Development and validation of an electronic daily control score for asthma (e-DASTHMA): a real-world direct patient data study

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Summary

Background Validated questionnaires are used to assess asthma control over the past 1–4 weeks from reporting. However, they do not adequately capture asthma control in patients with fluctuating symptoms. Using the Mobile Airways Sentinel Network for airway diseases (MASK-air) app, we developed and validated an electronic daily asthma control score (e-DASTHMA).

Methods We used MASK-air data (freely available to users in 27 countries) to develop and assess different daily control scores for asthma. Data-driven control scores were developed based on asthma symptoms reported by a visual analogue scale (VAS) and self-reported asthma medication use. We included the daily monitoring data from all MASK-air users aged 16–90 years (or older than 13 years to 90 years in countries with a lower age of digital consent) who had used the app in at least 3 different calendar months and had reported at least 1 day of asthma medication use. For each score, we assessed construct validity, test–retest reliability, responsiveness, and accuracy. We used VASs on dyspnoea and work disturbance, EQ-5D-VAS, Control of Allergic Rhinitis and Asthma Test (CARAT), CARAT asthma, and Work Productivity and Activity Impairment: Allergy Specific (WPAI:AS) questionnaires as comparators. We performed an internal validation using MASK-air data from Jan 1 to Oct 12, 2022, and an external validation using a cohort of patients with physician-diagnosed asthma (the INSPIRERS cohort) who had had their diagnosis and control (Global Initiative for Asthma [GINA] classification) of asthma ascertained by a physician.

Findings We studied 135 635 days of MASK-air data from 1662 users from May 21, 2015, to Dec 31, 2021. The scores were strongly correlated with VAS dyspnoea (Spearman correlation coefficient range 0·68–0·82) and moderately correlated with work comparators and quality-of-life-related comparators (for WPAI:AS work, we observed Spearman correlation coefficients of 0·59–0·68). They also displayed high test–retest reliability (intraclass correlation coefficients range 0·79–0·95) and moderate-to-high responsiveness (correlation coefficient range 0·69–0·79; effect size measures range 0·57–0·99 in the comparison with VAS dyspnoea). The best-performing score displayed a strong correlation with the effect of asthma on work and school activities in the INSPIRERS cohort (Spearman correlation coefficients 0·70; 95% CI 0·61–0·78) and good accuracy for the identification of patients with uncontrolled or partly controlled asthma according to GINA (area under the receiver operating curve 0·73; 95% CI 0·68–0·78).

Interpretation e-DASTHMA is a good tool for the daily assessment of asthma control. This tool can be used as an endpoint in clinical trials as well as in clinical practice to assess fluctuations in asthma control and guide treatment optimisation.

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Introduction

Asthma is defined by the variable intensity of symptoms and airflow obstruction that might resolve spontaneously or after treatment.[1] Poor symptom control is associated with an increased exacerbation risk.[2] The Global Initiative for Asthma (GINA) recommends that

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Research in context

Evidence before this study

Most validated questionnaires for asthma assess disease control for periods of 1 week or more. Complementing information from such questionnaires with information on daily asthma control might help to improve asthma control, allowing for a dual approach such as that used in diabetes (with HbA1c used for long-term monitoring and glycaemia for daily control). However, based on a MEDLINE search done on May 8, 2022, with no language restrictions, using the search terms "asthma" AND "control", we did not find any studies on daily control scores for asthma encompassing information on both symptoms and medication that were internationally validated and using mobile health. Valid and reliable daily asthma control scores are therefore needed to combine patients' symptoms and medications, potentially improving their monitoring in clinical practice.

Added value of this study

In this study, we used real-world data (obtained with an app) from patients with allergic rhinitis and asthma to generate an electronic daily asthma control score as well as to assess its construct validity, test–retest reliability, responsiveness, and accuracy. We assessed data corresponding to 135 635 days of Mobile Airways Sentinel Network for airway diseases use from 1662 users in 27 countries. We developed a set of data-driven candidate scores, which were found to have moderate-to-strong construct validity, high test–retest reliability, and moderate-to-high responsiveness. The best-performing daily asthma control score (e-DASTHMA) displayed high validity and good accuracy in an external validation cohort, with values less than 16·4 (on a 0–100 scale) indicating good asthma control and values more than 28·9 indicating poor asthma control. e-DASTHMA was highly correlated with the Global Initiative for Asthma classification of control in an independent cohort (INSPIRERS).

Implications of all the available evidence

The developed and assessed e-DASTHMA is a digital biomarker that can be used not only as an endpoint in clinical trials, real-world data-based studies, and observational studies, but also in clinical practice. In particular, the daily information provided by e-DASTHMA can complement information provided by questionnaires assessing asthma control for longer periods of time. This finding could be particularly relevant for the optimisation of the care of patients with asthma with fluctuating symptoms.

symptom control should be assessed at every opportunity during treatment.[1]

For asthma, validated questionnaires can be used to assess control for a period of 1–4 weeks[3] (eg, the Asthma Control Questionnaire [ACQ],[4] the Asthma Control Test [ACT],[5] and the Control of Allergic Rhinitis and Asthma Test [CARAT][6]). However, daily control tests are not available (only symptom diaries).[7] A validated daily control score for asthma is therefore needed, allowing short-term fluctuations to be captured and subsequently improving disease monitoring and shared management. Such a biomarker, particularly if mobile health (mHealth)-based, would enable patients and physicians to rapidly analyse results and have timely alerts for uncontrolled disease. However, the transfer of data to physicians requires mobile apps complying with the Medical Device Regulation class IIa.[8] In addition, mHealth tools used to develop and validate daily control scores should include validated questions or questionnaires. Among the 23 apps with more than 10 000 downloads identified when searching for the term asthma in the Google Play or Apple app stores, Mobile Airways Sentinel Network for airway diseases (MASK-air) is the only Medical Device Regulation class IIa app that enables patients to report daily asthma symptoms and medication use, and the only one with published assessments on the validity, reliability, and responsiveness of its daily asthma symptoms questions (appendix pp 3–4). In fact, MASK-air has already enabled the development of a daily control score for rhinitis: the combined symptom–medication score.[9]

We aimed to develop and validate an electronic daily control score for asthma (e-DASTHMA) on the basis of MASK-air data, supporting patients with asthma in the daily assessment of their disease, in terms of control, monitoring, and self-management. Given the common variables and challenges, we aimed to use an approach analogous to that applied to the development of the combined symptom–medication score,[9] with the development of data-driven candidate scores (applying clustering and regression methods) and the subsequent assessment of their validity, reliability, and responsiveness.

Methods

Study design and participants

We used MASK-air data[10] to develop and assess different daily control scores for asthma. Such scores were developed using patients treated for asthma using different data-driven methodological approaches given the absence of a single gold standard. For each score, we assessed construct validity, test–retest reliability, and responsiveness. We performed internal validation in a different MASK-air sample (the 2022 internal validation cohort). We also performed an external validation of the developed scores using data from a cohort of patients with physician-diagnosed asthma and who used the InspirerMundi app (INSPIRERS cohort).[11] This study followed the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) and the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis recommendations.[12] The protocol of this study is available in the appendix (pp 21–29).

MASK-air is Conformité Européene-registered and follows the EU General Data Protection Regulation. An independent review board approval was not required for this specific study because the use of MASK-air secondary data for research purposes was approved by an independent review board (Köln-Bonn, Germany; reference number 17–069), all data were anonymised before the study using k-anonymity, and users agreed to the analysis of their data for research purposes in the terms of use for MASK-air (translated into all languages and customised according to the legislation of each country). The INSPIRERS studies involved a physician evaluation and had ethics committee approval from participating centres.[11]

MASK-air is an app (that will become a DG Santé Good Practice in March 2023, which is a strategy, approach, or activity that has been shown through research and evaluation to be effective, efficient, sustainable, or transferable, or a combination, and to reliably lead to a desired result) for digitally enabled, patient-centred care in rhinitis and asthma multimorbidity.[10] This app is freely available in 27 countries. We included data collected from May 21, 2015, to Dec 31, 2021 for the development and validation of daily control scores (the derivation cohort). MASK-air data from Jan 1 to Oct 12, 2022 were used to further validate the developed scores (the 2022 internal validation cohort). The InspirerMundi app has been available since 2017 and is currently freely available in Portugal and Spain. We included data from Nov 15, 2019, to Dec 8, 2020 (the external validation cohort).

We included the daily monitoring data from all MASK-air users aged 16–90 years (or older than 13 years to 90 years in countries with a lower age of digital consent: Belgium, Denmark, Portugal, Sweden, Switzerland, the UK, Finland, Canada, Argentina, Mexico, Japan, Australia, Brazil, Türkiye, and Lebanon [minimum age 13 years]; Austria, Italy, Lithuania, and Spain [minimum age 14 years]; Czech Republic, Slovenia, and France [minimum age 15 years]; and the Netherlands, Poland, Germany, and Greece [minimum age 16 years]) who had used the app in at least 3 different calendar months and had reported at least 1 day of asthma medication use, as in a previous study.[13]

The developed scores were externally validated using data from Portuguese users of the InspirerMundi app older than 13 years up to 70 years, who had had their diagnosis and control (GINA classification) of asthma determined by a physician, had answered the daily monitoring questionnaire at least once, and had reported at least 1 day of asthma medication use (INSPIRERS cohort).[11] Medical visits for these patients took place in 32 hospital care centres and 17 primary care centres in Portugal.

Data sources and variables

MASK-air comprises daily monitoring questions using visual analogue scales (VASs; a 0–100 scale) on overall

	MASK-air days (n=135 635)
Number of users (average number of days per user)*	1662 (81·6)
Women	79 544 (58·6%)
Men	56 091 (41·4%)
Age, mean (SD)	41·8 (14·8)
Total days reporting asthma medication	82 701 (61·0%)
Inhaled corticosteroids without long-acting β-agonists	28 978 (21·4%)
Inhaled corticosteroids and long-acting β-agonists (except formoterol)	15 858 (11·7%)
Inhaled corticosteroids and formoterol	32 350 (23·9%)
Short-acting β-agonists or short-acting muscarinic antagonists	10 129 (7·5%)
Oral steroids	54 (<0·1%)
Biological drugs or long-acting muscarinic antagonists	3643 (2·7%)
Other asthma drugs†	19 155 (14·1%)
VAS asthma, median (IQR)	7 (20)
VAS dyspnoea,‡ median (IQR)	33 (37)
VAS global allergy symptoms, median (IQR)	10 (22)
VAS ocular symptoms, median (IQR)	5 (17)
VAS nasal symptoms, median (IQR)	11 (24)
VAS work,§ median (IQR)	8 (20)
CARAT,¶ median (IQR)	15 (12)
CARAT rhinitis,¶ median (IQR)	5 (8)
CARAT asthma,¶ median (IQR)	10 (7)
EQ-5D VAS,‖ median (IQR)	85 (26)
WPAI:AS activities,** median (IQR)	19 (46)
WPAI:AS work,†† median (IQR)	25 (55)
Self-reported allergic rhinitis	122 684 (90·5%)
Allergic rhinitis combined symptom–medication score, median (IQR)	11 (17)
Total days reporting rhinitis medication	74 247 (54·7%)
Oral antihistamines monotherapy	21 059 (15·5%)
Intranasal steroids monotherapy	15 892 (11·7%)
Azelastine–fluticasone monotherapy	5952 (4·4%)
Oral antihistamines and intranasal steroids	15 769 (11·6%)
Azelastine-fluticasone and other rhinitis medication	6396 (4·7%)
Conjunctivitis	96 371 (71·1%)

Data shown as n (%), unless otherwise stated. Data shown are from the MASK-air derivation cohort, collected from May 21, 2015, to Dec 31, 2021. Ethnicity data were not available. CARAT=Control of Allergic Rhinitis and Asthma Test. MASK-air=Mobile Airways Sentinel Network for airway diseases. VAS=visual analogue scale. WPAI:AS=Work Productivity and Activity Impairment: Allergy Specific. *Average MASK-air adherence (proportion of reported MASK-air days in the time period between the first use of the app and Dec 31, 2021): 10%. †Includes leukotriene receptor antagonists, mast cell stabilisers, and xanthines. ‡Number of observations, 60 210 (SD 24·3). §Number of observations, 12 339 (SD 18·1). ¶Number of observations, 1555 to CARAT complete, SD 7·7; to CARAT rhinitis, SD 4·2; to CARAT asthma, SD 4·5. ‖Number of observations, 16 535 (SD 19·7). **Number of observations, 1205 (SD 27·3). ††Number of observations, 803 (SD 29·2).

Table 1: **Description of the number of days on which participants used MASK-air from assessed MASK-air users on the basis of which daily control scores were developed and validated**

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***Panel*: Formula for the computation of data-driven electronic daily control scores for asthma**

Cluster-based scores

Clusters defined based on Control of Allergic Rhinitis and Asthma Test (CARAT) asthma and Work Productivity and Activity Impairment: Allergy Specific (WPAI:AS) activities: ([0·066 × visual analogue scale (VAS) asthma] + [2·505 if inhaled corticosteroids without long-acting β-agonists (LABA) are used] + [1·652 if inhaled corticosteroids with LABA, excluding formoterol, are used] + [1·275 if inhaled corticosteroids with formoterol are used] + [0·112 if short-acting β-agonists (SABA) or short-acting muscarinic antagonists (SAMA) are used] + [2·752 if biological drugs or long-acting muscarinic antagonists (LAMA) are used] + [1·896 if other asthma drugs* are used] + [2·240 if the patient is younger than 30 years]) × 6·209

Clusters defined based on CARAT asthma and WPAI:AS work: ([0·089 × VAS asthma] + [2·014 if inhaled corticosteroids without LABA are used] + [0·289 if inhaled corticosteroids with LABA, excluding formoterol, are used] + [1·485 if inhaled corticosteroids with formoterol are used] + [0·468 if SABA or SAMA are used] + [3·319 if biological drugs or LAMA are used]) × 6·802

Clusters defined based on CARAT asthma, WPAI:AS activities, and WPAI:AS work: ([0·086 × VAS asthma] + [1·756 if inhaled corticosteroids without LABA are used] + [0·859 if inhaled corticosteroids with LABA, excluding formoterol, are used] + [1·238 if inhaled corticosteroids with formoterol are used] + [0·559 if SABA or SAMA are used] + [4·022 if biological drugs or LAMA are used]) × 6·695†

Clusters defined based on CARAT complete and WPAI:AS activities: ([0·060 × VAS asthma] + [2·255 if inhaled corticosteroids without LABA are used] + [1·486 if inhaled corticosteroids with LABA, excluding formoterol, are used] + [1·220 if inhaled corticosteroids with formoterol are used] + [0·400 if SABA or SAMA are used] + [2·374 if biological drugs or LAMA are used] + [1·688 if other asthma drugs* are used] + [1·726 if the patient is younger than 30 years]) × 6·924

Clusters defined based on CARAT complete and WPAI:AS work: ([0·075 × VAS asthma] + [2·049 if inhaled corticosteroids without LABA are used] + [0·180 if inhaled corticosteroids with LABA, excluding formoterol, are used] + [1·480 if inhaled corticosteroids with formoterol are used] + [0·533 if SABA or SAMA are used] + [3·728 if biological drugs or LAMA are used]) × 7·241

Clusters defined based on CARAT complete, WPAI:AS activities, and WPAI:AS work: ([0·081 × VAS asthma] + [1·901 if inhaled corticosteroids without LABA are used] + [0·687 if inhaled corticosteroids with LABA, excluding formoterol, are used] + [1·380 if inhaled corticosteroids with formoterol are used] + [0·556 if SABA or SAMA are used] + [4·037 if biological drugs or LAMA are used]) × 6·852

Linear regression-based scores

Dependent variable corresponding to CARAT asthma: ([0·093 × VAS asthma] + [0·203 if inhaled corticosteroids without LABA are used] + [0·188 if inhaled corticosteroids with LABA, excluding formoterol, are used] + [0·547 if inhaled corticosteroids with formoterol are used] + [0·145 if SABA or SAMA are used] + [2·121 if biological drugs or LAMA are used] + [0·975 if other asthma drugs* are used] + [1·000 if the patient is female] + [1·240 if the patient is aged 30–64 years]) × 6·524

Dependent variable corresponding to CARAT complete: ([0·141 × VAS asthma] + [1·380 if inhaled corticosteroids without LABA are used] + [2·521 if inhaled corticosteroids with LABA, excluding formoterol, are used] + [2·325 if inhaled corticosteroids with formoterol are used] + [1·337 if SABA or SAMA are used] + [4·969 if biological drugs or LAMA are used] + [2·460 if other asthma drugs* are used] + [1·253 if the patient is female]) × 3·754

All scores are expressed on a scale of 0 to 100, with higher values indicating worse allergic rhinitis control. If no symptoms or medication are reported, scores should be recorded as 0. For each model, coefficients correspond to those obtained using multivariable regression models.

*Includes leukotriene receptor antagonists, mast cell stabilisers, and xanthines. †This is the score that corresponds to the electronic daily control score for asthma.

allergic, nasal, ocular, and asthma symptoms (appendix p 5). In addition, users reporting that they were working were asked how much allergic symptoms affected work activities on that day (VAS work). MASK-air VASs have been assessed on their validity, reliability, and responsiveness.[14] MASK-air users were also asked to provide the medication they used each day using a regularly updated list customised for each country and including all over-the-counter and prescribed asthma medications.

In addition to daily symptom monitoring, MASK-air users were able to respond (albeit non-mandatorily) to the other questionnaires that were used in this study as comparators of the developed scores (full description in the appendix pp 6–7). These questionnaires included: (1) CARAT, which assesses the control of allergic rhinitis and asthma in the previous 4 weeks,[15] and can be divided into two components: CARAT rhinitis questions (questions 1–4) and CARAT asthma questions (questions 5–10); (2) Work Productivity and Activity Impairment: Allergy Specific (WPAI:AS), which is a nine-item questionnaire assessing the productivity effect of allergies over the previous week[16] (both the percent overall work impairment due to allergy [WPAI:AS work] and the degree allergy affected regular activities [WPAI:AS activities], both expressed as percentages, were used as comparators); and (3) EQ-5D-5L, which assesses the respondents' health status through five dimensions or questions followed by a VAS assessing the

	VAS dyspnoea (n=12 339)	EQ-5D VAS (n=16 535)	CARAT (n=1555)	CARAT asthma (n=1555)	VAS work (n=60 208)	WPAI:AS activities (n=1205)	WPAI:AS work (n=803)
Cluster-based scores							
CARAT asthma and WPAI:AS activities	0·68 (0·67 to 0·69)	−0·31 (−0·32 to −0·29)	−0·34 (−0·39 to −0·30)	−0·42 (−0·47 to −0·38)*	0·43 (0·43 to 0·44)	0·51 (0·46 to 0·56)*	0·64 (0·59 to 0·68)
CARAT asthma and WPAI:AS work	0·79 (0·78 to 0·80)	−0·40 (−0·41 to −0·39)	−0·39 (−0·43 to −0·34)	−0·46 (−0·50 to −0·42)*	0·54 (0·54 to 0·55)	0·54 (0·49 to 0·59)	0·68 (0·63 to 0·72)*
CARAT asthma and WPAI:AS activities and work	0·79 (0·78 to 0·80)	−0·40 (−0·42 to −0·39)	−0·36 (−0·41 to −0·32)	−0·45 (−0·49 to −0·41)*	0·56 (0·55 to 0·56)	0·50 (0·44 to 0·54)*	0·65 (0·60 to 0·69)*
CARAT complete and WPAI:AS activities	0·69 (0·68 to 0·70)	−0·31 (−0·32 to −0·29)	−0·35 (−0·40 to −0·30)*	−0·43 (−0·47 to −0·38)	0·44 (0·44 to 0·45)	0·51 (0·46 to 0·56)*	0·64 (0·60 to 0·68)
CARAT complete and WPAI:AS work	0·75 (0·75 to 0·76)	−0·38 (−0·39 to −0·36)	−0·35 (−0·40 to −0·30)*	−0·42 (−0·47 to −0·38)	0·52 (0·51 to 0·53)	0·52 (0·47 to 0·56)	0·65 (0·59 to 0·69)*
CARAT complete and WPAI:AS activities and work	0·77 (0·76 to 0·78)	−0·39 (−0·40 to −0·37)	−0·35 (−0·40 to −0·31)*	−0·43 (−0·48 to −0·39)	0·54 (0·53 to 0·54)	0·50 (0·45 to 0·54)*	0·64 (0·59 to 0·68)*
Linear regression-based scores							
CARAT asthma as dependent variable	0·82 (0·81 to 0·83)	−0·46 (−0·47 to −0·45)	−0·47 (−0·51 to −0·43)	−0·55 (−0·59 to −0·51)*	0·61 (0·60 to 0·61)	0·49 (0·44 to 0·53)	0·65 (0·60 to 0·69)
CARAT complete as dependent variable	0·78 (0·77 to 0·79)	−0·39 (−0·40 to −0·38)	−0·35 (−0·40 to −0·31)*	−0·47 (−0·51 to −0·42)	0·56 (0·55 to 0·56)	0·43 (0·39 to 0·48)	0·59 (0·54 to 0·64)

Data shown as Spearman correlation coefficients (95% CIs) for the correlation between each score and each validated comparator. WPAI:AS work refers to the percent overall work impairment due to allergy, and WPAI:AS activities refers to the degree allergy affected regular activities. CARAT=Control of Allergic Rhinitis and Asthma Test. MASK-air=Mobile Airways Sentinel Network for airway diseases. VAS=visual analogue scale. WPAI:AS=Work Productivity and Activity Impairment: Allergy Specific. *The comparators used in the generation of the respective scores.

Table 2: **Construct convergent validity of electronic daily control scores for asthma (data from the MASK-air derivation cohort)**

	CARAT rhinitis (n=1555)	VAS nasal symptoms (n=135 530)	VAS ocular symptoms (n=135 530)
Cluster-based scores			
CARAT asthma and WPAI:AS activities	−0·18 (−0·23 to −0·13)	0·35 (0·34 to 0·35)	0·30 (0·30 to 0·31)
CARAT asthma and WPAI:AS work	−0·22 (−0·27 to −0·17)	0·44 (0·43 to 0·44)	0·42 (0·42 to 0·43)
CARAT asthma and WPAI:AS activity and work	−0·18 (−0·23 to −0·13)	0·44 (0·44 to 0·45)	0·43 (0·42 to 0·43)
CARAT complete and WPAI:AS activities	−0·18 (−0·23 to −0·13)	0·36 (0·35 to 0·36)	0·31 (0·31 to 0·32)
CARAT complete and WPAI:AS work	−0·19 (−0·24 to −0·14)	0·42 (0·41 to 0·42)	0·40 (0·40 to 0·41)
CARAT complete and WPAI:AS activities and work	−0·18 (−0·23 to −0·13)	0·43 (0·43 to 0·44)	0·41 (0·41 to 0·42)
Linear regression-based scores			
CARAT asthma as dependent variable	−0·27 (−0·31 to −0·23)	0·49 (0·49 to 0·50)	0·48 (0·48 to 0·49)
CARAT complete as dependent variable	−0·14 (−0·20 to −0·10)	0·46 (0·45 to 0·46)	0·43 (0·43 to 0·44)

Data shown as Spearman correlation coefficients (95% CIs) for the correlation between each score and each validated comparator. WPAI:AS work refers to the percent overall work impairment due to allergy, and WPAI:AS activities refers to the degree allergy affected regular activities. CARAT=Control of Allergic Rhinitis and Asthma Test. MASK-air=Mobile Airways Sentinel Network for airway diseases. VAS=visual analogue scale. WPAI:AS=Work Productivity and Activity Impairment: Allergy Specific.

Table 3: **Discriminant validity of electronic daily control scores for asthma (data from the MASK-air derivation cohort)**

general health status on that day;[17] in this study, we used the EQ-5D-VAS as a comparator.

Biases

Potential misclassification stemming from selecting patients solely based on self-reported asthma was addressed by identifying MASK-air users with asthma based on their treatment (ie, MASK-air users were deemed to have asthma by assessing their treatment). In addition, a cohort of patients with a physician-based asthma diagnosis was used for external validation. Difficulties in the identification of a single suitable comparator were overcome by the simultaneous use of several comparators.

Statistical analysis

We did not perform a sample size calculation, but rather analysed all data from users meeting the eligibility criteria. A full description of the data analysis is provided in the appendix (pp 1–2).

Derivation of the asthma daily control scores

In MASK-air users, we developed eight scores: six using k-means clustering-based approaches and two using multiple linear regression-based approaches. In the k-means-based approach, clusters were defined according to either: (1) CARAT or CARAT asthma; and (2) WPAI:AS activities or WPAI:AS work, or both. These approaches

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	Correlation with asthma effect on work or school activities (Spearman correlation coefficient [95% CI])	Accuracy of the identification of patients with uncontrolled or partly controlled asthma* (AUC-ROC [95% CI])
Cluster-based scores		
CARAT asthma and WPAI:AS activities	0·50 (0·41–0·59)	0·69 (0·64–0·75)
CARAT asthma and WPAI:AS work	0·66 (0·57–0·78)	0·75 (0·69–0·80)
CARAT asthma and WPAI:AS activities and work	0·70 (0·61–0·78)	0·73 (0·68–0·78)
CARAT complete and WPAI:AS activities	0·54 (0·43–0·63)	0·71 (0·65–0·76)
CARAT complete and WPAI:AS work	0·63 (0·52–0·72)	0·75 (0·70–0·80)
CARAT complete and WPAI:AS activities and work	0·68 (0·58–0·76)	0·74 (0·69–0·79)
Linear regression-based scores		
CARAT asthma as dependent variable	0·66 (0·57–0·74)	0·74 (0·69–0·79)
CARAT complete as dependent variable	0·64 (0·54–0·72)	0·74 (0·69–0·79)

N=425 days from 69 participants. WPAI:AS work refers to the "percent overall work impairment due to allergy", and WPAI:AS activities refers to the "degree allergy affected regular activities". AUC-ROC=area under the receiver operating characteristic curve. CARAT=Control of Allergic Rhinitis and Asthma Test. WPAI:AS=Work Productivity and Activity Impairment: Allergy Specific. *Global Initiative for Asthma definition.

Table 4: **Results of the validation of the electronic daily control scores in asthma using data from the INSPIRERS studies**

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allowed us to differentiate the worst controlled cases (the cluster containing the observations indicating the lowest asthma control and a highest effect of allergy on work or activities) from all other cases. This classification was used as the dependent variable in multivariable logistic regression models, whereas the independent variables consisted of VAS asthma, daily asthma medication use, gender, and age group (<30 years, 30–64 years, and ≥65 years). Regression coefficients were then used in the asthma daily control scores according to clinical and statistical criteria. In the linear regression-based approach, CARAT or CARAT asthma were used as the dependent variables. Independent variables consisted of VAS asthma, daily asthma medication use, gender, and age group. Regression coefficients were used in asthma daily control scores according to clinical and statistical criteria.

Validation of daily control scores using MASK-air data

We assessed the construct validity, test–retest reliability, and responsiveness of developed asthma daily control scores using MASK-air data. First, we assessed those properties in the MASK-air sample on the basis of which daily control scores were developed (the derivation cohort). Subsequently, we analysed a different MASK-air sample (the 2022 internal validation cohort).

For construct validity, Spearman correlation coefficients were computed to assess the correlation between each score and VAS dyspnoea, CARAT, CARAT asthma, VAS work, WPAI:AS work, WPAI:AS activities, and EQ-5D-VAS (convergent validity), as well as CARAT rhinitis, VAS nasal symptoms, and VAS ocular symptoms (discriminant validity).

Test–retest reliability was assessed in users who were clinically stable (ie, those who had been stable for 3 to 5 weeks), whereas responsiveness was assessed in users displaying a clinical change. Both clinical stability and clinical change were defined on the basis of the minimal important difference for validated comparators (appendix p 6) in different assessments (separate analyses were performed considering time periods of 3 weeks and 5 weeks apart).[18] Reliability was expressed by intraclass correlation coefficients.[19] Responsiveness was expressed by correlation coefficients between changes in scores and by effect size measures.[20]

External validation of the asthma daily control scores using INSPIRERS data

Asthma daily control scores were assessed using data from INSPIRERS patients with asthma. We assessed the correlation between each score and the reported daily effect of asthma symptoms in work or school activities (registered in the InspirerMundi app). We also compared, by computing areas under the receiver operating characteristic curves (AUC-ROC), the performance of the developed scores with the GINA classification of patients assessed at medical evaluation.[1]

Selection of the e-DASTHMA

The daily control score displaying the best performance was identified as being e-DASTHMA. To select the best performance score, we computed average correlation coefficients, intraclass correlation coefficients, effect size measures, and the AUC-ROC for each score, with relative values then being computed in function of the maximal obtained score; and we subsequently calculated the number of correlation coefficients, intraclass correlation coefficients, effect size measures, or AUC-ROC whose values were more than those indicated by COSMIN guidelines as corresponding to good validity (correlation coefficient more than 0·5), reliability (intraclass correlation coefficient more than 0·7), responsiveness (correlation coefficient [or effect size measure] more than 0·5), or accuracy (AUC-ROC more than 0·7).

Sensitivity analyses

The validity, reliability, and responsiveness of the asthma daily control score displaying the best performance (e-DASTHMA) were assessed in MASK-air users with and without self-reported allergic rhinitis and conjunctivitis. We also assessed the construct validity of the e-DASTHMA in individual countries reporting more than 200 observations.

Role of the funding source

There was no funding source for this study.

Results

We developed and validated daily control scores based on 135 635 observations (days) of MASK-air use from 1662 users (mean age 41·8 years, SD 14·8 years; 79 544 [58·6%] days from women, 56 091 [41·4%] days

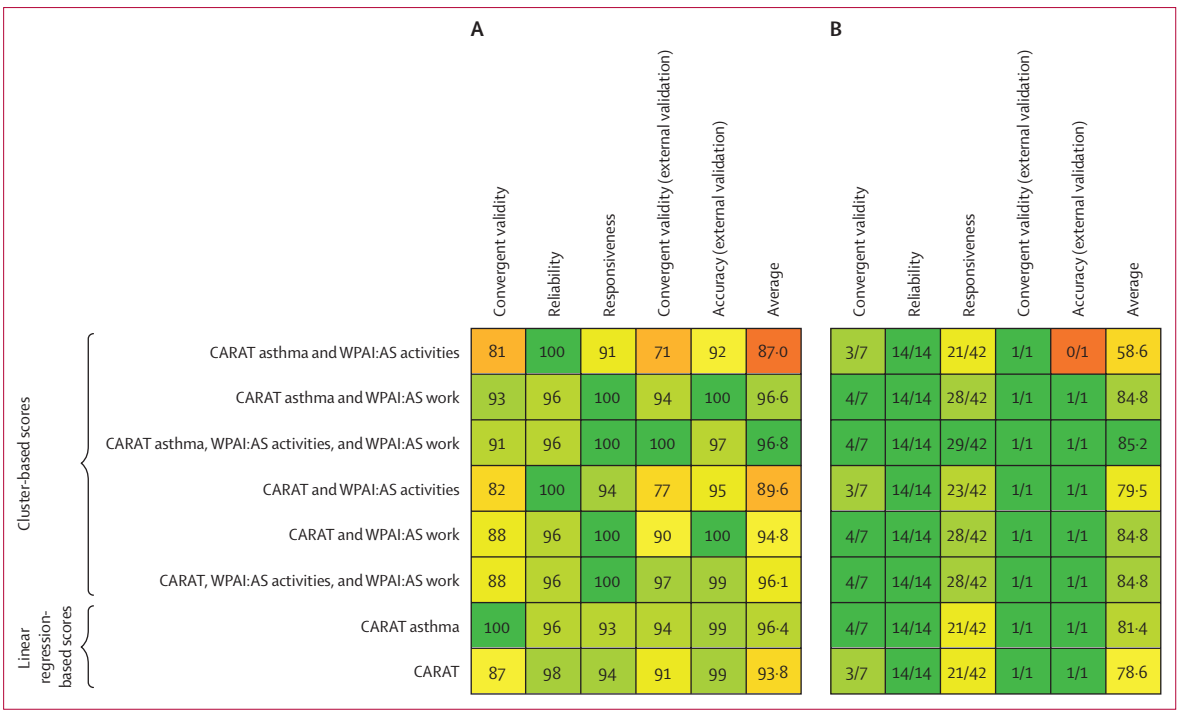

Figure 1: **Ranking of the properties of the developed electronic daily control scores for asthma**
(A) Average correlation coefficients, intraclass correlation coefficients, effect size measures, or AUC-ROC were computed for each score; relative values were then computed in function of the maximal obtained score (eg, for convergent validity, the maximum average of Spearman correlation coefficients was obtained with the linear regression-based score having CARAT asthma as the dependent variable; the average of Spearman correlation coefficients for the score obtained with linear regression-based methods with CARAT complete as the dependent variable was 87% of that of the maximum value). (B) The number of correlation coefficients, intraclass correlation coefficients, effect size measures, or AUC-ROC whose values were more than those indicated by COSMIN guidelines as corresponding to good validity (correlation coefficient more than 0·5), reliability (intraclass correlation coefficient more than 0·7), responsiveness (correlation coefficient [or effect size measure] more than 0·5), or accuracy (AUC-ROC more than 0·7). For both panels, the cluster-based score obtained based on CARAT asthma, WPAI:AS activities, and WPAI:AS work was the score that presented the highest average ranking. External validation data obtained from the INSPIRERS cohort (n=425 days). Otherwise, data obtained from the MASK-air derivation cohort (n days 135 635). WPAI:AS work refers to the percent overall work impairment due to allergy, and WPAI:AS activities refers to the degree allergy affected regular activities. AUC-ROC=area under the receiver operating characteristic curve. CARAT=Control of Allergic Rhinitis and Asthma Test. MASK-air=Mobile Airways Sentinel Network for airway diseases. WPAI:AS=Work Productivity and Activity Impairment: Allergy Specific.

from men) from May 21, 2015, to Dec 31, 2021 (table 1; appendix pp 8, 18). Ethnicity data were not available. A total of 24 384 additional days of MASK-air use from 489 users (the 2022 internal validation cohort; mean age 42·9 years, SD 16·6 years; 14 177 [58·1%] days from women, 10 207 [41·9%] days from men; appendix p 9) were used to further validate the developed scores. We assessed 69 participants from the INSPIRERS studies reporting a total of 425 days (mean age 33·2 years, SD 15·1 years; 326 [76·7%] days from women, 99 [23·3%] days from men; appendix p 9). The calculated asthma daily control scores are available in the panel. Further details on the underlying clusters and models are available in the appendix (pp 10, 19).

The construct convergent and divergent validity of the developed scores is shown in tables 2 and 3. The scores displayed their strongest correlations with VAS dyspnoea (Spearman correlation coefficients range 0·68 to 0·82) and WPAI:AS work (0·59 to 0·68). Correlations with VAS dyspnoea were stronger than those observed for VAS nasal or ocular symptoms (0·30 to 0·49). The developed scores presented stronger correlations with CARAT asthma (–0·55 to –0·42) than with CARAT rhinitis (–0·27 to –0·14).

The appendix (p 11) presents the results of the test–retest reliability analysis. Intraclass correlation coefficients ranged from 0·79 to 0·95. The appendix (pp 12–13) presents the results of the responsiveness of the developed scores. Strong correlations (0·69–0·79) and high effect size measures (0·57–0·99) were observed when the scores were compared with VAS dyspnoea, whereas moderate correlations and effect size measures were mostly observed when the scores were compared with VAS work (correlation coefficients range 0·49 to 0·57; effect size measures range 0·51 to 0·64), WPAI:AS (correlation coefficients range 0·30 to 0·56; effect sizes range 0·37 to 0·69), and CARAT asthma (correlation coefficients range –0·60 to –0·50; effect sizes range 0·47 to 0·72).

We obtained similar results when assessing daily asthma control scores in the 2022 MASK-air internal validation cohort (appendix pp 14–15). However, because of sample size limitations, we were not able to assess test–retest reliability and responsiveness with all comparators.

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See **Online** for appendix

For the **MASK-air app** see www.mask-air.com

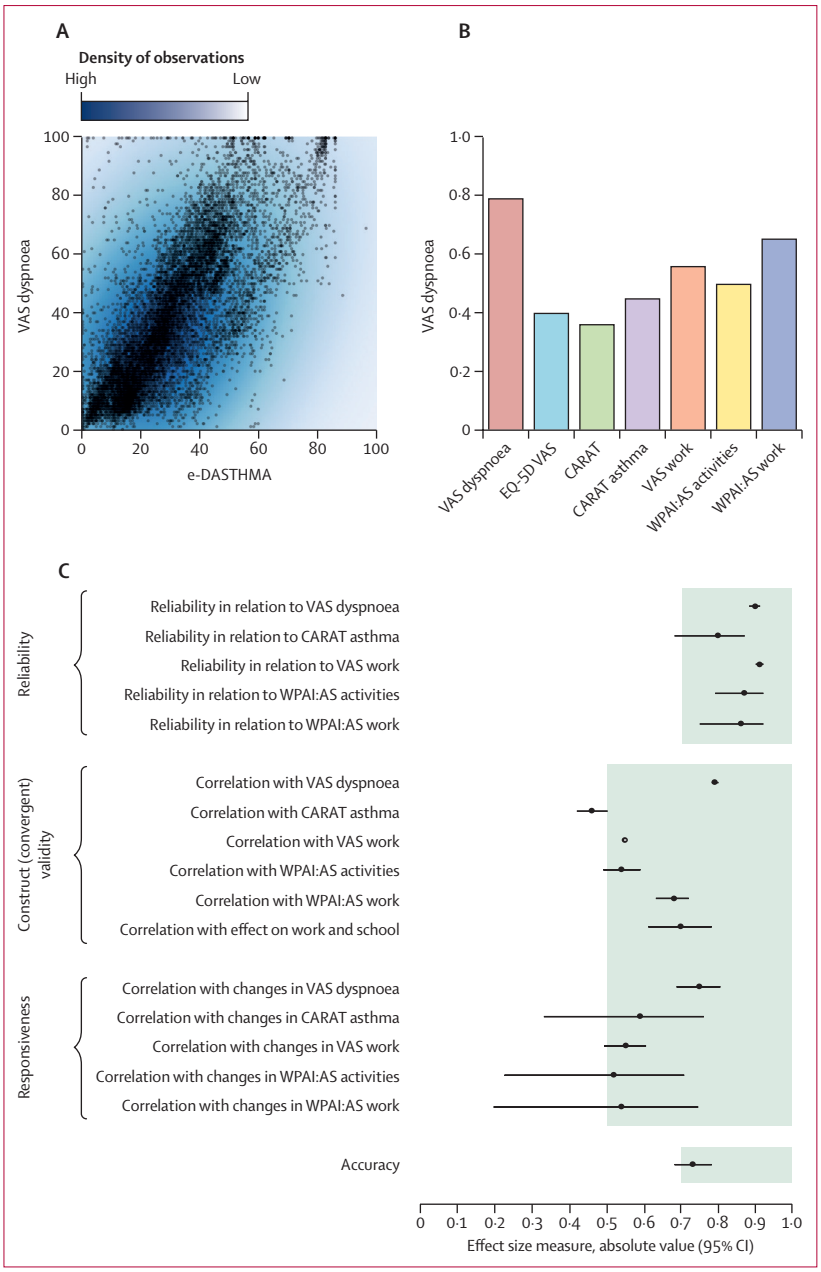

***Figure 2*: Graphical summary of the performance of e-DASTHMA**
(A) Scatter-dot graph on the association between e-DASTHMA and VAS assessing the effect of dyspnoea symptoms. (B) Spearman correlation coefficients of e-DASTHMA. (C) Overall summary of the properties of e-DASTHMA. The shaded part corresponds to the range of values higher than those indicated by COSMIN guidelines as corresponding to good validity (correlation coefficient more than 0·5), reliability (intraclass correlation coefficient more than 0·7), responsiveness (correlation coefficient [or effect size measure] more than 0·5), or accuracy (AUC-ROC more than 0·7). Intra-rater reliability was not assessed, because when users fill in the MASK-air daily monitoring questionnaire several times per day, only the VAS values are registered on a per-questionnaire basis (medication is registered on a daily basis). Considering only the potential changes in VAS asthma, an intra-rater reliability of 0·93 (95% CI 0·93–0·94; calculated similarly to Sousa-Pinto and colleagues[14]) would be obtained. External validation data obtained from the INSPIRERS cohort (n days 425). Otherwise, data obtained from the MASK-air derivation cohort (n days 135 635). WPAI:AS work refers to the percent overall work impairment due to allergy, and WPAI:AS activities refers to the degree allergy affected regular activities. CARAT=Control of Allergic Rhinitis and Asthma Test. e-DASTHMA=electronic daily asthma control score. MASK-air=Mobile Airways Sentinel Network for airway diseases. VAS=visual analogue scale. WPAI:AS=Work Productivity and Activity Impairment: Allergy Specific.

In the INSPIRERS cohort, the developed asthma daily control scores displayed a strong correlation with the daily effect of asthma on work or school activities (Spearman correlation coefficients range 0·50–0·70). These scores also showed good accuracy with regard to distinguishing patients with uncontrolled or partly controlled versus controlled asthma (AUC-ROC range 0·69–0·75; table 4; appendix p 20).

Considering the internal and external validation results, the e-DASTHMA was the score derived from clusters defined according to CARAT asthma, WPAI:AS work, and WPAI:AS activities (figures 1–2). The e-DASTHMA is based on the following formula: [(0·086×VAS asthma)+(1·756 if inhaled corticosteroids without long-acting β-agonists are used)+(0·859 if inhaled corticosteroids with long-acting β-agonists, excluding formoterol, are used)+(1·238 if inhaled corticosteroids with formoterol are used)+(0·559 if short-acting β-agonists or short-acting muscarinic antagonists are used)+(4·022 if biological drugs or long-acting muscarinic antagonists are used)]×6·695. In the INSPIRERS cohort, e-DASTHMA displayed a strong correlation with the effect of asthma on work and school activities (Spearman correlation coefficient: 0·70; 95% CI 0·61–0·78) and good accuracy for the identification of patients with uncontrolled or partly controlled asthma according to GINA (AUC-ROC 0·73; 95% CI 0·68–0·78; table 4). Identified using a distribution approach (SD divided by 2), the minimal important difference for the e-DASTHMA was 8 points. Following an outcome-based approach (with comparison of e-DASTHMA versus three classes of asthma control defined by CARAT asthma, WPAI:AS work, and WPAI:AS activities), we observed that values less than 16·4 indicated good asthma control (sensitivity 70% [95% CI 64–77%]; specificity 88% [84–92%]), whereas values of 28·9 or more indicated worse asthma control (sensitivity 95% [92–98%]; specificity 73% [68–78%]). The performance of e-DASTHMA was similar in patients with or without self-reported rhinitis and in those with or without self-reported conjunctivitis (appendix p 16). Results were also consistent across different individual countries (appendix p 17).

Discussion

This study involved the development of a data-driven asthma control score (e-DASTHMA) that was strongly correlated with daily dyspnoea symptoms and moderately correlated with work-comparators and quality-of-life-related comparators, had high test–retest reliability, and displayed moderate-to-high responsiveness (figure 2). e-DASTHMA was validated in an external cohort of patients with asthma enrolled by physicians, being associated with the GINA classification of asthma control.[1]

Several questionnaires assess the control of asthma for a period of 1–4 weeks (eg, ACT, ACQ, or CARAT[6]). e-DASTHMA (similar to patient symptom diaries)[7,21] assesses the period of a single day, but has the advantage

of combining asthma symptoms and medication use. As an analogy, e-DASTHMA might represent the equivalent of glycemia in the control of diabetes (with the advantage of taking treatment into consideration), whereas the scores of questionnaires such as ACQ, ACT, and CARAT are analogous to HbA1c. If this strategy is confirmed, it might represent a novel approach to help optimise asthma control.

e-DASTHMA might help in the follow-up of patients with uncontrolled asthma, in shared decision making, and in the generation of daily alerts for patients or physicians. Such a daily score avoids the recall biases associated with longer-term assessments, allowing for a better identification of exacerbations and their triggers. e-DASTHMA might help in stratifying patients for the selection of biological drugs (because physicians would be able to identify patients with poor or irregular asthma control, distinguishing those in which these issues occurred despite adherence to asthma treatment, and who might be candidates for biological drugs, from those who are not adherent) and in monitoring their effectiveness. e-DASTHMA can also be an endpoint in clinical trials or observational studies (eg, by informing on the percentage of well controlled or poorly controlled days), complementary to questionnaires already approved by regulatory agencies.

e-DASTHMA was strongly correlated with a frequently used asthma patient-reported outcome (VAS dyspnoea).[22] This questionnaire displayed good correlation with work-related and activity-related comparators (COSMIN guidelines indicate that correlation coefficients of more than 0·5 represent good correlation between patient-reported outcomes).[23] e-DASTHMA was less strongly correlated with the EQ-5D-VAS questionnaire, albeit that the correlations were similar to those observed for ACQ or Asthma Quality of Life Questionnaire.[24,25] In fact, the EQ-5D might not be the best quality-of-life measure for asthma,[24] because it does not react sensitively to small changes in asthma control[26] and its VAS is less sensitive than ACQ-6 for assessing asthma control.[27]

e-DASTHMA also showed strong test–retest reliability considering all assessed comparators. The COSMIN guidelines show that coefficients of more than 0·7 (observed in all analyses) indicate good reliability.[23] In the same guidelines, correlation coefficients of more than 0·5 (observed for VAS dyspnoea, WPAI:AS, VAS work, and CARAT asthma) indicate good responsiveness.

We only included patients reporting data in at least 3 different calendar months. This requirement meant the exclusion of 2955 participants reporting asthma treatment (leading to decreased precision) and might have possibly introduced a selection bias, because patients with higher MASK-air adherence might not be representative of all users (eg, they might be more concerned about their asthma control). However, this approach was adopted to decrease the risk or effect of misclassification—namely, of including patients with low respiratory symptoms and incorrect asthma medication use because of conditions other than asthma (eg, lower respiratory infections). In addition, this approach avoids an over-representation of observations provided on the first day of MASK-air use, which tend to be associated with worse reported symptoms than all other days.[28] This approach also addresses potential biases associated with low MASK-air reporting. Although each included participant reported an average of 82 MASK-air days, participants not providing data in at least 3 different months reported an average of only 5 days.

The use of secondary data directly provided by the patients enabled us to overcome two risks to construct validity—namely, experimenter expectancies and participant biases (ie, the possibility that researchers' or participants' expectations about a study bias the data collection or provision). Other potential threats—namely, poor construct operationalisation—were overcome by an a priori and simple definition of the construct, as corresponding to daily asthma control reflected by both reported symptoms and medication use.

This study has some limitations: first, not all patients were enrolled by physicians, and we relied on the reported use of asthma medication for identifying patients with asthma. The fact that, for MASK-air participants, we were unable to clinically confirm their diagnosis of asthma might have resulted in the exclusion of patients with asthma who do not use medication or the inclusion of patients without asthma. Therefore, either an under-representation or over-representation of patients with milder symptoms might have occurred. However, in a MASK-air sub-study of 69 patients, we found that 93% of the patients with an asthma treatment had a physician diagnosis of current or previous asthma.[13] In addition, we observed that e-DASTHMA results were reproduced in INSPIRERS, a cohort of patients enrolled by physicians. Second, there is no gold standard measure for the daily control of asthma (the closest measure regarding symptoms could be dyspnoea). We therefore simultaneously used multiple comparators to develop and validate e-DASTHMA (including comparators assessing periods longer than 1 day). Nevertheless, all comparators except WPAI:AS have been assessed on their validity (and other properties) in patients with asthma, with some even being specific to asthma (VAS dyspnoea and CARAT asthma). Third, of the 4617 MASK-air users reporting asthma treatment, only 1662 met the eligibility criteria (accounting to 36% of the users, but they reported approximately 90% of the days). A larger sample would have resulted in a higher precision of the estimates. There were small sample sizes for the assessment of reliability and responsiveness, not only in relation to comparators such as EQ-5D-VAS, CARAT, or WPAI:AS, but also precluding the external assessment of these properties in the INSPIRERS cohort. Although this limitation might result in optimistic estimates for these

properties, the overestimation of effect sizes associated with such optimistic estimates is not expected to be high (as observed by the assessment of convergent validity in INSPIRERS, where strong correlations were obtained). Fourth, e-DASTHMA might not be generalisable to patients with asthma in low-income or lower-middle-income countries, because these data were obtained from high-income or upper-middle-income countries. In these countries, there is a potential over-representation of younger adults, of patients more concerned about their health (and more likely to use mHealth apps), and of more affluent patients.[29–31] And finally, the derivation and external validation cohorts displayed some relevant differences in median VASs, possibly reflecting different eligibility criteria, different app reporting patterns, or even selection biases. However, the good external validation results obtained in such different cohorts might point to the potential generalisability of e-DASTHMA.

This study also has several strengths: (1) the assessment of patients in a real-world context; (2) the application of different methodological approaches to generate asthma daily control scores; (3) the external validation of e-DASTHMA in a dataset of patients with physician-confirmed asthma; (4) the consistency of results obtained in sensitivity analyses; (5) the use of a VAS asthma questionnaire whose validity, reliability, and responsiveness have been assessed; and (6) the use of comparators that measure quality of life and the effect of allergy on work.

e-DASTHMA is generalisable to asthma with or without rhinitis and probably to most high-income or upper-middle-income countries. Because this study used previously collected data, future prospective evaluations are required, as well as studies comparing e-DASTHMA with other validated tools to assess asthma control, such as ACQ (which does not, however, have an electronic version) or ACT.

In conclusion, we developed and assessed the properties of the data-driven e-DASTHMA. This digital biomarker was obtained with moderate–high convergent validity, high test–retest reliability, and moderate responsiveness, making it a potential candidate for clinical practice and as an endpoint in clinical trials. In line with international initiatives aiming to harmonise outcome measures in asthma for better comparability of intervention effects, this study is an important contribution to the optimisation of the future care of patients with asthma.

Contributors

BS-P participated in the study design, data analysis, and manuscript writing (original draft). JB participated in the conceptualisation, study design, data analysis, supervision, and manuscript writing (original draft). JAF participated in the design and data collection of the INSPIRERS study, supervision, and manuscript writing (revision and editing). CJ, AMP, RAm, RAl, PV-M, and AS-S participated in the design and data collection of the INSPIRERS study, and in manuscript writing (revision and editing). TZ, JMA, and LFA participated in the study design, supervision, and manuscript writing (revision and editing). All other authors participated in data collection and manuscript writing (revision and editing). All authors had access to all data. BS-P and JB verified the raw data and JB was responsible for the decision to submit the manuscript for publication. All authors have seen and approved this version of the manuscript.

Declaration of interests

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Data sharing

Individual participant data underlying the results reported in this Article can be made available (after de-identification) between 12 and 36 months after Article publication. These data can be supplied to researchers who provide a methodologically sound proposal. Proposals should be directed to the corresponding author (jean.bousquet@orange.fr). We made every effort to follow the EU General Data Protection Regulation; therefore, we can transfer data only if there is a protocol and an agreement between the owner of the data and the person (or institution) requesting the data. To gain access, data requestors will need to sign a data access agreement. The source code used in this study can be supplied to researchers who provide a methodologically sound proposal directed to the corresponding author. The study protocol is available in the appendix.

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