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Predicting asthma attacks using connected mobile devices and machine learning; the AAMOS-00 observational study protocol

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ABSTRACT

Introduction:

Supported self-management empowering people with asthma to detect early deterioration and take timely action reduces the risk of asthma attacks. Smartphones and smart monitoring devices coupled with machine learning could enhance self-management by predicting asthma attacks and providing tailored feedback.

We aim to develop and assess the feasibility of an asthma attack predictor system based on data collected from a range of smart devices.

Methods and Analysis:

A 2-phase, 7-month observational study to collect data about asthma status using three smart monitoring devices, and daily symptom questionnaires. We will recruit up to 100 people via social media and from a severe asthma clinic, who are at risk of attacks and who use a pressurised metered dose relief inhaler (that fits the smart inhaler device).

Following a preliminary month of daily symptom questionnaires, 30 participants able to comply with regular monitoring will complete six months of using smart devices (smart peak flow meter, smart inhaler, smartwatch) and daily questionnaires to monitor asthma status. The occurrence of asthma attacks (definition: ATS/ERS Task Force 2009) will be detected by self-reported use (or increased use) of oral corticosteroids. Monitoring data will be analysed to identify predictors of asthma attacks. At the end of the monitoring, we will assess users' perspectives on acceptability and utility of the system with an exit questionnaire.

Ethics and Dissemination:

Ethics approval was provided by the East of England - Cambridge Central Research Ethics Committee. IRAS project ID: 285505 with governance approval from ACCORD (Academic and Clinical Central Office for Research and Development), project number: AC20145. The study sponsor is ACCORD, the University of Edinburgh.

Results will be reported through peer-reviewed publications, abstracts, and conference posters. Public dissemination will be centred around blogs and social media from the Asthma UK network and shared with study participants.

Key Words

Asthma Attacks, Machine Learning, mHealth, Smart Monitoring Devices, Prediction

ARTICLE SUMMARY

Strengths and limitations of this study

- This study combines objective data collected from multiple smart monitoring devices available on the market.

- Stratified analysis and individualised asthma attack prediction models are not expected, due to the limited number of participants and study period.
- Participants are limited to patients with severe asthma at risk of acute attacks, and to those using a pressurised metered dose relief inhaler that fits our smart device.

INTRODUCTION

Asthma is a variable condition, affecting around 5.4 million people in the UK.[1] Every 10 seconds in the UK alone, someone has an asthma attack. Some of these attacks are life-threatening with over 1400 annual deaths estimated in the UK.[1,2] Since there is no known cure for asthma, self-management is a key part of patient care; this involves detecting deterioration and taking appropriate action to maintain control and prevent the threatened attack.[3] The most common symptoms of asthma are wheezing, cough, chest tightness and shortness of breath.

Traditional self-management action plans use symptom scores, sometimes supplemented by peak flow measurements, to determine a patient's asthma condition.[4–6] Keeping track of relief inhaler usage can also help measure asthma control.[7] However, patients may regard this level of monitoring as tedious as it involves high levels of active engagement on their part.

Increasingly, smart monitoring devices and "mobile-health" (mHealth) technologies are being developed to support asthma self-management.[8] Some notable examples include myAsthma [9] and Asthma MD.[10] myAsthma stores personalised action plans, includes instructional videos about inhaler techniques, tracks symptoms and peak flow, and provides local weather forecasts. AsthmaMD [10] has similar features to support self-management and can provide customised notifications. However, these tools still require a high level to active engagement to monitor one's asthma.

There has been an increasing number of mHealth studies to predict asthma attacks and develop passive monitoring to support asthma self-management, including the use of smart peak flow meters,[11] activity tracking,[12,13] smartphone administrated questionnaires,[6,14] and weather data.[15,16] However, the combined use of the monitoring devices available to asthma patients to develop asthma attack prediction models is largely unexplored. In addition, whilst there have been some studies that explored the use of machine learning algorithms for chronic disease management with home-monitoring data,[17] there is still no mHealth system that is widely used by asthma patients. One of the key bottlenecks for the limited progress is the difficulty of collecting asthma monitoring data and the lack of availability of such datasets from existing studies. Apart from the Asthma Mobile Health Study,[18] no other asthma mHealth dataset is publicly available to be able to investigate the development and validation of asthma attack prediction algorithm.

In this study, we will collect novel asthma monitoring data that will facilitate the development of an asthma attack prediction algorithm leveraging available, approved asthma monitoring devices in the market. This study will also enable us to test whether unobtrusive, passive monitoring and machine learning could help minimise the need for active patient data collection whilst maintaining accuracy for predicting attacks. We envisage that an mHealth system that leverages machine learning to predict asthma attacks with passive monitoring will enhance patient adherence and improve patient self-management.

The overarching aim of this study is to develop and assess the feasibility and acceptability of an asthma self-management system using existing smart devices, collect novel monitoring data and leverage machine learning to develop asthma attack prediction algorithm.

METHODS AND ANALYSIS

Study population

To maximise the chances of collecting data related to attacks in a short time-span, we will focus on patients with moderate to severe risk of attacks. Two key predictors are a recent history of attacks and people with severe asthma.[19,20] We will thus focus on adult asthma patients who have had at least one course of oral corticosteroid for an acute asthma attack in the past 12 months, and people attending a secondary care severe asthma clinic. See Table 1 for inclusion and exclusion criteria.

Social media recruitment consists of sending tweets on Twitter and posting on Facebook via the Asthma + Lung UK and Asthma UK Centre for Applied Research (AUKCAR) accounts, which total around 175,000 followers. The Norfolk and Norwich University Hospital will help identify potentially eligible patients for the study and direct them to the online information and expression of interest.

Table 1: Inclusion and exclusion criteria

Inclusion criteria:	• Aged 18 and above • Self-reported or doctor-diagnosed asthma • Possession of a smartphone (from 2016 onwards) that can support the Mobistudy and FindAir mobile apps (Android 4.4+, iOS 10+) and has Bluetooth capabilities • Has had at least one course of oral corticosteroids for an acute asthma attack in the past 12 months • Prescribed with pressurised metered dose relief inhaler that is compatible with FindAir ONE (e.g. Ventolin and other versions of salbutamol if the inhaler is a compatible shape inhaler as Ventolin; Salamol; Airomir; Fostair; Budiair)[21]
Exclusion criteria:	• Comorbidities that have overlapping symptoms (e.g. wheezing, cough, chest tightness and shortness of breath) • Aged under 18 • Unable to provide valid consent (e.g. cognitive impairment, learning disabilities) • Unable to use an app and respond to questions in English

Potential participants will complete an online questionnaire to identify whether they are eligible to participate. Informed consent will be collected via Online Surveys, a secure online platform for collecting questionnaire data. Potential participants will be given time to read the participant information sheet before deciding whether to participate.

Sample size calculation

To achieve the objectives of this study, we need to collect sufficient data need to train an asthma attack prediction model.

In the study population of UK Optimum Patient Care Research Database (OPCRD) and Clinical Practice Research Datalink (CPRD), 41% of the patients who had multiple (2 or more) attacks in the baseline year also had multiple attacks in the following year.[20]

Based on 30 participants with daily monitoring, 3,470 recordings (= 30 people × 30 days × (89% adherence at baseline, 58% adherence at 3 months, 52% adherence at 6 months [22])) for each of the daily measurements can be expected in phase 2. Also, 12 recorded asthma attacks are expected, assuming an average of one attack observed per participant in 41% of phase 2 participants during the study period.[20] To use the novelty detection algorithm iForest (which can be trained even if the data collected does not include any attacks), a sample of 256 recordings or data points would suffice.[23] Other machine learning classification algorithms will also obtain high accuracy on this sample size.

Recruitment strategy

Using a similar recruitment method, Hui et al. recruited 87 participants using social media alone, the majority within the first month after the initial invitational message, although the number of those who continued to use the app dropped to 15 (17% of the total initially recruited participants) after 30 days.[24] Moreover, only 5% of identified participants through practices agreed to join their study, which totalled 28 participants from five practices.[24] However, the attrition rate for participants recruited through practices was lower, 63% vs 83% reduction in social media participants; only 25% of users were still using the app after 30 days.[24] The eligibility criteria (≥16 years, an asthma prescription in the previous year, registered with a UK general practitioner) is more relaxed than the proposed criteria. However, this study incentivises entry of data in the first 28 days by giving adherent participants access to phase 2 which is likely to result in much more than 25% passing 30 days of participation.

Following the previous research, which recruited participants through Asthma UK's social media (at the time of writing had 175,000 followers), around 87 participants are expected to be eligible and join this study. In addition, around six participants identified and invited via are expected to be eligible and join from Norfolk and Norwich University Hospital. Of which, 47 people (50% of 93 respondents) are expected to complete phase 1. Thus, including 30 participants is achievable using the outlined recruitment method.

Outcomes

Primary endpoints

The primary endpoints of this study are severe asthma attacks, as defined in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force 2009 statement.[25] The definition is as follows:

- *Severe asthma attacks* are events that require urgent action on the part of the patient and physician to prevent a serious outcome. Such attacks are defined as a deterioration requiring use of systemic corticosteroids (or an increase from a stable maintenance dose).[25]

Severe asthma attacks will be identified using the use of systemic corticosteroids question on the weekly self-reported questionnaire. Courses of corticosteroids separated by 1 week or more will be treated as separate severe attacks.

Secondary endpoints

The secondary endpoints of this study are moderate asthma attacks, as defined in the ATS/ERS Task Force 2009 statement.[25] The definition is as follows:

- A *moderate asthma attack* is an event that, when recognised, should result in a temporary change in treatment to prevent the attack from becoming severe. Such attacks are defined as a deterioration that does not require use of systemic corticosteroids.[25] Moderate asthma attacks include a deterioration in symptoms, lung function, and/or increased rescue bronchodilator use that lasts for 2 days or more but are not severe enough to warrant systemic corticosteroid use.

Moderate asthma attacks will be identified using the questions about relief inhaler usage, symptoms (day symptoms, nocturnal symptoms, interference with usual activities, shortness of breath, wheezing), and unscheduled care (GP, emergency room, and hospitalisations) in the daily and weekly self-reported questionnaires.

Data collection

The data collection period is split into two phases:

1. *Questionnaire monitoring, daily for one month.*
2. *Smart device and questionnaire monitoring, daily for six months.* 30 participants who keep a regular diary in phase 1 will be given three smart devices (smart inhaler, smart peak flow meter, smartwatch) to collect data automatically as they use the devices, in addition to completing daily and weekly questionnaires. We will choose participants for this phase with a range of ages, gender, and smoking status, and with different types of asthma triggers.

At the end of phase 2, we will send a questionnaire asking for feedback about using the smart devices and whether participants think they could be useful to help them look after their asthma.

We will be using Mobistudy to centralise most of the data collection, only the smart inhaler usage and exit questionnaire will not be collected via Mobistudy (see Figure 1).

Data collection mobile app (Mobistudy)

Mobistudy [26] is an open-source platform facilitating mHealth studies available on Android and iOS managed by Malmö University, Sweden. The platform has three key components: a mobile app for participants, a REST API server, and a web portal for researchers (see Figure 2). The platform

supports multiple studies and participants of the AAMOS-00 study will be given a study invite code to join the AAMOS-00 study within Mobistudy.

Each daily and weekly assessment, such as questionnaires and peak flow measurement, will appear as an individual task of the home page on the participant's app (see Figure 3). Once the task is completed, it will be removed from today's to-do list and the data is sent directly to the server via the phone Internet connection. In real-time, the research team will be able to view the collected data via the online web portal for researchers.

Phase 1

There will be a total of four questionnaires:

- A daily questionnaire that asks six questions about daily symptoms experienced, medication usage, and the triggers encountered. This will take around 2 minutes to complete.
- A weekly questionnaire that asks 10 questions about asthma symptoms in more detail, medication usage, and healthcare engagement. This will take around 5 minutes to complete.
- A questionnaire that asks 11 questions at the start of phase 1 about current asthma condition and history.
- A questionnaire that asks five questions about race and smoking status. Additionally, some demographic information will be collected from the Mobistudy profile of participants, such as height, weight, and age.

The completion rate (50%) of the daily and weekly questionnaire will be used to determine the eligibility of a participant to join phase 2.

Phase 2

In addition to the daily and weekly questionnaires (see Figure 4), in phase 2 participants will be asked to collect data using three smart monitoring devices: Smart Peak Flow Meter (by Smart Asthma [27]), FindAir ONE (by FindAir [21]) smart inhaler, and MiBand3 (by Xiaomi [28]) smartwatch.

Participants will be given the smart peak flow meter to take a peak expiratory flow measurement twice a day, once in the morning and once at night; each measurement takes the best of three tries (see Figure 5). They will also be provided in-app written instructions before each set of measurements on using the peak flow meter. Furthermore, participants recruited through the Norfolk and Norwich University Hospital have been trained to use a peak flow meter by the practice. To connect the smart peak flow meter to the smartphone, participants can either use the audio-jack connection or a Bluetooth adapter.

The FindAir ONE smart inhaler attaches to the top of pressurised metered dose relief inhalers, it records the time at which the inhaler is used. The device can be moved to a new inhaler if participants change medication. The device will be connected to participants' smartphone by Bluetooth to the FindAir mobile app. The data will be transferred from the FindAir server and thence to the research team using FindAir's Application Programming Interface (API). The data collection will happen in the background once the participant has set up the connection between their mobile app and the AAMOS-00 study.

Using the MiBand3, we will collect minute-by-minute data on heart rate, step count, activity intensity, and activity type. The watch will connect to the participant's smartphone via Bluetooth and to the Mobistudy app. Participants will be asked to upload the data from the watch at least once every three days. This also gives a chance for users to review their activity (see Figure 6).

Local daily weather reports will be obtained using the phone's location combined with the data from Open Weather Maps' [29] and Ambee's [30] API. The weather data will include the temperature, humidity, clouds, wind, air quality index, and pollen levels of grass, tree, and weeds measured at a one-kilometre resolution (see Figure 7).

Exit questionnaire at the end of Phase 2

At the end of phase 2, a survey will gather data regarding users' perspective of the acceptability and utility of the monitoring system. The survey combines validated questionnaires on usability and acceptance (SUS [31] and uMARS [32]) with questions about motivations to use technology (mTEI [33]) and desired features in an asthma management system.

See Table 2 for a summary of the study's activities.

Table 2. Summary of data collection

Assessment	Screening	Day 1 baseline	Phase 1	Day 31 baseline	Phase 2	Study Exit
Assessment of Eligibility Criteria	Once			Once		
Written informed consent	Once					
Demographic data, contact details		Once				
Weight/height		Once				
Known triggers		Once				
Peak flow					Twice daily	
Heart rate					Automated	
Activity					Automated	
Location, air quality and allergens					Daily	
Inhaler Usage			Daily & Weekly		Automated	
Symptoms			Daily & Weekly		Daily	
Triggers encountered			Daily		Daily	
Healthcare Usage			Weekly		Weekly	

Feedback						Once at the end

Data analysis plan

Feasibility (from usage data)

Combining the usage data from phase 1 and 2 of questionnaire completion and device usage will compute compliance to the monitoring regime to assess if it is feasible for patients to use the monitoring devices in their daily lives.

We will also use activity logs on the server, and communication over email with patients, to identify major technical issues and shortcomings of the technology.

Acceptability (from survey data)

The data from the final questionnaire will be mostly ordinal data, with some free text answers. Free text will be processed for thematic text analysis, identifying overall acceptability and recurring topics present in the feedback. The ordinal data from answers on a Likert scale will provide measures of acceptability.

Prediction of asthma attacks (using monitoring data)

Severe asthma attacks will be identified by the reports of oral corticosteroid usage (or an increased dose from normal). Moderate and severe asthma attacks will be identified from the daily and weekly data, to observe a change in control from the norm lasting two days or more. Sensitivity analysis will be conducted using different features to define an asthma attack, such as hospitalisations and changes in peak flow.

The methods of linear fit and bin-algorithms will be used to collate and produce summary variables over irregular time-series and to handle missing data;[6] though, the longitudinal data collected in this study are likely to be more complete than the Asthma Mobile Health Study.[34] Data collected from participants who have withdrawn from the study will be used up to the last recording. After processing the data, machine learning classifiers will be trained to predict asthma attacks.

The primary classifiers that will be used in the study include Bayesian networks, decision trees, iForest, logistic regression, and support vector machines.[35,36] From the classifiers, a severe asthma attack predictor will be built on the device and questionnaire data, at a patient-level and population-level. Also, feature selection will be used to identify the most useful features in the prediction models.

Furthermore, retrospective analysis will simulate the effects of limiting the use of active monitoring data, to simulate patients only taking active measurements (e.g., peak flow and symptom diary) when prompted. In other words, the training set will be considered as all data before a certain date in the study period and the test set everything after. Moreover, there will be simulation of the general population using samples of the data, where adherence to monitoring might be lower than the selected population. For assessing the performance of the models built in this study, we will use

k-fold cross validation.[35] The performance metrics will include the common machine learning metrics such as area under the receiver operating characteristic curve (AUC-ROC), sensitivity, and specificity.

PATIENT AND PUBLIC INVOLVEMENT

Patient and public involvement (PPI) is part of the project from the beginning. This study is nested within the Asthma UK Centre for Applied Research and has been reviewed by their AUKCAR PPI members.

All the participant and public-facing documents and study objectives have been reviewed by AUKCAR PPI members before the start of the study and edited accordingly. Such a close PPI involvement ensures that the participant and public facing material is accessible. As an example, we attempted to explain several technical terms (such as “pMDI”) in more detail in the participant documents and added pictures of pressured metered dose inhalers after feedback from PPI members.

DISSEMINATION

We will be reporting the results in peer-reviewed journal publications and conference presentations. Dissemination of the results will also include the AUKCAR network with blogs and social media to reach an audience who is interested in the used of smart monitoring devices for asthma.

We will also be sharing links to publications and summaries with study participants.

ETHICS

This study has received ethics approval by the East of England - Cambridge Central Research Ethics Committee. IRAS Project ID: 285505.

DATA AVAILABILITY

At the end of the study, the anonymised research data will be stored at Edinburgh DataShare (a digital repository of research data produced at the University of Edinburgh) in perpetuity.

CONCLUSIONS

The present study will collect an important and novel dataset, where asthma patients use a combination of multiple market-available mHealth monitoring devices in the real world. We plan to use the rich dataset to improve existing asthma attack prediction algorithms and use the feedback from participants to design a patient-centred asthma self-management system. This study is the first

step in developing the Asthma Attack Management Online System (AAMOS) which will support asthma patients with real-time tailored feedback based on machine learning driven by mHealth data.

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AUTHOR CONTRIBUTIONS

KCHT, HP, AMW, and SAS designed the study. SAS is the study guarantor. KCHT and DS set up the data collection system. KCHT drafted the manuscript which was critically revised by HP, AMW, DS, and SAS. All authors approved the final version of the manuscript.

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COMPETING INTEREST STATEMENT

None declared.

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FIGURE LEGENDS

Figure 1. AAMOS-00 system overview

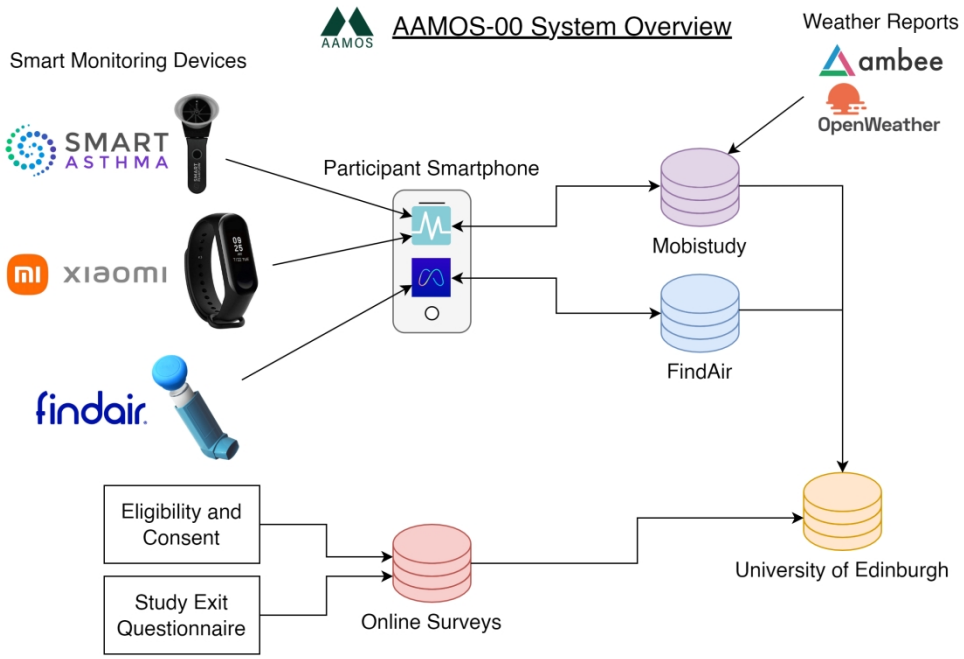

Figure 1: AAMOS-00 system overview

817x542mm (72 x 72 DPI)

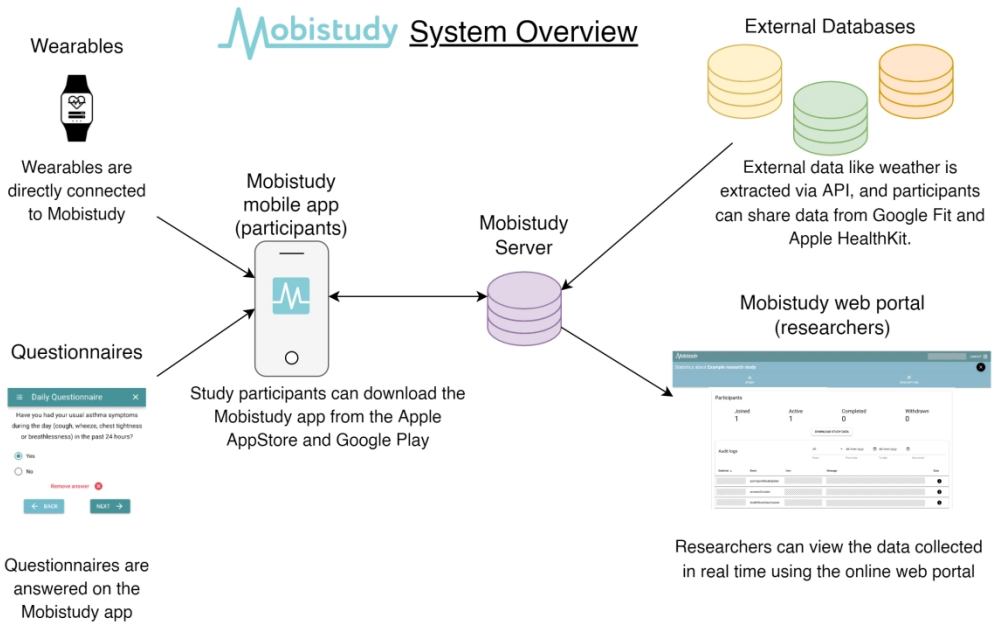

Figure 2: Mobistudy system overview

862x533mm (72 x 72 DPI)

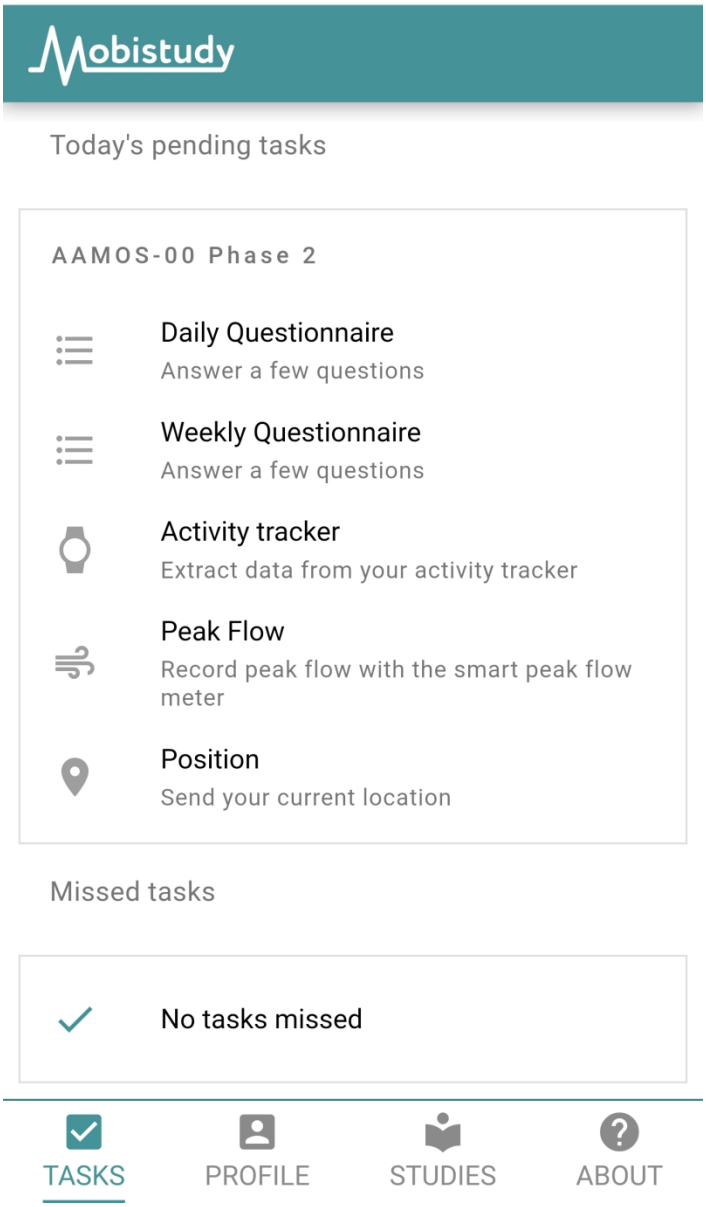

Figure 3: Participant's app home page

962x1649mm (38 x 38 DPI)

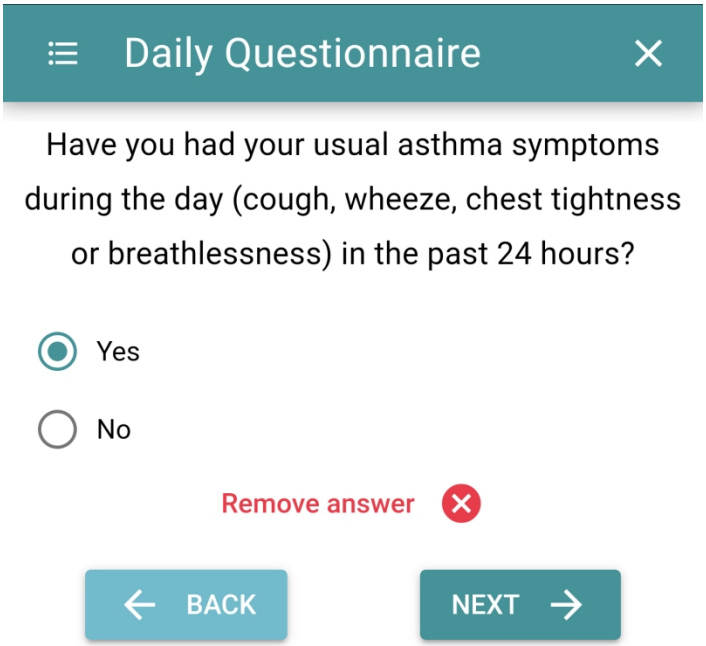

Figure 4: Questionnaire delivered by Mobistudy

962x1647mm (38 x 38 DPI)

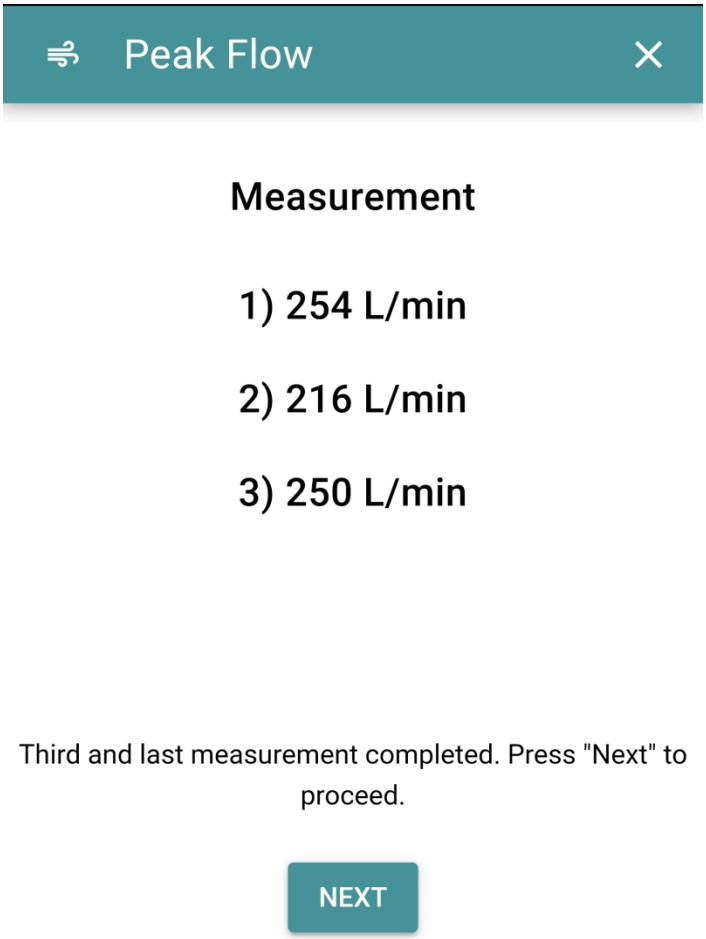

Figure 5: Smart peak flow meter task

962x1649mm (38 x 38 DPI)

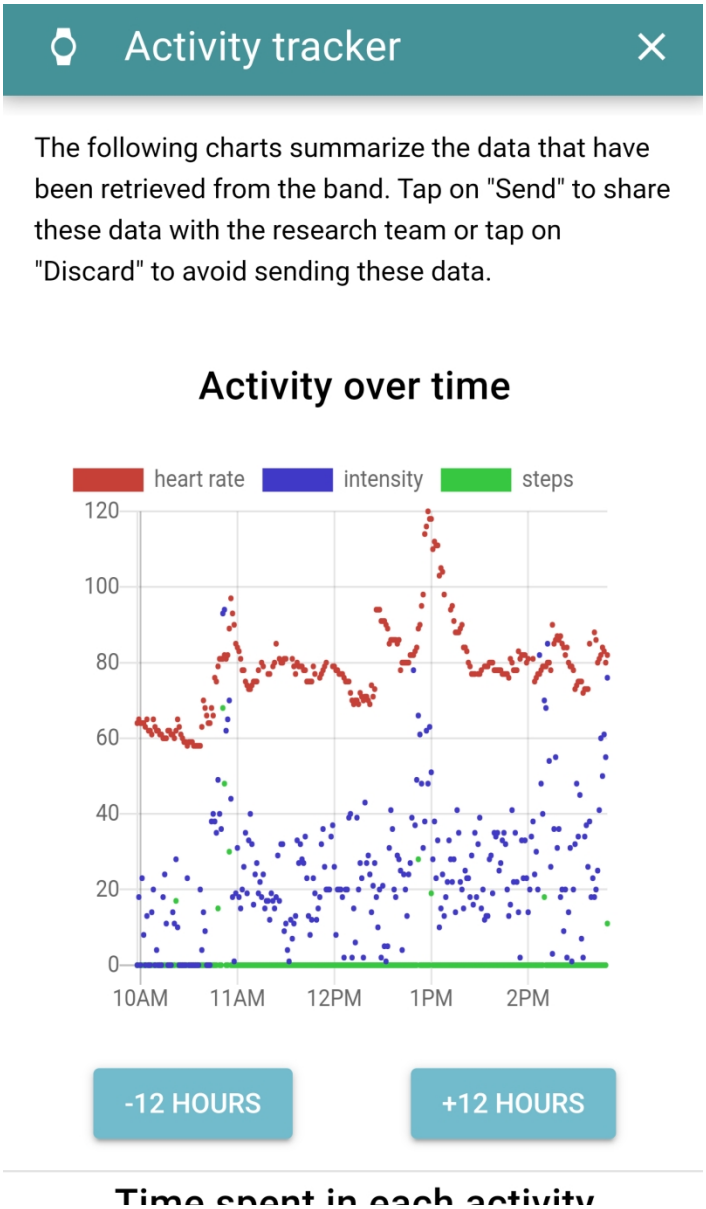

Figure 6: Smartwatch data

957x1637mm (38 x 38 DPI)

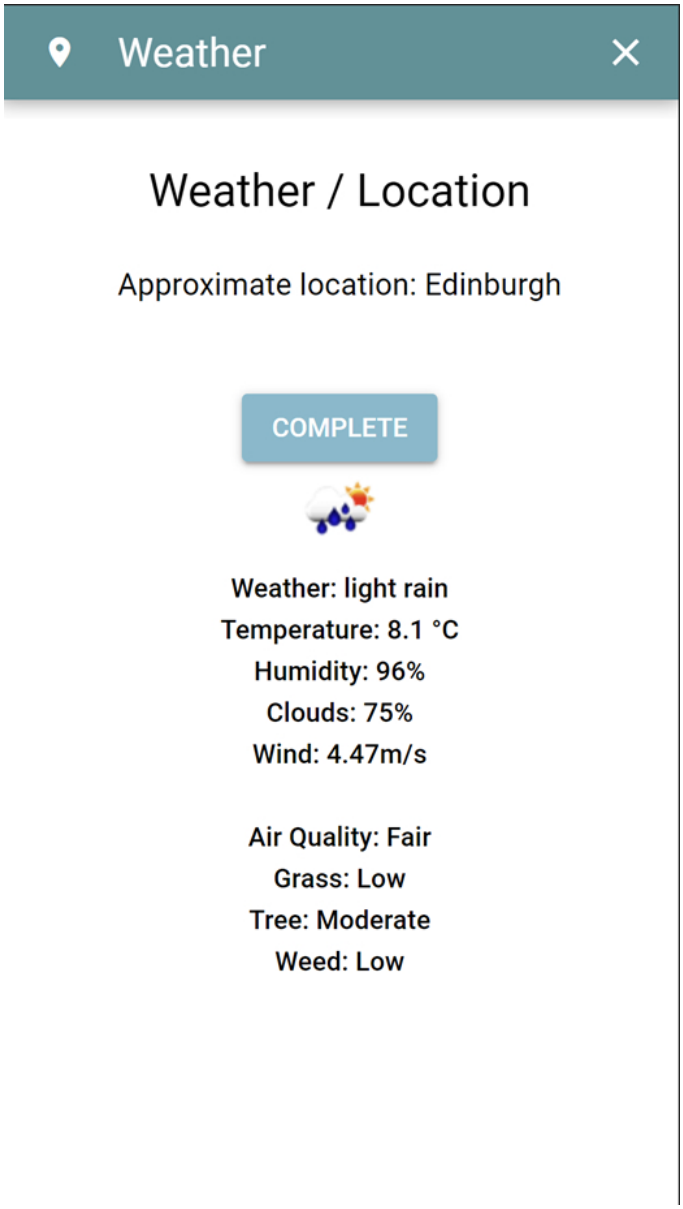

Figure 7: Local weather data

347x616mm (38 x 38 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	10

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	NA
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Predicting asthma attacks using connected mobile devices and machine learning; the AAMOS-00 observational study protocol

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Predicting asthma attacks using connected mobile devices and machine learning; the AAMOS-00 observational study protocol

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Word count: 3544

ABSTRACT

Introduction:

Supported self-management empowering people with asthma to detect early deterioration and take timely action reduces the risk of asthma attacks. Smartphones and smart monitoring devices coupled with machine learning could enhance self-management by predicting asthma attacks and providing tailored feedback.

We aim to develop and assess the feasibility of an asthma attack predictor system based on data collected from a range of smart devices.

Methods and Analysis:

A 2-phase, 7-month observational study to collect data about asthma status using three smart monitoring devices, and daily symptom questionnaires. We will recruit up to 100 people via social media and from a severe asthma clinic, who are at risk of attacks and who use a pressurised metered dose relief inhaler (that fits the smart inhaler device).

Following a preliminary month of daily symptom questionnaires, 30 participants able to comply with regular monitoring will complete six months of using smart devices (smart peak flow meter, smart inhaler, smartwatch) and daily questionnaires to monitor asthma status. The feasibility of this monitoring will be measured by the percentage of task completion. The occurrence of asthma attacks (definition: ATS/ERS Task Force 2009) will be detected by self-reported use (or increased use) of oral corticosteroids. Monitoring data will be analysed to identify predictors of asthma attacks. At the end of the monitoring, we will assess users' perspectives on acceptability and utility of the system with an exit questionnaire.

Ethics and Dissemination:

Ethics approval was provided by the East of England - Cambridge Central Research Ethics Committee. IRAS project ID: 285505 with governance approval from ACCORD (Academic and Clinical Central Office for Research and Development), project number: AC20145. The study sponsor is ACCORD, the University of Edinburgh.

Results will be reported through peer-reviewed publications, abstracts, and conference posters. Public dissemination will be centred around blogs and social media from the Asthma UK network and shared with study participants.

Key Words

Asthma Attacks, Machine Learning, mHealth, Smart Monitoring Devices, Prediction

ARTICLE SUMMARY

Strengths and limitations of this study

- This study combines objective data collected from multiple smart monitoring devices available on the market.

- Stratified analysis and individualised asthma attack prediction models are not expected, due to the limited number of participants and study period.
- Participants are limited to patients with severe asthma at risk of acute attacks, and to those using a pressurised metered dose relief inhaler that fits our smart device.

INTRODUCTION

Asthma is a variable condition, affecting around 5.4 million people in the UK.[1] Every 10 seconds in the UK alone, someone has an asthma attack. Some of these attacks are life-threatening with over 1400 annual deaths estimated in the UK.[1,2] Since there is no known cure for asthma, self-management is a key part of patient care; this involves detecting deterioration and taking appropriate action to maintain control and prevent the threatened attack.[3] The most common symptoms of asthma are wheezing, cough, chest tightness and shortness of breath.

Traditional self-management action plans use symptom scores, sometimes supplemented by peak flow measurements, to determine a patient's asthma condition.[4–6] Keeping track of relief inhaler usage can also help measure asthma control.[7] However, patients may regard this level of monitoring as tedious as it involves high levels of active engagement on their part.

Increasingly, smart monitoring devices and "mobile-health" (mHealth) technologies are being developed to support asthma self-management.[8] Some notable examples include myAsthma [9] and Asthma MD.[10] myAsthma stores personalised action plans, includes instructional videos about inhaler techniques, tracks symptoms and peak flow, and provides local weather forecasts. AsthmaMD [10] has similar features to support self-management and can provide customised notifications. However, these tools still require a high level to active engagement to monitor one's asthma.

There has been an increasing number of mHealth studies to predict asthma attacks and develop passive monitoring to support asthma self-management,[11] including the use of smart peak flow meters,[12] night-time activity tracking,[13,14] smart inhalers,[15] smartphone administrated questionnaires,[6,16,17] and weather data.[18,19] However, the combined use of the monitoring devices available to asthma patients to develop asthma attack prediction models is largely unexplored. In addition, whilst there have been some studies that explored the use of machine learning algorithms for chronic disease management with home-monitoring data,[20] there is still no mHealth system that is widely used by asthma patients. One of the key bottlenecks for the limited progress is the difficulty of collecting asthma monitoring data and the lack of availability of such datasets from existing studies. Apart from the Asthma Mobile Health Study,[21] no other asthma mHealth dataset is publicly available to be able to investigate the development and validation of asthma attack prediction algorithm.

A related study is the myAirCoach study,[22] which investigated asthma home-monitoring using connected devices. However, their participants conducted daily monitoring for the first month with an additional randomly allocated two weeks, compared to seven months in total proposed in this study. To our knowledge, the dataset from myAirCoach is not publicly available and it has not yet been used to test any machine learning-based algorithms for asthma attack prediction.[23,24]

In this study, we will collect novel asthma monitoring data that will facilitate the development of an asthma attack prediction algorithm leveraging available, approved asthma monitoring devices in the market. This study will also enable us to test whether unobtrusive, passive monitoring and machine learning could help minimise the need for active patient data collection whilst maintaining accuracy for predicting attacks. We envisage that an mHealth system that leverages machine learning to predict asthma attacks with passive monitoring will enhance patient adherence and improve patient self-management.

The overarching aim of this study is to develop and assess the feasibility and acceptability of an asthma self-management system using existing smart devices, collect novel monitoring data and leverage machine learning to explore the feasibility of an asthma attack prediction algorithm based on passive monitoring.

METHODS AND ANALYSIS

Study population

To maximise the chances of collecting data related to attacks in a short time-span, we will focus on patients with moderate to severe risk of attacks. Two key predictors are a recent history of attacks and people with severe asthma.[25,26] We will thus focus on adult asthma patients who have had at least one course of oral corticosteroid for an acute asthma attack in the past 12 months, and people attending a secondary care severe asthma clinic. See Table 1 for inclusion and exclusion criteria.

Social media recruitment consists of sending tweets on Twitter and posting on Facebook via the Asthma + Lung UK and Asthma UK Centre for Applied Research (AUKCAR) accounts, which total around 175,000 followers. The Norfolk and Norwich University Hospital will help identify potentially eligible patients for the study and direct them to the online information and expression of interest.

Table 1: Inclusion and exclusion criteria

Inclusion criteria:	• Aged 18 and above • Self-reported or doctor-diagnosed asthma • Possession of a smartphone (from 2016 onwards) that can support the Mobistudy and FindAir mobile apps (Android 4.4+, iOS 10+) and has Bluetooth capabilities • Has had at least one course of oral corticosteroids for an acute asthma attack in the past 12 months • Prescribed with pressurised metered dose relief inhaler that is compatible with FindAir ONE (e.g. Ventolin and other versions of salbutamol if the inhaler is a compatible shape inhaler as Ventolin; Salamol; Airomir; Fostair; Budiair)[27]
Exclusion criteria:	• Comorbidities that have overlapping symptoms (e.g. wheezing, cough, chest tightness and shortness of breath) • Aged under 18 • Unable to provide valid consent (e.g. cognitive impairment, learning disabilities) • Unable to use an app and respond to questions in English

Potential participants will complete an online questionnaire to identify whether they are eligible to participate. Informed consent will be collected via Online Surveys, a secure online platform for collecting questionnaire data. Potential participants will be given time to read the participant information sheet before deciding whether to participate.

Sample size calculation

To achieve the objectives of this study, we need to collect sufficient data need to train an asthma attack prediction model.

In the study population of UK Optimum Patient Care Research Database (OPCRD) and Clinical Practice Research Datalink (CPRD), 41% of the patients who had multiple (2 or more) attacks in the baseline year also had multiple attacks in the following year.[26]

Based on 30 participants with daily monitoring, 3,098 recordings (= 30 people × 30 days × (85% retention at baseline,[28–30] 50% retention at 6 months[28,29,31,32]) × 85% adherence[30,31]) for each of the daily measurements can be expected in phase 2. Also, 12 recorded asthma attacks are expected, assuming an average of one attack observed per participant in 41% of phase 2 participants during the study period.[26] To use the novelty detection algorithm iForest (which can be trained even if the data collected does not include any attacks), a sample of 256 recordings or data points would suffice.[33] Other machine learning classification algorithms will also obtain high accuracy on this sample size.

Recruitment strategy

Using a similar recruitment method, Hui et al. recruited 87 participants using social media alone, the majority within the first month after the initial invitational message, although the number of those who continued to use the app dropped to 15 (17% of the total initially recruited participants) after 30 days.[28] Moreover, only 5% of identified participants through practices agreed to join their study, which totalled 28 participants from five practices.[28] However, the attrition rate for participants recruited through practices was lower, 63% vs 83% reduction in social media participants; only 25% of users were still using the app after 30 days.[28] The eligibility criteria (≥16 years, an asthma prescription in the previous year, registered with a UK general practitioner) is more relaxed than the proposed criteria. However, this study incentivises entry of data in the first 28 days by giving adherent participants access to phase 2 (where participants are sent smart devices) which is likely to result in much more than 25% passing 30 days of participation. The adherence to four weeks of monitoring with daily questionnaires and activity monitors has seen values upwards of 95%.[30]

Following the previous research, which recruited participants through Asthma UK's social media (at the time of writing had 175,000 followers), around 87 participants are expected to be eligible and join this study. In addition, around six participants identified and invited via are expected to be eligible and join from Norfolk and Norwich University Hospital. Of which, 47 people (50% of 93 respondents) are expected to complete phase 1. Thus, including 30 participants is achievable using the outlined recruitment method.

Outcomes

Primary endpoints

The primary endpoints of this study are adherence to monitoring, which are defined by the collection of data using different devices. For each task, we will measure the percentage of total days completed.

Secondary endpoints

The secondary endpoints of this study are asthma attacks. Primarily, we use severe asthma attacks as defined in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force 2009 statement.[34] The definition is as follows:

- *Severe asthma attacks* are events that require urgent action on the part of the patient and physician to prevent a serious outcome. Such attacks are defined as a deterioration requiring use of systemic corticosteroids (or an increase from a stable maintenance dose).[34]

Severe asthma attacks will be identified using the use of systemic corticosteroids question on the weekly self-reported questionnaire. Courses of corticosteroids separated by 1 week or more will be treated as separate severe attacks.

We will also explore the use of moderate asthma attacks, as defined in the ATS/ERS Task Force 2009 statement.[34] The definition is as follows:

- A *moderate asthma attack* is an event that, when recognised, should result in a temporary change in treatment to prevent the attack from becoming severe. Such attacks are defined as a deterioration that does not require use of systemic corticosteroids.[34] Moderate asthma attacks include a deterioration in symptoms, lung function, and/or increased rescue bronchodilator use that lasts for 2 days or more but are not severe enough to warrant systemic corticosteroid use.

Moderate asthma attacks will be identified using the questions about relief inhaler usage, symptoms (day symptoms, nocturnal symptoms, interference with usual activities, shortness of breath, wheezing), and unscheduled care (GP, emergency room, and hospitalisations) in the daily and weekly self-reported questionnaires.

Data collection

The data collection period is split into two phases:

1. *Questionnaire monitoring, daily for one month.*
2. *Smart device and questionnaire monitoring, daily for six months.* 30 participants who keep a regular diary in phase 1 will be given three smart devices (smart inhaler, smart peak flow meter, smartwatch) to collect data automatically as they use the devices, in addition to completing daily and weekly questionnaires. We will choose participants for this phase with a range of ages, gender, and smoking status, and with different types of asthma triggers.

At the end of phase 2, we will send a questionnaire asking for feedback about using the smart devices and whether participants think they could be useful to help them look after their asthma.

We will be using Mobistudy to centralise most of the data collection, only the smart inhaler usage and exit questionnaire will not be collected via Mobistudy (see Figure 1).

Data collection mobile app (Mobistudy)

Mobistudy [35] is an open-source platform facilitating mHealth studies available on Android and iOS managed by Malmö University, Sweden. The platform has three key components: a mobile app for participants, a REST API server, and a web portal for researchers (see Figure 2). The platform supports multiple studies and participants of the AAMOS-00 study will be given a study invite code to join the AAMOS-00 study within Mobistudy.

Each daily and weekly assessment, such as questionnaires and peak flow measurement, will appear as an individual task of the home page on the participant's app (see Figure 3). Once the task is completed, it will be removed from today's to-do list and the data is sent directly to the server via the phone Internet connection. In real-time, the research team will be able to view the collected data via the online web portal for researchers.

Phase 1

There will be a total of four questionnaires:

- A daily questionnaire that asks six questions about daily symptoms experienced, medication usage, and the triggers encountered. This will take around 2 minutes to complete.
- A weekly questionnaire that asks 10 questions about asthma symptoms in more detail, medication usage, and healthcare engagement. This will take around 5 minutes to complete.
- A questionnaire that asks 11 questions at the start of phase 1 about current asthma condition and history.
- A questionnaire that asks five questions about race and smoking status. Additionally, some demographic information will be collected from the Mobistudy profile of participants, such as height, weight, and age.

The completion rate (50%) of the daily and weekly questionnaire will be used to determine the eligibility of a participant to join phase 2.

Phase 2

In addition to the daily and weekly questionnaires (see Figure 4), in phase 2 participants will be asked to collect data using three smart monitoring devices: Smart Peak Flow Meter (by Smart Asthma [36]), FindAir ONE (by FindAir [27]) smart inhaler, and MiBand3 (by Xiaomi [37]) smartwatch.

Participants will be given the smart peak flow meter to take a peak expiratory flow measurement twice a day, once in the morning and once at night; each measurement takes the best of three tries (see Figure 5). They will also be provided in-app written instructions before each set of measurements on using the peak flow meter. Furthermore, participants recruited through the Norfolk and Norwich University Hospital have been trained to use a peak flow meter by the practice.

To connect the smart peak flow meter to the smartphone, participants can either use the audio-jack connection or a Bluetooth adapter.

The FindAir ONE smart inhaler attaches to the top of pressurised metered dose relief inhalers, it records the time at which the inhaler is used. The device can be moved to a new inhaler if participants change medication. The device will be connected to participants' smartphone by Bluetooth to the FindAir mobile app. The data will be transferred from the FindAir server and thence to the research team using FindAir's Application Programming Interface (API). The data collection will happen in the background once the participant has set up the connection between their mobile app and the AAMOS-00 study.

Using the MiBand3, we will collect minute-by-minute data on heart rate, step count, activity intensity, and activity type. The watch will connect to the participant's smartphone via Bluetooth and to the Mobistudy app. Participants will be asked to upload the data from the watch at least once every three days. This also gives a chance for users to review their activity (see Figure 6).

Local daily weather reports will be obtained using the phone's location combined with the data from Open Weather Maps' [38] and Ambee's [39] API. The weather data will include the temperature, humidity, clouds, wind, air quality index, and pollen levels of grass, tree, and weeds measured at a one-kilometre resolution (see Figure 7).

Exit questionnaire at the end of Phase 2

At the end of phase 2, a survey will gather data regarding users' perspective of the acceptability and utility of the monitoring system. The survey combines validated questionnaires on usability and acceptance (SUS [40] and uMARS [41]) with questions about motivations to use technology (mTEI [42]) and desired features in an asthma management system.

See Table 2 for a summary of the study's activities.

Table 2. Summary of data collection

Assessment	Screening	Day 1 baseline	Phase 1	Day 31 baseline	Phase 2	Study Exit
Assessment of Eligibility Criteria	Once			Once		
Written informed consent	Once					
Demographic data, contact details		Once				
Weight/height		Once				
Known triggers		Once				
Peak flow					Twice daily	
Heart rate					Automated	
Activity					Automated	
Location, air quality and allergens					Daily	
Inhaler Usage			Daily & Weekly		Automated	
Symptoms			Daily & Weekly		Daily	
Triggers encountered			Daily		Daily	
Healthcare Usage			Weekly		Weekly	
Feedback						Once at the end

At the end of the study, participants will be compensated for mobile data charges that may have incurred from participating in the study, £5 per month. Participants are also able to continue using the smart devices beyond the study.

Following ethics approval in December 2020, we aim to complete the study by June 2023.

Data analysis plan

Feasibility (from usage data)

Combining the usage data from phase 1 and 2 of questionnaire completion and device usage will compute compliance to the monitoring regime to assess if it is feasible for patients to use the monitoring devices in their daily lives.

We will also use activity logs on the server, and communication over email with patients, to identify major technical issues and shortcomings of the technology.

Acceptability (from survey data)

The data from the final questionnaire will be mostly ordinal data, with some free text answers. Free text will be processed for thematic text analysis, identifying overall acceptability and recurring topics present in the feedback. The ordinal data from answers on a Likert scale will provide measures of acceptability.

Exploring asthma attack prediction (using monitoring data)

Severe asthma attacks will be identified by the reports of oral corticosteroid usage (or an increased dose from normal). Moderate and severe asthma attacks will be identified from the daily and weekly data, to observe a change in control from the norm lasting two days or more. Sensitivity analysis will be conducted using different features to define an asthma attack, such as hospitalisations and changes in peak flow. Data collected from participants who have withdrawn from the study will be used up to the last recording.

The methods of linear fit and bin-algorithms will be used to collate and produce summary variables over irregular time-series and to handle missing data.[6] After processing the data, machine learning classifiers will be trained to predict asthma attacks. Evaluation of these classifiers will allow comparison with the benchmarks set using daily questionnaires alone.[6] However, due to the selection of participants with higher adherence to monitoring in phase 2 of this AAMOS-00 study, the longitudinal data collected in this study are likely to be more complete than the data collected by the wide range of participants in the Asthma Mobile Health Study.[43]

Using different subsets of the data and features, we will test the performance of predictions made using different modes of monitoring, such as self-reported data alone, self-reported and objective data (active and passive monitoring), and passive monitoring data only (see Figure 8). Our previous analysis using only self-reported data achieved AUC > 0.87 and we expect the performance to increase with the addition of objective data.[6]

There is no consensus on the optimal algorithm for classification as previous studies are not comparable.[11] Therefore, we have taken a broad approach to use five state-of-the-art algorithm classes including Bayesian networks, decision trees, iForest, logistic regression, and support vector machines.[44,45] From the classifiers, a severe asthma attack predictor will be built on the device and questionnaire data, at a patient-level and population-level. Also, feature selection will be used to identify the most useful features in the prediction models.

Furthermore, if there are sufficient data, retrospective analysis will simulate the effects of limiting the use of active monitoring data, to simulate patients only taking active measurements (e.g., peak flow and symptom diary) when prompted. Moreover, there will be simulation of the general population using samples of the data, where adherence to monitoring is lower than the select population. For assessing the performance of the models built in this study, we will use k-fold cross validation.[44] The performance metrics will include the common machine learning metrics such as area under the receiver operating characteristic curve (AUC-ROC), sensitivity, and specificity.

Strengths and limitations

This study combines objective data collected from multiple smart monitoring devices available on the market. Not only will this independently test the monitoring devices in the real-world, but also patients will be able to continue using the devices they have found useful beyond the study. It also allows other researchers to reproduce the study with the current or latest versions of the devices.

Due to the limited number of participants and study period, stratified analysis and individualised asthma attack prediction models are not expected. However, seven months of daily monitoring per participant will provide insightful data.

This study is limited to patients with severe asthma at risk of acute attacks, and the findings may not generalise to the wider asthma population. Furthermore, only participants using a pressurised metered dose relief inhaler that fits our smart device are able to join the study, which is around 80% of the UK's asthma population.[46] If there are sufficient data, we will explore the generalisability of the results through simulating different adherence to monitoring.

The anonymised research data will be stored at Edinburgh DataShare (a digital repository of research data produced at the University of Edinburgh),[47] which researchers can access for their own research.

PATIENT AND PUBLIC INVOLVEMENT

Patient and public involvement (PPI) is part of the project from the beginning. This study is nested within the Asthma UK Centre for Applied Research and has been reviewed by their AUKCAR PPI members.

All the participant and public-facing documents and study objectives have been reviewed by AUKCAR PPI members before the start of the study and edited accordingly. Such a close PPI involvement ensures that the participant and public facing material is accessible. As an example, we attempted to explain several technical terms (such as "pMDI") in more detail in the participant documents and added pictures of pressured metered dose inhalers after feedback from PPI members.

The findings about feasibility and acceptability will be interpreted with input from PPI members. Furthermore, we plan to continue working with PPI members to develop a system that supports asthma self-management.

DISSEMINATION

We will be reporting the results in peer-reviewed journal publications and conference presentations. Dissemination of the results will also include the AUKCAR network with blogs and social media to reach an audience who is interested in the used of smart monitoring devices for asthma.

We will also be sharing links to publications and summaries with study participants.

ETHICS

This study has received ethics approval by the East of England - Cambridge Central Research Ethics Committee. IRAS Project ID: 285505.

DATA AVAILABILITY

At the end of the study, the anonymised research data will be stored at Edinburgh DataShare (a digital repository of research data produced at the University of Edinburgh) in perpetuity. Researchers will be able to access and download the data from the website for their own research.

CONCLUSIONS

The present study will collect an important and novel dataset, where asthma patients use a combination of multiple market-available mHealth monitoring devices in the real world. We plan to use the rich dataset to improve existing asthma attack prediction algorithms and use the feedback from participants to design a patient-centred asthma self-management system. This study is the first step in developing the Asthma Attack Management Online System (AAMOS) which will support asthma patients with real-time tailored feedback based on machine learning driven by mHealth data.

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AUTHOR CONTRIBUTIONS

KCHT, HP, AMW, and SAS designed the study. SAS is the study guarantor. KCHT and DS set up the data collection system. KCHT drafted the manuscript which was critically revised by HP, AMW, DS, and SAS. All authors approved the final version of the manuscript.

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COMPETING INTEREST STATEMENT

None declared.

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FIGURE LEGENDS

Figure 1. AAMOS-00 system overview

Figure 2. Mobistudy system overview

Figure 3. Participant's app home page

Figure 4. Questionnaire delivered by Mobistudy

Figure 5. Smart peak flow meter task

Figure 6. Smartwatch data

Figure 7. Local weather data

Figure 8. Exploring asthma attack prediction.

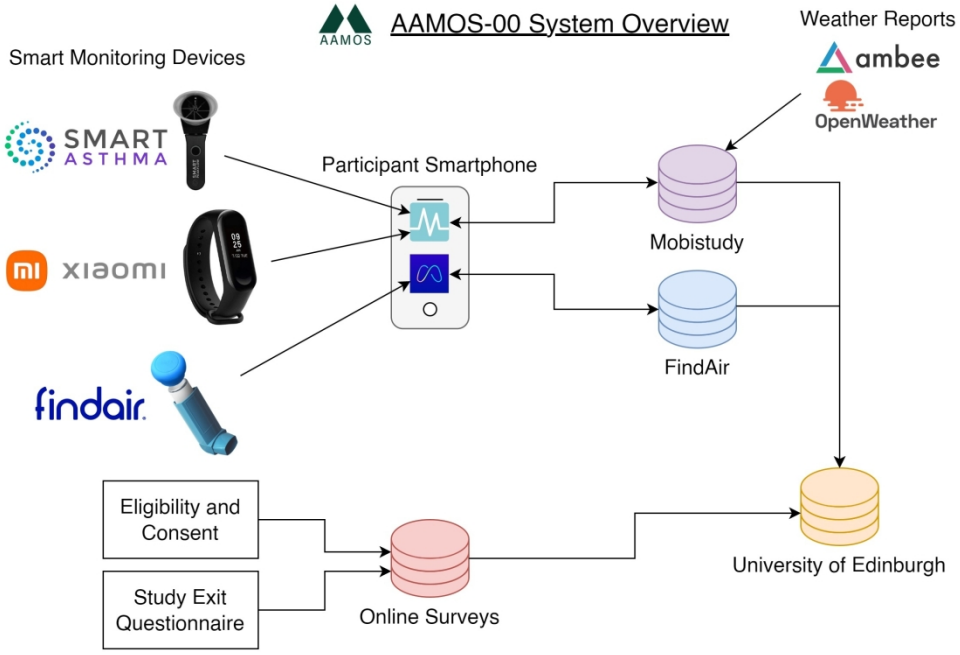

Figure 1: AAMOS-00 system overview

819x545mm (72 x 72 DPI)

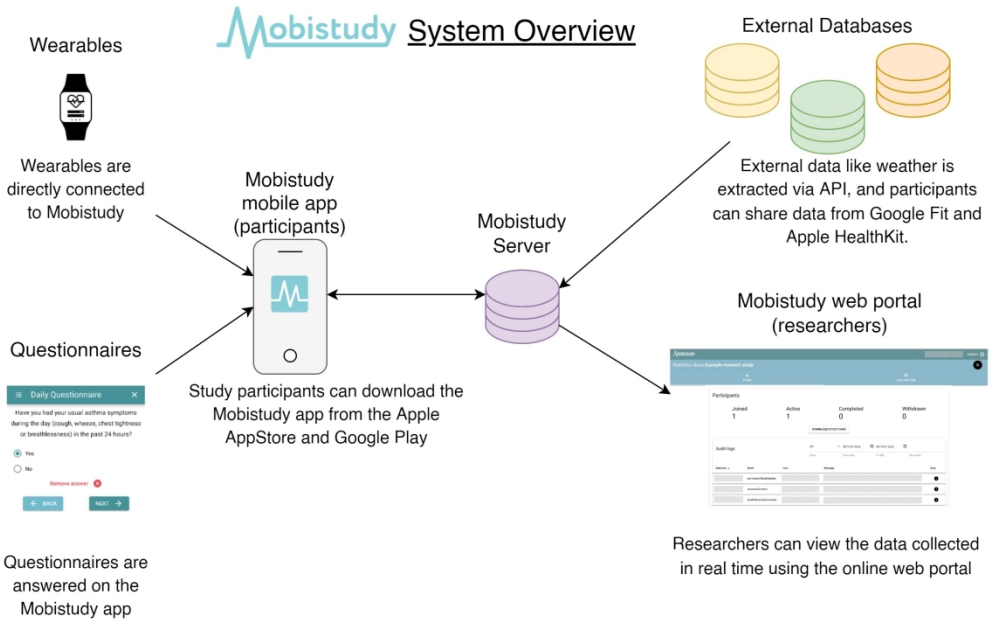

Figure 2: Mobistudy system overview

864x535mm (72 x 72 DPI)

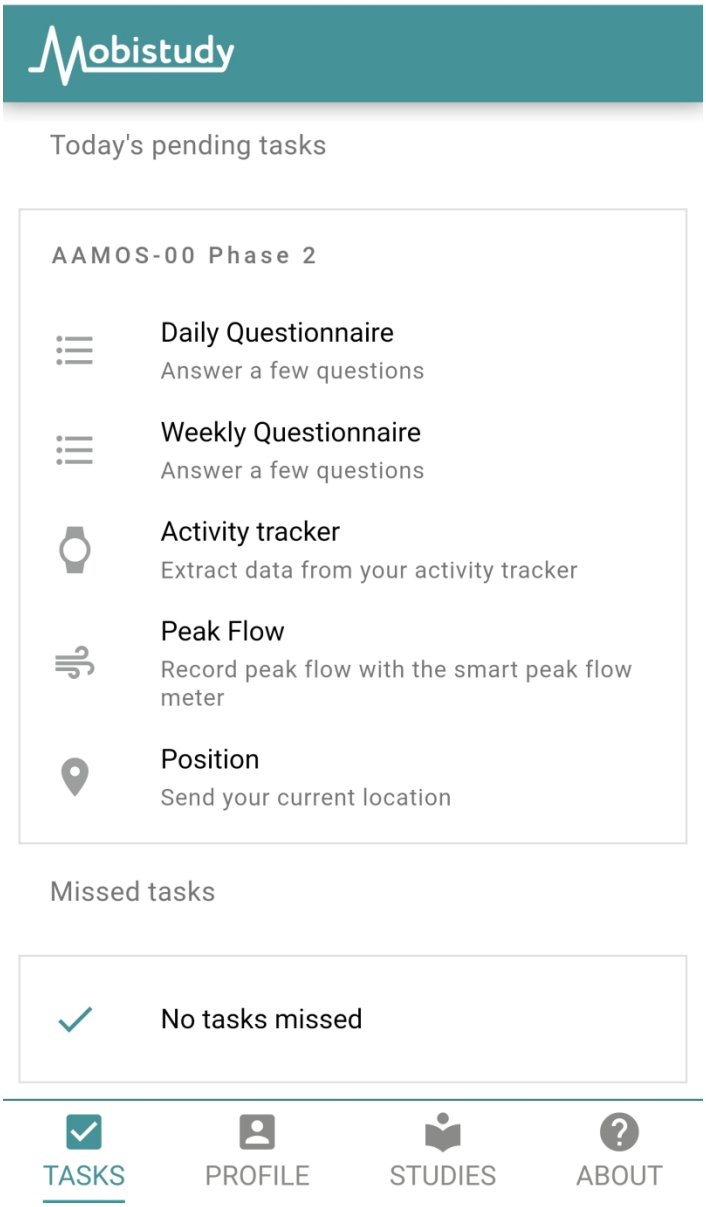

Figure 3: Participant's app home page

121x208mm (300 x 300 DPI)

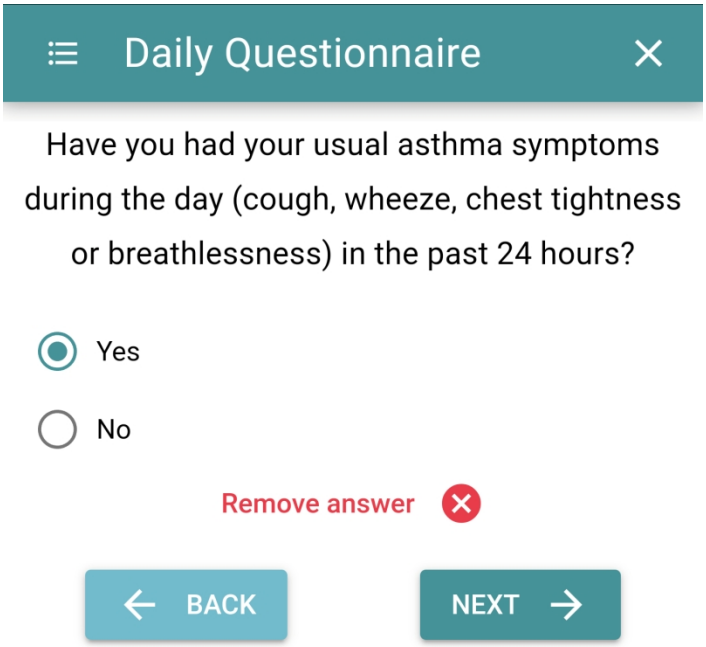

Figure 4: Questionnaire delivered by Mobistudy

121x208mm (300 x 300 DPI)

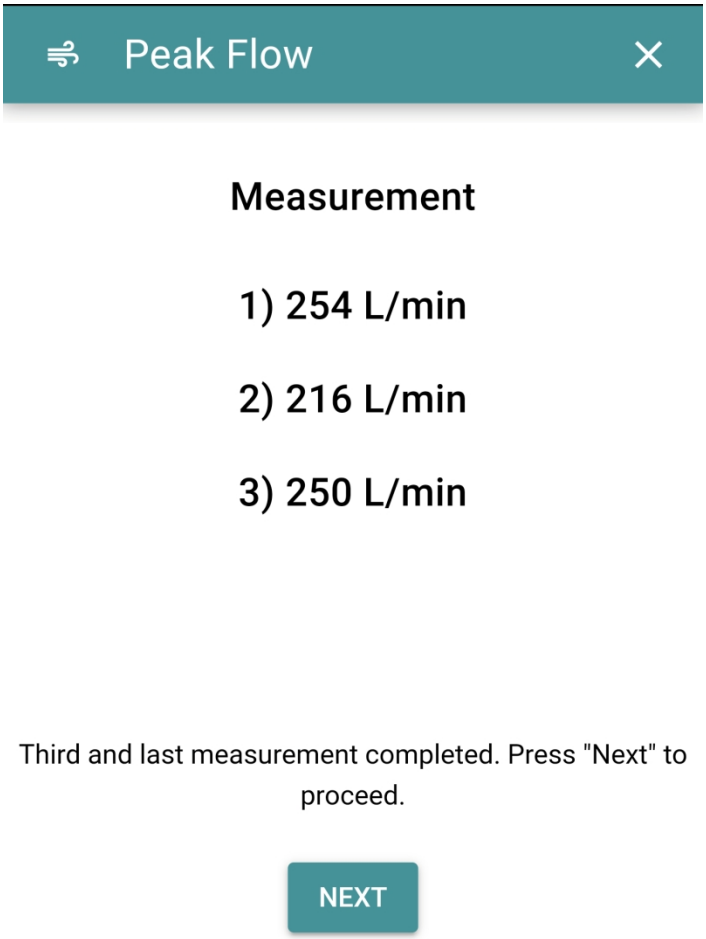

Figure 5: Smart peak flow meter task

121x208mm (300 x 300 DPI)

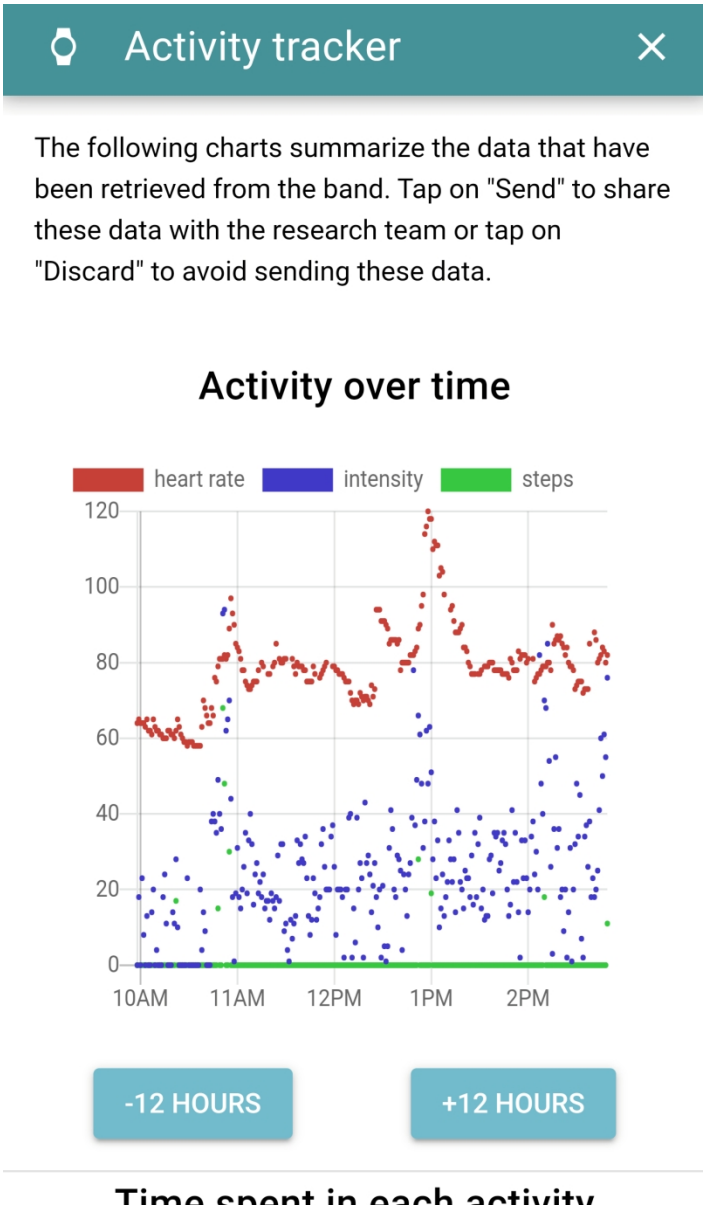

Figure 6: Smartwatch data

121x207mm (300 x 300 DPI)

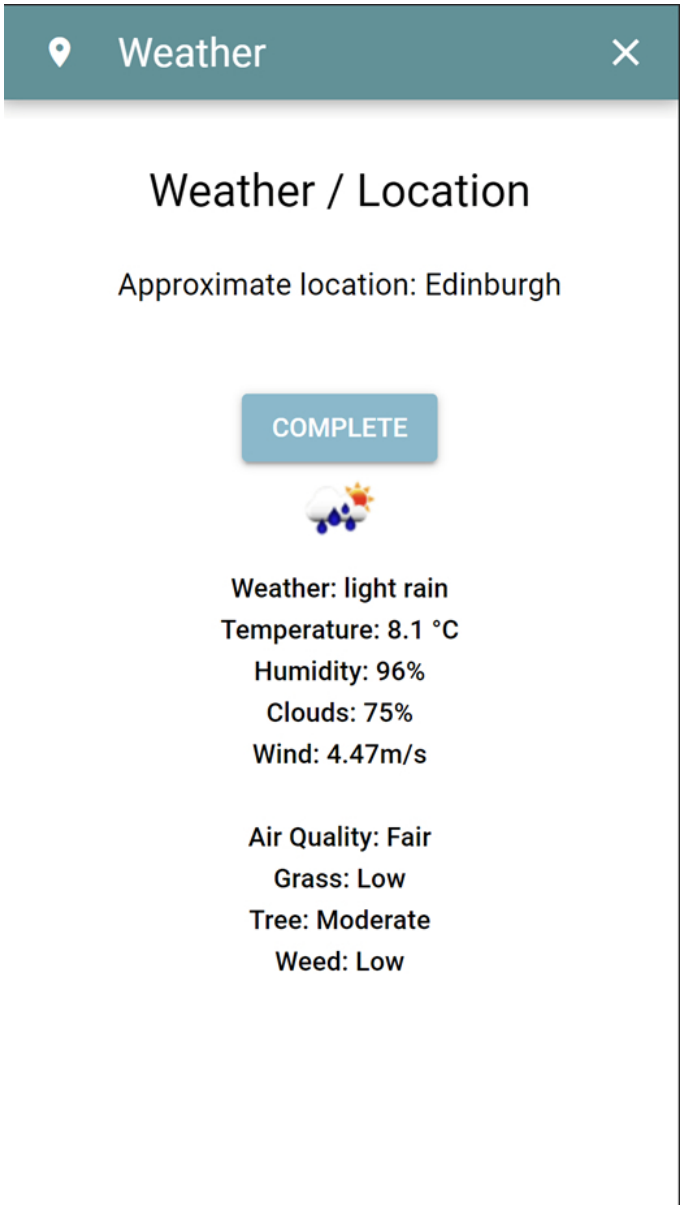

Figure 7: Local weather data

44x78mm (300 x 300 DPI)

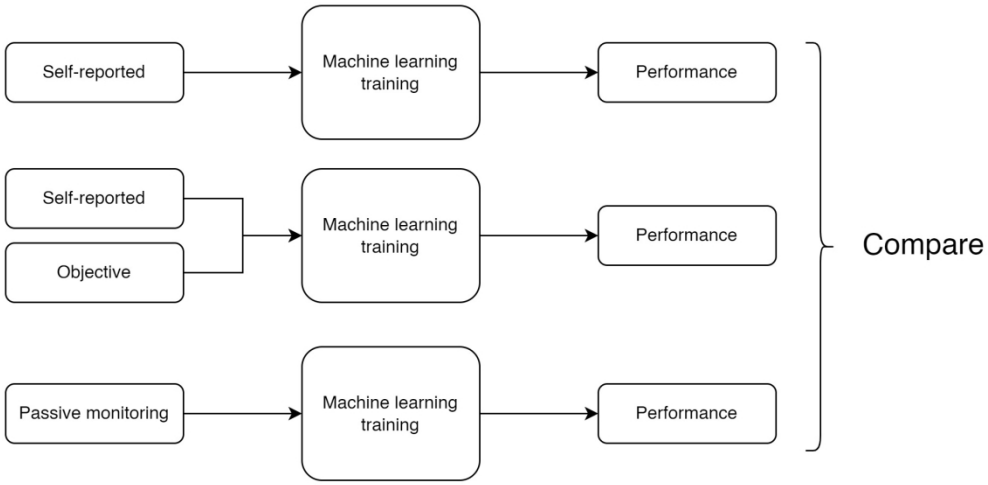

Figure 8. Exploring asthma attack prediction

714x407mm (72 x 72 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7*
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	10

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*NA*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	*NA*
		Cross-sectional study—Report numbers of outcome events or summary measures	*NA*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	NA
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.