Digital markers of asthma exacerbations: a systematic review

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Shareable abstract (@ERSpublications)
Increasing heart rate, short-acting β-agonist use and cough were found in this systematic review to be associated with increased risk of asthma attacks. These could form the foundation of a set of digital markers of asthma attacks. https://bit.ly/4ezcGbR

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Abstract

Background and objective With the increase in use of digital technologies, there is growing interest in digital markers, where technology is used to detect early markers of disease deterioration. The aim of this systematic review is to summarise the evidence relating to digital markers of asthma exacerbations.

Methods A systematic search of the following databases was conducted, using key search terms relating to asthma, digital and exacerbations: Ovid MEDLINE, EMBASE, Psycinfo, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials. Studies that aimed to explore the relationship between any digitally measured marker and asthma exacerbations using any form of portable digital sensor technology were included.

Results 23 papers were included. The digital markers related to five key categories: environmental, physiological, medication, lung function and breath-related parameters. The most commonly studied marker was lung function, which was reported in over half (13 out of 23) of the papers. However, studies were conflicting in terms of the use of lung function parameters as a predictor of asthma exacerbations. Medication parameters were measured in over a third of the studies (10 out of 23) with a focus on short-acting β-agonist (SABA) use as a marker of exacerbations. Only four and two studies measured heart rate and cough, respectively; however, both parameters were positively associated with exacerbations in all reported studies.

Conclusion Several digital markers are associated with asthma exacerbations. This suggests a potential role for using parameters such as heart rate, SABA use and, potentially, cough as digital markers of asthma exacerbations.

Introduction

Worldwide, asthma affects ~339 million people and causes 455 000 deaths each year [1, 2]. The greatest cause of morbidity from asthma is from asthma exacerbations, which due to their heterogeneous nature, can be difficult to predict [3, 4]. With the widespread availability of digital technologies and the potential for scalability, there has been increasing interest in the use of digital technologies in the management of asthma [5]. Recent data has shown that approximately seven in 10 people have access to some form of mobile phone or digital technology [6], highlighting the potential for technology to be used to monitor markers related to asthma attacks. Digital predictors are markers of asthma attacks which can be identified using digital technologies and may help reduce morbidity from asthma exacerbations by enabling real time monitoring of asthma control. These digital markers can also be used as clinical end-points [7], yet there has been limited research into such markers. Identifying which markers have been studied and their relationship with asthma exacerbations is a first step towards identifying a set of digital markers for asthma that can be used in clinical studies as potential end-points and for self-monitoring of asthma control [8]. There are two applications for digital markers – one to signal a general increased risk of exacerbation at a population level, for example from high pollen levels, and the other to signal a more imminent risk to the patient at an individual level, for example higher reliever risk or reduced peak flow [9].

One example of an individual level digital marker of asthma exacerbation is heart rate. This can be easily monitored and measured by a smart watch [10], which allows for easy detection of heart rate fluctuations

to alert the asthma patient that they could be at risk of an asthma attack. A recent cohort study in the Netherlands measured heart rate using a smart watch in asthma subjects and found that the heart rate of people with asthma was significantly higher than people in the control group [8]. KRUIZINGA *et al.* [8] reported a similar finding with increases in heart rate in the period preceding an exacerbation. A study by PATEL *et al.* [11] involving electronic monitoring of short-acting β-agonist (SABA) inhaler use in people with asthma reported that an increase in SABA use was a significant indicator of an asthma attack [12]. Environmental factors such as levels of particulate matter (*e.g.* PM2.5) levels and air pollutants can also be measured using digital technologies such as air quality sensors and smart phones [13], and have been found to be related to the risk of asthma attacks [14, 15]. Other parameters that can be measured using digital devices, for example lung function and breath-related parameters such as peak expiratory flow rate (PEFR) and exhaled nitric oxide (F_{ENO}), have also been found to be associated with an increased risk of asthma attacks [16, 17].

A recent systematic review by ALHARBI *et al.* [18] explored predictive models for asthma attacks based on environmental factors and biophysical signals. The focus of the review was to synthesise the evidence relating to asthma predictive models; as such, the review did not examine other markers that could be associated with asthma exacerbations such as SABA use and heart rate. There have also been some conflicting studies reporting different findings about the relationship between certain digital markers such as forced expiratory volume in 1 s (FEV_1) and asthma attacks. One study found that there was no difference in FEV_1 in asthma patients and healthy subjects [19], whilst another study found that a decrease in FEV_1 was a predictor of an asthma attack [8].

Given the range of studies examining markers that could potentially be captured using digital technologies and the opportunity that digital technologies present for the management of asthma attacks, a systematic review was undertaken to systematically identify studies that report on digital markers and to synthesise the evidence to date relating to digital markers and asthma exacerbations. The aim of this systematic review is to summarise the evidence relating to digital markers of asthma that are captured using digital technology and the relationship with asthma exacerbations.

Materials and methods

Eligibility criteria

Studies that aimed to explore the relationship between any digitally measured marker and asthma exacerbations using any form of portable digital sensor technology were included. Digital sensor technology was defined as a device or system that can detect changes in its environment objectively and coverts this into a measurable digital signal, based on search terms from other similar reviews of digital technologies [20, 21], and included smart watches, smart phones and other digital devices (supplementary appendix A1). Studies on digitally measured patient-reported measures were excluded based on this definition of digital sensor technology. Studies that did not investigate the relationship with asthma exacerbations were excluded, for example, studies reporting the use of digital markers for asthma diagnosis. There was no limitation on study design. Randomised controlled trials (RCTs), controlled clinical trials, interrupted time series, controlled before-and-after studies, cohort and case-control studies that were published between 2000 and 2022 and written in English, were included. No age limitation or limitation to study population was applied though only published full texts or conference abstracts were included.

Search strategy

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the review protocol is registered with PROSPERO (CRD42022377611). We conducted a bibliographic search to find eligible studies using the following databases: Ovid MEDLINE, EMBASE, Psycinfo, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials. These databases were searched using keywords that were identified in a brainstorming session before commencing the review. Key search terms used included asthma, digital, exacerbations and their other related terms. MeSH terms were used alongside the keywords to broaden the search. A manual search of the reference list of included studies was conducted to find other useful resources. The initial search was conducted in November 2022 with the screening process occurring between December 2022 and January 2023.

Data collection and analysis

Selection process and data extraction

The selection process was a two-part process. In the first part, all articles extracted from the search were reviewed by two reviewers based on the title and abstract. This screening was done using Rayyan [22].

Where there was conflict in the decision-making, and a third party was included as necessary until a consensus agreement was reached. The second part of the selection process involved a full text review of the included articles.

Once the full text review was completed, data extraction was conducted. A data extraction table was developed based on prior literature and was organised into two sections. The first section included information about the study characteristics, and the second section extracted information about the devices and markers investigated, and their relationship with the asthma outcome (either exacerbation or worsened asthma control, or both). The digital markers were classified into five categories. The first category, environmental, relates to a general increased risk of exacerbation. The remaining four categories, physiological, medication, lung function and breath-related parameters, relate to an individual's imminent risk. This data extraction table was piloted on two studies before being used to extract the remaining studies. Data were then synthesised descriptively and narratively. The possibility of conducting a pooled estimates and meta-analysis was explored but not conducted due to the heterogeneity between study designs including the differences in the definitions of the digital marker and of the outcomes and data reporting.

Quality assessment

The quality assessment was done using the Newcastle–Ottawa scale or Cochrane Risk of Bias 2 tool, depending on the study type. RCTs were assessed using the Risk of Bias 2 tool. In this tool, each individual domain (selection, performance, detection, attrition, reporting and other bias) was judged as low, unclear or high risk of bias. Non-randomised studies were assessed using the Newcastle–Ottawa scale, which covers selection, comparability and outcome domains. The quality of these studies was either poor, fair or good. The Newcastle–Ottawa scale was also customised for cross-sectional, case–control and cohort studies.

Results

The database search resulted in 1472 articles being retrieved. After eliminating 433 duplicates, 1039 studies were screened by the title and abstract of the article using Rayyan. Once these articles were screened, 60 articles were sought for retrieval, which resulted in only 55 studies for the full text analysis. Finally, of the 55 reviewed, 23 studies met the inclusion criteria and were analysed.

The studies included a range of designs such as reviews, RCTs, observational studies, retrospective dataset and case studies. A study flowchart is shown in figure 1.

The markers of asthma were divided into five main categories: environmental (population risk) and physiological, medication, lung function and breath-related parameters (individual risk) (table 1). Most studies only focused on one parameter, whilst others measured a range of factors.

Digital markers indicating changes in general risk

Environmental parameters

Out of the included papers, six papers focused on the relationship between environmental factors and asthma attacks. Environmental parameters such as PM2.5 levels, NO_2 levels, temperature and humidity were the most common parameters measured across these six papers, though data on general weather was also reported [13, 18, 23–26]. In Downen *et al.* [23], participants were given NO_2 sensors to monitor levels. In this pilot study, the data captured by the sensors was then combined with hospital records to see if there was any relationship between elevated NO_2 levels and asthma exacerbations. Results from this study show that increased NO_2 levels are associated with hospital admissions from asthma exacerbations ($p=0.037$). The other four studies measured PM2.5 levels, temperature, humidity and air pollutant levels using air pollution portable sensors, smart phone applications and environmental sensors [13, 18, 24, 27]. These studies used these environmental markers to investigate the relationship with asthma exacerbations. Park *et al.* [13] used air monitors and smart wearables to monitor particulate matter and gaseous pollutants. It was found that long-term exposure to PM2.5 levels and ozone (O_3) were associated with uncontrolled asthma and exacerbations. Similarly, Lucas *et al.* [24] also found that there were strong associations between asthma attacks and environmental factors; however, this was reported in a single case study of a 42-year-old male. The study reported that PM2.5 level was the factor that was most associated with the patient's asthma control ($p<0.001$), and an increase in these levels was related to an increased risk of attack. Not only were PM2.5 levels associated with an increased risk of attack, but also these levels were reported in the Alharbi *et al.* [18] review to impact on the rate of asthma hospitalisation. These results highlight the role of PM2.5 levels and air pollutants such as O_3 in increasing the risk of an asthma exacerbation in people with asthma.

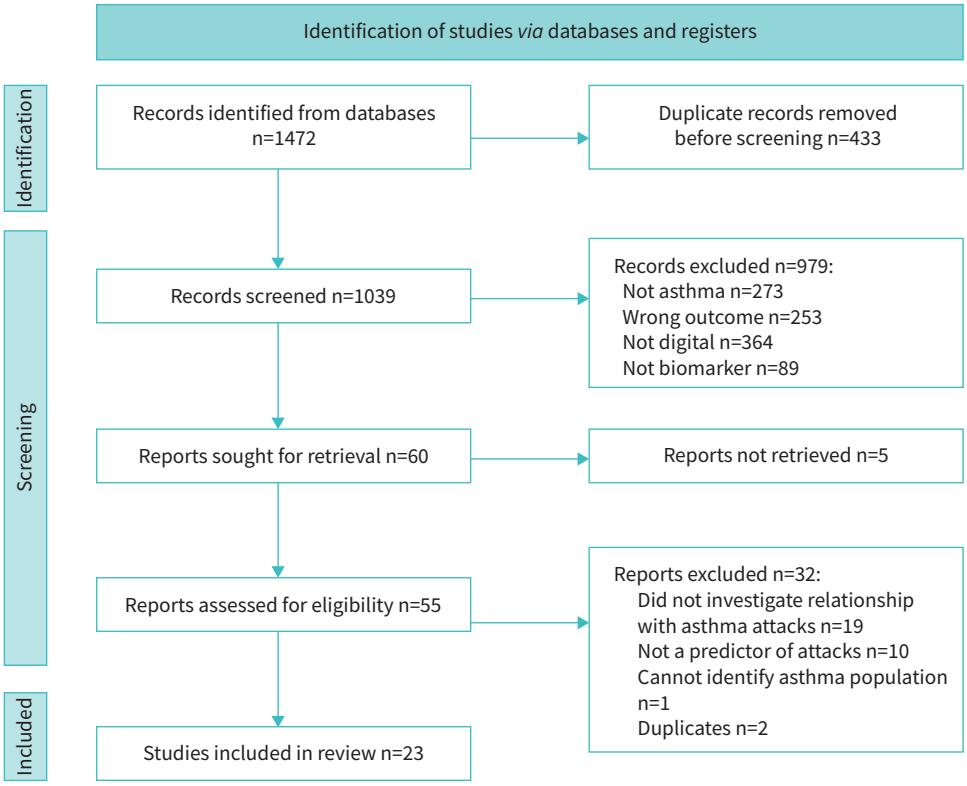

FIGURE 1 PRISMA flow diagram.

Digital markers indicating changes in individual risk

Physiological parameters

Four studies measured heart rate to investigate the relationship between heart rate and decrease in asthma control and increased risk of asthma attacks [7, 19, 25, 28]. In an observational study done in the USA, participants were given a bed sensor device to measure their heart rate, and data were collected every 2 weeks to see if there was any change in their asthma control [28]. The study found that an increase in heart rate and heart rate parameters such as stroke volume were associated with the loss of asthma control. Increases in nocturnal heart rate also correlated with asthma symptoms. Kruizinga *et al*. [8] measured nocturnal heart rate in asthma subjects comparing them to a control group of healthy subjects. Heart rate was measured using a smart watch and a questionnaire was used alongside the smart device to gather data about the participants' daily asthma symptoms. The authors found that the mean nocturnal heart rate of asthma subjects was significantly higher compared to the control group ($p<0.001$). In relation to asthma attacks, heart rate increased 7 days prior to an attack and decreased once rescue medication was given [8]. Khusial *et al*. [19] measured heart rate using the myAirCoach system and found that an increase in heart rate was related to loss of asthma control.

Medication parameters: SABA use

10 out of the 23 included papers reported on medication parameters as a predictor of asthma attacks. Most studies reported on the relationship between SABA use and the risk of asthma attacks [11, 12, 16, 17, 26, 29–32], though in one study that reported on the SMART regimen, budesonide/formoterol inhaler use was also explored [12]. One study measured time of inhaler use [25, 27]. There have been studies showing that asthma exacerbations can be predicted by monitoring SABA use with an electronic adherence monitoring device or a digital inhaler. A digital inhaler can also measure inhalation volume, number of inhalations and inhalation volume. Levy *et al*. [29] monitored SABA use over 12 weeks using a digital inhaler and found that there was a gradual increase in mean inhalations of SABA from the 15- to 30-day window prior to an exacerbation, and also in the 14 days prior. Overall, the mean daily SABA use was greater in those participants who had an exacerbation than those who did not. Two other studies [11, 30] reported similar

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TABLE 1 Characteristics of included studies and their findings

First author [ref.]	Country	Method	Devices	Digital parameters measured		Asthma attack definition	Asthma outcome measured	Findings
				Increased population attack risk	Increased individual risk			
Alharbi [18]	Saudi Arabia	Systematic review of research articles introducing asthma attack prediction models that uses biosignal, environmental and both risk factors.	Smartwatch, home-based telemonitoring technology (participant datasets); networked sensors, IoT sensors (environmental datasets).	Environmental: $PM_{2.5}$ level, temperature, humidity, SO_2, NO_2, CO, O_3	Lung: PEFR, FEV_1	Worsening of asthma symptoms, *i.e.* coughing, shortness of breath, wheezing	Asthma attack: yes Asthma symptoms (ACT/ACQ): no	Asthma biosignals used in prediction model show some evidence of being linked to asthma exacerbations. Models using PEFR showed high accuracy if combined with additional biosignal risk factors (model accuracy 0.87); increase in CO, NO_2 and $PM_{2.5}$ significantly impacted the rate of asthma hospitalisation (0.79, 0.79, 0.93=positive correlation coefficient). O_3 non-significant relationship (relationship=0.03). People with asthma in urbanised areas and sparsely vegetated areas have a higher risk of asthma attacks leading to hospital admissions (correlation=0.6). Predicting asthma attacks becomes more accurate and gives better performance when both biosignal and environmental risk factors are used (model accuracy up to 0.87).
Bos [37]	UK	Review to examine the current performance of breathomics and its ability to contribute to the treatment of chronic airway diseases. It also evaluates the data obtained by breathonomics in predicting risk for asthma exacerbations.	Electronic nose		Breath: VOCs, breathonomics		Asthma attack: yes Asthma symptoms (ACT/ACQ): yes	The eNose can detect the breath of patients with both mild and severe asthma. The VOCs detected are related to the disease state itself rather than its severity or phenotype. Noninvasive breath analysis allows for monitoring of asthma and the prediction of exacerbations. Classification of exacerbations was very good: model comprising six VOCs was able to classify exacerbations when comparing baseline samples with the exacerbation samples within the patient (sensitivity 100%; specificity 93%). Between-patient analysis (comparing exacerbation and non-exacerbation samples of other patients) gave a lower accuracy (sensitivity 79%, specificity 100% with seven VOCs). Markers did not correlate with asthma control.
Bui [33]	France	Review of telemonitoring of a range of paediatric respiratory diseases including asthma.	Electronic spirometers		Lung: FEV_1		Asthma attack: yes Asthma symptoms (ACT/ACQ): no	Daily monitoring of FEV_1 over 12 months with medical feedback did not reduce severe asthma exacerbations in an included study in 50 children aged 6–16 years with severe uncontrolled allergic asthma, though the referenced study did not examine the direct relationship between FEV_1 and exacerbation onset. Review also referred to Huffaker *et al.* [28] (which is extracted below).

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TABLE 1 Continued

First author [ref.]	Country	Method	Devices	Digital parameters measured		Asthma attack definition	Asthma outcome measured	Findings
				Increased population attack risk	Increased individual risk			
Claxton [36]	Australia	A cough-centred smartphone algorithm was developed for patients aged 12 years and older, using five coughs recorded on a smartphone combined with four patient-related symptoms (acute/productive cough, fever and wheeze). A non-standard reference test was performed to compare the accuracy of the software diagnosis with the reference test made after specialist review.	Smart phone-based algorithm		Breath: cough	Worsening asthma symptoms and positive response to bronchodilator test	Asthma attack: yes Asthma symptoms (ACT/ACQ): no	Cough-based algorithm showed a high positive percentage agreement with the reference test, with the greatest positive percentage agreement (96%) for patients aged 22–65 years with similar negative percentage agreement (81%) compared to the whole sample (positive agreement 89%; negative agreement 84%).
Downen [23]	USA	Participants were given a home-based personal sensor to monitor NO_2, O_3, humidity and temperature in the participant's home, though only NO_2 exposure was the focus for the study. Hospital records from 12 months prior were analysed for trends of exacerbations to see if there were any observed short- and long-term correlations between gas appliances, elevated NO_2 levels and exacerbations. ACT and medication data were also collected.	NO_2 sensor	NO_2 levels		Hospitalisation	Asthma attack: yes (hospital admissions) Asthma symptoms (ACT/ACQ): yes	Frequency of elevated acute NO_2 exposure (>21 ppb) correlates with number of hospital admissions due to asthma in the 12 months prior to monitoring (correlation=0.662, p=0.037).

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TABLE 1 Continued

First author [ref.]	Country	Method	Devices	Digital parameters measured		Asthma attack definition	Asthma outcome measured	Findings
				Increased population attack risk	Increased individual risk			
Fleming [16]	UK	Review on asthma attacks and predictors of exacerbations.	Electronic monitoring device, spirometer		Medication: adherence, SABA Lung: PEFR Breath: F_{ENO}, VOC	Requiring high-dose oral corticosteroids for 3 or more days, increase in maintenance dose, ED visit or hospitalisation.	Asthma attack: yes Asthma symptoms (ACT/ACQ): no	Steep decline in PEF with no increased variability related to attacks, whilst wide diurnal PEF variation related to loss of control. Decreased ICS adherence leads to increased risk of attacks and hospital admissions; excessive SABA use is associated with risk of asthma attack (high daily use (>2 actuations/day) and use on 2 or more days in 2 weeks increase the odds ratio of an asthma attack with mean daily use the strongest predictor). Single measurements of F_{ENO} show low predictive value for asthma exacerbations even 2 weeks before an attack, but an approach involving analysis of variation in daily F_{ENO} with symptoms shows some promise for predicting exacerbations (but limited by need for daily F_{ENO} measurements). Two studies found that patterns of VOCs can be used for exacerbation prediction in children; predictive value improved the closer the VOCs measurement was taken to an exacerbation. A meta-analysis found NO_2, SO_2 and $PM_{2.5}$ are significantly associated with increased risk of asthma attacks.
Huffaker [28]	America	A bed sensor device was strapped to the participant's mattress to measure HR every 2 weeks; data were collected from the subject on any changes of asthma control. A random forest method was used to build a prediction model using the variables from the device to predict asthma symptoms each night and to see which variable was closely associated with asthma symptoms.	Commercial ballistocardiography accelerometer-based passive bed sensor: device was attached to the mattress using an elastic strap without contact with the participant.		Physiological: HR including HR variability, respiratory rate, relative stroke volume	ACT score (every 2 weeks)	Asthma attack: no Asthma symptoms (ACT/ACQ): yes	A random forest model to predict asthma symptoms 14 days before each date of symptom onset had high specificity and accuracy but low sensitivity (sensitivity 47.2%, specificity 96.3%, accuracy 87.4%) but model performance was highly variable between participants. Overall, HR and respiratory parameters were the most important variables in this model. Increases in HR parameters were better associated with loss of asthma control than RR. In up to 35% of instances, the model generated was able to predict loss of asthma control before participants perceived symptoms. Increases in nocturnal HR and RR correlate with asthma symptoms, and in some cases, these changes can precede perception of symptoms.

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TABLE 1 Continued

First author [ref.]	Country	Method	Devices	Digital parameters measured		Asthma attack definition	Asthma outcome measured	Findings
				Increased population attack risk	Increased individual risk			
Khusial [19]	The Netherlands (study 1)/UK (study 2)	Study 1 (RCT): participants randomised to either usual care or usual care plus the myAirCoach management Study 2 (3 months before and after study): all participants used the myAirCoach system. Participants completed questionnaires and lung function and F_{ENO} were measured.	myAirCoach app; portable spirometer and F_{ENO} sensor; indoor air quality monitor for NO_2, SO_2, $PM_{2.5}$ and PM_{10}, humidity, air pressure, temperature; inhaler adaptor to capture adherence and improve inhalation technique; Fitbit Charge HR smartwatch.	NO_2, SO_2, $PM_{2.5}$ and PM_{10}	Phsysiological: HR Medication: adherence Lung: lung function, FEV_1 Breath: exhaled F_{ENO}	Asthma related hospitalisations, ED visits or use of oral corticosteroids for ≥3 days for attack definition. Asthma control assessed by ACQ at 4-week intervals.	Asthma attack: yes (exacerbation as secondary outcome) Asthma symptoms (ACT/ACQ): yes	Overall authors found that monitoring a diverse range of factors improved asthma control and exacerbation rate, but it is unclear which of the individual components relate to the improvements. In study 1, the intervention group had, statistically significant improvement of asthma control compared with control group, the difference in ACQ was 0.70 (p=0.006); the number of severe exacerbations was lower in the intervention group compared with the control group (6 *versus* 12, p=0.06); in study 2 asthma control improved by 0.86 (p=0.007) compared with baseline; no change in FEV_1 measured in both studies; quality of life was also improved in both studies for those using the myAirCoach management system.
Kruizinga [8]	The Netherlands	Participants were instructed to: wear a smartwatch (Steel HR) which measures HR and calculates several sleep-related parameters; perform daily home-based spirometry; and complete a daily symptom questionnaire at baseline and throughout the 28 days. The asthma participants were compared with healthy children (control) to see if there was a relationship between the parameters and asthma exacerbations.	Portable spirometer and smart watch	Rain duration and temperature	Physiological: HR, sleep paramaeters Lung: FEV_1 and FVC	Worsening of asthma requiring use of systemic corticosteroids to prevent serious outcome. Asthma control assessed using ACD-6	Asthma attack: yes Asthma symptoms (ACT/ACQ): yes	Daytime HR for participants with uncontrolled asthma was 1.6 bpm higher per point increase in symptom score (95% CI 0–3.3; p=0.05), whilst nocturnal HR was 2.8 bpm higher (95% CI 1.2–4.3; p=0.001). Uncontrolled asthma participants had a 0.25 lower FEV_1 z-score for each point increase in symptom score (95% CI 00–0.49; p=0.05) with no correlation found for FVC. Symptom scores did not correlate with sleep parameters. The mean nocturnal HR of participants with uncontrolled asthma was significantly higher compared with healthy controls (p<0.001). The mean FEV_1 in patients with uncontrolled asthma was lower compared to healthy controls with no asthma (p=0.002). Estimated mean trajectory of symptom scores found that HR increases 7 days prior to an attack and decreases after rescue medication is given. FEV_1 decreases 7 days prior to the attack and increases slowly after.
Levy [29]	USA	Participants used a digital inhaler with salbutamol (1–2 inhalations every 4 h) as needed to see whether there is a relationship between SABA use and exacerbations.	Digital inhaler		Medication: SABA	Not defined in abstract	Asthma attack: yes Asthma symptoms (ACT/ACQ): no	Increased mean±SD daily inhalations of SABA from 30 days (2.0±3.2) to 15 days (3.3±3.7) prior to an exacerbation. Mean daily SABA use further increased 14 days (2.6±3.1) prior to the day of exacerbation (3.8±3.9). Overall the mean daily SABA use was greater in patients who had an exacerbation compared to those who did not.

Continued

TABLE 1 Continued

First author [ref.]	Country	Method	Devices	Digital parameters measured		Asthma attack definition	Asthma outcome measured	Findings
				Increased population attack risk	Increased individual risk			
Lugogo [30]	USA	Participants were given a digital inhaler with albuterol to monitor their inhaler use. The digital inhaler contained sensors that can record inhaler use, PIF, inhalation volume, duration and time to PIF. These parameters were measured at baseline. These data were then combined with demographic information and clinical data to develop a predictive model of impending exacerbations using machine learning. This model was able to predict impending exacerbation over the following 5 days.	Digital inhaler with integrated sensors		Medication: SABA (albuterol) Lung: PIF, inhalation volume, inhalation duration, time to PIF	Moderate exacerbation: worsening asthma and requiring systemic corticosteroids above baseline for at least 3 days, and/or unscheduled HCP visit. Severe exacerbation: requiring both systemic corticosteroids and an unscheduled HCP visit.	Asthma attack: yes Asthma symptoms (ACT/ACQ): no	Mean daily albuterol use increased in the days leading up to the exacerbation peak (mean±SD number of inhalations in the 24-h preceding an exacerbation was 7.3±17.3) and decreased in the days following. PIF and inhalation volume decreased in the days prior to exacerbation and increased after. Those who had exacerbations: mean±SD number of daily albuterol inhalations was 1.8±2.78 (outside the 14-day window around an exacerbation), increasing to 2.43 ±3.67 during the exacerbation window *versus* a mean number of 1.14±2.35 inhalations for non-exacerbators. Albuterol inhalations (47% contribution to predictive model performance) and inhalation parameters (11% contribution) in the 4 days prior to exacerbation were the main predictors of attacks.

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TABLE 1 Continued

First author [ref.]	Country	Method	Devices	Digital parameters measured		Asthma attack definition	Asthma outcome measured	Findings
				Increased population attack risk	Increased individual risk			
Merchant [31]	USA	Participants enrolled were given a ProAir Digihaler to use when needed (see study by Lugogo *et al.*). The inhaler had integrated sensors which record inhalation variables. These data were then combined with case report data (demographics, medical history, baseline vital signs) to a machine learning algorithm to develop a model capable of predicting exacerbations.	Digital inhaler		Medication: SABA (albuterol) Lung: PIF, inhalation volume, time to PIF	Not reported in abstract but assumed same as Lugogo *et al.*	Asthma attack: yes Asthma symptoms (ACT/ACQ): no	Overall, 64 patients experienced 78 asthma exacerbations. The combination of inhalation parameters, albuterol usage pattern and case report data was subjected to a machine learning algorithm. The generated model using case report information, SABA use patterns and inhalation patterns was shown to increase the model performance from a ROC AUC value of 0.75 (based on Digihaler data only) to 0.83. Final model sensitivity was 68.8% and specificity 89.1%. Addition of patient data to inhalation data improved model performance.
Navanandan [17]	USA	Commentary review on strategies that have potential to allow accurate and reliable prediction of children at risk of exacerbations.	Electronic monitoring devices, mobile health apps, personal smart devices (*i.e.* smart watch)		Medication: SABA (albuterol) Lung: PEF Breath: exhaled F_{ENO}	Requires medical intervention including systemic corticosteroid treatment, ED visit and/or hospitalisation.	Asthma attack: yes Asthma symptoms (ACT/ACQ): no	Strongest risk factor for future asthma exacerbation is having one in the previous year; change in % F_{ENO} is associated with poor asthma outcomes but not exacerbation risk, baseline F_{ENO} and absolute change in F_{ENO} were not associated with exacerbation risk or asthma outcomes; machine learning can be used as an analytical tool for the prediction of asthma exacerbations when incorporating telemonitoring data to predict exacerbations in a 7-day window; changes in cough, albuterol use and PEF were evident 12–3 days before an exacerbation and more abruptly within the 2 days before.

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TABLE 1 Continued

First author [ref.]	Country	Method	Devices	Digital parameters measured		Asthma attack definition	Asthma outcome measured	Findings
				Increased population attack risk	Increased individual risk			
Park [13]	Korea	Review discussing how the use of digital technologies can help in the management of asthma by looking at the relationship between environmental exposures and exacerbations.	Air pollution portable sensors, smartphones, smart wearable devices	$PM_{2.5}$ level, gaseous pollutants			Asthma attack: yes Asthma symptoms (ACT/ACQ): no	Air monitors can be used to measure concentrations of particulate matter and gaseous pollutants; wearable devices can also be used to measure personal environmental exposure data; long-term exposure to O_3 and PM_{10} is associated with uncontrolled asthma, exacerbations and decreased lung function; air pollution exposure is associated with adverse health outcomes, in particular symptoms of chronic airway disease are heavily affected by environmental exposure.
Patel [11]	New Zealand	Participants were randomly assigned to either the SMART regimen (single budesonide–formoterol inhaler as maintenance and reliever therapy) or the standard (fixed-dose salbutamol as reliever) group. The inhalers dispensed were all fitted with a smart inhaler tracker to monitor medication use. The aim of this study was to investigate the relationships between SABA use metrics and future adverse outcome such as asthma exacerbations. Baseline measurements of daily salbutamol use were performed.	Electronic monitoring of inhaler use by using a smart inhaler tracker		Medication: SABA (salbutamol)	Use of ICS for at least 3 days; or hospitalisation or ED visit due to asthma, requiring systemic corticosteroids. Courses of corticosteroids separated by 7 days or more were treated as separate severe exacerbations.	Asthma attack: yes Asthma symptoms (ACT/ACQ): no	Mean±SD daily SABA use was 5.5±9.7 in exacerbators compared to 1.8±3.3 in non-exacerbators. Mean±SD number of days of SABA use over 2 weeks was 7.2±5.4 in exacerbators and 5.3±5.0 in non-exacerbators. Max number of inhalations of SABA in a day was 14.6±25.8 in exacerbators and 5.3±7.8 in non-exacerbators. These parameters are significant predictors of asthma exacerbations.

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TABLE 1 Continued

First author [ref.]	Country	Method	Devices	Digital parameters measured		Asthma attack definition	Asthma outcome measured	Findings
				Increased population attack risk	Increased individual risk			
Patel [12]	New Zealand	*Post hoc* analysis of data that was undertaken from a 24-week RCT (Patel *et al.* [11]). The analysis is restricted to patients with severe asthma exacerbations that resulted in acute presentation to hospital ED during the 24-week study period. The main outcome of interest was the median daily use of budesonide/formoterol in the SMART group and of budesonide/formoterol and SABA 14 days preceding hospital attendance with a severe exacerbation and median maximum number of budesonide/formoterol (SMART group) and SABA actuations and median number of budesonide/formoterol actuations on the day of maximum salbutamol (standard group) in a 24-h period.	Smart inhaler tracker		Medication: SABA (salbutamol) in the standard group; budesonide/formoterol in the SMART group	Medication use was analysed as the attack indicator, not attack definition.	Asthma attack: yes Asthma symptoms (ACT/ACQ): no	Both budesonide/formoterol (SMART group) and SABA use (standard group) increased 5 days before hospital attendance with a median maximum number of daily inhaler actuations of 14 (budesonide/formoterol) in the SMART group and 46 (SABA) in the standard group. Inhaler use progressively increased 5 days before hospital attendance and peaked in the 24 h preceding attendance, though in the standard group, salbutamol use increased at 10 days but reduced to a lower level before increasing again in the 5 days before hospital attendance. Patients commonly take high doses of SABA in the 2-week period leading up to hospital attendance with severe exacerbations of asthma. Those on the SMART regimen had reduced non-adherence with ICS therapy likely because patients on SMART used their combination ICS/formoterol inhaler "as needed" in response to symptoms in the lead up to the exacerbation, rather than as per the formal SMART regimen.

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TABLE 1 Continued

First author [ref.]	Country	Method	Devices	Digital parameters measured		Asthma attack definition	Asthma outcome measured	Findings
				Increased population attack risk	Increased individual risk			
Lucas [24]	USA	Cloud computing and a smartphone-based platform was used to track asthma symptom severity for one individual (male). The app tracks medication adherence and environmental data by capturing the geographical location. This was done to see if there was a link between relevant environmental data and asthma symptom severity.	Smart phone application (Asthma Ally)	$PM_{2.5}$ and PM_{10} level, pollen concentration, CO, NO, NO_2, SO_2, weather		Not defined	Asthma attack: no Asthma symptoms (ACT/ACQ): yes (Pediatric Asthma Control and Communication Instrument)	Strong associations between asthma symptom severity and environmental factors. $PM_{2.5}$ level and pollen concentrations ($p<0.001$) were the factors most associated with the patient's asthma severity contributing 37% and 31% to the coefficient of variation. Of the 21 increases in severity of symptoms, 18 of these points were preceded by a peak in $PM_{2.5}$ with a mean lag of 0.9 days.
Safioti [32]	USA	Participants were given a digital inhaler (ProAir Digihaler) to use as needed. The inhaler recorded each use and inhalation variables. These data were combined with clinical data subjected to a machine learning algorithm to develop a predictive model of exacerbations defined by the need of OCS. The relationship between the pattern and amount of albuterol use and inhalation parameters preceding exacerbations was evaluated. Baseline measurements were also performed for comparison.	Digital inhaler		Medication: SABA (albuterol) use Lung: PIF, inhalation volume, inhalation duration, time to peak flow	Need for OCS	Asthma attack: yes Asthma symptoms (ACT/ACQ): no	This study examined inhalation measures and relationship with severe exacerbations. During the exacerbation window, patients had a lower mean PIF than their baseline (outside the exacerbation window of 14 days) and compared to patients who did not have exacerbations. Mean±SD daily albuterol inhalations were higher during the time of an attack (2.43±3.67 compared to patients without exacerbations 1.14±2.35). The strongest predictive factor during the 5 days before an exacerbation was mean number of albuterol inhalations per day (61% of the prediction model). The model was stronger if other inhalation features of PIF (13%), inhalation volume (8%), night-time usage (2%) and inhalation trends over time (16%) were added to the model in addition to number of inhalations.

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TABLE 1 Continued

First author [ref.]	Country	Method	Devices	Digital parameters measured		Asthma attack definition	Asthma outcome measured	Findings
				Increased population attack risk	Increased individual risk			
Sankaran [38]		Measurements were made using a handheld collector to measure H_2O_2 and analysed using a biosensor-based real time analyser. F_{ENO} was also measured. These measurements were performed to assess its relationship in stable and exacerbated airway disease.	H_2O_2 hand-held collector, F_{ENO} *via* NIOX MINO, spirometry		Breath: exhaled breath H_2O_2, exhaled F_{ENO}	Acute exacerbation, admitted to hospital	Asthma attack: yes Asthma symptoms (ACT/ACQ): no	H_2O_2 was higher in exacerbated airways (asthma and COPD) (p=0.04); F_{ENO} was not significant.
Tinschert [35]	Switzerland	Questionnaire and sensor data were collected *in situ* with a smartphone application based on MobileCoach. Nocturnal cough and sleep quality were investigated to see whether they are useful markers for predicting asthma exacerbations. Nocturnal cough frequencies were obtained each night by manually labelling audio recordings from the built-in microphone of the smartphone.	Smart phone		Physiological: sleep quality Breath: nocturnal cough		Asthma attack: yes Asthma symptoms (ACT/ACQ): yes	Nocturnal cough and sleep quality were associated with asthma control (p<0.05). Sleep quality was more useful for detecting weeks with uncontrolled asthma; nocturnal cough was better at detecting weeks with asthma control deteriorations. Cut-offs that used both markers predicted asthma attacks up to 5 days before.

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TABLE 1 Continued

First author [ref.]	Country	Method	Devices	Digital parameters measured		Asthma attack definition	Asthma outcome measured	Findings
				Increased population attack risk	Increased individual risk			
Tsang [24]	UK	Participants given smart devices for regular monitoring of their asthma symptoms. Daily questionnaires were also performed to monitor asthma status. These asthma monitoring data were used to test the feasibility of an asthma attack prediction algorithm based on passive monitoring.	Smart peak flow meter, smart inhaler, smart watch	Temperature, humidity, pollen level	Physiological: HR Medication: time inhaler used Lung: PEF	Seven-item daily questionnaire to measure daily asthma control; 11-item weekly questionnaire to capture control, symptoms in the last week, and unscheduled care. Severe attacks identified based on use of OCS from weekly self-report questionnaire. Moderate attacks identified from questions about relief inhaler use, symptoms and unscheduled care.	Asthma attack: yes Asthma symptoms (ACT/ACQ): yes	Data from the daily questionnaire, environment, smart watch, smart peak flow meter and smart inhaler informed a prediction model with good performance (AUC=0.93 and AUPRC=0.55). No information presented on relationship between each of the digital parameters collected and outcomes of asthma control or attacks.
Tsang [25]	UK	Review: included peer-reviewed studies that applied machine learning to mHealth data from asthma management.	Smartphone, smartwatch, peak flow meters, electronic noses, smart inhalers, pulse oximeters, wireless wearable sensors.	Weather, air quality	Physiological: Sleep quality, HR, RR Medication: SABA use Lung: PEF Breath: VOCs		Asthma attack: yes Asthma symptoms (ACT/ACQ): yes	Decreasing PEF is a big indicator of asthma attacks; PEF in the morning and before bedtime are particularly important predictors. Combining multiple data sources can help improve asthma attack prediction; VOCs can be used to understand the development of asthma attacks but evidence is inconsistent; sleep quality can be used in predicting asthma exacerbations (70% in predicting attacks, night symptoms-related features were two of the four most predictive features); SABA use was an important predictor of attacks.
Wong [34]		Three participants were given a commercial FOT device to be installed in each subject's home for daily FOT measurements. Medication adherence was tracked using electronic data loggers and daily symptoms and medication diaries.	Commercial FOT device		Lung: FOT	Deterioration in asthma symptoms or increased reliever use over 2 consecutive days. First day in 7 days without symptom and reliever free = end of attack.	Asthma attack: no Asthma symptoms (ACT/ACQ): yes	Results from these three case studies report an association between increased day-to-day FOT variability prior to an exacerbation. The authors suggest that daily FOT measurements could be used to detect and prevent exacerbations in paediatric asthma.

IoT: Internet of things; $PM_{2.5}$: particulate matter with aerodynamic diameter <25 µm; SO_2: sulfur dioxide; NO_2: nitrogen dioxide; CO: carbon monoxide; O_3: ozone; PEFR: peak expiratory flow rate; FEV_1: forced expiratory volume in 1 s; VOCs: volatile organic compounds; ACT: Asthma Control Test; SABA: short-acting β-agonist; F_{ENO}: fractional exhaled nitric oxide; ED: emergency department; PEF: peak expiratory flow; ICS: inhaled corticosteroid; HR: heart rate; RR: respiratory rate; RCT: randomised controlled trial; ACQ: Asthma Control Questionnaire; ACD: Asthma Control Diary; FVC: forced vital capacity; PIF: peak inspiratory flow; HCP: healthcare professional; ROC AUC: receiver operating characteristic area under the curve; OCS: oral corticosteroid; H_2O_2: hydrogen peroxide; AUPRC: area under the precision-recall curve; FOT: forced oscillation technique.

results with mean daily SABA use increasing in the 7-day window prior to the exacerbation. There were also changes in inhalation parameters. Inhalation volume decreased in the days prior to the exacerbation and then increased after the attack. Participants who experienced exacerbations had a higher number of mean inhalations compared to subjects who did not. In a study by Patel *et al.* [12], a retrospective analysis of a large dataset found that use of budesonide/formoterol for patients on the SMART regimen and use of SABA for those in the standard regimen increased 5 days before hospital attendance and peaked in the 24 h preceding hospital admission. Interestingly, for patients taking SABA there was a stepped change in SABA use with an initial increase 10 days before hospital attendance, which reduced to a lower level before increasing again 5 days before hospital attendance. Excessive SABA use and decreased adherence are also associated with hospital admission and the risk of experiencing an asthma attack. Safioti *et al.* [32] found that the strongest predictive factor of asthma exacerbations was the mean number of SABA inhalations per day, 5 days prior to an attack.

Lung function parameters

Peak expiratory flow and spirometry measures

PEFR, peak expiratory flow (PEF) and FEV_1 were the most common measures of pulmonary function explored across 13 papers [8, 16–19, 25, 26, 30–34]. Of the 13 papers, four reported on FEV_1 [8, 18, 19, 33], three on PEF [17, 25, 26], two on PEFR [16, 18] and one reported on forced oscillation technique (FOT) [34]. Electronic spirometers were used to measure these lung function parameters across these studies. There were conflicting data on whether measurements of lung function can be used for the prediction of asthma exacerbations. Interestingly, two studies [19, 33] found that monitoring FEV_1 did not reduce the risk of severe asthma exacerbations and that there was no change in the FEV_1 measurements of asthma participants compared to their baseline values. However, one study in paediatric patients [8] found a relationship between FEV_1 and asthma exacerbations, with the mean FEV_1 being lower in asthma patients compared to healthy subjects and FEV_1 decreasing 7 days prior to an attack. In a review by Fleming [16], some studies reported a weak association and poor predictive value between PEFR and the prediction of asthma attacks. However, in a review by Alharbi *et al.* [18], predictive models using PEFR showed higher prediction accuracy asthma attacks. Studies measuring PEF [17, 25] showed similar results unlike the other markers FEV_1 and PEFR, where greater heterogeneity in findings were seen. The three PEF studies found that decrease in PEF was a consistent indicator of asthma attacks, with Tsang *et al.* [26] noting that PEF in the morning and before bedtime were important predictors. Navanandan *et al.* [17] also found that the changes in PEF were more evident 3–12 days prior to an exacerbation. In the single study examining FOT and exacerbations, increased day-to-day FOT variability prior to an exacerbation were seen, which decreased to baseline levels after the exacerbation [34]. Interestingly there were three studies that reported on inspiratory flow [30–32].These were conducted in the same sample, but modelled different aspects of inhalation data [32] with and without other clinical information [30, 31]. Whilst the biggest contributor to the model was number of SABA actuations, the model was strengthened with addition of peak inspiratory flow and other inhalation features such as inhalation volume and trends [30, 32].

Nocturnal cough and sleep quality

Two studies investigated the association of nocturnal cough and asthma exacerbation risk [35, 36]. Nocturnal cough refers to cough occurring during the night when the individual sleeps, usually between the time of going to bed and the time of waking up. In an observational study, a smart phone was used to investigate whether sleep quality and nocturnal cough are useful markers for predicting attacks [35]. Nocturnal cough frequencies were obtained each night by manually labelling the audio recordings from the built-in microphone of the smart phone. Results showed that participants who coughed more or had worse sleep quality had worse asthma control. In turn, participants also had an increased risk of asthma attacks. Nocturnal cough was found to be better at detecting asthma control deteriorations whilst sleep quality was more useful for detecting uncontrolled asthma. Kruizinga *et al.* [8] reported no correlation between asthma control and sleep parameters, whilst a review by Tsang *et al.* [26] reported that night symptoms-related features including night-time waking were key variables selected for prediction. Similarly, Claxton *et al.* [36], found that nocturnal cough can be used in models to accurately identify exacerbations of asthma.

Breath-related parameters

Seven papers investigated breath-related parameters [16, 17, 19, 25, 26, 37, 38]. Some of these measurements include F_{ENO}, volatile organic compounds (VOCs) and hydrogen peroxide (H_2O_2). Two recent studies have shown that F_{ENO} has low predictive value of asthma exacerbations [16, 38]. A review by Navanandan *et al.* [17] found that the change in percentage of F_{ENO} is associated with poor asthma outcomes but not necessarily related to exacerbation risk. The change in F_{ENO} levels from baseline was not associated with other asthma outcomes. Although the approach of using F_{ENO} may be useful in predicting asthma attacks, the use of this measurement to predict asthma attacks is limited by the cost and availability

of daily measurements. One study showed that measurements of H_2O_2 had some association in predicting asthma attacks. H_2O_2 levels were higher in the airways of participants with an attack compared to those who did not experience an attack during the study [38]. There is limited evidence about the use of other exhaled VOCs to predict asthma attacks. Four papers report that patterns of exhaled VOCs can be used for prediction of attacks and to understand the development and mechanisms of asthma attacks, but the evidence was inconsistent [16, 25, 26, 37].

Quality of studies included

Of the 23 studies included, two [11, 19] were RCTs and five [7, 27, 28, 34, 35] were observational studies. Using the Cochrane Risk of Bias 2 tool, both RCTs were found to have low risk of bias. The quality of the other five studies was assessed using the Newcastle–Ottawa scale. Only one study had "good" quality after assessing the study design [28]. The other four studies were rated as "fair" quality as they were all lacking in the "comparability" domain of the Newcastle–Ottawa scale [8, 27, 34, 35].

Discussion

Digital technologies are an increasingly important part of asthma self-management [5, 39]. As asthma is a condition which varies within and between individuals, and over time, the availability of accessible technologies to monitor a patient's asthma control status objectively has the potential to change the face of asthma care. This systematic review summarises the evidence on the relationship between digital markers of asthma and the risk of asthma exacerbations. We identified 23 studies that reported on asthma digital markers and asthma exacerbations. The digital parameters measured in these studies were categorised into five types: environmental, physiological, medication, lung function and breath-related. The most commonly studied parameter was lung function, reflecting the long-standing use of lung function tests in traditional asthma monitoring. However, other parameters were also associated with exacerbations. Environmental factors, such as increased PM2.5 levels and air pollutants, which can be detected using wireless digital sensors [13–15], were associated with asthma exacerbations. In terms of physiological parameters, the only physiological marker that has been measured in studies is heart rate, with studies showing that an increase in heart rate was associated with an increased risk of an attack. Heart rate could be a significant predictor of asthma exacerbations and may be a useful marker for asthma patients, particularly as this parameter is easily measurable using accessible wearables such as smart watches.

SABA use, number of inhalations and inhalation volume were factors associated with asthma exacerbations. The findings highlight that whilst SABA use is an important predictor of exacerbations, inhalation parameters may also form an essential part of the picture when considering prediction models [30]. Whilst smart inhalers are not yet a part of routine care, there are methods that could capture similar information such as electronic dispensing data, which could be used to generate an alert to patients of an increase in asthma exacerbation risk. However, with the shift away from SABA monotherapy for asthma treatment [40], a more useful future medication marker may be the use of inhaled corticosteroid (ICS)–formoterol or the combination of SABA with ICS rather than SABA alone as a digital marker. For lung function parameters, a decrease in PEF was related to increased risk of asthma exacerbations. It is well documented that PEF variability is a marker of asthma deterioration [41, 42] and is used in asthma action plans to guide the use of medication. However, although PEF could be an easily accessible marker, in practice, obtaining sufficiently regular PEF readings to calculate variability is difficult due to poor adherence to regular peak flow monitoring. If PEF monitoring could be digitised, for example using a smart peak flow meter as part of a digitised action plan [43, 44], then there could be potential for using this in practice as an indicator of exacerbation risk. However, a recent National Institute for Health and Care Excellence (NICE) Medtech Innovation briefing [45] of smart peak flow meters highlighted the limited evidence and small sample sizes of available studies. Further research evaluating the effect of smart peak flow meters on outcomes, clinical decision-making and user satisfaction are warranted. For breath-related parameters, patterns of VOCs could have potential for identifying exacerbations; however, the evidence is conflicting [16, 46]. There are also no easily available digital tools currently available in practice that can monitor VOCs, which limits the current relevance of exhaled breath as a digital marker. Further research into the exact VOCs that are consistently related to asthma exacerbations, and how VOCs can be easily measured in practice, is needed [47].

Our findings add to the growing evidence on digital markers for asthma. There are few existing systematic reviews exploring this. A review by Alharbi *et al*. [18] reported on asthma attack prediction models and their performance and compared these based on whether they used biosignals or environmental factors as predictors. The review focused on modelling and performance rather than examining what digital markers have been explored in the literature and their relationship with exacerbations. Nevertheless, our findings relating to the relationship between environmental parameters and asthma exacerbations were similar to

those of Alharbi *et al*. We found that long-term exposure to environmental parameters such as PM2.5 levels and NO_2 was significantly associated with the increased risk of asthma exacerbations. In contrast, for lung function parameters, Alharbi *et al*. found that PEFR could be used to improve the accuracy of predictive models for exacerbations. However, we found conflicting studies which reported that PEFR had a low predictive value and weak association with the risk of asthma exacerbations. These conflicting data suggest that further research is needed to establish whether lung function parameters remain as significant markers of asthma exacerbations or if other digital markers are more strongly predictive. Our review is also limited as it includes only studies that have captured these parameters digitally, and studies that have examined the same or similar parameters using non-digital or "analogue" methods were part of our inclusion criteria. Older studies looking at non-digital markers of exacerbations may provide important clues as to which markers may be associated with exacerbation, and in some cases, it may be the combination of parameters rather than isolated parameters that is important. For example, a review of 425 severe exacerbations by Tattersfield *et al*. [9] showed that the combination of increased symptoms, decreasing PEF and increased SABA use showed parallel changes prior to an exacerbation of asthma, suggesting that no one parameter was superior to another in detecting earlier changes in exacerbation risk. These findings are similar to those by Lugogo *et al*. [30], which are included in this review. Gibson *et al*. [48] describe asthma self-management activities to include these measures – namely peak flow and symptom monitoring. Our findings highlight the potential opportunities for digital technology to support these self-management activities, though we recognise this review did not explore the use of technology for monitoring of patient-reported symptoms, which could be the subject of a future review.

Whilst our review found a growing number of studies that consistently support heart rate and SABA use as positive correlates with asthma exacerbations, there are still areas for more research. In the eight studies that measured medication parameters, all of them measured SABA use only. Questions remain as to whether it is SABA use itself that is the most important digital marker, or if other medication parameters are more important, such as the ICS:SABA ratio. More research is needed to fully understand which other medication factors may be associated with asthma exacerbations. Of note, Merchant *et al*. [31] compared the performance of a model using only inhalation data *versus* inhalation and patient data and found the latter model had higher predictive accuracy, highlighting the importance of considering patient-related factors in addition to only medication markers. Cough is another parameter warranting further research. Out of the included studies, only two studies investigated nocturnal cough, but both showed a positive association with asthma attacks. This parameter is an important one to explore further as it is highly likely that cough is associated with asthma exacerbations. With the increasing availability of AI-trained cough monitors [49], this could become an easily accessible marker for asthma patients to measure to monitor risk of asthma exacerbations.

Although this review found several markers that could be used to identify changes in asthma control and increased exacerbation risk, there remain challenges to be overcome before these digital markers can be used as part of clinical care. Patient acceptability and adherence to using digital technology regularly as part of asthma management; concerns about reliability and accuracy of the data collected; and data privacy and security are issues that have been reported as possible barriers to implementation [50]. There are also policy-level barriers such as considering health professional training and acceptability, funding structures and integration into existing health systems [51, 52]. However, there are clear advantages that digital technologies provide that traditional self-management methods do not, such as the ability to provide continuous monitoring, remote data transmission, personalised feedback and treatment, and 24/7 educational support, which has the potential to improve patient outcomes [50]. Globally, digital technologies have been recognised to have the potential to strengthen health systems [53, 54], and further work to promote the successful implementation of digital respiratory technologies in routine care is under way [55]. Compared to the vast and growing research on digital interventions, only a small proportion of interventions studied become implemented as part of routine care. Most of the studies in our review report on the relationship between digital markers and asthma exacerbations but few report on how the digital intervention or devices were developed. Future interventions should consider the patient perspective [56], ideally being co-designed with end users, and consider economic modelling to support successful implementation [57].

Our review is one of the first to examine a range of digital markers and their relationship with asthma exacerbations. This allowed for a diverse set of markers and parameters to be investigated, with no limit on study design or ages of the asthma population. Whilst we found digital markers that may indicate a change in asthma control status or increased risk of an exacerbation, there are likely different and confounding mechanisms at play that vary from patient to patient. For example, increased heart rate prior to an attack may be due to anxiety in one patient or overuse of SABA in another. The underlying drivers of the changes in digital markers need to be considered if these markers are used as part of clinical decision-making.

There are also some limitations to the review. The date of the search was limited from the year 2000 onwards as studies relating to technology and digital devices are likely to have only been studied over the last two decades. There is a possibility that this date range limit may have missed older studies that may have had relevant information about the digital markers of asthma exacerbations. However, any technologies prior to 2000 are unlikely to still be relevant or available. The review also included only studies that reported on markers that have been measured using digital devices rather than any markers that could be measured using digital methods. This means there are likely other markers of asthma exacerbations that could be included as part of a set of digital markers and have not been included in this review. Lastly, the heterogeneity observed in the definitions of the digital markers and the asthma outcome, and data reporting, meant that we were unable to conduct a meta-analysis or generate forest plots of the data. Nevertheless, this review provides an important starting point for identifying a clinically relevant set of digital markers that can be used in research and practice for monitoring asthma exacerbation risk.

Conclusion

As the asthma population increases and patients become more empowered to self-manage their own health, there is growing interest in the role of digital markers and their relationship with asthma exacerbation risk. This review identifies several digital markers that are associated with asthma exacerbations. The growing body of evidence suggests a role for monitoring heart rate, SABA use and potentially cough when considering asthma exacerbation risk. Further research is needed to clarify the relationship between peak flow, and other lung function and breath parameters, and asthma exacerbations.

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