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Daily digital biomarkers in the follow-up and clustering of patients with asthma

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ABSTRACT

Background and Research question: We aimed to assess whether levels of digital biomarkers can reflect monthly patterns of asthma control

Study design and methods: We performed a longitudinal study on patients with asthma and comorbid rhinitis who filled ≥26 days of data in a month in the MASK-air® app and who reported at least 1 day of treatment with an inhaled corticosteroid with or without a long-acting β_2-agonist (ICS ± LABA). We applied k-means cluster analysis to define clusters of months according to daily asthma control and medication use. Clusters were compared using digital biomarkers (visual analogue scale [VAS] on asthma symptoms and electronic daily asthma control score [e-DASTHMA]). We compared patients who did not switch with patients who switched their ICS ± LABA.

Results: We assessed 243 patients and 1358 months. We identified three clusters of poor asthma control despite high ICS ± LABA adherence, one cluster of poor asthma control and poor ICS ± LABA adherence, one cluster of good asthma control and high ICS ± LABA adherence and one cluster of good asthma control despite poor ICS ± LABA adherence. These clusters displayed relevant differences in VAS asthma and e-DASTHMA levels. Similar clusters were found in 'non-switchers' *versus* 'switchers'.

Conclusion: Levels of digital biomarkers reflect asthma control patterns and might be used to monitor patients with asthma.

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Asthma; mHealth; inhaled corticosteroids; electronic symptom-medication score; PROMs

Introduction

A digital biomarker is 'a characteristic or set of characteristics, collected from digital health technologies, measured as an indicator of pathogenic processes or responses to an intervention, including therapeutic interventions'.[1] Depending on their individual characteristics, digital biomarkers – which may correspond to patient-reported outcome measures (PROMs) – have the potential to monitor patient health, predict outcomes and/or identify exacerbations at an early stage.[2]

Mobile health apps can be particularly valuable tools for collecting digital biomarkers. In the context of allergic diseases, MASK-air® (Mobile Airways Sentinel NetworK) – an OECD (Organisation of Economic Cooperation and Development) Best Practice in integrated care for chronic diseases[3] – includes several daily PROMs that can be used as digital biomarkers to monitor asthma. They include a visual analogue scale (VAS) assessing the daily impact of asthma symptoms (VAS asthma)[4] and the electronic daily asthma control score (e-DASTHMA).[5,6] VAS asthma is strongly correlated with VAS on dyspnoea[4,7] and small airways resistance.[8] e-DASTHMA is also correlated with VAS dyspnoea and has been validated against the Global Initiative for Asthma (GINA) classification of control.[5] Using these daily PROMs to monitor patients may allow for an assessment of their asthma control and medication-use patterns between consultations. This may facilitate the tailoring of treatment plans – for example, by helping to identify whether patients could benefit from additional medication (e.g., biologics or long-acting muscarinic antagonists, LAMAs) or whether they should increase their treatment adherence to ICS-containing inhalers.

In this study, in patients with asthma under maintenance medication, we aimed to determine whether levels of digital biomarkers (VAS asthma and e-DASTHMA) measured during the first month of treatment can be used to identify relevant patterns of asthma control. We hypothesised that levels of these two biomarkers would differ across distinct patterns of asthma control, adherence to maintenance treatment and use of rescue medication. Our secondary aim was to assess whether similar patterns would be observed in patients who did not switch their asthma maintenance medication versus those who did switch. This study was produced in the context of the ARIA-EAACI Task Force on patient-centred digital biomarkers for allergic diseases and asthma,[2] a project which assessed users of the MASK-air® app with self-reported asthma or rhinitis and which aimed to develop and validate digital PROMs for these two diseases.

Materials and methods

Design of the study

A longitudinal observational study was carried out on patients (i) with asthma and (ii) who reported the use of inhaled corticosteroids (ICS) with or without long-acting β_2 agonists (LABA) during their follow-up. All months with at least 26 days of MASK-air data from patients fulfilling these characteristics were assessed. We clustered months of MASK-air® data (applying a k-means algorithm) to identify patterns of reported symptoms and medication use. We compared clusters on VAS asthma[4] and e-DASTHMA[5] levels. A sensitivity analysis was performed comparing patients using the same maintenance treatment and patients switching their treatments.

Settings and participants

MASK-air® is a mobile app that was launched in 2015. It is freely available on the Google Play and Apple App Stores (www.mask-air.com).[9] We assessed MASK-air® users (i) with self-reported asthma, (ii) with self-reported anytime use of an ICS or an ICS+LABA for at least 1 day and (iii) aged between the age of digital consent (13–16 years depending on the country)[10] and 90 years.[11] We selected all users who had provided at least 26 days of MASK-air® data per month (i.e., at most an average of one missing day per week). We assessed data reported between June 2015 and December 2022 by users from 27 countries. In addition to asthma, all assessed users reported rhinitis symptoms.

Ethics

MASK-air® complies with the General Data Protection Regulation (GDPR).[12] All data are anonymously introduced by users, and geolocation-related data are 'blurred' using k-anonymity.[13] Users consented to having their data analysed for scientific purposes in the terms of use. The use of MASK-air® data has been approved by an independent review board (Köln-Bonn, Germany).[14] Due to this prior approval and to the fact that this is an observational study, a specific ethics committee approval was not required.

Data sources and variables

MASK-air® is an app whose prospective ongoing digital study was initiated in 2015. MASK-air® includes a daily monitoring questionnaire assessing the impact of allergy and asthma symptoms. This questionnaire includes VAS asthma and three other validated VASs on a 0 to 100 scale (with higher values indicating worse symptoms) (Supplementary Table S1). In addition, in the daily monitoring questionnaire, MASK-air® users provide their medication use through a scroll list customised for each country and regularly updated.

Daily symptom and medication data provided by patients allow the calculation of two validated daily combined symptom-medication scores from formulae previously published – the Combined Symptom-Medication Score (CSMS)[15] and e-DASTHMA.[5] The formulae for CSMS and e-DASTHMA used in this study are presented in Supplementary Table S1. Exacerbations were defined not only by the reporting of a poor control of asthma (daily VAS asthma ≥ 36)[16] but also by an increase in VAS asthma levels of at least 80% for three consecutive days from the mean baseline levels of the previous 10 days. This approach was designed

so as to replicate the pattern of the asthma score in the context of exacerbations, as described by Tattersfield et al.[17]

Statistical analysis

When responding to the MASK-air® daily monitoring questionnaire, it is not possible to skip any of the questions, and data are saved to the dataset only after the final answer. This precludes any missing data within each questionnaire. We assessed all data meeting eligibility criteria, with no sample size calculation being performed. All analyses were performed using R (version 4.3.1.).

We performed a cluster analysis of months (at least 26 reporting days) of eligible MASK-air® users. In our main analysis, in order to avoid having multiple months from each user, we selected the first month from users who had reported multiple months. We performed k-means cluster analysis[18] in order to identify clusters of months based on the proportion of days (i) with partly or poorly controlled asthma (VAS asthma >20/100),[16] (ii) with ICS or ICS-LABA use, (iii) with SABA use and (iv) with LAMA or biologics use. The identification of the optimal number of clusters was carried out based on the silhouette method,[19] with need of an average silhouette >0.5.

Obtained clusters were compared on (i) VAS asthma levels, (ii) e-DASTHMA levels, (iii) the adherence to ICS or ICS-LABA (defined as the percentage of days on which these medications were used), (iv) the percentage of days with SABA use and (v) the percentage of days with LAMA or biologics use. Comparisons were performed by calculating effect sizes (which quantify how large the differences between groups are): values <0.2 indicate non-meaningful differences, between 0.2 and 0.5 small differences, between 0.5 and 0.8 moderate differences, and >0.8 large differences.[20]

Sensitivity analysis

Sensitivity analyses were carried out by performing a separate analysis on non-switchers and switchers. Patients were classified into (i) 'non-switchers' if they had only reported one type of the following medication – ICS alone, ICS + formoterol, ICS + salmeterol or ICS + vilanterol and (ii) 'switchers' if they had reported more than one of these medications. In order for patients to be classified as 'switchers' or 'non-switchers', we considered the whole period during which users reported MASK-air® data (i.e., not just the first complete month). That is, the classification of patients as 'switchers' or 'non-switchers' considered data irrespective of the period of time in which the different medications were reported. The rationale for comparing switchers and non-switchers is grounded on the fact that previous MASK-air® studies performed in patients with rhinitis have found that strategies involving the use of co-medication and/or medication from different classes are common, with the use of these strategies being associated to a poor disease control.[21] Switchers and non-switchers were compared by computing effect sizes and by hypothesis tests (e.g., chi-square test for categorical variables and Mann–Whitney U test for continuous variables).

In addition, a sensitivity analysis was performed, clustering all months with at least 26 reporting days from users meeting eligibility criteria (and not solely the first month of MASK-air® use).

Results

Characteristics of the patients

We assessed 243 patients who met the eligibility criteria. In total, these patients reported 1358 months. In our main analysis, we assessed only the first 243 months (i.e., 1 month per patient; corresponding to a total of 7107 reported days) (Supplementary Figure S1). Most patients were female ($N = 146$; 60.1%) and the patients' mean age was of 41.5 years (SD = 14.2). Characteristics of the patients and of the reported days are presented in Table 1.

Table 1. Characteristics of the users and of the reported months.

	Assessed users
N users [*N* reported days][a]	243 [7107]
Age (years) – mean (SD)	41.5 (14.2)
Females – *N* (%)	146 (60.1)
VAS asthma	
Maximum – median (IQR)	30 (45)
Median – median (IQR)	8 (26)
Full/good control days – *N* (%)	4975 (70.0)
Medium control days – *N* (%)	800 (11.3)
Poor control days – *N* (%)	1276 (18.0)
e-DASTHMA	
Maximum – median (IQR)	27.1 (27.4)
Median – median (IQR)	12.9 (20.1)
Asthma treatment days – *N* (%)	4978 (70.0)
Months with exacerbations – *N* (%)	23 (9.5)
ICS/ICS+LABA days – *N* (%)	3993 (56.2)
ICS/ICS+LABA reported – *N* users (%)	
ICS alone	109 (44.9)
ICS + formoterol	101 (41.6)
ICS + salmeterol	34 (14.0)
ICS + vilanterol	20 (8.2)
Other reported asthma treatments – *N* days (%)	
SABA	692 (9.7)
LAMA	241 (3.4)
Biologics	53 (0.7)

e-DASTHMA = Electronic daily control score for asthma; ICS = Inhaled corticosteroids; IQR = Interquartile range; LAMA = Long-acting muscarinic antagonists; SABA = Short-acting beta agonists; SD = Standard-deviation; VAS = Visual analogue scale; [a]The number of users corresponds to the number of reported months.

Clusters in the first month of survey

An optimal number of six clusters was identified from the analysis of the first month of each of the 243 patients (Table 2; an example of each cluster is given in Figure 1 and their interpretability is summarised in Box 1):

Table 2. Characteristics of the clusters of assessed months.

	Cluster A	Cluster B	Cluster C	Cluster D	Cluster E	Cluster F
N months (%)[a]	15 (6.2)	10 (4.1)	30 (12.3)	23 (9.5)	99 (40.7)	66 (27.2)
ICS alone	1 (6.7)	0	11 (36.7)	6 (26.1)	36 (36.4)	32 (48.5)
ICS + formoterol	5 (33.3)	2 (20.0)	8 (26.7)	10 (43.5)	29 (29.3)	20 (30.3)
ICS + salmeterol	0	1 (10.0)	3 (10.0)	1 (4.3)	9 (9.1)	4 (6.1)
ICS + vilanterol	2 (13.3)	0	2 (6.7)	1 (4.3)	7 (7.1)	3 (4.5)
Switchers	7 (46.7)	7 (70.0)	6 (20.0)	5 (21.7)	18 (18.2)	7 (10.6)
VAS asthma						
Maximum – median (IQR)	60 (40)	46 (56)	59 (29)	64 (24)	20 (26)	22 (31)
Median – median (IQR)	37 (32)	22 (21)	33 (20)	33 (23)	5 (11)	0 (5)
Full control days – *N* (%)	6 (1.4)	25 (8.5)	2 (0.2)	10 (1.5)	852 (29.5)	972 (50.2)
Good control days – *N* (%)	132 (30.1)	106 (36.1)	101 (11.6)	167 (24.8)	1800 (62.3)	858 (44.3)
Medium control days – *N* (%)	60 (13.7)	70 (23.8)	270 (30.9)	167 (24.8)	170 (5.9)	63 (3.3)
Poor control days – *N* (%)	241 (54.9)	93 (31.6)	501 (57.3)	329 (48.9)	69 (2.4)	43 (2.2)
e-DASTHMA						
Maximum – median (IQR)	46.6 (18.3)	61.7 (31.8)	46.1 (17.4)	41.7 (18.7)	21.0 (15.3)	16.0 (20.2)
Median – median (IQR)	36.6 (14.7)	47.9 (14.7)	31.9 (9.6)	21.0 (14.0)	12.3 (5.4)	0.3 (4.0)
Months with exacerbations – *N* (%)	0	1 (10.0)	2 (6.7)	6 (26.1)	8 (8.1)	6 (9.1)
Days of ICS/ICS-LABA use – *N* (%)	424 (96.6)	265 (90.1)	853 (97.6)	138 (20.5)	2737 (94.7)	188 (9.7)
Days of SABA use – *N* (%)	402 (91.6)	28 (9.5)	50 (5.7)	95 (14.1)	56 (1.9)	61 (3.2)
Days of LAMA or biologics use – *N* (%)	1 (0.2)	287 (97.6)	1 (0.1)	0	14 (0.5)	0
N females (%)	10 (66.7)	6 (60.0)	20 (66.7)	13 (56.5)	58 (58.6)	39 (59.1)
Age – mean (SD)	48.0 (13.5)	40.8 (8.9)	46.4 (13.8)	43.1 (15.9)	42.2 (14.0)	35.1 (13.3)

ICS = Inhaled corticosteroids; IQR = Interquartile range; LABA = Long-acting beta agonists; LAMA = Long-acting muscarinic antagonists; SABA = Short-acting beta-agonists; VAS = Visual analogue scale; [a]The number of months is the same as the number of patients, as we only considered one month per patient.

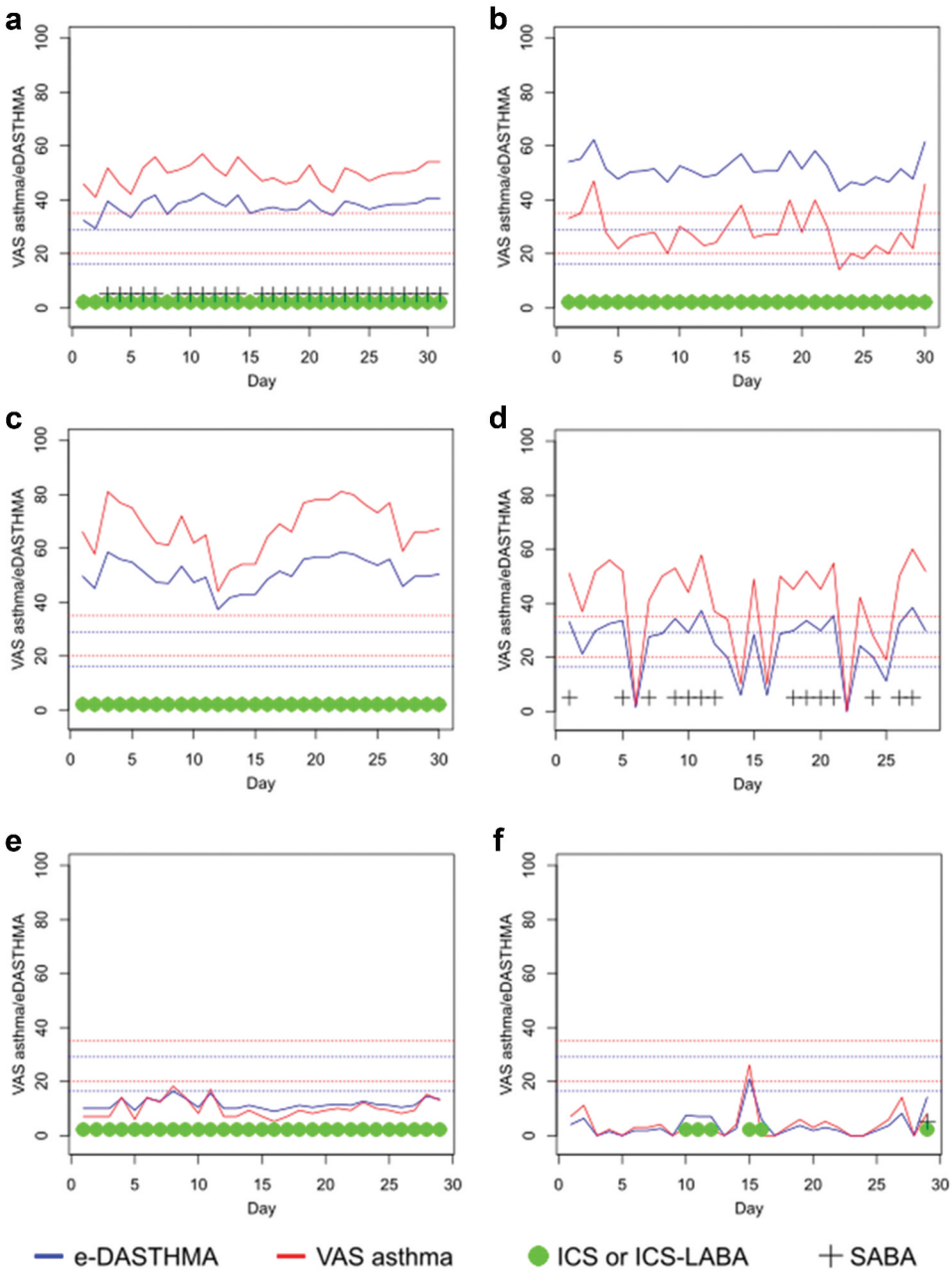

Figure 1. Examples of representative months for each of the clusters. e-DASTHMA = Electronic daily control score for asthma; ICS = Inhaled corticosteroids; LABA = Long-acting beta-agonists; SABA = Short-acting beta-agonists; VAS = Visual analogue scale

Box 1. Interpretability of the identified clusters

Clusters A and B included patients who had poor asthma symptom control despite adherence to treatment. Cluster A was distinguishable from Cluster B by the use of rescue medications, which was higher in Cluster A (in fact, high SABA use was limited to cluster A, which only represents 6% of the cohort). On the other hand, Cluster A was characterised by a lower frequency of use of LAMA or biologics. Patients of this cluster would therefore most probably be those who would benefit the most from the use of these medications. The reason why some patients use SABA, despite a similar low level of asthma control, while others do not, remains elusive and should prompt further research on the motivation of using SABA in patients with uncontrolled asthma.

Cluster C was characterised by less severe patients (less often treated with LAMA or biologicals) with a good adherence to ICS-containing treatments but still symptomatic and not frequently using SABA medications. These patients would possibly benefit from stepping up of treatment, either by LAMA or biologics, according to their immune-inflammatory profile.

Cluster D included patients with asthma who were poorly controlled (including displaying the highest frequency of exacerbations) but were not adherent to their inhalation therapy. These patients should possibly be managed with education on the proper use of medications before considering a step-up in treatment. The reasons for non-adherence have to be evaluated, and switching to a more tailored treatment according to patients' preferences should be considered.

Cluster E was characterised by patients with a good asthma symptoms control associated with a good adherence to asthma treatment. Surprisingly, this subgroup was the largest, as patients with few symptoms would be thought to be less prone to filling in the MASK-air® app every day. However, these results may reflect the 'healthy adherer effect', with patients with good treatment adherence tending to display overall more healthy behaviours (which may include the possibly of answering more often to the MASK-air® daily monitoring questionnaire).

In Cluster F, patients had few asthma symptoms despite low adherence to treatment. This reflects a subgroup of patients with intermittent or mild asthma not requiring daily asthma medications. In fact, this cluster may include those patients in which ICS + formoterol as needed is sufficient to prevent exacerbations and maintain well-controlled asthma. For patients of this group, sharing the information on asthma control and adherence with the treating physician may be important in allowing physicians to properly adapt their prescription to the reality of the patients' needs.

- Cluster A ('high ICS/ICS-LABA adherence, high SABA use, poor control'): This cluster encompassed 15 (6.2%) months. Adherence to ICS/ICS-LABA was high (96.6% of days, respectively). However, SABA use was frequent (91.6%) and most of the days (54.9%) were associated with poor asthma control, with the median VAS asthma and e-DASTHMA both being high (37/100 and 36.6/100, respectively).
- Cluster B ('high ICS/ICS-LABA adherence, high LAMA/biologics use, poor control'): This cluster included 10 (4.1%) months. Both adherence to ICS/ICS-LABA and LAMA or biologics use were high (90.1% and 97.6% of days, respectively). SABA were used occasionally (9.5% days). More than half of the days were associated either with medium or poor asthma control.
- Cluster C ('high ICS/ICS-LABA adherence, low SABA use, poor control'): This cluster included 30 (12.3%) months. Adherence to ICS/ICS-LABA was high (97.6% of days), and SABA, LAMA or biologics use was infrequent. Most days were associated either with poor (57.3%) or medium asthma control (30.9%).
- Cluster D ('low ICS/ICS-LABA adherence, moderate SABA use, poor control'): This cluster comprised 23 (9.5%) months. It was associated with low adherence to ICS/ICS-LABA (20.5% of days) and occasional SABA use (14.1%). In most days, asthma control was poor (48.9%) or medium (24.8%). This was the cluster with the highest frequency of months with exacerbations (26.1%).
- Cluster E ('high ICS/ICS-LABA adherence, low SABA use, good control'): This cluster included 99 (40.7%) months. It was associated with high adherence to ICS/ICS-LABA (94.7% of days) and infrequent use of SABA, LAMA or biologics. Most days were associated with full (29.5%) or good asthma control (62.3%).
- Cluster F ('low ICS/ICS-LABA adherence, low SABA use, good control'): This cluster encompassed 66 (27.2%) months. It was associated with low adherence to ICS/ICS+LABA (9.7% of days), as well as with low use of other asthma drugs. Most days were associated with full (50.2%) or good asthma control (44.3%).

Sensitivity analysis: Clustering months of 'non-switchers' and 'switchers'

One hundred and ninety-three patients (79.4%) were classified as 'non-switchers', while 50 (20.6%) were classified as 'switchers'. Compared to 'non-switchers', 'switchers' displayed higher maximum (median values = 44 *versus* 26; $p = 0.050$, effect size = 0.54) and median (16 *versus* 6; $p = 0.003$; effect size = 0.85) VAS asthma levels, as well as higher maximum (37.4 *versus* 24.4; $p < 0.001$; effect size = 0.61) and median (20.5 *versus* 11.8; $p < 0.001$; effect size = 0.63) e-DASTHMA levels (Supplementary Table S2). The frequency of medium or poorly controlled days was also higher for switchers (37.6%) than non-switchers (27.0%). In addition, 'switchers' displayed a higher frequency of days with SABA use (18.7% *versus* 7.4%; $p < 0.001$; effect size =

Table 3. Interpretation of the clusters of months reported by MASK-air® users.

Asthma control	Adherence to ICS ±LABA	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	C (12.3%)	C′ (14.5%)	–
	Low	Medium		D (9.5%)	D′ (5.2%)	–
Volatile			High	–	–	G″ (12.0%)
Good	High	Low	Low	E (40.7%)	E′ (43.0%)	E″ (18.0%)
	Low			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 maintenance treatment: High > 80%, Low < 80%.
SABA use: High > 80% days, medium 25%, Low < 20%.
LAMA = Long-acting muscarinic antagonists; SABA = Short-acting beta-agonists.

0.34) or with LAMA use (14.7% *versus* 0.5%; $p < 0.001$; effect size = 0.65). The frequency of days of ICS/ICS-LABA use (adherence to maintenance treatment) was higher in the non-switchers than in the switchers (62.1% *versus* 33.1%; $p < 0.001$; effect size = 0.59).

An optimal number of five clusters was identified for 'non-switchers' (Supplementary Table S3), while an optimal number of four clusters was identified for 'switchers' (Supplementary Table S4). Among 'non-switchers', all obtained clusters resembled those of the main analysis (the only exception was cluster B of the main analysis, which did not have a correspondence among clusters of non-switchers). Among 'switchers', there were three clusters analogous to those of the main analysis (clusters A″, E″ and F″). In addition, there was one cluster (G″) characterised by no adherence to ICS/ICS-LABA, occasional SABA use (15.8% of days) and frequent LAMA or biologics use (97.7%). An overall summary and interpretation of clusters is given in Table 3.

Sensitivity analysis: Clustering all months from eligible users

We performed a k-means cluster analysis of all months ($N = 1358$) reported by eligible MASK-air® users. We obtained similar results to those registered when considering only 1 month of reporting per user both when considering the percentage of months per cluster and the characteristics of the clusters in terms of distribution of PROMs and the frequency of use of each medication class (Table 4).

Discussion

This study using validated daily monitoring digital biomarkers shows that patients with asthma treated with ICS ± LABA and using the app regularly can be ascribed to six distinct groups of clinical relevance (Clusters A–F). These groups reflect distinct patterns of asthma control, medication adherence and use of SABA or other

Table 4. Characteristics of the clusters of all reported months by eligible MASK-air® users ($N = 1358$).

	Cluster A	Cluster B	Cluster C	Cluster D	Cluster E	Cluster F
N months (%)	55 (4.1)	34 (2.5)	153 (11.3)	92 (6.8)	632 (46.5)	392 (28.9)
VAS asthma						
Maximum – median (IQR)	36 (52)	52 (68)	55 (24)	55 (35)	17 (22)	17 (28)
Median – median (IQR)	19 (47)	27 (36)	37 (24)	27 (15)	5 (11)	1 (8)
Full control days – *N* (%)	11 (0.7)	37 (3.9)	6 (0.1)	14 (0.5)	4822 (26.5)	5355 (47.4)
Good control days – *N* (%)	780 (50.5)	362 (38.3)	615 (14.2)	597 (22.6)	12,359 (67.6)	5272 (46.7)
Medium control days – *N* (%)	124 (8.0)	172 (17.4)	1255 (28.6)	1119 (42.1)	822 (4.5)	456 (4.1)
Poor control days – *N* (%)	636 (40.7)	392 (40.4)	2530 (57.1)	908 (34.8)	238 (1.3)	201 (1.8)
e-DASTHMA						
Maximum – median (IQR)	38.0 (32.9)	67.0 (38.4)	45.7 (15.6)	36.1 (18.9)	20.4 (15.8)	12.7 (18.7)
Median – median (IQR)	27.6 (31.3)	50.6 (22.1)	30.8 (17.0)	16.7 (9.5)	12.3 (5.1)	1.2 (5.8)
Days of ICS/ICS-LABA use – *N* (%)	1503 (96.8)	893 (92.8)	4258 (96.6)	249 (9.3)	17,584 (96.4)	712 (6.3)
Days of SABA use – *N* (%)	1463 (94.4)	127 (13.0)	190 (4.4)	252 (9.5)	377 (2.1)	180 (1.6)
Days of LAMA or biologics use – *N* (%)	1 (0.1)	942 (97.8)	22 (0.5)	14 (0.5)	58 (0.3)	89 (0.8)
N females (%)	41 (74.5)	27 (79.4)	84 (54.9)	39 (42.4)	353 (55.9)	208 (53.1)
Age – mean (SD)	51.5 (12.1)	43.7 (9.8)	50.5 (11.7)	45.5 (14.9)	45.9 (13.1)	38.6 (15.2)

ICS = Inhaled corticosteroids; IQR = Interquartile range; LABA = Long-acting beta agonists; LAMA = Long-acting muscarinic antagonists; SABA = Short-acting beta-agonists; VAS = Visual analogue scale.

medications. They also differ on their VAS asthma and e-DASTHMA levels. Two-thirds of the patients (i.e., those included in clusters E and F) displayed good asthma control despite displaying different levels of adherence to ICS or ICS-LABA as well as different levels of SABA use. On the other hand, patients from clusters A–D were found to be poorly controlled (with variable levels of adherence), possibly benefitting from referral to a secondary care centre where specific asthma expertise could be obtained. Regarding the comparison between 'non-switchers' and 'switchers', the former displayed a higher frequency of full/good control days and a substantially higher adherence to the ICS/ICS-LABA treatment. The results obtained with the first 243 months of observation were confirmed when using the full dataset of 1358 months.

Limitations and strengths

In this study, only regular MASK-air® users were included. They represent less than 10% of patients, suggesting that possibly only a minority of patients with asthma are expected to answer to the daily monitoring questionnaire on a regular basis (and, therefore, benefit from this type of monitoring between healthcare visits). In addition, these patients may exhibit more of a distinct behavioural profile than the less regular users, limiting the generalisability of the findings and posing the risk of selection biases. The relatively small amount of patients meeting the eligibility criteria also limits the possibility of dividing our sample into a training set and a testing (validation) set. Having a validation sample would allow us to assess whether consistent across-clusters differences would be found when replicating our methodology in a different set of participants. It should be noted that the frequency of patients regularly reporting MASK-air® data increases when patients are actively encouraged by their physicians to use the app and taught how to do so. In fact, this study includes both patients who downloaded the app by themselves and those who started using the app through indication of their physicians. Of note, the demographic and clinical characteristics of the included patients are similar to those of the full dataset (participants who reported at least 1 day of ICS or ICS-LABA even if they did not report at least 1 month of MASK-air® data), with all effect sizes corresponding to trivial differences except in the comparison of the frequency of users reporting ICS alone and of the days under treatment (Supplementary Table 5).

Asthma diagnosis was not made by a physician since we wanted to have a real-life assessment of patients. Therefore, we cannot exclude the possibility of having some misclassified participants, including patients with chronic obstructive pulmonary disease (COPD) without asthma. However, the age distribution of the patients, the female predominance and the presence of nasal symptoms[22] strongly suggest that the frequency of patients with COPD alone may be residual (even though we cannot exclude the possibility of having patients with an asthma-COPD overlap).[23,24] In order to minimise the risk of misclassification of patients with asthma by relying on self-reported asthma alone, we included patients who reported asthma and at least 1 day of ICS or ICS-LABA use. In a previous study, we assessed a sample of MASK-air® patients who had also been assessed by a physician, observing that more than 90% of patients with rhinitis, self-reported asthma and receiving asthma treatment had a physician-made diagnosis of asthma (even when considering that misdiagnosis is common in the primary care setting).[25,26] Thus, although this study does not include patients necessarily recruited by physicians, the diagnosis of asthma is highly likely for most of its participants.

Information on medication use was self-reported by the patients, so that we were not able to confirm its accuracy although a study showed similarity.[25] We do not have information on the dose of ICS, which precludes any firm conclusion on the real severity of asthma. Therefore, although patients from clusters A-C are uncontrolled despite regular maintenance ICS or ICS-LABA treatment, they cannot unequivocally be considered as severe asthmatics. By contrast, cluster D – featuring poor disease control and poor adherence – can be more certainly considered a cluster of 'difficult-to-treat asthma'. Further relevant variables for which we do not have information include those related to the use of healthcare services (e.g., unplanned outpatients visits or emergency department visits). Comparisons based on these outcome variables would further allow to assess the clinical relevance of the identified clusters (that is, if they do not only differ on asthma control levels but also in the need for healthcare services).

Another limitation stems from the possibility of misclassification of 'non-switchers'. In fact, we considered 'non-switchers' as those who only reported an ICS or ICS-LABA during the period in which they reported MASK-air® data. Therefore, we cannot exclude the possibility that some of these participants may have

switched their asthma maintenance treatment in a period during which they did not answer to the MASK-air® daily monitoring questionnaire. However, the most likely effect of this misclassification bias is to 'attenuate' differences between 'non-switchers' and 'switchers' – if all non-switchers would have been correctly classified, we would expect the differences between these two groups of patients to be even larger.

Finally, we have not distinguished patients using ICS + formoterol on a daily basis *versus* those using it on demand (in that case, patients may not be using SABA but ICS + formoterol instead). It is possible that patients using ICS + formoterol on demand are particularly overrepresented in cluster F, as the latter displays a higher frequency of patients with ICS + formoterol and is overall characterised by low ICS/ICS-LABA adherence, low SABA use and good asthma control.

Several apps have been reported in asthma. Some use a pulmonary function test but we did not include this, as asthma control tests do not usually require the reporting of such measurements. In fact, in one study, the Asthma Control Questionnaire (ACQ) was found to be more efficient without than with FEV_1 for the identification of not well controlled asthma.[27] There are also apps that require the use of an inhaler count. However, requiring additional devices could threaten the feasibility of this study. In fact, in order to render it accessible to the largest possible number of patients, the MASK-air® app has been designed to be used without any wearables (being solely based on validated PROMs), making it totally free of charge.

This study also has important strengths. First, it uses validated digital biomarkers. The VAS asthma and the e-DASTHMA were found to have high concurrent validity and intra-rater reliability, and moderate-high responsiveness.[5,28,29] Their cut-offs differentiating good, medium and poor control had also been previously determined.[5,16] Second, this study points to the possibility of classifying patients based on a relatively small number of variables, namely symptoms and medication use data provided during the period of 1 month. This may have relevant clinical implications, helping to easily identify patients who would benefit from increased medication adherence and from a more adequate tailoring of treatment plans. Third, we were able to analyse a relatively large number of MASK-air® users for a full month using validated questionnaires. Finally, this is a study that uses direct patient data, providing a glimpse on the real-life behaviours of patients.

Interpretation

This study is an observational study and is only hypothesis-generating. These clusters need to be confirmed in patients enrolled by specialists after having undergone a full clinical assessment. However, the obtained clusters have a relevant clinical interpretation (Box 1).

This study indicates how a mobile health tool and its digital biomarkers can be used to more adequately follow and manage patients with asthma. In particular, such a tool can retrieve daily monitoring data between consultations, which can then be made available in electronic health records. The obtained clusters can be helpful for informing the patient and the physician about asthma control as well as for supporting therapeutic decisions. It is expected that the classification proposed may be the basis for an algorithm supporting practicing physicians on (i) the stratification of patients for biologics or LAMAs, (ii) the follow-up of patients during treatment and (iii) asthma remission and identification of patients who may be over-treated. MASK-air® is a Medical Device Regulation (MDR) Class IIa, allowing mHealth interactions between physicians and patients as well as recommendations to the patient according to a pre-defined asthma action plan.

While previous studies have applied k-means cluster analysis to group patients with asthma, their goal has been mostly been to classify phenotypes of the disease and not so much their control.[30,31] This is reflected in the fact that the variables used for clustering frequently encompassed some patient baseline characteristics and/or inflammatory biomarkers.

Generalisability

Patients with asthma who did not report rhinitis symptoms were not included and this study cannot be generalised in these patients. However, most patients with allergic asthma have concomitant rhinitis.[32] A recent MASK-air® study found that most of these patients had either under-reported or under-treated rhinitis. It is likely that patients using an app regularly represent a specific subgroup of patients with asthma.

Conclusion

This study enabled the identification of six clusters of monthly patterns of asthma control. However, these results should be confirmed in observational studies of patients with a full phenotypic evaluation. These clusters reflect different levels of asthma symptoms, medication adherence, use of rescue medications and occurrence of exacerbations. Overall, this study demonstrates how a mobile health app and its digital biomarkers can be used to more closely follow and classify patients with asthma, particularly providing information on asthma control and medication adherence between consultations. Such information can support shared decision making on aspects such as the need for stepping up or stepping down asthma medication, or on the provision of education.

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