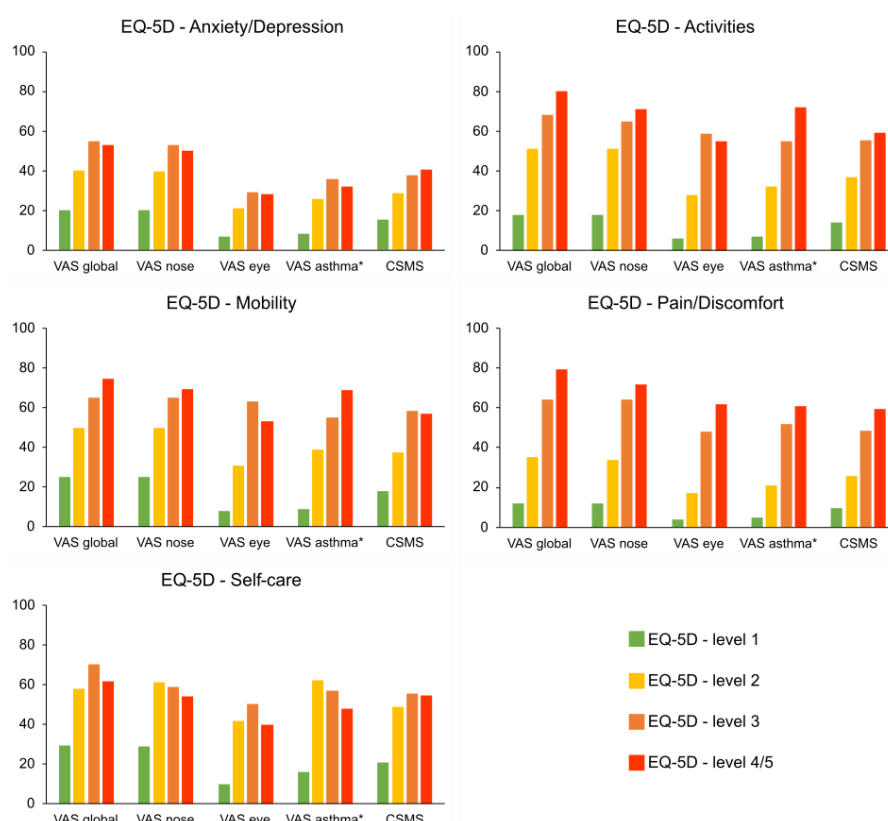
Very few studies in allergic rhinitis and asthma have assessed each of the five EQ-5D domains individually. A cross-sectional MASK-air[®] study assessed the association between rhinitis or asthma control and the different EQ-5D-5L domains in 5354 days from 3092 different users.¹⁰³ Mobility was particularly associated with VAS asthma (Figure 50). The expected differences in the EQ-5D “mobility” domain between VAS asthma and the other comparators strengthen the validity of VAS asthma.

Figure 50: EQ-5D-5L domains and different outcomes (N=5354) (from ¹⁰³)



Worse control of rhinitis, conjunctivitis or asthma (median VASs and CSMS) was associated with an impairment of EQ-5D levels. Mobility was particularly associated with VAS asthma (Figure 51). On the other hand, VAS asthma is less well correlated with the EQ-5D “daily activities” domain, in accordance with the results of the European Community Respiratory Health Study in QOL.²⁰²

Figure 51: VAS or CSMS levels depending on EQ-5D-5L levels (from ¹⁰³)

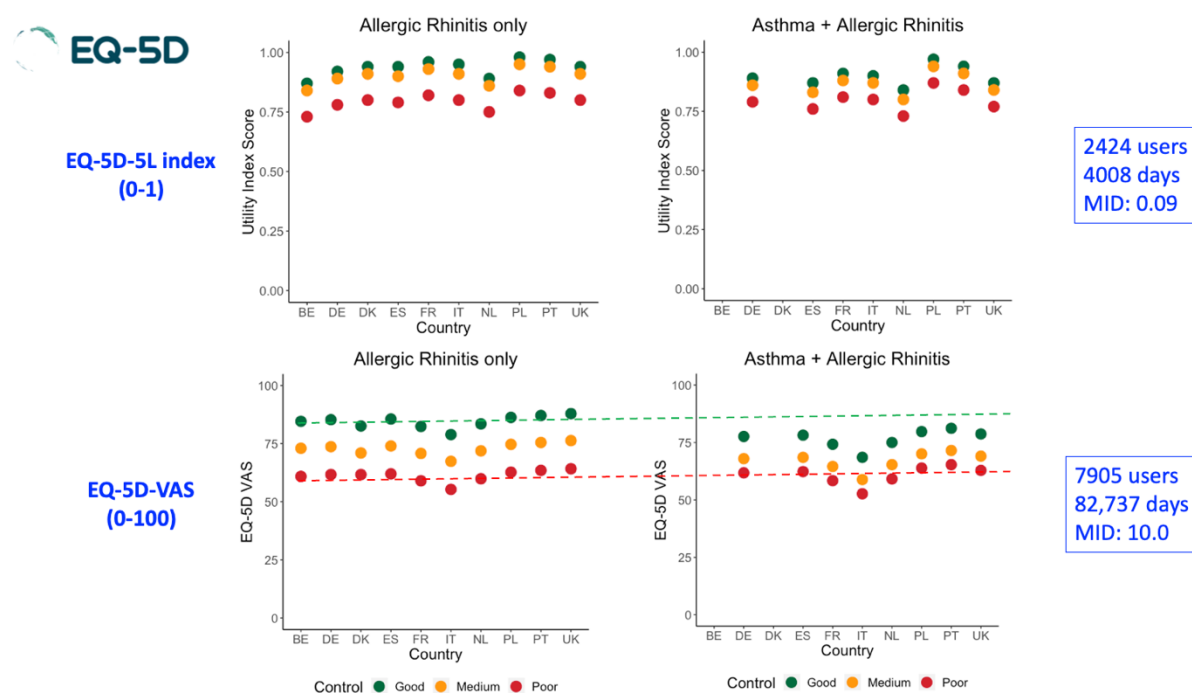


Limitations of the studies: Possible selection biases; EQ-5D is not allergy specific and may be affected by “non-allergic” comorbidities.

13.3.2. Impact of control on EQ-5D-5L utilities and VAS

In a cross-sectional study in European users, EQ-5D-5L utilities and VAS were compared with the control of the disease. Spearman rank test coefficients were correlated between (i) the EQ-5D utility index score or the EQ-5D VAS and (ii) symptom VAS (eye, nose and asthma). Each symptom VAS was characterised into “good”, “partial” and “poor” control (Figure 52).⁶ There were differences between rhinitis alone and rhinitis + asthma.

Figure 52: Differences in utilities and EQ-5D VAS levels associated with uncontrolled nose, eye and asthma symptoms in European countries



BE: Belgium, DE: Germany, DK: Denmark, ES: Spain, FR: France, IT: Italy, NL: The Netherlands, PL: Poland, UK: United Kingdom
MID: minimum important difference

Overall, poor control of any symptom was associated with decreased QoL assessed by either utility values or EQ-5D VAS. Poor control of eye and nose symptoms seems to have a similar impact on QoL in patients with AR alone and AR+asthma, underscoring the importance of controlling both ocular and nasal symptoms in patients with AR, while also considering and integrating patients' preferences into care⁸. The largest differences in QoL concerned comparisons between poor *versus* other levels of control for all symptoms, particularly for the EQ-5D VAS.

This study's limitations include the fact that mHealth users may not be representative of the general patient population. Another limitation is that AR is characterised by variable control levels across and within the same individual. To minimise this potential effect modification of AR control, analyses were performed with stratification by symptom control levels. Finally, utilities were estimated from EQ-5D-5L health profiles, instead of the standard gamble method.

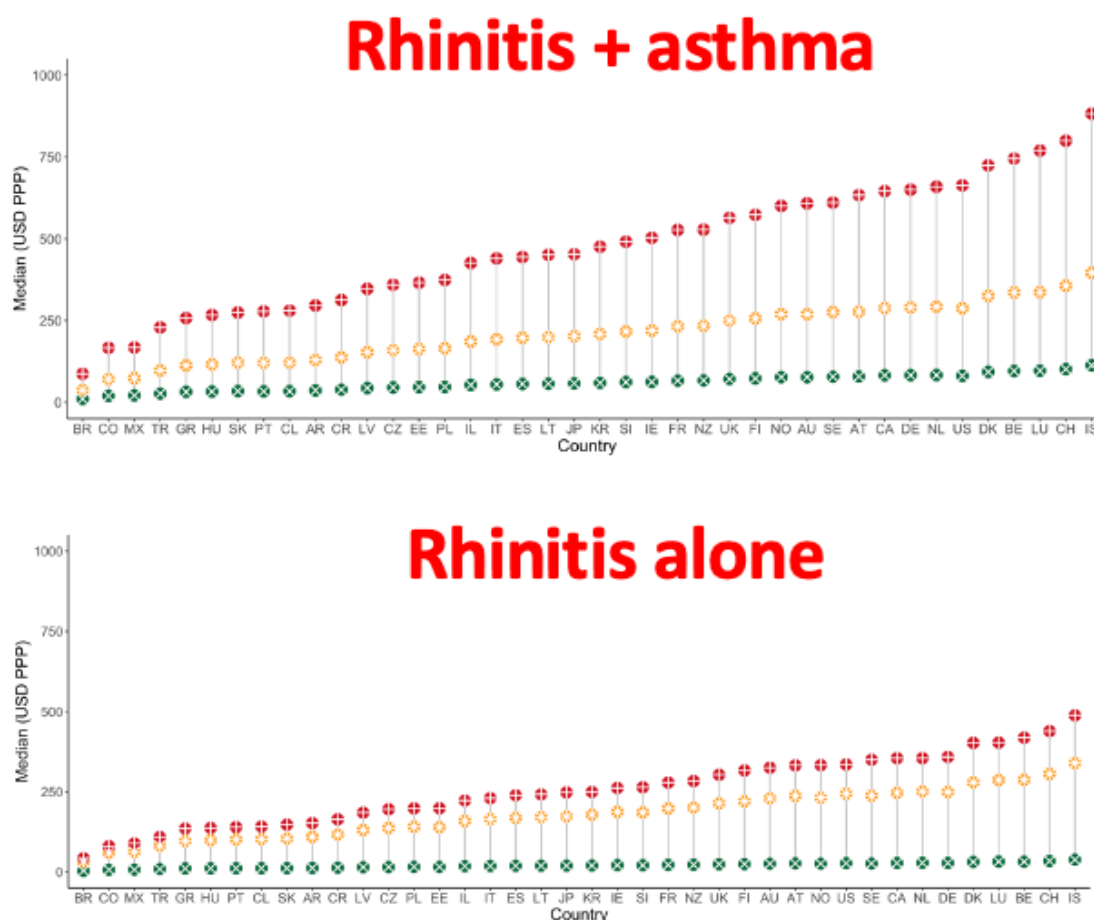
Limitations of the studies: For some countries, estimates of the prevalence of AR or asthma were unavailable in sufficient detail; “nonallergic” comorbidities were not assessed; small sample size for some countries (particularly Belgium and Denmark).

13.4. Economic impact

13.4.1. Weekly indirect costs estimated per country

The monetary impact (indirect costs) of AR was assessed on work productivity for all OECD countries and countries where MASK-air[®] is available by using the human-capital method (that is, by considering productivity to be measured by the wages received by a worker)²⁰³. They were estimated for each level of rhinitis control (defined using VAS data), and considering patients with and without asthma. In poorly controlled weeks, presenteeism was associated with indirect costs ranging from 65.7 US\$ purchase power parity (US\$ PPPs) (P25-P75=29.2-143.2) in Brazil to 693.6 US\$ PPP (P25-P75=405.2-1094.9) in Iceland. Patients with rhinitis + asthma showed higher overall work impairment than patients with AR alone, particularly in poorly controlled weeks (median work impairment in AR alone=39.1% [P25-P75=12.5-71.9%]; median work impairment in rhinitis + asthma =68.4% [P25-P75=54.6-80.2%]). Results per country are presented in Figure 53. Differences exist between rhinitis alone and rhinitis + asthma.

Figure 53: Median weekly costs of allergic rhinitis due to total work impairment (absenteeism and presenteeism) per country and level of rhinitis control for all patients with allergic rhinitis alone (A), and allergic rhinitis + asthma (B)



AR: Argentina, AT: Austria, AU: Australia, BE: Belgium, BR: Brazil, CA: Canada, CH: Switzerland, CL: Chile, CO: Colombia, CR: Costa Rica, CZ: Czech Republic, DE: Germany, DK: Denmark, EE: Estonia, ES: Spain, FI: Finland, FR: France, GR: Greece, HU: Hungary, IE: Ireland, IL: Israel, IS: Iceland, IT: Italy, JP: Japan, KR: South Korea, LT: Lithuania, LU: Luxembourg, LV: Latvia, MX: Mexico, NL: Netherlands, NO: Norway, NZ: New Zealand, PL: Poland, PT: Portugal, SE: Sweden, SI: Slovenia, SK: Slovakia, TR: Turkey, UK: United Kingdom, US: United States.

Well controlled impaired control uncontrolled

Limitations of the study: Since MASK-air does not collect information on income or occupation, the indirect costs of AR were modelled based on the human capital method considering mean and median wages for each country; fringe costs were not considered.

13.4.2. Estimating work-related indirect costs in allergic rhinitis and asthma using daily combined symptom-medication score

Allergic rhinitis and asthma can impair work productivity. VAS work (work productivity) correlated with WPAI:AS. We then quantified how allergy control relates to work impairment and indirect costs using a cross-sectional study. We estimated the cost of CSMS and e-DASTHMA induced by loss of work productivity using mixed-effects linear regression models. Each 1-point increase in CSMS and e-DASTHMA was associated with mean 0.97 and 0.79-point increases in VAS work (Table 26).

Table 26. Daily estimated indirect costs associated (i) with a 1-point increase in CSMS or e-DASTHMA) and (ii) with well-, partially, and poorly controlled disease as assessed by CSMS or e-DASTHMA.

Country	Median 1-point cost (USD) (P25–P75)	Daily estimated indirect costs		
		Good control (USD) – Median (P25-P75)	Partial control (USD) – Median (P25-P75)	Poor control (USD) – Median (P25-P75)
A. Values based on allergic rhinitis control (combined symptom medication score)				
Australia	1.70 (1.12-2.50)	3.9 (0-14.7)	36.7 (18.7-66.0)	80.9 (46.3-135.0)
Brazil	0.13 (0.06-0.23)	0.2 (0-1.1)	2.6 (1.1-5.9)	5.8 (2.6-12.3)
Canada	1.60 (1.17-2.19)	3.9 (0-14.1)	35.8 (19.3-61.0)	78.4 (48.1-122.3)
France	1.14 (0.75-1.85)	2.7 (0-10.6)	26.2 (13.1-48.5)	57.2 (32.2-98.3)
Germany	1.52 (1.09-2.09)	3.7 (0-13.1)	33.4 (18.0-56.7)	72.9 (44.8-113.3)
Italy	0.86 (0.53-1.38)	1.9 (0-7.7)	19.2 (9.4-36.0)	41.8 (23.1-72.7)
Japan	0.86 (0.60-1.20)	2.1 (0-7.5)	19.0 (10.2-32.4)	41.7 (25.5-65.3)
Mexico	0.28 (0.18-0.45)	0.6 (0-2.4)	6.1 (3.1-11.1)	13.3 (7.5-22.7)
Portugal	0.48 (0.27-0.88)	1.0 (0-4.3)	10.2 (4.6-21.0)	22.5 (11.3-43.1)
Spain	0.82 (0.56-1.26)	1.9 (0-7.3)	18.4 (9.4-32.7)	39.9 (23.3-66.0)
United Kingdom	1.49 (0.99-2.17)	3.4 (0-13.1)	32.5 (16.8-57.9)	72.1 (41.8-117.1)
United States	2.04 (1.14-3.72)	4.1 (0-18.1)	43.3 (19.6-89.9)	95.9 (47.3-183.8)
B. Values based on asthma control (electronic daily asthma score)				
Australia	1.39 (0.91-2.05)	9.1 (0-27.3)	36.2 (17.4-68.3)	63.6 (30.1-114.6)
Brazil	0.11 (0.05-0.19)	0.6 (0-2.2)	2.5 (1.0-5.9)	4.3 (1.7-9.9)
Canada	1.31 (0.95-1.79)	9.0 (0-25.8)	35.1 (18.0-62.1)	62.3 (30.7-106.3)
France	0.93 (0.62-1.51)	6.5 (0-19.5)	26.0 (12.4-49.4)	44.6 (21.2-83.0)
Germany	1.25 (0.89-1.71)	8.4 (0-23.9)	32.8 (16.6-58.1)	58.4 (29.2-98.2)
Italy	0.71 (0.43-1.12)	4.7 (0-14.4)	18.5 (8.7-36.1)	32.5 (15.1-61.8)
Japan	0.71 (0.50-0.98)	4.8 (0-13.8)	18.6 (9.5-33.5)	33.3 (16.3-56.4)
Mexico	0.23 (0.14-0.36)	1.5 (0-4.6)	6.1 (2.9-11.4)	10.5 (5.0-19.3)
Portugal	0.39 (0.22-0.72)	2.4 (0-8.1)	10.0 (4.3-21.2)	17.4 (7.6-36.2)
Spain	0.68 (0.46-1.03)	4.5 (0-13.5)	18.0 (8.9-33.2)	31.6 (15.3-56.5)

United Kingdom	1.21 (0.81-1.77)	8.0 (0-23.9)	32.4 (15.8-60.2)	56.3 (27.4-100.3)
United States	1.66 (0.93-3.04)	10.1 (0-34.4)	43.0 (18.4-90.8)	73.8 (31.8-155.6)

P25-P75=Percentiles 25-75; USD=US Dollar. Values are expressed in US Dollars without adjustment for power purchase.

14. Planetary Health and climate change

14.1. Planetary Health

In December 2019, a conference entitled "Europe That Protects: Safeguarding Our Planet, Safeguarding Our Health" was held in Helsinki. It was co-organised by the Finnish Institute for Health and Welfare, the Finnish Environment Institute and the European Commission, under the auspices of Finland's Presidency of the EU.^{204,205} As a side event, a symposium organised as the final POLLAR (Impact of air POLLution on Asthma and Rhinitis) meeting explored the digital transformation of health and care to sustain planetary health in airway diseases.¹³⁵ The Finnish Allergy Programme²⁰⁶ collaborates with MASK and can be considered as a proof-of-concept to impact Planetary Health.

14.2. CATALYSE (Horizon Europe)

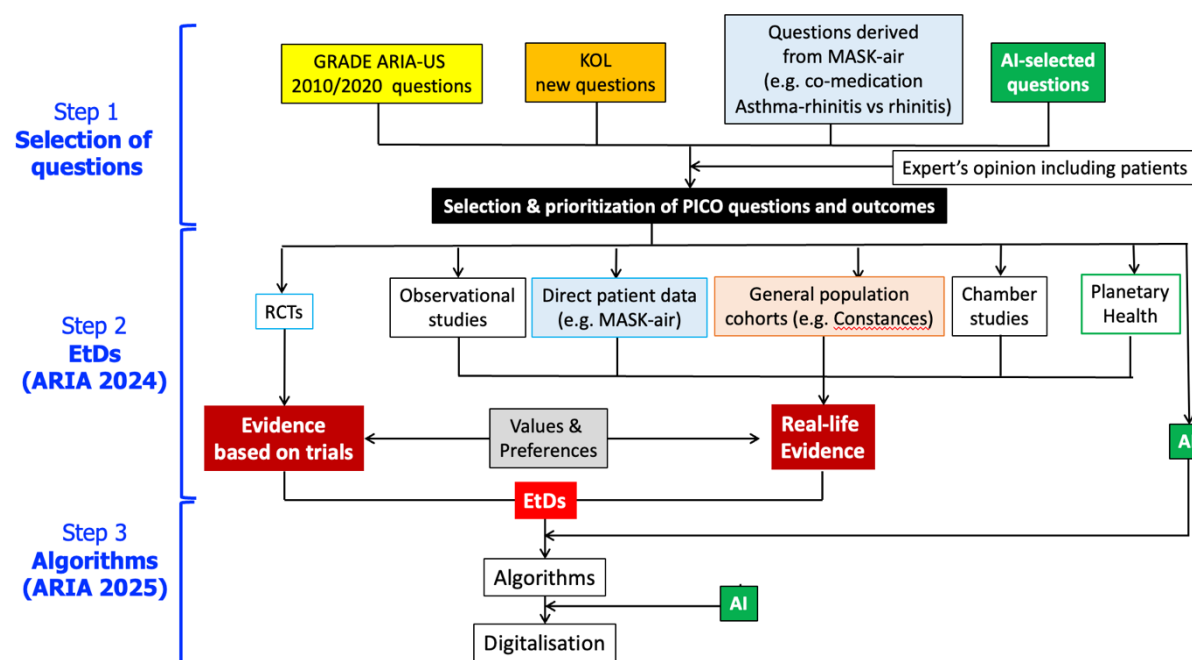
A new Horizon Europe grant started in September 2022 in order to better understand climate change and how to counteract it. Pollens were selected as one of the indicators of climate change. In collaboration with the FMI and Porto University, MASK-air® will be used to correlate pollen counts with the clinical impact. For this project, preliminary methodologic studies are undergoing that will help to better assess the impact of the pollen season on symptoms.²²

The integration of information technology tools for climate, weather, air pollution and aerobiology in MASK-air® will enable the development of an alert system. Citizens will thus be informed about personal environmental threats, which may also be linked to indicators of Planetary Health and sustainability.

15. ARIA 2024 guidelines

ARIA has evolved from a guideline using the best evidence-based approach (GRADE)¹⁶³ to integrated care pathways using mobile technology in patients with allergic rhinitis (AR) and asthma multimorbidity.²⁰⁷ The proposed next phase of ARIA is change management.¹⁶⁷ The aim of this phase is to provide an active and healthy life to patients with rhinitis and to those with asthma multimorbidity across the lifecycle, irrespective of their sex or socioeconomic status, to reduce health and social inequities incurred by the disease. ARIA will follow the 8-step model of Kotter (i) to assess and implement the effect of rhinitis on asthma multimorbidity and (ii) to propose person-centred, digitally enabled, artificial intelligence-assisted guidelines (Figure 54). MASK-air® data will be used to develop PICO (patient/population, intervention, comparison and outcomes) questions and recommendations on real-world data to triangulate RCTs.

Figure 54: Stepwise approach for the development of ARIA 2024 recommendations (from²⁰⁸)



AI: Artificial intelligence, KOL: Key opinion leaders, RCT: Randomised controlled trials, EtDs: Evidence to decision

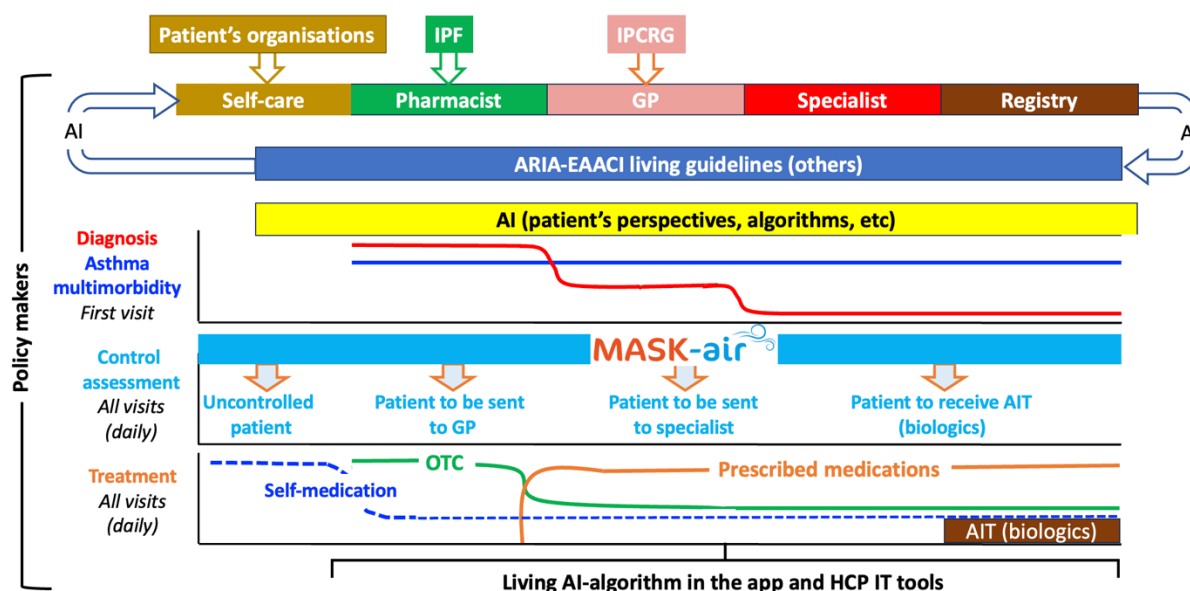
16. Person-centred, digitally enabled and artificial intelligence-assisted change management in airway diseases: An OECD Best Practice for integrated care for chronic diseases

Up until 2017, ARIA® was a guideline using the best evidence (Grading of Recommendations, Assessment, Development and Evaluation, GRADE) and developed as a change management strategy (CM).

A CM strategy in collaboration with the European Academy of Allergy and Clinical Immunology (ARIA-EAACI) was developed as a person-centred, digitally enabled, AI-assisted care with strong political involvement (Bousquet et al., in press). The digital tools of ARIA are mainly based on MASK-air®, an OECD Best Practice for integrated care for chronic diseases. Artificial intelligence was used, in particular, to approach patients' views and expectations. The steps to build and achieve a new CM strategy were based on the Kotter's stepwise approach.²⁰⁹ They include (i) the development of ARIA® 2024-2025 guidelines, (ii) the new ARIA-MeDALL classification of single and multimorbid airway diseases and (iii) embedding MASK-air® in a registry for severe allergic diseases. The ultimate goal of the ARIA-EAACI CM strategy will be the transformation of health and care in R and R+A multimorbidity, the development of novel person-centred guidelines and policies in a cost-effective manner improving shared-decision-making.

MASK-air® will be used as the central tool integrating patients, HCPs, primary care physicians and specialists for a better integration of care (Figure 55).

Figure 49: Person-centred, digitally enabled, AI-assisted care pathways based on ARIA-EAACI guidelines using MASK-air® as a common tool: OECD Best Practice



17. Policy agenda

Building an alliance among patients, healthcare providers and policy makers is therefore essential to save healthcare costs and provide better care for the patients. Healthcare providers or insurers could provide a financial reward for patients with chronic disease using digital health tools or HCPs.ALB

It is of upmost importance to transfer the knowledge of any person-centred care approach to policy makers. ARIA has already been involved in several initiatives to inform policy makers ²¹⁰⁻²¹².

In a 2023 report of the Organisation for Economic Coordination and Development (OECD) on Best Practices for Integrating Care to Prevent and Manage Chronic Diseases, an app on rhinitis and asthma (MASK-air[®]) was listed. The OECD is a reliable source of evidence-based policy analysis and economic data largely used by governments. It has published several BPs on Public Health. On the 10th of May 2023, the OECD published 13 BPs for Integrating Care to Prevent and Manage Chronic Diseases in the European Union. The report did not cover all models of integrated care, rather, it *“focuse(d) on those that are of key strategic interest to policy makers.”* New MASK-air[®] studies (not published in the report) include equity, usability of the app in old age adults, economic impact, quality-of-life and allergen immunotherapy.

MASK-air[®] has already been approved by the Ministries of Health of Ukraine (March 2023) and Poland (May 2024). In January 2025, it was referenced by the French MoH and National Fund (CNAM) on the *“Mon Espace Santé”*.

18. Equity and UCRAID: Ukrainian Citizen and Refugee Electronic Support in Respiratory, Allergy, Immunology and Dermatology action plan

A special effort needs to be undertaken to globalise care pathways. The first ARIA report involved low- and middle-income countries.²¹³ A specific group of members of developing countries **will be involved have been included in ARIA 2024.** **ALB** Smartphone ownership is growing rapidly around the world. In 2015, there were more than 7 billion mobile telephone subscriptions across the world, over 70% of which were in low- or middle-income countries²¹⁴. The joint WHO-ITU (International Telecommunication Union) initiative “Be He@lthy, Be Mobile” for the prevention and management of noncommunicable diseases, their comorbidities and their risk factors, including improving disease diagnosis and tracking, is of great importance. MASK is one of the examples of the “Be He@lthy, Be Mobile” handbook on how to implement mBreatheFreely for asthma and COPD.²¹⁵

OECD specifically identified MASK-air[®] as an equity-enhancing app given that it is available in 30 countries, and pointed out that MASK-air[®] “*offers the same level of care for AR and asthma to people across the world.*”

Eight million Ukrainians have taken refuge in the European Union. Many have asthma and/or allergic rhinitis and/or urticaria, and around 100,000 may have a severe disease. Cultural and language barriers are a major obstacle to appropriate management. Two mHealth apps - MASK-air[®] (Mobile Airways Sentinel Network), for the management of rhinitis and asthma and CRUSE[®] (Chronic Urticaria Self Evaluation) for CSU patients - are available in many countries and languages. The Ukrainian patients fill in the questionnaires and daily symptom-medication scores for asthma, rhinitis (MASK-air) or urticaria (CRUSE) in Ukrainian. Following the GDPR, patients grant their physician access to the app by scanning a QR code displayed on the physician’s computer enabling the physician to read the app contents in his/her own language. This service is available freely. It takes less than a minute to show patient data to the physician in the physician’s web browser. UCRAID - developed by ARIA (Allergic Rhinitis and its Impact on Asthma) and UCARE (Urticaria Centers of Reference and Excellence) - is under the auspices of the Ministry of Health of Ukraine as well as European (European Academy of Allergy and Clinical immunology, EAACI, European Respiratory Society, ERS, European Society of Dermatologic Research, ESDR) and national societies.

Conclusions

Current digital health tools such as MASK-air[®] were developed initially for rhinitis and asthma. However, the technology itself is generic and can be applied to other diseases (e.g. Chronic Urticaria Self Evaluation [CRUSE] mobile app in urticaria).⁶ The digital tool allows patients to be guided for an integrated care pathway supporting them in adapting the medication based on symptom load but also to allow better SDM. The success strongly depends on the patients' adherence, particularly among the elderly, to these digital tools.

Overall, the innovations of MASK-air[®] are summarised in Table 27.

Table 27: Innovations of MASK-air[®]

1. Allergic rhinitis

i. When the full database is analysed, most patients:

- are not adherent¹²⁰ and do not follow guidelines,
- use as-needed treatment,^{124,216}
- often use over-the-counter medications,
- do not take medication when feeling healthy,^{124,216}
- increase their treatment based on symptoms similarly in all European countries,¹²⁴ irrespective of the culture¹³⁶ and the treatments bought in the pharmacies,^{124,140}
- do not use the recommended treatment.

Moreover,

- Control (symptoms, work productivity, educational performance) is not necessarily improved by increasing medications, including co-medication.^{47,113,122-124}
- Co-medication of an intra-nasal and oral medication is usually associated with worse control than a single medication (cross-sectional and longitudinal analyses).^{47,113,122-124}
- Medication satisfaction is reduced on days with co-medication by comparison to monotherapy.

Overall, patients treat themselves when they are not well, self-medicate, and increase their medications when their symptoms are not controlled, showing that they do not follow guidelines and physician's prescriptions.

ii. When patients adherent to the app are analysed:

4. They are also often adherent to medications, and adherence to the app appears to be associated with adherence to medications.
5. But, except for INCS, increased adherence is not associated with an increased level of control.
6. In patients with an adherence level over 80%, INCS are more effective than AzeFlu for nasal but not ocular symptoms. For an adherence level under 80%, AzeFlu is more effective.
7. Most studies were cross-sectional and confirmed by longitudinal studies.⁹⁸
8. Switching of medications is common (longitudinal analyses).⁹⁸

iii. A CSMS has been validated under the auspices of EAACI and ARIA.¹⁸

2. Allergen-specific immunotherapy

- Evidence regarding the efficacy of allergen immunotherapy (AIT) on AR has been provided mostly by RCTs. A MASK-air[®] pilot study showed that AIT improved symptoms and work productivity.¹³²
- Using a Bayesian model, sublingual was found to be more effective than subcutaneous immunotherapy on VAS symptoms, VAS work and CSMS.¹⁰²
- AIT is likely to have an effect that differs from pharmacotherapy as shown by the effects on education.¹³
- MASK-air[®] was considered as a PCC for AIT.⁴⁰

3. Asthma

i. When patients adherent to the app are analysed (longitudinal studies):

- 3- Adherence to ICS or ICS-LABA was high (56.3-81.2% days).
- 4- Adherence was higher for ICS+other LABA than for ICS+formoterol (ICS+F). However, control was similar in both groups, ICS+F was associated with a meaningful lower SABA use and with similar VAS asthma, e-DASTHMA or VAS work.
- 5- Overall, increased adherence to either ICS+F or ICS+other LABA was associated with decreased SABA use.
- 6- For a drug or a drug class, co-medication days were less well controlled than days with single medication (fixed dose combination therapy considered as single medication).
- 7- A longitudinal observational study was carried out on asthmatic patients who filled at least 26 days in the first month of reporting the MASK-air® app and received a treatment with ICS or ICS/LABA. Based on control, adherence to ICS±LABA, short-acting β -agonist use and biologics as well as long-acting anti-muscarinics, six distinct groups of different clinical relevance were retrieved in patients who used the same treatment (non-switchers).

ii. Severe asthma

- Applicability of the MASK-air® app was explored in severe asthmatic patients in a longitudinal (observational) study. Highly variable trends were found for VAS asthma, and asthma remission can be assessed using daily e-DASTHMA and VAS asthma.

iii. e-DASTHMA has been validated under the auspices of EAACI and ARIA. ⁷⁵

iv. Risk factors: Info-epidemiology studies have been carried out to assess the risk factors for asthma exacerbations and can be added to MASK-air® (e.g. rhinovirus ⁵³). Pollen and pollution are already embedded in MASK-air® for Europe. ^{21,35,76}

4. Towards personalised medicine: MASK-air® realises a bridge between clinical practice, randomised controlled trials and real-life observations, enabling a strategy for personalised medicine.

The global applicability of MASK-air is summarised in Table 28.

Table 28: Global applicability of MASK-air® (adapted from ⁹)

Applicability	MASK-air®
Patient empowerment and engagement	• Self-management: The patient takes control of his/her own disease to improve autonomy because: ○ Better understanding of the symptoms ○ Aerobiology (pollen and pollution) data embedded in control ○ Improved adherence • MASK-air® as a medical device (MDR class IIa) has the potential to link patients, counselling (messaging and warnings) and physician advice.
Clinical practice	• MASK-air® provides support tools for doctors to assess daily symptoms and adjust treatment. • MASK-air® is an essential tool in providing personalised medicine in AR and asthma. • Optimised shared-decision making. Physicians will be able to read the daily files of the patients in order to: • Assess exacerbations and their link with pollen and pollution. • Assess and increase the adherence to treatment. • Daily assess patients' satisfaction to the treatment. • Optimise treatment for the patient and, in particular, the current or the next pollen season. • Prescribe allergen immunotherapy (AIT) more rapidly when the patient is not controlled despite optimal pharmacologic treatment and determine AIT efficacy. • Assess and manage severe asthma.

	Implement global strategies based on local data and specific patterns of each region.
Registries	- Daily symptom-medication scores, adherence and satisfaction are of great interest for registries. - MASK-air® may become the link between different registries (common tool used in different languages)
Cost-effectiveness and indirect societal costs	- Several tools in MASK-air® can be used for costs (work productivity, WPAI-AS, daily medication costs) and utilities (EQ-5D). - Identify the most effective treatment strategy based on real-life data, taking into account adherence and treatment persistence. - Using real-life data from MASK-air® provides added value by making the pharmacoeconomic simulation more accurate and reliable.
Clinical trials	- MASK-air can help design and conduct "remote" studies, which can cut the cost of new drug (or AIT) development and reach a more diverse population. For RCTs, it is essential to have clarity on definitions and relevant tools. MASK-air® enables: - Better stratification of the patients needing treatment, both in terms of predicted response (stratification by effect modification) and better qualifiers/characteristics and outcomes to be measured in trials (better profiling). - Assessment of the onset and magnitude of treatment efficacy during the trial. - Assessment of the efficacy when the treatment is stopped. Observational studies in real life: - Are of key importance to fine-tune RCTs. - Can compare different treatment strategies. - Provide insight into delivery of care in routine practice to all patients. - Can provide answers to questions that have not or cannot be evaluated in RCTs, especially effectiveness on a longer timescale. - Can reflect changes of attitude to treatment over time in a rapidly changing overall medical landscape. - Can include cost-effectiveness. - Develop new hypotheses for the treatment of AR and asthma.
Registration and reimbursement of treatments	- Better understanding of direct and indirect costs - Controlled trials designed with a uniform approach will be more easily evaluated by easily evaluated by the Health Technology Assessment agencies (such as NICE) for reimbursement. MASK-air® uses EQ-5D, a validated measure of utility
Public health planning	For public health purposes, a perfect patient characterisation in real life is needed to identify the prevalence, burden and costs incurred by patients in order to improve quality of care and optimise healthcare planning and policies.
Reduction of inequities	Inequities still exist in the EU for the prevalence and burden of allergic diseases (not only sex/gender inequities). In deprived areas, asthma is often severe. OECD specifically identified MASK-air® as an equity-enhancing app.
Employers	- AR and asthma represent a major burden for employers, and the estimated annual costs in the EU range from 30 to 60 B€. Better control of the disease was shown to reduce costs. MASK-air® has the potential to improve the control of allergic diseases and asthma and to significantly improve work productivity at the EU level. - MASK-air® as an MDR class IIa may help to propose and implement preventive strategies of occupational diseases.
Guideline development	Real-life data of MASK-air® represent an asset for ARIA 2024.
Research on mechanisms and genetics	A uniform definition and a collaborative approach to research - including genetic and mechanistic research - are important and will be enhanced by the stratification of patients using MASK-air®.

	• Different levels of phenotype characterisation (granularity) can be applied to assess phenotypic characterisation in different groups of patients (e.g. rhinitis alone and rhinitis and asthma) including gender and old-age patients.
Epidemiology	• In epidemiologic population studies, standardised definitions and tools are fundamental. MASK-air® allows novel approaches combining classical cross-sectional and longitudinal studies with real-life studies in large populations. • MASK-air® may become the link between different epidemiologic studies.
Humanitarian actions	• UCRAID: Ukrainian Citizen and Refugee Electronic Support in Respiratory, Allergy, Immunology and Dermatology action plan. • From UCRAID to travels.
From MASK-air® to symptomatic chronic diseases	• The MASK approach is a prototype of digital health for symptomatic chronic diseases without objective measurements (e.g. arterial pressure, glycemia).

MASK-air® is an essential component of change management in allergic rhinitis.

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