Cut-off values of MASK-air® Patient-Reported Outcome Measures (PROMs)

Short-title: Cut-off values in allergic diseases

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Conflicts of Interest:

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Dr. Bosnic-Anticevich reports grants from TEVA, personal fees from TEVA, personal fees from TEVA, personal fees from AstraZeneca, personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Boehringer Ingelheim, personal fees from GSK, personal fees from Sanofi, personal fees from Mylan, outside the submitted work.
Dr. Bousquet reports personal fees from Cipla, Menarini, Mylan, Novartis, Purina, Sanofi-Aventis, Teva, Uriach, other from KYomed-Innov, other from Mask-air-SAS, outside the submitted work.
Dr. Canonica reports grants from Menarini, grants from AstraZeneca, grants from Glaxo Smith Kline, grants from Sanofi, grants from Genzyme/Regeneron, grants from Stallergenes, outside the submitted work.
Dr. Cardona reports personal fees from ALK, personal fees from Allergopharma, personal fees from GSK, grants from Thermofisher, outside the submitted work.
Dr. Cecchi reports personal fees from Thermofisher, personal fees from Astra Zeneca, personal fees from Sanofi, personal fees from Novartis, outside the submitted work.
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Dr. Devillier reports personal fees and non-financial support from Astra Zeneca, personal fees from Chiesi, personal fees and non-financial support from Boehringer Ingelheim, personal fees from GlaxoSmithKline, personal fees from Menarini, personal fees and non-financial support from Stallergenes, personal fees and non-financial support from ALK Abello, personal fees from IQVIA, outside the submitted work.
Dr. Gemicioglu reports grants from AstraZeneca, grants from Sanofi, grants from Deva, grants from Abdi Ibrahim, grants from Sandoz, grants from GSK, grants from Chiesi, grants from Novartis, outside the submitted work.
Dr. Haahtela reports personal fees and other from Orion Pharma, outside the submitted work.
Dr. Ivancevich reports personal fees from Laboratorio Casasco, personal fees from Abbott Ecuador, personal fees from Laboratorio Bago Bolivia, outside the submitted work.
Dr. Kuna reports personal fees from Adamed, personal fees from Berlin Chemie Menarini, personal fees from Boehringer Ingelheim, personal fees from AstraZeneca, personal fees from Glenmark, personal fees from Krka,

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Dr. Kvedariene reports other from Norameda, other from BerlinChemie Menarini, outside the submitted work.
Dr. Larenas Linnemann reports personal fees from ALK, Allakos, Amstrong, Astrazeneca national and global, Chiesi, DBV Technologies, Grunenthal, GSK national and global, Mylan/Viatris, Menarini, MSD, Novartis, Pfizer, Sanofi, Siegfried, UCB, Carnot, grants from Abbvie, Lilly, Sanofi, Astrazeneca, Lilly, Pfizer, Novartis, Circassia, UCB, GSK, Purina institute., outside the submitted work.
Dr. Louis reports and Grants from GSK, Chiesi and AZ and adboard and lecture fees from AZ, GSK, Chiesi.
Dr. Makris reports personal fees from NOVARTIS, personal fees from MENARINI, personal fees from GSK, personal fees from ASTRA ZENECA, personal fees from SANOFI, personal fees from PFIZER, personal fees from CHIESI, outside the submitted work.
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The other authors have nothing to disclose, outside the submitted work.

Abstract

Background: In clinical and epidemiological studies, cut-offs of Patient-Reported Outcome Measures (PROMs) can be used to classify patients into groups of statistical and clinical relevance. However, visual analog scale (VAS) cut-offs in MASK-air® have not been tested.

Objective: To calculate cut-offs for VAS global, nasal, ocular, and asthma symptoms.

Methods: In a cross-sectional study design of all MASK-air® participants, we compared (i) approaches based on the percentiles (tertiles or quartiles) of VAS distributions, and (ii) data-driven approaches based on clusters of data from two comparators (VAS work and VAS sleep). We then performed sensitivity analyses for individual countries and for VAS levels corresponding to full allergy control. Finally, we tested the different approaches using MASK-air® real-world cross-sectional and longitudinal data to assess the most relevant cut-offs.

Results: We assessed 395,223 days from 23,201 MASK-air® users with self-reported allergic rhinitis. The percentile-oriented approach resulted in lower cut-off values than the data-driven approach. We obtained consistent results in the data-driven approach. Following the latter, the proposed cut-off differentiating "controlled" and "partly-controlled" patients was similar to the cut-off value which had been arbitrarily used (20/100). However, a lower cut-off was obtained to differentiate between "partly-controlled" and "uncontrolled" patients (35 *versus* the arbitrarily-used value of 50/100).

Conclusion: Using a data-driven approach, we were able to define cut-off values for MASK-air® VASs on allergy and asthma symptoms. This may allow for a better classification of rhinitis and asthma patients according to different levels of control, supporting improved disease management.

Highlights

What is already known about this topic? Visual analog scales are patient-reported outcome measures which have been widely used to monitor allergic rhinitis and asthma control. Their validity and reliability have been assessed.

What does this article add to our knowledge? Using a data-driven approach, this study identified cut-offs for visual analog scales assessing allergic rhinitis and asthma control.

How does this study impact current management guidelines? The identified cut-offs allow for an improved classification of rhinitis and asthma patients according to different levels of control, supporting a better disease management.

Key words: rhinitis, asthma, conjunctivitis, cut-offs, MASK-air

Abbreviations

AUC-ROC: Area under the receiver operating characteristic
CARAT; Control of Allergic Rhinitis and Asthma Test
GDPR: General Data Protection Regulation
INAH: Intranasal antihistamines
ICS: Inhaled steroids
INCS: Intranasal steroids
LABA: Long-acting beta-agonists
LAMA: Long-acting muscarinic antagonists
MDR: Medical Device Regulation
OAH: Oral antihistamines
PROMs: Patient-reported outcome measures
SABA: Short-acting beta-agonists
VAS: Visual analog scales
WHO: World Health Organization

Introduction

Portable devices, such as smartphones and mobile Internet access, have become ubiquitous in the last decades, and their application to rhinitis and asthma widespread.[1] However, few apps have been validated.[2] The MASK-air® (Mobile Airways Sentinel NetworK for airway diseases) app is a Good Practice of DG Santé for digitally-enabled, patient-centered care in rhinitis and asthma multimorbidity.[3-5] It can be downloaded freely from the Google Play and Apple App Stores in 27 countries (www.mask-air.com). In MASK-air®, patients report their daily symptoms through visual analog scales (VASs) for overall, nasal, ocular, and asthma symptoms (Table E1). These VASs therefore represent patient-reported outcome measures (PROMs)[6] and may be understood as digital biomarkers.

In clinical and epidemiological studies, PROMs can be used to classify patients into groups of statistical and clinical relevance. Patient classification into groups based on the value of a PROM (cut-off) may help in the decision to provide different care or procedures. The MASK-air® cut-offs for the different MASK-air® VASs have been arbitrarily defined according to (i) the World Health Organization (WHO) definition of cut-offs for the International Classification of Functioning, Disability and Health ICF grading[7], and (ii) the results of a large study assessing VAS cut-offs in ARIA (Allergic Rhinitis and its Impact on Asthma) classes.[8] Four classes of control and the respective cut-offs have been defined for all four symptom VASs: 0/100 (full control), 1-19/100 (good control), 20-49/100 (partial control) and ≥50/100 (poor control). However, cut-off values should be validated, and there may be differences in cut-offs between VASs.

There are two statistical approaches for determining a cut-off value: percentile-oriented (i.e., "PROM distribution-oriented") and outcome-oriented. The percentile-oriented approach splits a continuous marker according to percentiles of data distribution or to the arithmetic or geometric means of PROM values. In contrast, the outcome-oriented approach selects the PROM cut-off that considers the association between outcome and PROM. The outcome-oriented approach is expected to provide a better cut-off value than the percentile-oriented approach,[9] but requires a gold-standard outcome measure. In the absence of such an outcome, analogous data-driven approaches can be used.

In this study, we aimed: (i) To calculate cut-offs for VAS global, nasal, ocular, and asthma symptoms in order to propose a better discriminative value for cut-off points. We compared data-driven[10,11] and percentile-oriented approaches in a cross-sectional study design. (ii) To perform sensitivity analyses for individual countries and for VAS levels corresponding to full allergy control. (iii) To test the different approaches using MASK-air® real-world data in order to assess the most relevant cut-offs.

Methods

1- Study design

We assessed different approaches for the estimation of cut-offs for MASK-air® symptom VASs. We first followed the percentile-oriented approach based on the percentiles (tertiles or quartiles) of VAS distributions. We then followed a machine learning data-driven approach based on clusters of data from two comparators (comparator VASs: VAS work and VAS sleep). We performed sensitivity analyses for individual countries and for different symptom VAS levels corresponding to full allergy control, and tested the obtained cut-offs according to data on medication use and seasonality.

2- Setting and participants

MASK-air® has been launched in 27 countries (www.mask-air-com). It has been freely available in the Google Play and Apple App Stores since 2015.

In this study, we included data from MASK-air® users from May 21, 2015 to December 2021. The users (i) had a self-reported diagnosis of allergic rhinitis, and (ii) were ranging in age from 16 to 90 years (or lower than 16 years in countries with a lower age of digital consent).[12] For the identification of VAS asthma cut-offs, we considered only participants with self-reported asthma.

3- Ethics

MASK-air® is CE1 and Medical Device Regulation (MDR) class IIa registered. It follows the European Union General Data Protection Regulation (GDPR) for privacy.[13] An independent review board approval was not required for this specific study as all data were anonymized prior to the study using k-anonymity (transformation of data to hamper the determination of the identity of the individuals in a dataset; [14] for a description of the application of such methods to MASK-air® geolocation data using the GDPR, please check Samreth et al.)[15], and users agreed to the analysis of their data in the terms of use (translated into all languages and customized according to the legislation of each country, allowing the use of the results for research purposes).

4- Data sources and variables

MASK-air® comprises mandatory daily monitoring questions whose responses are provided by means of four symptom VASs on overall, nasal, ocular, and asthma symptoms (Table E1).[16] VASs are reported on a 0 to 100 scale (with higher values indicating worse symptoms). In addition, the daily monitoring questionnaire comprises two VASs (comparator VASs) assessing the impact of allergic symptoms on sleep and on work (if users report to be working on that day). Then, users are asked to

provide their daily medication using a regularly updated scroll list customized for each country and including all over-the-counter and prescribed rhinitis and asthma medications.

5- Data analysis

When responding to the MASK-air® daily monitoring questionnaire, it is not possible to skip any of the questions. This precludes missing data.

Categorical variables were described using absolute and relative frequencies, while continuous variables were described using means and standard-deviations or medians and interquartile ranges. All analyses were performed using software R (version 4.0).

a. Estimation of cut-off points: percentile-oriented approach

After excluding days of VAS=0 (considered to correspond to full allergy control), we estimated the tertiles and quartiles of VAS global, VAS nose, VAS eye, and VAS asthma (which were used as potential cut-offs in scenarios generating three and four groups beyond "full allergy control"). The distributions of MASK-air® VASs are skewed (Figure E1), rendering the estimation of cut-offs based on percentiles appropriate.

b. Estimation of cut-off points: data-driven approach

In the absence of a single categorical variable (i) indicating daily allergy control, and (ii) independent of assessed VASs, we applied k-means cluster approaches[17-19] to create a categorical "outcome variable" based on VAS work and VAS sleep (as work and sleep are two domains affected by allergy symptoms).[20-25] In particular, for each assessed symptom VAS, and after excluding days of VAS=0 ("full allergy control"), we applied k-means approaches so that we obtained three and four clusters. We subsequently determined the symptom VAS cut-off points that best distinguished three or four levels of allergy control (beyond "full allergy control"), maximizing the Youden index (compromise between sensitivity and specificity).

c. Sensitivity analyses

For each symptom VAS, we estimated cut-offs using either the percentile- or the machine learning data-driven approaches by (i) not considering full allergy control (and, thus, considering all available data), (ii) excluding observations with VAS<2 as corresponding to full allergy control, and (iii) excluding observations with VAS<3 as corresponding to full allergy control.

We also performed sensitivity analyses by estimating cut-off points for each country with more than 1,000 observations, assessing whether there are countries with outlier cut-offs. We used the following

definition for considering outliers: (i) low outlier: Quartile 1 - 1.5 × interquartile range, and (ii) high outlier: Quartile 3 + 1.5 × interquartile range.

We performed cross-sectional analyses of MASK-air® data, obtaining reported median VAS global, VAS nose, and VAS eye for different rhinitis medication schemes by day of MASK-air® use (oral or intranasal antihistamines (OAH or INAH); intranasal corticosteroids (INCS); INCS+INAH; INCS+INAH + other rhinitis medication; INCS+OAH; INCS+OAH + other rhinitis medication; no medication). Similar analyses were performed for VAS asthma, but the considered medication schemes included inhaled steroids (ICS), long-acting beta-agonists (LABA, with or without inhaled steroids), short-acting beta-agonists (SABA), long-acting muscarinic antagonists (LAMA) or biologics and other asthma drugs (including leukotriene receptor antagonists, mast cell stabilizers and xanthines). In addition to these cross-sectional analyses (where median values from all patients reporting each medication scheme were calculated for each day of MASK-air® use), longitudinal analyses were also performed, namely in patients who reported MASK-air® data on the first fifteen days after the first use, reporting at least fourteen days on the same medication scheme.

Results

1- Demographic characteristics

We assessed 395,223 days from 23,201 MASK-air® users with self-reported allergic rhinitis (Figure E2). More than half of the days (55.6%) were from females, and the mean participants' age was of 38.0 years (Table 1; Table E2). For the estimation of cut-offs based on the percentile approach, we included all days/observations, while for the estimation of cut-offs based on the machine learning data-driven approach, we only included days/observations for which information was provided simultaneously for VAS work and VAS sleep (*N* days=77,217; *N* users=7019).

2- Evaluation of cut-offs

Cut-offs obtained with percentile-based and data-driven approaches are displayed in Table 2. The percentile-based approach resulted in overall lower cut-off values than those obtained in the data-driven approach. In the data-driven approach, the estimation of four levels of allergy control (beyond full control) often resulted in cut-off points that were very close to each other. Therefore, we proposed cut-offs identifying three levels of control beyond full control (Table 3; Figure E3), namely those estimated by the data-driven approach (as they were obtained based on variables estimating the impact of allergy symptoms). Given the similarities of the cut-off points obtained with the data-driven approach for the different VASs, we suggest - for simplicity purposes - the use of the cut-off points 20 and 35 for all assessed VASs. Four groups were identified: full control (VAS=0), good control (VAS

1-20), partial control (VAS: 21-35), and poor control (VAS>35). Of note, the groups in which each cut-off point was included reflect the cut-offs obtained for the VAS global allergy symptoms, as the latter is the most comprehensive of all symptom VASs.

3- Sensitivity analyses

Results of the sensitivity analyses estimating the VAS cut-offs based on different assumptions of full allergy control are displayed in Table E3. Lower cut-off points were obtained in the percentile-based approach when there was no exclusion of VAS values indicating full allergy control. For the remaining analyses, similar cut-off estimates were obtained.

Results of the sensitivity analyses estimating VAS cut-offs for individual countries are displayed in Tables E4 and E5. For most countries, consistent results were found. There were no outlier countries but there were some divergent ones.

4- Application of cut-offs to real-world MASK-air® data

We assessed obtained cut-offs in real-world MASK-air® data. Examples of results of the cross-sectional analysis are displayed in Figure 1, while examples of results for longitudinal analyses are provided in Figure 2 (results for all VASs are available upon contact to the authors). For all medication classes, both in cross-sectional and longitudinal analyses, we observed that the highest reported VAS values were those registered on the first day of MASK-air® reporting. Among those first day median VAS values, 19% indicated poor control when considering the arbitrary cut-offs *versus* 52% when considering the machine learning data-driven cut-offs. After the first days, a plateau in VAS values was reached for most medication classes (in 69% of cases, all median values during the plateau stage fell within the "good control" group). With the arbitrary cut-off points, there were seven cases in which the classification of the first day of MASK-air® reporting and at least some of the days of the plateau stage were in the same group. With the proposed data-driven cut-offs, this occurred in only six cases. Therefore, by comparison with the arbitrary cut-offs, the proposed cut-off points allowed a better discrimination between median VASs of days under different medication schemes according to the day of MASK-air® reporting.

In a more detailed perspective, in the cross-sectional analysis of rhinitis/VAS global allergy symptoms (Figure 1A), day 1 would not have been detected as uncontrolled for no treatment, INCS, and INCS+OAH. Uncontrolled days following day 1 were detected for OAH or INAH (1 day), INCS+OAH (1 day), INCS+INAH+other (3 days), and INCS+OAH+other (2 days) only with the data-driven cut-offs. For VAS asthma (Figure 1B), in SABA reporting, 14/15 days had a cut-off of over 36/100 whereas only one day had uncontrolled days using the arbitrary cut-offs. For LAMA or

biologics (probably the most severe group), 14/15 days were uncontrolled using the data-driven cut-offs versus 0/15 using the arbitrary cut-offs.

Discussion

This study is of great importance since it allowed the identification of cut-off values for MASK-air® PROMs for rhinitis, conjunctivitis or asthma. The percentile-based approach resulted in lower cut-off values than those which had been arbitrarily used (20 and 50) as well as than those which had been identified in previous studies using paper-based VASs (4 out of 10 and 7 out of 10).[27] However, we considered the machine learning data-driven values. The proposed cut-off differentiating "controlled" and "partly-controlled" patients was similar to the cut-off value which had been arbitrarily used (20). However, a lower cut-off was obtained to differentiate between "partly-controlled" and "uncontrolled" patients (35 *versus* the arbitrarily used value of 50).

This paper has some limitations. The obtained cut-offs reflect the patterns of rhinitis severity of MASK-air® users, particularly the cut-offs related to the percentile-based approach. Therefore, it is expectable that different cut-off values might have been observed if, overall, MASK-air® users displayed more or less severe rhinitis. This limits the direct generalization of the results of this study beyond MASK-air®. In spite of that, the approach followed in this study can be a methodological example (i) for the determination of cut-offs in other PROMs from any chronic disease, particularly in the context of mHealth, where the number of consistently provided relevant variables is often scarce and missing observations are frequent, and (ii) for other mHealth apps once they provide enough data.

Moreover, there may be a selection bias, with the potential overrepresentation of younger patients and patients more concerned about their health among MASK-air® users. Nevertheless, reported symptoms and medication use patterns may not be too dissimilar to those of the general population with rhinitis.[28] However, data for asthma are lacking. The possibility of selection biases does not solely concern the characteristics of the patients who are more prone to using the MASK-air® app, but also the characteristics of the days that tend to be more often reported (i.e., it is expected that patients systematically tend to use MASK-air® more often when they are feeling worse). In fact, we observed that a relatively large number of patients provided a small number of observations. In addition to that limitation, we had a smaller sample when considering days reporting only VAS work and VAS sleep. The lower number of days with VAS work data stems from the fact that (i) not all MASK-air® users are employed, and (ii) employed patients do not work every day. On the other hand, VAS sleep was added to MASK-air® later than the remaining VASs. Finally, we did not assess hospitalizations or emergency visits since (i) allergic rhinitis does not prompt emergency care visits or hospitalizations, and (ii) these events are relatively rare in asthma in Europe. Systemic steroid use was also rare, with less than 100 observations in our dataset. Thus, the obtention of cut-offs according to the data-driven

approach was not based on any healthcare-related use outcome variable, but rather on two variables associated with the impact of rhinitis or asthma symptoms (VAS work and sleep).

This study also has important strengths: (i) the fact that the MASK-air® VASs have been studied on their validity, reliability, and responsiveness, (ii) the large number of patients assessed, (iii) the robustness of the obtained results in the performed sensitivity analyses (e.g., when estimating cut-off points by country), and (iv) the relatively simple selection of clustered variables given that we used two variables quantifying the impact of daily allergy symptoms in relevant domains of patients' lives (namely work productivity and sleep). This favors the use of cut-offs obtained following the machine-learning data-driven approach.

Converting a continuous variable into a categorical variable has some disadvantages from a statistical point of view, including loss of information and potential separation of patients (not too dissimilar) into different categories (namely those with values close to the cut-off points). However, from a clinical point of view, the adoption of cut-offs and the classification of patients into several categories is particularly helpful, supporting the clinical decision process and the patients' disease self-management. In fact, the definition of cut-offs for MASK-air® VASs will assist clinicians in having a good distinction between partly-controlled and uncontrolled patients which is important for clinical practice. That is, these cut-off values could facilitate the identification of patients who are most in need of improving their rhinitis and/or asthma control. MASK-air® VAS cut-off values can be applied in the clinical practice alongside the minimal important difference established for such VASs.[29] Therefore, clinicians may not only assess patients' level of control, but also whether during certain periods of time there were clinically important changes in reported symptoms.

When applying the different cut-offs to real-world data, we observed that the highest median symptom VAS values concerned the first day of MASK-air® reporting. This may have several possible explanations: (i) the fact that patients may tend to start using the MASK-air® app on days when they are not feeling particularly well due to their allergy symptoms, (ii) an improved allergy control associated with the use of medication (as observed in the longitudinal analyses), and/or (iii) an improved allergy control associated with the use of MASK-air® (e.g., app use prompting higher medication adherence).

Future studies should assess the performance of the proposed VAS classification into four groups in comparison with other asthma and rhinitis PROMs and their cut-offs. In particular, it may be of particular relevance to perform comparisons with other validated allergic rhinitis and asthma questionnaires, such as the Control of Allergic Rhinitis and Asthma Test (CARAT)[30] which is available in MASK-air®. In addition, future studies may assess whether the adoption of these cut-off points may result in a better allergy self-management in MASK-air® users. In fact, for each day,

MASK-air® indicates whether the patient's symptoms are well-controlled or not. Changing from the arbitrarily defined cut-offs to those stricter ones identified in this study may lead MASK-air® users to further improve their symptoms. Such a hypothesis should be tested in a subsequent study.

In conclusion, in this study, we proposed cut-off values for MASK-air® VASs on allergy and asthma symptoms, following different approaches and testing their robustness in sensitivity analyses. This may allow for the classification of rhinitis and asthma patients according to different levels of control, supporting a better disease management.

Acknowledgments: MASK-air® has been supported by Charité Universitätsmedizin Berlin, EU grants (EU Structural and Development Funds; POLLAR, EIT Health, Twinning, EIP on AHA and H2020) and educational grants from Mylan-Viatris, ALK, GSK, Novartis and Uriach.

Data availability statement: Data can be made available upon reasonable request to the corresponding author.

Author contributions: BSP participated in methodology, formal analysis and writing – original manuscript; JB participated in conceptualization, formal analysis, supervision and writing – original manuscript. All remaining authors participated in data collection and writing – review & editing.

527 **Table 1. Description of the days from assessed MASK-air® users**

	Days assessed for cut-off estimation in the percentile-based approach (*N*=395,223)	Days assessed for cut-off estimation in the machine learning data-driven approach (*N*=77,217)
N users (average days per user) [a]	23,201 (17.0)	7019 (11.0)
Females – *N* (%)	219,660 (55.6)	43,569 (56.4)
Age – mean (SD)	38.0 (14.4)	40.2 (12.6)
VAS global allergy symptoms – median (IQR) [b]	11 (27)	15 (26)
VAS nose – median (IQR) [b]	12 (29)	15 (28)
VAS eyes – median (IQR) [b]	4 (18)	8 (21)
VAS asthma – median (IQR) [b]	0 (10)	4 (14)
Users with self-reported asthma	7 (23)	9 (22)
VAS work – median (IQR) [b]	8 (22) [c]	12 (23)
VAS sleep – median (IQR) [b]	16 (29) [d]	17 (30)
Allergic rhinitis CSMS – median (IQR) [b]	10 (18)	12 (18)
Total days reporting rhinitis medication – *N* (%)	181,006 (45.8)	38,140 (49.4)
Oral antihistamines monotherapy	59,523 (15.1)	12,525 (16.2)
INCS monotherapy	35,941 (9.1)	7831 (10.1)
Azelastine-fluticasone monotherapy	14,747 (3.7)	2944 (3.8)
Oral antihistamines + INCS	35,346 (8.9)	7107 (9.2)
Azelastine-fluticasone + other rhinitis medication	12,897 (3.3)	2400 (3.1)
Self-reported asthma – *N* (%)	155,484 (39.3)	33,390 (43.2)
Total days reporting asthma medication – *N* (%)	82,390 (20.9)	18,996 (24.6)
SABA	9727 (2.5)	2444 (3.2)
ICS	25,697 (6.5)	6100 (7.9)
ICS+LABA	45,940 (11.6)	11,106 (14.4)
LAMA or biologics	3264 (0.8)	1060 (1.4)
Other medications	19,589 (5.0)	3978 (5.2)
Conjunctivitis – *N* (%)	285,398 (72.2)	59,749 (77.4)

528 CSMS=Combined symptom-medication score; ICS=Inhaled corticosteroids; INCS= intranasal corticosteroids; IQR=Interquartile range;
529 LABA=Long-acting beta-agonists; LAMA=Long-acting muscarinic antagonists; SABA=Short-acting beta-agonists; SD=Standard-deviation;
530 VAS=Visual analog scale; [a] Median number of reported days per user: 2 for both approaches; [b] Scale: 0-100; [c] 182,245 days provided by
531 15,216 users; [d] 171,918 days provided by 9952 users.

Table 2. Cut-off points obtained for MASK-air® visual analog scales (VASs) according to the percentile-oriented and machine learning data-driven approaches

	VAS global [a]	VAS nose [a]	VAS eye [a]	VAS asthma [a]
Percentile-oriented approach				
Identification of tertiles				
Cut-off 1 - Percentile 33	10	10	7	8
Cut-off 2 - Percentile 67	28	29	23	24
Identification of quartiles				
Cut-off 1 - Percentile 25	8	8	5	6
Cut-off 2 - Percentile 50	17	18	13	14
Cut-off 3 - Percentile 75	36	38	30	32
Data-driven approach				
Obtention of three clusters				
Cut-off 1	20	21	17	19
Cut-off 2	36	38	30	35
Obtention of four clusters				
Cut-off 1	16	17	13	14
Cut-off 2	32	32	25	30
Cut-off 3	39	42	30	37

[a] Scale: 0-100

Table 3. Proposed groups and cut-off points for MASK-air® visual analog scales (VASs) according to the percentile-oriented and data-driven approaches

	Percentile-oriented approach	Data-driven approach
VAS global		
Full control	0	0
Good control	1-10	1-20
Partial control	11-27	21-35
Poor control	28-100	36-100
VAS nose		
Full control	0	0
Good control	1-10	1-21
Partial control	11-28	22-37
Poor control	29-100	38-100
VAS eye		
Full control	0	0
Good control	1-7	1-17
Partial control	8-22	18-29
Poor control	23-100	30-100
VAS asthma		
Full control	0	0
Good control	1-8	1-19
Partial control	9-23	20-34
Poor control	24-100	35-100

Figure captions

Figure 1. Cross-sectional analysis of reported allergy symptoms with depiction of median values of the visual analog scales (VASs) on global allergy symptoms and asthma according to the day of MASK-air® use and for each reported medication scheme

ICS=Inhaled corticosteroids; INAH=Intranasal antihistamines; INCS=Intranasal corticosteroids; LABA=Long-acting beta-agonists; LAMA=Long-acting muscarinic antagonists; OAH=Oral antihistamines; SABA=Short-acting beta-agonists

Figure 2. Longitudinal analysis of reported allergy symptoms with depiction of median values of the visual analog scales (VASs) on global allergy symptoms according to the day of MASK-air® use. Included patients encompassed those who, on the first fifteen days of MASK-air® use, reported at least fourteen days on the same medication scheme

INAH=Intranasal antihistamines; INCS=Intranasal corticosteroids; OAH=Oral antihistamines. INCS+INAH not depicted on account of the low number of participants

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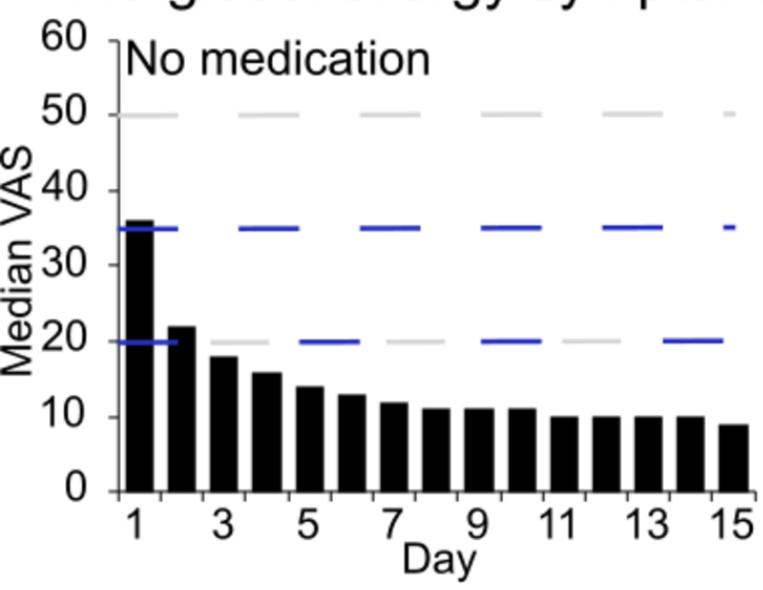
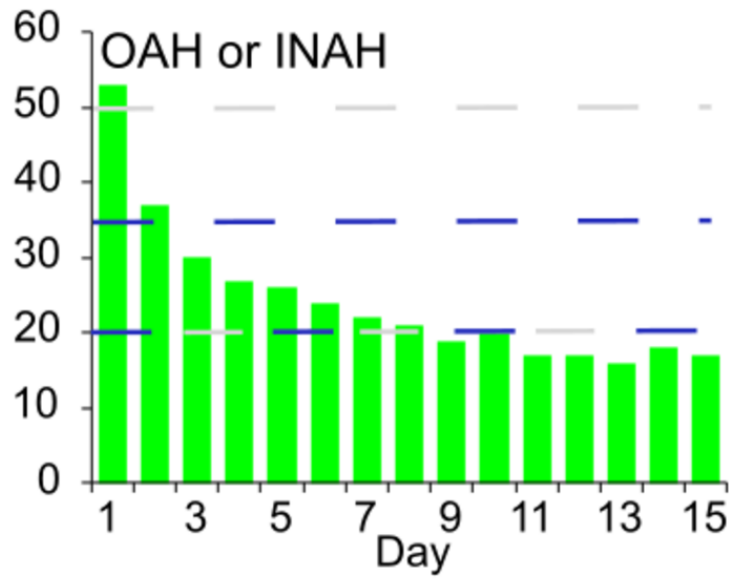
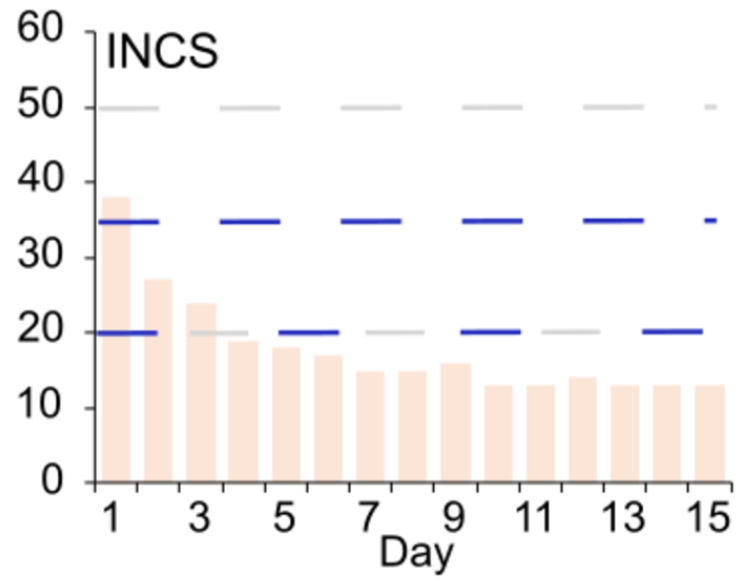
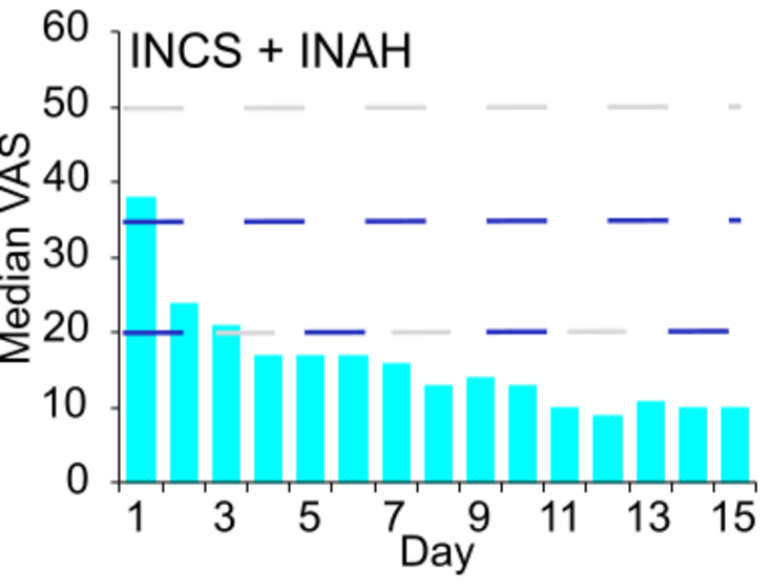
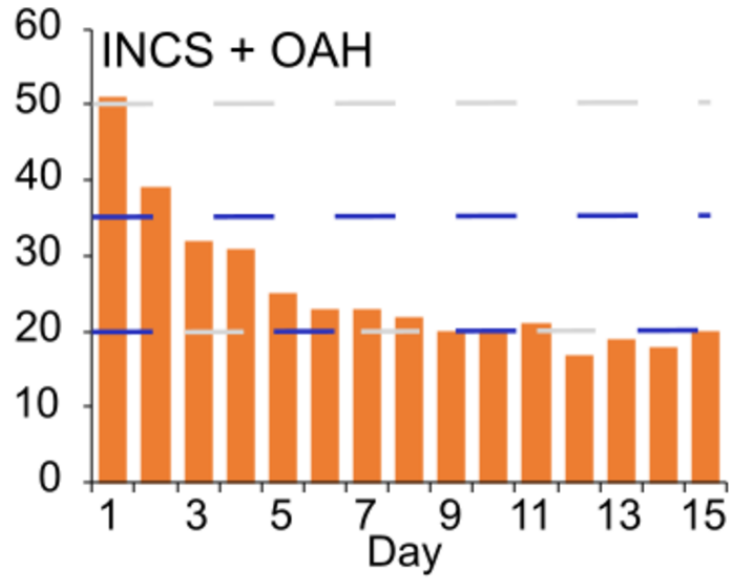
VAS global allergy symptoms

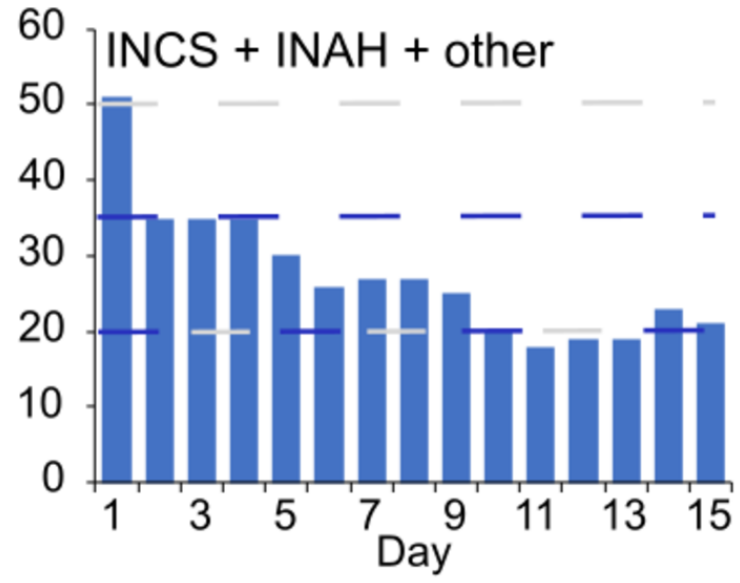


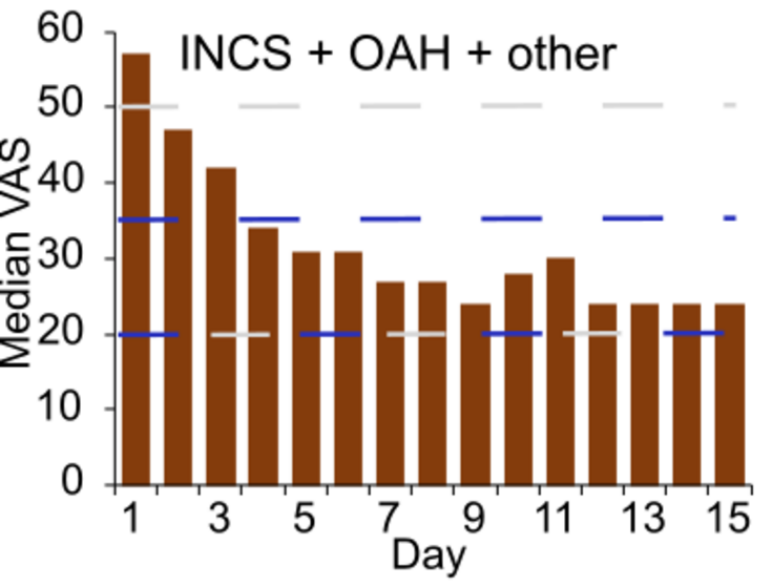


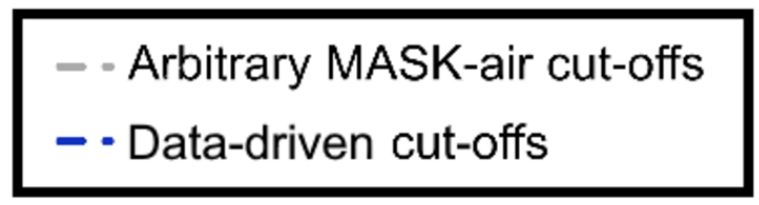




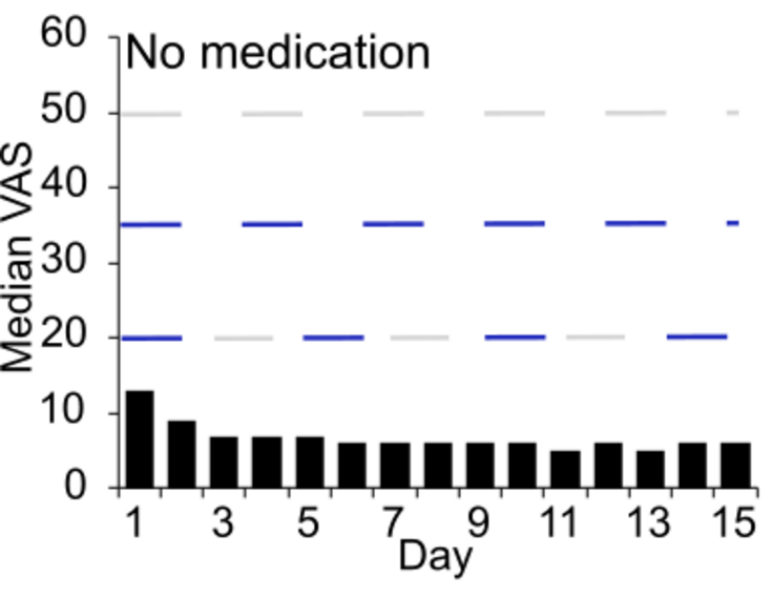


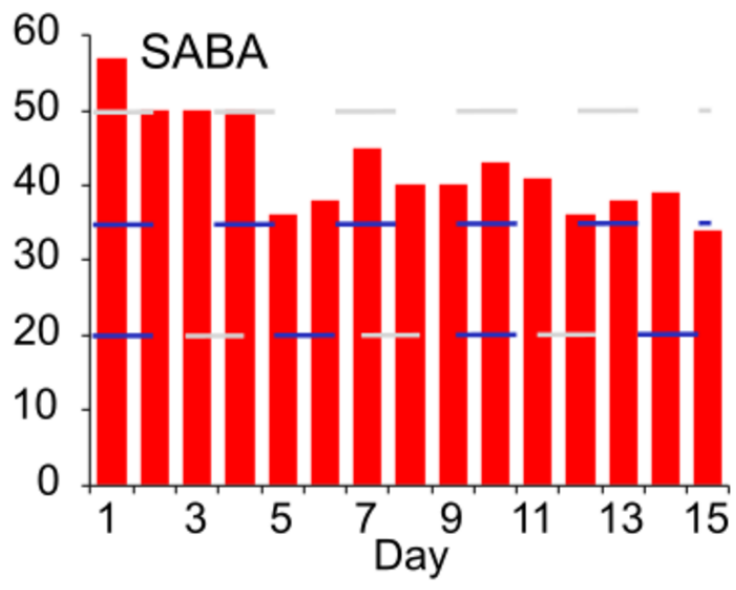


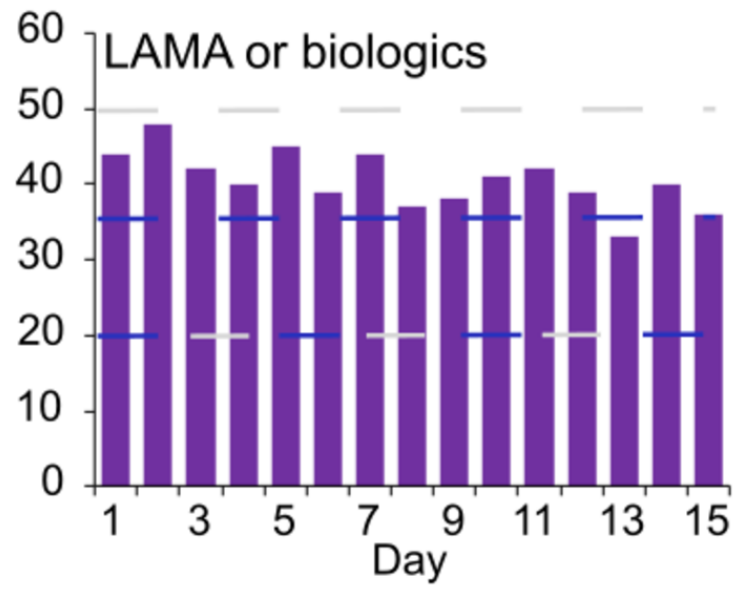


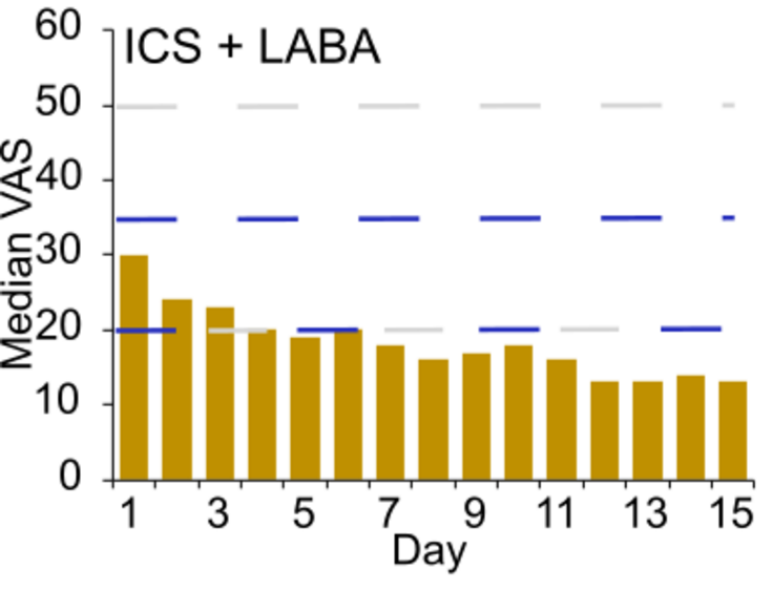


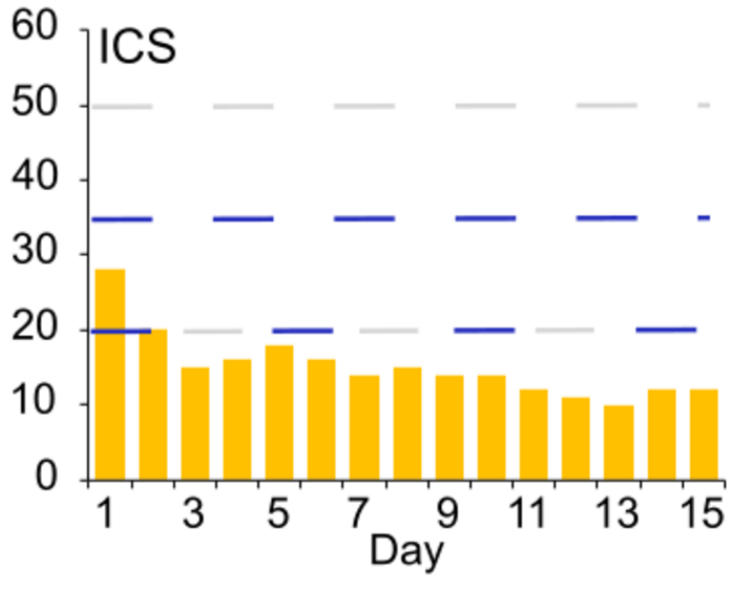
VAS asthma

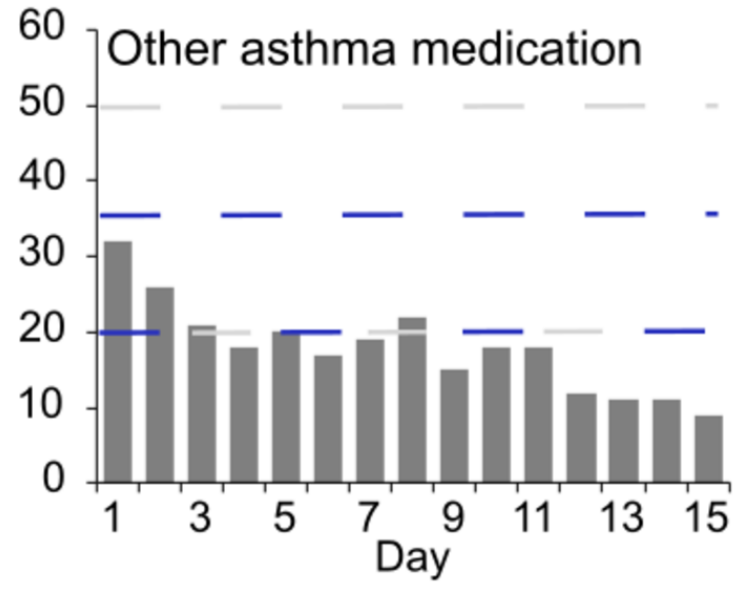


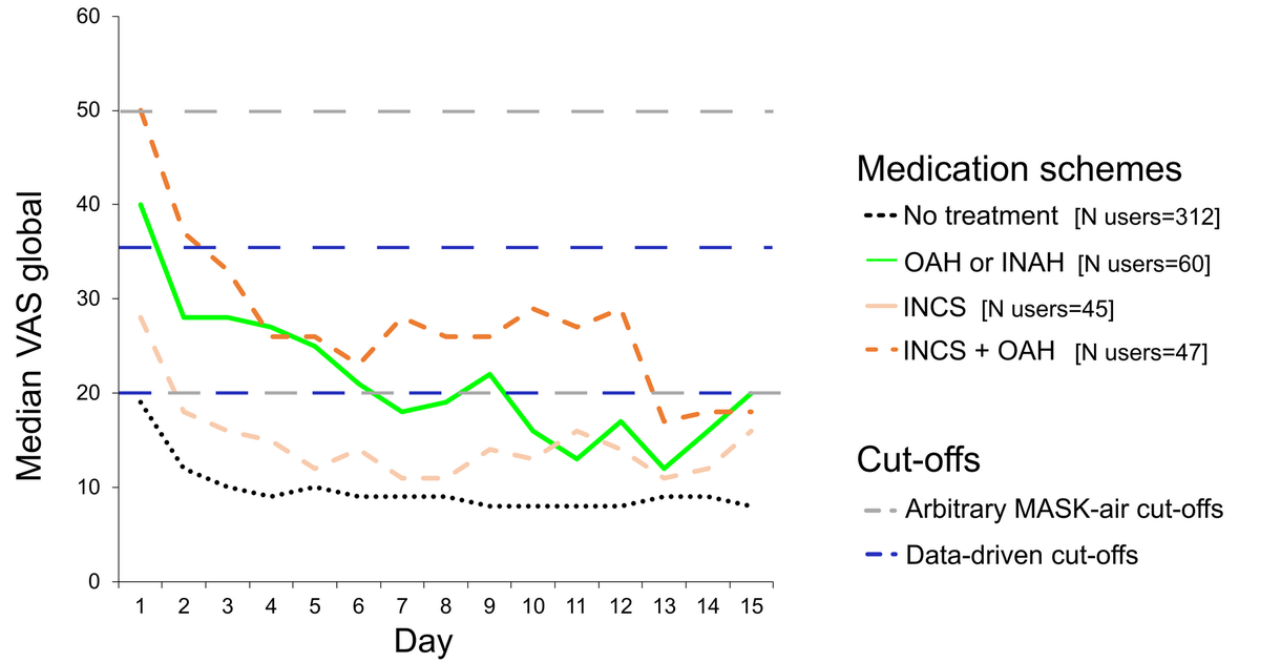








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Day
Medication schemes
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OAH or INAH [N users=60]
INCS [N users=45]
INCS + OAH [N users=47]
Cut-offs
Arbitrary MASK-air cut-offs
Data-driven cut-offs