Consistent trajectories of rhinitis control and treatment in 16,177 weeks

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ORIGINAL ARTICLE

Rhinitis, Sinusitis and Upper Airway Disease

Consistent trajectories of rhinitis control and treatment in 16,177 weeks: The MASK-air® longitudinal study

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Abstract

Introduction: Data from mHealth apps can provide valuable information on rhinitis control and treatment patterns. However, in MASK-air®, these data have only been analyzed cross-sectionally, without considering the changes of symptoms over time. We analyzed data from MASK-air® longitudinally, clustering weeks according to reported rhinitis symptoms.

Methods: We analyzed MASK-air® data, assessing the weeks for which patients had answered a rhinitis daily questionnaire on all 7 days. We firstly used k-means clustering algorithms for longitudinal data to define clusters of weeks according to the trajectories of reported daily rhinitis symptoms. Clustering was applied separately for weeks when medication was reported or not. We compared obtained clusters on symptoms and rhinitis medication patterns. We then used the latent class mixture model to assess the robustness of results.

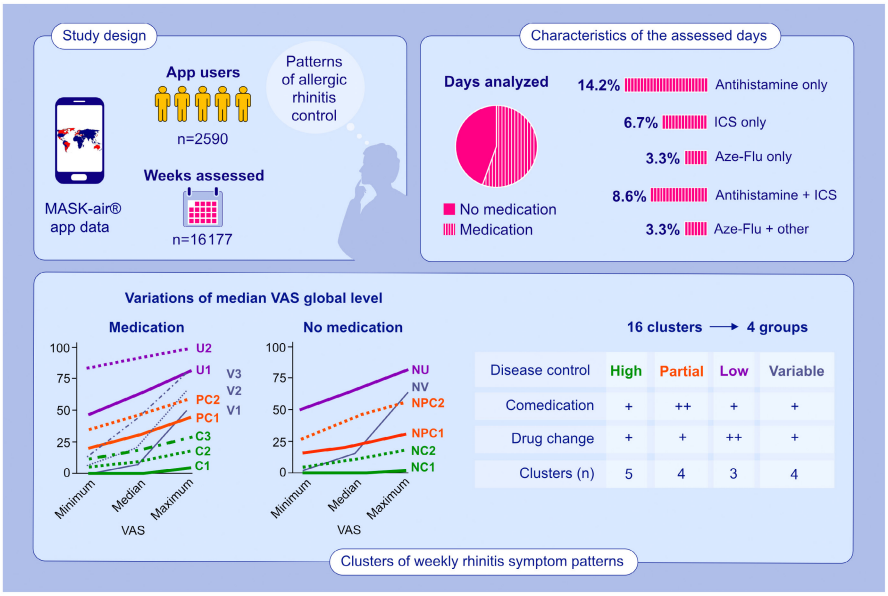
Results: We analyzed 113,239 days (16,177 complete weeks) from 2590 patients (mean age ± SD = 39.1 ± 13.7 years). The first clustering algorithm identified ten clusters among weeks with medication use: seven with low variability in rhinitis control during the week and three with highly-variable control. Clusters with poorly-controlled rhinitis displayed a higher frequency of rhinitis co-medication, a more frequent change of medication

schemes and more pronounced seasonal patterns. Six clusters were identified in weeks when no rhinitis medication was used, displaying similar control patterns. The second clustering method provided similar results. Moreover, patients displayed consistent levels of rhinitis control, reporting several weeks with similar levels of control.

Conclusions: We identified 16 patterns of weekly rhinitis control. Co-medication and medication change schemes were common in uncontrolled weeks, reinforcing the hypothesis that patients treat themselves according to their symptoms.

KEYWORDS

mobile health, patient-reported outcomes, real-world data, rhinitis



GRAPHICAL ABSTRACT

This study analyzed MASK-air® data longitudinally, analysing and clustering (according to VAS levels) 16,177 complete weeks, of which 55.5% involved the use of medication. Among weeks with medication use, 10 clusters were identified: 7 with low variability in rhinitis control during the week and 3 with highly-variable control. Six clusters were identified in weeks with no rhinitis medication use. Clusters with poorly-controlled rhinitis displayed higher frequency of co-medication, more frequent changes in medication schemes and more pronounced seasonal patterns.

Abbreviations: Aze-Flu, azelastine-fluticasone; C1-C3, clusters with low median and maximum VAS global during weeks with medication; ICS, intranasal corticosteroid; MASK-air®, Mobile Airways Sentinel NetworK for airway diseases; NC1-NC2, clusters with low median and maximum VAS global during weeks without medication; NPC1-NPC2, clusters with medium VAS global during weeks without medication; NU, cluster with high VAS global during weeks without medication; NV, cluster with large differences between minimum, median, and maximum VAS global during weeks without medication; PC1-PC2, clusters with medium VAS global during weeks with medication; U1-U2, clusters with high VAS global during weeks with medication; V1-V3, clusters with large differences between minimum, median, and maximum VAS global during weeks with medication; VAS, visual analog scale

1 | INTRODUCTION

The MASK-air® (Mobile Airways Sentinel NetworK for airway diseases) app is a Good Practice of DG Santé for digitally-enabled patient-centred care in rhinitis and asthma multimorbidity.[1,2] It assesses the daily control of allergic rhinitis and asthma through visual analogue scales (VASs), which have been validated in relation to their independence,[3] concurrent validity, reliability and responsiveness.[4] Data from MASK-air® have enabled the finding of novel phenotypes of allergic diseases,[5] the assessment of adherence to rhinitis medications[6,7] and the assessment of the control associated with reported rhinitis medications.[6,8,9] The results of MASK-air® have thus allowed the development of next-generation guidelines, incorporating real-world data.[10]

However, MASK-air® data were analyzed cross-sectionally, and several limitations exist for both mHealth-based studies[6,8,9] and studies with a cross-sectional design. Cross-sectional studies cannot provide definite information about temporal relationships, let alone cause-and-effect relationships (causal inference). Such studies may also provide differing results if different time frames are chosen, which has prompted the comparison of data during and outside the pollen season.[9] By contrast, longitudinal studies can establish sequences of events, even though participants may drop out of the study, thereby decreasing the amount of data collected (selective

attrition).[11,12] In allergic rhinitis, a longitudinal assessment can provide information on the trajectories of patients with rhinitis (i.e., how rhinitis symptoms and medication use vary throughout certain time periods), allowing the identification of patterns of trajectories.

The aim of this study was to perform a longitudinal assessment of MASK-air® data, identifying weeks with 7 days of reporting and clustering them according to VAS levels. Clusters were then compared on rhinitis and asthma control and on medication use, testing previous hypotheses posed in cross-sectional analyses (e.g., that days under co-medication can be associated with worse allergic rhinitis control than those under monotherapy or no medication).[6,8,9]

2 | METHODS

2.1 | Study design

We performed a longitudinal analysis using the MASK-air® database. We identified the weeks for which patients had answered to the MASK-air® daily monitoring questionnaire on all 7 days. To identify patterns of allergic rhinitis weeks, we applied cluster analysis methods for longitudinal data separately for weeks during which: (i) medication was used for at least 1 day and (ii) medication was not used on any day. The phenotypic characteristics of the different clusters were subsequently compared.

2.2 | Setting and participants

MASK-air® can be downloaded via the Apple App and Google Play Stores (www.mask-air.com). We included data from MASK-air® users (25 different countries) (i) aged 16–90 years, (ii) with self-reported allergic rhinitis and (iii) reporting data from May 21, 2015 to December 6, 2020. In particular, we included all weeks (defined as sets of consecutive days) during which patients answered to the MASK-air® daily monitoring questionnaire on all days.

2.3 | Ethics

MASK-air® has a CE1 marking. It follows the General Data Protection Regulation (GDPR).[13] All data are anonymized using k-anonymity.[14] An Independent Review Board (Bohn-Köln) approval was obtained for the MASK-air studies,[15] but individual boards in different countries were not required since the study is observational and users agree to the analysis of their data in the terms of use.

2.4 | Data sources

The MASK-air® app comprises a daily monitoring questionnaire assessing the impact of asthma and rhinitis symptoms on a daily basis by means of 0–100 visual analogue scales (VASs). In addition, users are asked to enter their daily medications via a regularly-updated scroll list that contains country-specific prescribed and over-the-counter medications.

2.5 | Size of the study

In this study, data from all complete weeks meeting inclusion criteria were included. No sample size calculation was performed.

2.6 | Biases

There are potential information biases related to the self-reported nature of the data collection. Potential selection biases might occur given that app users are not representative of all rhinitis patients (e.g., there may be an overrepresentation of users suffering from moderate-to-severe rhinitis and of younger individuals who may be more familiar with apps). Furthermore, complete weeks introduced by users in MASK-air® may not be representative of all yearly weeks.

2.7 | Data analysis

Categorical variables were described by absolute and relative frequencies, while continuous variables were described by means and standard deviations (SDs) or medians and interquartile ranges (IQRs). When responding to the MASK-air® daily monitoring questionnaire, it is not possible to skip any of the questions and data are saved only after the final answer. This precludes any missing data.

Since selective attrition is common in MASK-air® (given that many patients use the app for only a few days and/or intermittently[6,8,9]), days from complete weeks were compared with all days of the full MASK-air® database on the characteristics of patients, VAS data and frequency of medication use. The computation of effect sizes was based on standardized differences.

Longitudinal k-means (an adaptation of k-means clustering algorithms for longitudinal data trajectories) was applied to cluster weeks during which medication was used for at least 1 day. Such methods were applied to identify—in an unsupervised way and taking into account the longitudinal nature of the data—groups/patterns of weeks defined based on the VAS assessing the impact of global allergy symptoms ("VAS global") reported during the different days of each week[16] (i.e., considering their values on the different days and their variation throughout the week; no other variables were considered for clustering). A detailed description of adopted clustering methods and sensitivity analyses (along with key concepts on clustering) is included in the Method S1. Obtained clusters were then compared, regarding not only VAS global values but also (i) rhinitis medication use, (ii) patients' demographic and clinical characteristics, (iii) the ARIA-EAACI combined symptom-medication score (CSMS) assessing the daily control of allergic

rhinitis, (iv) the use of asthma medication, (v) several VAS levels assessing daily allergy symptoms (including VASs on the reported impact of asthma, eye symptoms, nose symptoms and the impact of allergy symptoms on work) and (vi) seasonality (i.e., distribution of the weeks of each cluster throughout the months of the year). Comparisons between clusters relied on effect sizes computed based on standardized differences. We assumed that values between 0.2 and 0.5 correspond to small effect sizes (differences), values between 0.5 and 0.8 to moderate differences, and values over 0.8 to large differences.[17]

Similar analyses were performed for weeks during which no medication was used. Clustering was performed separately for weeks during which at least one medication was used versus those during which no medication was used. This helped to better explore and compare the reported severity of symptoms in weeks with and without medication use and to characterize patients' pathways across weeks with and without medication use.

Sensitivity analyses were performed adopting a different method for clustering longitudinal data, namely the latent class mixture model (also known as "latent class growth modelling").[18] This allowed us to assess the consistency of clusters obtained in the main—nonparametric—clustering method compared to those obtained with a different—model-based—method.

Finally, we estimated, for each cluster, the risk (along with credible intervals—CrI) of a user reporting another week belonging to the same cluster or to a different cluster. This risk was estimated using Bayesian models weighted by the number of reported weeks.[19]

All analyses were performed using software R (version 4.0.0).

3 | RESULTS

3.1 | Characteristics of the assessed days

We analyzed a total of 16,177 complete weeks of which 8981 (55.5%) involved the use of medication (Figure S1). These weeks corresponded to 113,239 days of MASK-air® use provided by a total of 2590 users (mean age ± SD = 39.1 ± 13.7 years) (Table 1; Table S1). There were 61,299 (54.1%) days for women. Differences between assessed days and days from the full MASK-air® database were very small (Table 1).

Days with single medication involved, most commonly, the use of an antihistamine (14.2%), an intranasal steroid (8.4%) or azelastine-fluticasone (3.3%). Regarding co-medication schemes, intranasal steroids + antihistamines were registered in 8.6% of the days and azelastine-fluticasone + other medication in 3.5% (Table 1).

TABLE 1 Characteristics of the assessed sample (observations/days from complete weeks) and of observations from the full MASK-air® database

	Observations from complete weeks	Observations from the full MASK-air® database	Effect size
N (*N* users)	113,239 (2590)	317,176 (17,780)	–
Females – *N* (%)	61,299 (54.1)	177,067 (55.8)	0.03
Age – mean (SD)	39.1 (13.7)	38.3 (13.8)	0.06
Days from European users – *N* (%)	80,654 (71.2)	222,025 (70.0)	0.03
Asthma – *N* (%)	41,846 (37.0)	125,639 (39.6)	0.05
Conjunctivitis – *N* (%)	84,315 (74.5)	236,862 (74.7)	0.01
VAS global – median (IQR)	9 (22)	11 (27)	0.07
VAS eyes – median (IQR)	3 (13)	4 (18)	0.10
VAS nose – median (IQR)	9 (24)	12 (28)	0.10
VAS asthma – median (IQR)	0 (7)	0 (10)	0
VAS work – median (IQR)	6 (17)	8 (23)	0.10
Total days reporting rhinitis medication – *N* (%)	48,949 (43.2)	127,801 (40.3)	0.06
Antihistamines only	16,121 (14.2)	53,685 (16.9)	0.07
Intranasal steroids only	7569 (6.7)	25,380 (8.0)	0.05
Azelastine-fluticasone only	3721 (3.3)	12,745 (4.0)	0.04
Antihistamines + intranasal steroids	9786 (8.6)	25,061 (7.9)	0.03
Azelastine-fluticasone + other rhinitis medication	3997 (3.5)	9433 (3.0)	0.03
Total days reporting asthma medication – *N* (%)	18,619 (16.4)	50,492 (15.9)	0.01

Abbreviations: IQR, interquartile range; SD, standard deviation; VAS, visual analogue scale.

3.2 | k-means cluster analysis

3.2.1 | Weeks when at least one medication was reported

We identified 10 clusters among weeks when at least one medication was reported (Table 2). Three of these clusters displayed low median and maximum VAS global (named as clusters C1-C3, pointing to overall good weekly rhinitis control, with the best control being observed for C1, followed by C2 and C3), two displayed medium VAS global (clusters PC1 and PC2, indicating weekly partial rhinitis control) and two displayed high VAS global (clusters U1 and U2, suggesting weeks with poor rhinitis control). In addition, we identified three clusters with large differences between maximum, median and minimum VAS global (clusters V1-V3, with the lowest maximum VAS being observed for V1, followed by V2 and V3) (Table 2; Figure 1). Overall, the median values of VAS nose and eyes accompanied those of median VAS global (Figure 1). For VAS asthma, this was also observed for all clusters except those with high VAS global variability (clusters V1-V3) and cluster U2. The latter appears to be associated with very poor global, nasal and ocular control but with no/mild asthma symptoms.

Regarding rhinitis medication reporting, the percentage of days without medication varied between 11.8% (cluster U2) and 39.4% of the days (cluster V1). The frequency of co-medication days increased with severity from clusters C1 (25.5%) to U2 (65.2%). In variable clusters, it increased from 19.9% (V1) to 33.5% (V3).

Modification of treatment schemes in rhinitis medication within the same week varied from 15.9% (cluster C1) to 45.0% (cluster U2) (Figure 2). Moreover, over 10% of weeks comprised three medication schemes in clusters U1 and U2.

Regarding asthma medications, ICS-LABAs were reported from 16.3 to 22.7% of days in clusters C1 to U1. In the variable clusters (V1-V3), ICS-LABA were reported in 9.6 to 11.2% of days (Figure S2), with the reporting of ICS-LABA increasing with VAS global level.

3.2.2 | Weeks when no medication was reported

Six clusters were identified among weeks for which no medication was reported (Table 3). Two clusters displayed low median and maximum VAS global values (clusters NC1 and NC2), two displayed medium VAS global values (clusters NPC1 and NPC2) and one displayed high VAS global values (cluster NU). We also identified one cluster with large differences between maximum, median and minimum VAS global values (cluster NV) (Table 3). Median values of VAS nose and eyes increased similarly to the median values of VAS global.

3.3 | Sensitivity analyses

Consistent results were observed in the sensitivity analyses considering the specific weekdays for which VASs were registered. For weeks when medication was reported, three highly-variable clusters and eight (instead of seven) additional clusters were identified (Table S2). For weeks when no medication was reported, five clusters were identified (Table S3).

3.4 | Latent class mixture model

Using the latent class mixture model, an optimal number of eight clusters was identified for weeks when medication was used (Table S4). The main difference between the results obtained with this approach compared with k-means lies in the identification of a single cluster with controlled rhinitis (low median and maximum VAS global) instead of three clusters. For weeks when no medication was used, the latent class mixture model also identified an optimal number of six clusters, although these encompassed a single controlled cluster (low median and maximum VAS global) and two clusters with highly-variable VAS (Table S5). The consistency of the results between the two clustering approaches was higher for weeks when medication was used than for those with no medication (Figure S3; Table S6).

3.5 | Seasonality of clusters

Regarding clusters of weeks with reported medication use, a more pronounced seasonal pattern was observed for clusters associated with worse or more variable rhinitis control. In fact, for clusters PC2, U1-U2 and V1-V3, there was at least one spring month with over 15% of observations. Clusters of untreated weeks did not show such a seasonal pattern (Figures S4 and S5).

3.6 | Consistency of clusters by users

For each cluster, we estimated the risk of a user reporting another week belonging to the same cluster or to a different cluster (Table S7; Figure 3).

For a patient reporting a week with medication, there was a low risk of this patient reporting a subsequent week with no medication (8.5%; 95%CrI = 6.5–10.8%). For a patient reporting a week with no medication, the risk of reporting a subsequent week with medication was 24.3% (95%CrI = 19.9–29.2%).

In clusters with reported medication use, the risk that a patient in clusters C1-C3 reported another week in the same cluster ranged from 10.6% (cluster C3) to 20.8% (cluster C1). Such percentages were progressively lower for clusters PC1-PC2 (range = 6.1–7.5%), U1–U2 (range = 4.2–4.7%) and V1-V3 (range = 1.5–2.1%) (Figure S6). Similar observations were found for four of the clusters with no reported medication use.

4 | DISCUSSION

In this study, we clustered full weeks of MASK-air® data reporting in order to assess longitudinal patterns of rhinitis symptoms. We identified 16 clusters, which not only differed in VAS global patterns but

TABLE 2 Clusters obtained when considering full weeks with at least 1 day of medication for allergic rhinitis

	Cluster C1	Cluster C2	Cluster C3	Cluster PC1	Cluster PC2	Cluster U1	Cluster U2	Cluster V1	Cluster V2	Cluster V3	Effect size[a]
N weeks (%)	2352 (26.2)	2030 (22.6)	1476 (16.4)	882 (9.8)	580 (6.5)	342 (3.8)	80 (0.9)	427 (4.8)	494 (5.5)	318 (3.5)	–
N days	16,464	14,210	10,332	6174	4060	2394	560	2989	3458	2226	–
N users (average *N* weeks per user)	534 (4.4)	692 (2.9)	559 (2.6)	405 (2.2)	285 (2.0)	210 (1.6)	32 (2.5)	325 (1.3)	390 (1.3)	270 (1.2)	–
Females – *N* (%)	1273 (54.1)	1096 (54.0)	832 (56.4)	530 (60.1)	406 (70.0)	269 (78.7)	63 (78.9)	218 (51.1)	298 (60.3)	209 (65.7)	0.6
Age – mean (SD)	39.3 (12.8)	40.0 (13.4)	39.3 (12.5)	39.6 (13.3)	39.6 (13.8)	38.0 (14.1)	46.2 (9.1)	35.7 (12.6)	35.5 (12.6)	34.4 (12.8)	1.0
VAS global allergy symptoms											
Maximum week value – median (IQR)	5 (7)	17 (9)	28 (9)	44 (12)	58 (11)	81 (17)	99 (7)	49 (17)	66 (20)	80 (22)	20.9
Minimum week value – median (IQR)	0 (1)	4 (6)	11 (7)	20 (9)	35 (13)	46 (18)	83 (22)	0 (3)	6 (9)	13 (15)	9.3
Weekly range – median (IQR)	4 (6)	12 (12)	16 (15)	24 (20)	23 (21)	36 (24)	11 (18)	48 (17)	58 (20)	67 (25)	4.9
Median week value – median (IQR)	0 (4)	9 (4)	18 (5)	30 (7)	47 (9)	62 (11)	91 (11)	7 (10)	20 (9)	43 (15)	19.3
Days with VAS >50 – *N* (%)	0	0	1 (0.01)	244 (4.0)	1501 (37.0)	1931 (80.7)	559 (99.8)	196 (6.6)	576 (16.7)	911 (40.9)	3.1
Rhinitis medication reporting – *N* (%)											
No medication days	3623 (22.0)	3249 (22.9)	2166 (21.0)	956 (15.5)	604 (14.9)	416 (17.4)	66 (11.8)	1178 (39.4)	1120 (32.4)	540 (24.3)	0.7
Single medication days	8636 (52.5)	6782 (47.7)	4950 (47.9)	2628 (42.6)	1787 (44.0)	904 (37.8)	129 (23.0)	1215 (40.6)	1462 (42.3)	941 (42.3)	0.6
Co-medication days	4205 (25.5)	4179 (29.4)	3216 (31.1)	2590 (42.0)	1669 (41.1)	1074 (44.9)	365 (65.2)	596 (19.9)	876 (25.3)	745 (33.5)	1.0
Total days reporting AR medication – *N* (%)											
Only AH	4163 (25.3)	3464 (24.4)	2606 (25.2)	1564 (25.3)	1126 (27.7)	510 (21.3)	63 (11.3)	793 (26.5)	1137 (32.9)	695 (31.2)	0.5
Single AH use	4099 (24.9)	3305 (23.3)	2452 (23.7)	1437 (23.3)	998 (24.6)	420 (17.5)	39 (7.0)	748 (25.0)	1004 (29.0)	651 (29.2)	0.6
Several AH use	64 (0.4)	159 (1.1)	154 (1.5)	127 (2.1)	128 (3.2)	90 (3.8)	24 (4.3)	45 (1.5)	133 (3.8)	44 (2.0)	0.3
Only INCS	2736 (16.6)	1918 (13.5)	1235 (12.0)	513 (8.3)	277 (6.8)	198 (8.3)	72 (12.9)	235 (7.9)	262 (7.6)	123 (5.5)	0.4
Only AzeFlu	1343 (8.2)	863 (6.1)	667 (6.5)	257 (4.2)	182 (4.5)	159 (6.6)	0	99 (3.3)	92 (2.7)	59 (2.7)	0.6
AH + INCS	2111 (12.8)	1482 (10.4)	835 (8.1)	684 (11.1)	478 (11.8)	321 (13.4)	109 (19.5)	276 (9.2)	312 (9.0)	266 (11.9)	0.3
AH + INCS + others	259 (1.6)	832 (5.9)	660 (6.4)	397 (6.4)	228 (5.6)	170 (7.1)	48 (8.6)	54 (1.8)	117 (3.4)	147 (6.6)	0.3
AzeFlu + others	777 (4.7)	884 (6.2)	775 (7.5)	715 (11.6)	271 (6.7)	244 (10.2)	41 (7.3)	102 (3.4)	100 (2.9)	88 (4.0)	0.4
OCS	63 (0.4)	126 (0.9)	68 (0.7)	228 (3.7)	209 (5.1)	116 (4.8)	26 (4.6)	6 (0.2)	38 (1.1)	35 (1.6)	0.4
N medication schemes per week (%)											
One scheme	1979 (84.1)	1509 (74.3)	1034 (70.1)	618 (70.1)	422 (72.8)	219 (64.0)	44 (55.0)	324 (75.9)	357 (72.3)	222 (69.8)	0.7
Two different schemes	336 (14.3)	442 (21.8)	381 (25.8)	221 (25.1)	127 (21.9)	86 (25.1)	24 (30.0)	89 (20.8)	112 (22.7)	76 (23.9)	0.4
Three or more different schemes	37 (1.6)	79 (3.9)	61 (4.1)	43 (4.9)	31 (5.3)	37 (10.8)	12 (15.0)	14 (3.3)	25 (5.1)	20 (6.3)	0.5

(Continues)

TABLE 2 (Continued)

	Cluster C1	Cluster C2	Cluster C3	Cluster PC1	Cluster PC2	Cluster U1	Cluster U2	Cluster V1	Cluster V2	Cluster V3	Effect size[a]
N weeks according to the number of medication use days (%)											
1 day of medication use	246 (10.5)	196 (9.7)	120 (8.1)	36 (4.1)	26 (4.5)	20 (5.8)	3 (3.8)	97 (22.7)	73 (14.8)	22 (6.9)	0.6
2 days of medication use	128 (5.4)	123 (6.1)	87 (5.9)	36 (4.1)	25 (4.3)	11 (3.2)	1 (1.3)	56 (13.1)	43 (8.7)	19 (6.0)	0.5
3 days of medication use	115 (4.9)	117 (5.8)	70 (4.7)	42 (4.8)	23 (4.0)	15 (4.4)	2 (2.5)	30 (7.0)	43 (8.7)	22 (6.9)	0.3
4 days of medication use	127 (5.4)	120 (5.9)	77 (5.2)	41 (4.6)	25 (4.3)	16 (4.7)	1 (1.3)	25 (5.9)	39 (7.9)	33 (10.4)	0.4
5 days of medication use	173 (7.4)	156 (7.7)	133 (9.0)	67 (7.6)	35 (6.0)	33 (9.6)	5 (6.3)	28 (6.6)	52 (10.5)	35 (11.0)	0.2
6 days of medication use	320 (13.6)	318 (15.7)	234 (15.9)	135 (15.3)	86 (14.8)	67 (19.6)	22 (27.5)	65 (15.2)	74 (15.0)	56 (17.6)	0.4
7 days of medication use	1243 (52.8)	1000 (49.3)	755 (51.2)	525 (59.5)	360 (62.1)	180 (52.6)	46 (57.5)	126 (29.5)	170 (34.4)	131 (41.2)	0.7
Combined symptom-medication score											
Maximum weekly value – median (IQR)	6.5 (5.7)	14.0 (7.3)	21.0 (8.9)	31.9 (13.3)	43.6 (15.1)	56.4 (19.7)	73.2 (18.5)	32.2 (16.7)	42.0 (19.4)	55.4 (19.6)	4.7
Median weekly value – median (IQR)	3.7 (3.9)	8.6 (5.5)	14.6 (7.0)	23.1 (9.6)	35.0 (14.7)	44.1 (15.9)	69.5 (13.9)	6.7 (7.0)	14.7 (10.1)	29.7 (15.0)	4.7
Weeks during the pollen season – *N* (%)[b]	348 (20.2)	443 (26.9)	310 (27.1)	170 (27.2)	133 (30.2)	75 (27.1)	8 (22.2)	94 (29.8)	122 (34.3)	76 (32.6)	0.3
Maximum weekly VAS eyes – median (IQR)	3 (7)	11 (14)	20 (22)	34 (31)	51 (32)	71 (47)	95 (14)	27 (45)	43 (45)	69 (38)	14.0
Median weekly VAS eyes – median (IQR)	0 (3)	4 (8)	9 (15)	19 (25)	35 (37)	42 (51)	85 (25)	1 (7)	9 (20)	25 (36)	7.7
Maximum weekly VAS nose – median (IQR)	6 (10)	18 (13)	30 (14)	46 (18)	60 (15)	82 (21)	99 (9)	50 (28)	66 (28)	81 (27)	17.0
Median weekly VAS nose – median (IQR)	2 (5)	9 (7)	19 (8)	31 (10)	48 (13)	62 (19)	91 (15)	7 (12)	20 (16)	43 (24)	13.4
Maximum weekly VAS work – median (IQR)	3 (6)	11 (10)	21 (14)	36 (18)	50 (19)	65 (20)	89 (22)	21 (31)	42 (34)	55 (33)	12.2
Median weekly VAS work – median (IQR)	0 (3)	7 (8)	14 (12)	27 (15)	39 (22)	52 (18)	83 (26)	4 (10)	16 (18)	32 (25)	8.3
Baseline *N* AR symptoms – mean (SD)	4.5 (2.1)	4.7 (1.9)	5.0 (1.7)	4.9 (1.7)	4.7 (1.9)	4.9 (1.9)	4.8 (1.4)	4.8 (1.9)	5.0 (1.8)	5.1 (1.8)	0.3
Baseline *N* domains of AR impact – mean (SD)	1.8 (1.5)	1.9 (1.4)	2.1 (1.4)	2.1 (1.4)	2.0 (1.5)	2.1 (1.5)	2.2 (1.2)	1.9 (1.4)	2.0 (1.4)	2.0 (1.3)	0.3
Conjunctivitis – *N* (%)	1643 (69.9)	1534 (75.6)	1180 (79.9)	717 (81.3)	431 (74.3)	259 (75.7)	65 (81.3)	324 (75.9)	401 (81.2)	269 (84.6)	0.4
Self-reported asthma – *N* (%)	921 (39.2)	864 (42.6)	590 (40.0)	357 (40.5)	253 (43.6)	155 (45.3)	27 (33.8)	150 (35.1)	167 (33.8)	112 (35.2)	0.2
VAS asthma											
Maximum value – median (IQR)	1 (6)	6 (15)	6 (23)	11 (40)	28 (55)	51 (75)	60 (87)	5 (31)	9 (46)	18 (67)	1.4
Minimum week value – median (IQR)	0 (0)	0 (4)	0 (7)	0 (15)	5 (35)	9 (47)	3 (56)	0 (0)	0 (3)	0 (8)	1.0

TABLE 2 (Continued)

	Cluster C1	Cluster C2	Cluster C3	Cluster PC1	Cluster PC2	Cluster U1	Cluster U2	Cluster V1	Cluster V2	Cluster V3	Effect size[a]
Weekly range – median (IQR)	1 (5)	4 (10)	4 (15)	9 (23)	9 (25)	21 (38)	9 (33)	4 (27)	8 (41)	15 (53)	1.1
Median week value – median (IQR)	0 (3)	0 (8)	1 (13)	4 (26)	14 (46)	26 (63)	7 (77)	0 (4)	0 (12)	2 (26)	1.0
Total days reporting asthma medication – *N* (%)											
SABA	192 (1.2)	291 (2.0)	314 (3.0)	257 (4.2)	394 (9.7)	358 (15.0)	51 (9.1)	64 (2.1)	98 (2.8)	91 (4.1)	0.6
LABA/LABA + ICS	2687 (16.3)	2872 (20.2)	1777 (17.2)	1050 (17.0)	920 (22.7)	530 (22.1)	48 (8.6)	286 (9.6)	354 (10.2)	249 (11.2)	0.4
ICS	846 (5.1)	539 (3.8)	549 (5.3)	318 (5.2)	257 (6.3)	143 (6.0)	26 (4.6)	97 (3.2)	110 (3.2)	72 (3.2)	0.1
Other	88 (0.5)	121 (0.9)	124 (1.2)	242 (3.9)	86 (2.1)	39 (1.6)	11 (2.0)	7 (0.2)	29 (0.8)	28 (1.3)	0.3

Abbreviations: AH, antihistamines; AR, allergic rhinitis; AzeFlu, Azelastine-fluticasone; ICS, inhaled corticosteroids; INCS, intranasal corticosteroids; IQR, interquartile range; LABA, long-acting beta-agonist; OCS, oral corticosteroids; SABA, short-acting beta-agonist; SD, standard deviation; VAS, visual analogue scale.

[a]Effect size for the largest difference between clusters. All comparisons have a p-value <.001 using classical inferential hypothesis tests (chi-square test for categorical variables and Kruskal–Wallis test for continuous variables). In linear discriminant analysis, the first linear discriminant function achieved a proportion of trace (percentage of separation) of 91.3%. A linear discriminant analysis model based on daily VASs in a training dataset (80% of the assessed sample) was able to correctly predict the cluster for 95.4% of the weeks in a test dataset.

[b]Considering only the weeks reported by European patients, and whose total value is of 1724 for cluster A, 1644 for cluster B, 1143 for cluster C, 626 for cluster D, 441 for cluster E, 356 for cluster F, 315 for cluster G, 277 for cluster H, 233 for cluster I, 36 for cluster J.

also in VASs for specific symptoms and in medication use patterns. Novel findings of this study are summarized in Box S1.

4.1 | Limitations and strengths

As in any cohort study, there are several biases to be considered.[20] In the present study, selection biases mostly concern the fact that MASK-air® users may not be representative of the general population with allergic rhinitis (being younger and, potentially, more affluent and with higher access to care). Nevertheless, the impact of such selection biases may be limited. In a preliminary study, we found that data from patients aged between 65 and 74 years are similar to those of younger patients regarding symptoms and medication use patterns (Taborda-Barata et al., submitted). Symptom and medication use patterns observed in MASK-air® were also consistent with patterns observed from other data sources including online searches on Google Trends, antihistamine sales and classical epidemiologic studies.[21] On the other hand, the assessed sample appears representative of the full MASK-air® database, as the characteristics of the assessed days/users are similar to those of the entire database (Table 1), although the existence of unmeasured confounders (e.g., related to the severity or to the quality of/access to medical care) explaining differences in MASK-air® reporting patterns cannot be discarded. Observational data are also subject to information biases.[22] While the tools for symptom measurement have been largely studied in MASK-air®,[6,8,9,23] users may often provide incorrect information on medication use or on their profile data. Another limitation of this study concerns the impossibility of assessing the effect of medication. Even though we assessed consecutive days of data reporting and compared medication patterns across different clusters, we were not able to assess the modifying effect of different medication classes on reported symptoms. We were also not able to measure potentially-relevant variables for cluster characterisation (which could help, at least partly, to explain differences in symptoms and drug use patterns across clusters), such as patients' ease of access to the healthcare system.

This study also has important strengths. It is the first study to assess MASK-air® data in a longitudinal way, pointing to the possibility of assessing relevant amounts of real-world longitudinal data from patients with allergic rhinitis. Another strength concerns the fact that clusters were obtained based on VAS global, which displays high concurrent validity and reliability as well as moderate responsiveness.[24] Finally, the obtained clusters may not only have face validity (as they correspond—according to a consensus of ARIA experts involved in this study—to medically relevant and recognizable week patterns) but also construct validity. The latter was assessed based on the adoption of two different clustering methods for longitudinal data. That is, the consistency of results obtained with the two different approaches points to the validity of the clusters obtained with our main (longitudinal k-means) approach. However, we were not able to assess criterion validity due to the absence of long-term outcome measures.

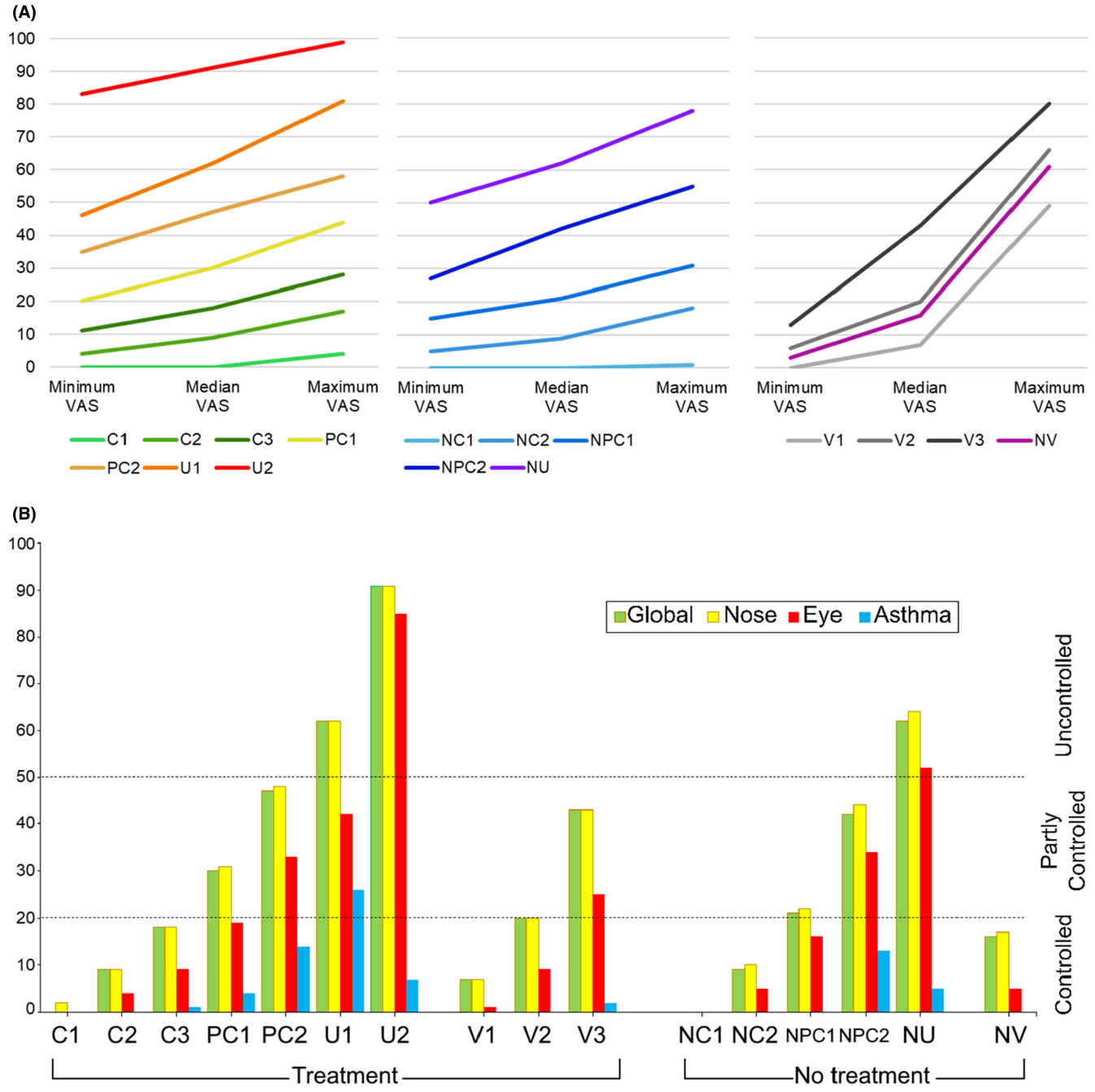


FIGURE 1 Variation of median VAS global levels (A) and median VAS global, nose, eye and asthma levels (B) in the different clusters

4.2 | Interpretation of the data

In the MASK-air® analyses carried out so far,[6,8,9] the unit of analysis had been the days. This implies that symptom trajectories within the same patient cannot be mapped and that results at the day level cannot be inferred at the patient level (the same patient can provide different information on different days). Otherwise, there would be a cross-level bias (from day to patient). In the present study, we moved from days to weeks. Weeks have the advantage of providing information allowing the assessment of the variability of symptoms (in VAS) within a given week. However, we cannot infer from clusters of weeks to clusters of users without incurring again in a cross-level bias, this time from week to patient. In the present study, in order to have an indication of the user diversity over weeks, we estimated the probabilities of users changing from one cluster to another. On the other hand, despite the methods adopted in this study, inferences cannot be made about the temporal relationships between treatments and symptoms. As treatments are used each day and their effect lasts for some hours, establishing such relationships would require obtaining symptom information immediately before and some hours after medication use.

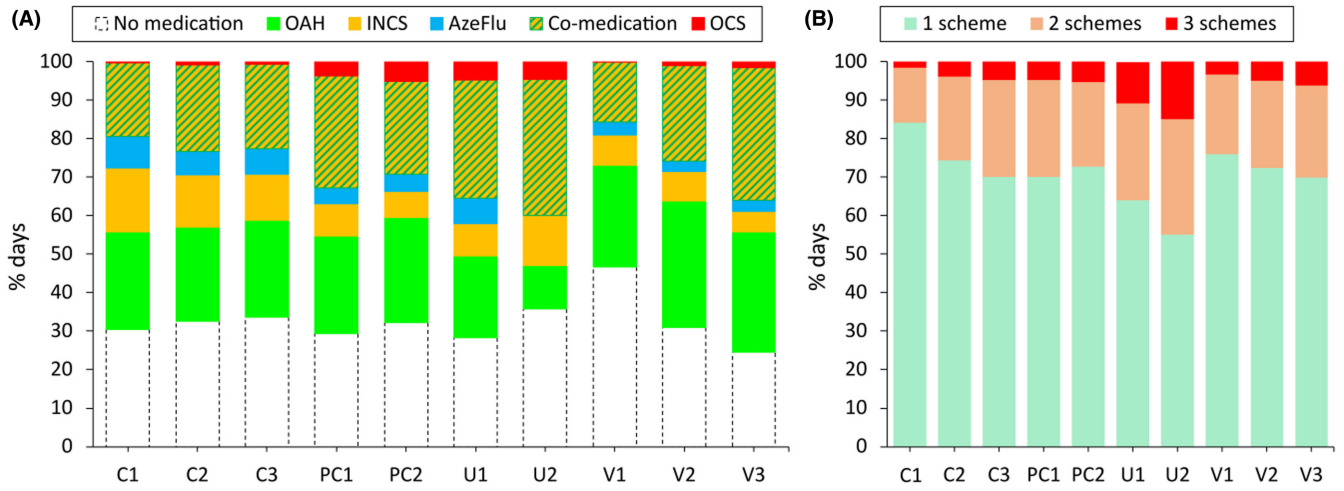


FIGURE 2 Percentage of days under rhinitis medication (A) and percentage of different weekly rhinitis medication schemes (B) for the 10 clusters reporting at least one medication day per week

We identified ten clusters based on VAS global patterns among weeks with medication use and six clusters among weeks when no medication was used. Overall, both for weeks when medication was used and weeks when no medication was used, we identified clusters, which, throughout the whole week, displayed (i) good rhinitis control (low VAS global), (ii) intermediate control, (iii) poor control and (iv) variable control. The latter, however, comprised a minority of weeks.

The study suggests correct discrimination of clusters as shown by VAS for nose, eyes and work as well as medications and the CSMS. Homologous clusters were observed in the "medication" and "no medication" groups, possibly pointing to the fact that control is independent of treatment.[25] Thirty-two (1.3%) users displayed weeks with uncontrolled rhinoconjunctivitis and controlled asthma (U2 cluster). However, such users do not seem to consistently report weeks of cluster U2, having a higher chance of reporting a subsequent week on the cluster U1 than another week on the cluster U2. Therefore, the U2 cluster may not correspond to a specific phenotype of rhinitis patients.

The identified clusters differed in medication use patterns, and the results from this study are consistent with those obtained in previous cross-sectional studies.[6,8,9] In particular, we observed that co-medication and the use of several different medication schemes were more common in weeks of poor rhinitis control, suggesting that (i) when patients are well-controlled, they continue their treatment without major changes, (ii) when patients are poorly controlled, they tend more often to use co-medication and/or to change their medication schemes and (iii) patients with low adherence to their treatments tend to behave differently. These results also suggest that patients are uncertain on how to amend their medication according to their symptoms. They tend to use trial-and-error strategies rather than follow guidelines. Indication on how to step-up and step-down medication depending on symptoms and on expected pollen exposure may be a relevant future step. For this purpose, MASK-air® may play a decisive role, as it could provide alerts to users according to pollen levels, making data easily available (with the patients' consent) to their doctors.

Previous cross-sectional studies have suggested that co-medication cannot be associated with better symptom control at a population level, neither with improved control when compared to individual medications. We had compared data during and outside the pollen season and found similar results concerning monotherapy and co-medication, excluding the bias of performing the study during specific time frames.[9]

In this study, weeks with medication use and with poorer or more variable rhinitis control tended to occur most often in the spring, with the remaining clusters having a less pronounced seasonal profile. This may be associated with the lack of adherence observed in cross-sectional studies,[7] as, in this study, only around 50% of patients reported medication use. However, along with our results on cluster trajectories, this suggests that certain patients may tend to report controlled or partly-controlled weeks for most of the year as well as occasional uncontrolled or variably-controlled weeks during the pollen season.

Cross-sectional studies cannot provide definite information on causal inference. This study is the first longitudinal study with results consistent with those from cross-sectional studies. However, future studies clustering patients reporting several full weeks of data should be performed in order to strengthen these findings.

4.3 | Generalizability

Previously, only AllergyMonitor® had provided longitudinal direct patient data on rhinitis and multimorbidities.[26–28] However, there was no focus on medication use except for adherence. This is, therefore, the first study using mHealth longitudinal direct patient data to assess both symptoms and treatment.

The present study was carried out in 25 countries. We could not assess individual countries due to sample size constraints. However,

TABLE 3 Clusters obtained when considering full weeks with no medication for allergic rhinitis

	Cluster NC1	Cluster NC2	Cluster NPC1	Cluster NPC2	Cluster NU	Cluster NV	Effect size[a]
N weeks (%)	3623 (50.3)	1777 (24.7)	824 (11.5)	466 (6.5)	175 (2.4)	331 (4.6)	–
N days	25,361	12,439	5768	3262	1225	2317	–
N users (average *N* weeks per user)	556 (6.5)	538 (3.3)	291 (2.8)	206 (2.3)	100 (1.8)	234 (1.4)	–
Females – *N* (%)	1602 (44.2)	869 (48.9)	448 (54.4)	332 (71.2)	116 (66.3)	196 (59.2)	0.6
Age – mean (SD)	38.9 (13.9)	40.0 (14.8)	42.3 (15.8)	39.2 (14.4)	39.4 (15.1)	32.6 (11.9)	0.7
VAS global allergy symptoms							
Maximum week value – median (IQR)	1 (6)	18 (10)	31 (11)	55 (16)	78 (23)	61 (20)	6.7
Minimum week value – median (IQR)	0 (0)	5 (7)	15 (8)	27 (16)	50 (19)	3 (7)	5.3
Weekly range – median (IQR)	1 (5)	12 (12)	15 (14)	27 (29)	28 (34)	55 (22)	5.1
Median week value – median (IQR)	0 (1)	9 (5)	21 (7)	42 (12)	62 (12)	16 (14)	11.8
Days with VAS >50 – *N* (%)	0	13 (0.1)	14 (0.2)	744 (22.8)	1032 (84.2)	323 (13.9)	2.3
Combined symptom-medication score							
Maximum weekly value – median (IQR)	1.8 (4.5)	11.6 (7.1)	20.5 (8.8)	40.5 (16.5)	54.8 (19.0)	35.6 (17.6)	5.2
Median weekly value – median (IQR)	0 (1.9)	6.8 (4.7)	15.1 (6.9)	30.0 (15.3)	43.6 (17.6)	10.9 (9.8)	4.9
Weeks during the pollen season – *N* (%)[b]	278 (10.7)	193 (18.0)	92 (19.9)	68 (26.1)	31 (27.9)	58 (26.2)	0.5
Maximum weekly VAS eyes – median (IQR)	0 (4)	11 (15)	24 (18)	50 (31)	69 (35)	36 (47)	3.9
Median weekly VAS eyes – median (IQR)	0 (0)	5 (9)	16 (16)	34 (35)	52 (47)	5 (14)	2.8
Maximum weekly VAS nose – median (IQR)	2 (7)	19 (14)	33 (15)	56 (22)	80 (24)	63 (27)	6.7
Median weekly VAS nose – median (IQR)	0 (2)	10 (7)	22 (9)	44 (14)	64 (16)	17 (21)	8.7
Maximum weekly VAS work – median (IQR)	0 (4)	12 (10)	26 (16)	48 (18)	67 (18)	35 (31)	7.1
Median weekly VAS work – median (IQR)	0 (1)	8 (8)	18 (13)	38 (19)	57 (16)	12 (16)	6.8
Baseline *N* AR symptoms – mean (SD)	4.5 (1.9)	4.6 (1.9)	5.0 (1.8)	4.8 (2.3)	4.8 (2.1)	4.9 (1.9)	0.3
Baseline *N* domains of AR impact – mean (SD)	1.9 (1.4)	1.7 (1.3)	1.9 (1.3)	1.9 (1.4)	2.3 (1.4)	1.8 (1.5)	0.4
Conjunctivitis – *N* (%)	2451 (67.7)	1318 (74.2)	710 (86.2)	346 (74.2)	138 (78.9)	259 (78.2)	0.5
Self-reported asthma – *N* (%)	1300 (35.9)	601 (33.8)	199 (24.2)	129 (27.7)	48 (27.4)	105 (31.7)	0.3
VAS asthma							
Maximum value – median (IQR)	0 (3)	5 (15)	3 (25)	26 (53)	12 (72)	5 (40)	0.9
Minimum week value – median (IQR)	0 (0)	0 (5)	0 (10)	4 (28)	1 (38)	0 (2)	1.0
Weekly range – median (IQR)	0 (3)	4 (10)	3 (14)	10 (26)	8 (25)	5 (35)	0.7
Median week value – median (IQR)	0 (0)	0 (9)	0 (18)	13 (42)	5 (57)	0 (8)	1.0
Total days reporting asthma medication – *N* (%)							
SABA	176 (0.7)	112 (0.9)	31 (0.5)	60 (1.8)	9 (0.7)	37 (1.6)	0.1
LABA/LABA+ICS	1158 (4.6)	1057 (8.5)	365 (6.3)	99 (3.0)	25 (2.0)	108 (4.7)	0.3
ICS	715 (2.8)	573 (4.6)	81 (1.4)	10 (0.3)	7 (0.6)	30 (1.3)	0.3
Other	30 (0.1)	94 (0.8)	6 (0.1)	0	0	2 (0.1)	0.2

Abbreviations: AR, allergic rhinitis; ICS, inhaled corticosteroids; IQR, interquartile range; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist; SD, standard deviation; VAS, visual analogue scale.

[a]Effect size for the largest difference between clusters. All comparisons have a *p*-value <.001 using classical inferential hypothesis tests (chi-square test for categorical variables and Kruskal–Wallis test for continuous variables). In the linear discriminant analysis, the first linear discriminant function achieved a proportion of trace (percentage of separation) of 94.2%. A linear discriminant analysis model based on daily VASs in a training dataset (80% of the assessed sample) was able to correctly predict the cluster for 94.1% of the weeks in a test dataset.

[b] Considering only the weeks reported by European patients, and whose total value is of 2600 for cluster AA, 1071 for cluster BB, 463 for cluster CC, 261 for cluster DD, 221 for cluster EE and 111 for cluster FF.

in previous studies, we had found consistent results in sensitivity analyses for several outcomes in individual countries.[29] Thus, the results presented herein are likely to be generalizable to many developed countries.

5 | CONCLUSIONS

Using MASK-air® data longitudinally, we identified 16 clusters of patterns of weekly rhinitis symptoms. The observed results were

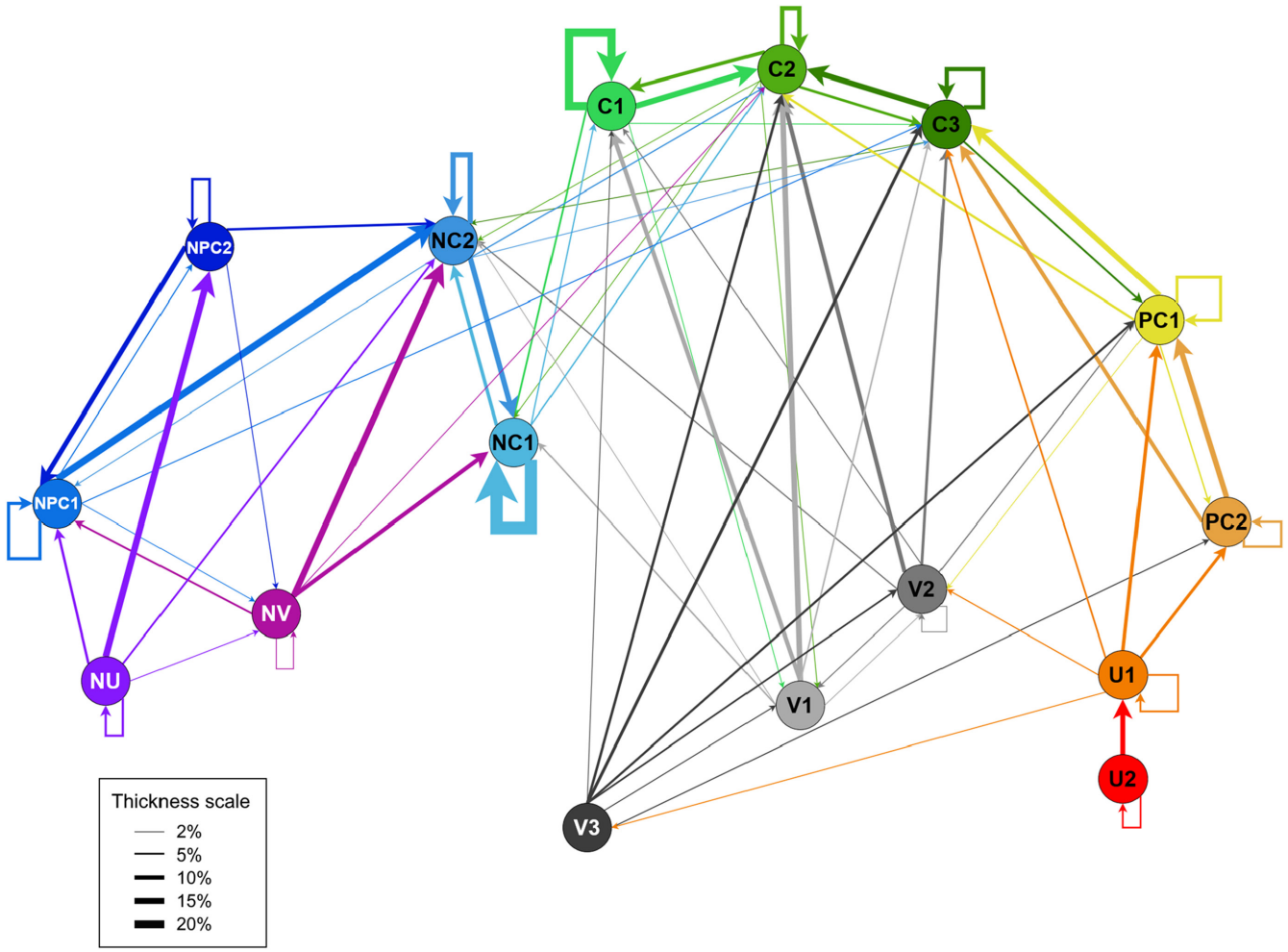


FIGURE 3 Risks of a user reporting another week belonging to the same cluster or to a different cluster. The thickness of the arrows is proportional to the risk. Risks below 2% are not plotted

consistent with those found in previous cross-sectional studies, albeit with a more robust design. In particular, co-medication and changes in medication schemes appear to be common in weeks with higher levels of symptoms, indicating poorer rhinitis control. Such findings reinforce the hypothesis that patients treat themselves according to their symptoms rather than based on guideline recommendations. These findings suggest that guidelines proposing to increase treatment to achieve control need to be revised in order to be centred around the patients.

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AUTHOR CONTRIBUTION

B Sousa-Pinto and J Bousquet proposed the concept of the hypothesis and wrote the paper. B Sousa-Pinto performed the analyses. HJ Schünemann, JM Anto, T Zuberbier and JA Fonseca worked on the concept of the paper and the analysis of the results and reviewed the paper. A Sá-Sousa, RJ Vieira and Rita Amaral participated in the analysis of the data and reviewed the paper. L Klimek, W Czarlewski, J Mullol, O Pfaar and A Bedbrook discussed the analyses and reviewed the paper. L Brussino, V Kvedariene, DE Larenas-Linnemann, Y Okamoto, MT Ventura, KC Bergmann, S Bosnic-Anticevich, V Cardona, P Carreiro-Martins, L Cecchi, C Cingi, AA Cruz, WJ Fokkens, B Gemicioglu, JC Ivancevich, P Kuna, H Kraxner, M Makris, R Monti, M Morais-Almeida, R Mösges, M Niedoszytko, NG Papadopoulos, V Patella, N Pham-Thi, FS Regateiro, S Reitsma, PW Rouadi, B Samolinski, M Sova, A Todo-Bom, L Taborda-Barata, S Toppila-Salmi, J Sastre and I Tsiligianni recruited patients. I Agache, IJ Ansotegui, GW Canonica, T Casale, T Chivato, DK Chu, EM Costa, S Del Giacco, P Devillier, P Eklund, T Haahtela, Z Ispayeva, M Jutel, I Kaidashev, M Khaitov, D Laune, B Lipworth, R Louis, A Sheikh, A Valiulis, O Vandenplas and D Wallace are MASK members. They participated in the concept and in reviewing the analyses. All authors read the paper, most gave some comments and all agreed on its publication. M Khaitov (Moscow) is not a member of the Russian government. M Khaitov participated in the paper in his own capacity.

CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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