Digipredict

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DIGIPREDICT: physiological, behavioural and environmental predictors of asthma attacks—a prospective observational study using digital markers and artificial intelligence—study protocol

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ABSTRACT

Introduction Asthma attacks are a leading cause of morbidity and mortality but are preventable in most if detected and treated promptly. However, the changes that occur physiologically and behaviourally in the days and weeks preceding an attack are not always recognised, highlighting a potential role for technology. The aim of this study 'DIGIPREDICT' is to identify early digital markers of asthma attacks using sensors embedded in smart devices including watches and inhalers, and leverage health and environmental datasets and artificial intelligence, to develop a risk prediction model to provide an early, personalised warning of asthma attacks.

Methods and analysis A prospective sample of 300 people, 12 years or older, with a history of a moderate or severe asthma attack in the last 12 months will be recruited in New Zealand. Each participant will be given a smart watch (to assess physiological measures such as heart and respiratory rate), peak flow meter, smart inhaler (to assess adherence and inhalation) and a cough monitoring application to use regularly over 6 months with fortnightly questionnaires on asthma control and well-being. Data on sociodemographics, asthma control, lung function, dietary intake, medical history and technology acceptance will be collected at baseline and at 6 months. Asthma attacks will be measured by self-report and confirmed with clinical records. The collected data, along with environmental data on weather and air quality, will be analysed using machine learning to develop a risk prediction model for asthma attacks.

Ethics and dissemination Ethical approval has been obtained from the New Zealand Health and Disability Ethics Committee (2023 FULL 13541). Enrolment began in August 2023. Results will be presented at local, national and international meetings, including dissemination via community groups, and submission for publication to peer-reviewed journals.

Trial registration number Australian New Zealand Clinical Trials Registry ACTRN12623000764639; Australian New Zealand Clinical Trials Registry.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There are physiological and behavioural changes occurring in the days to weeks before an asthma attack but are not always easily recognised.

WHAT THIS STUDY ADDS

⇒ This DIGIPREDICT study will identify early digital markers of asthma attacks.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND OR POLICY

⇒ Identifying these markers will enable early detection and management of attacks and inform the development of a risk prediction model for asthma attacks based on these digital markers.

INTRODUCTION

Asthma is one of the most common long-term conditions in New Zealand (NZ), affecting one in five children and one in eight adults.[1] These rates are among the highest in the world, particularly in Māori and Pacific people.[2] Globally, more than 1000 people die from asthma each day, a number that is largely unchanged since 2006[3] with asthma remaining the second leading cause of death among chronic respiratory diseases.[4] Asthma attacks, also known as exacerbations, are the primary cause of asthma deaths and place a huge burden on the NZ health system costing >NZ$120 million each year.[2] Early recognition of deterioration, timely adjustment of treatment and prompt seeking of emergency medical advice, is critical to prevent severe

attacks and potential death. Too often, patients do not recognise the severity of their asthma deterioration and delay timely action,[5] losing the self-management opportunity to prevent further deterioration and poor outcomes. There is a need to identify novel, preferably passive (ie, requiring little/no effort on the part of the patient) markers of attacks to facilitate early detection of attacks and trigger action.

There also remain unanswered questions about risk factors for attacks and the underlying mechanisms.[6] Notably, it is difficult to predict attacks before they occur, as the risk varies between and within individuals over time and is influenced by multiple health and non-health factors, including genetics, demographics, medications and comorbidities. Contextual elements such as socioeconomic, behavioural and environmental factors can also play a role. While single risk factors have been identified, each factor alone has limited predictive value.[7] Moreover, current risk prediction models have primarily been developed using data from retrospective healthcare data sets rather than from prospective real-time data.[7] The time scales from these retrospective data sets are often too long for meaningful action to be taken to prevent attacks; for example, many algorithms identify individuals who are more likely to experience attacks in the next months or year, rather than when an attack is imminent.

Digital technologies offer dual opportunities of monitoring in real-time (a) factors that increase the risk of an attack (eg, environmental triggers, individual history of attacks, poor adherence to preventer medication) to promote strategies to reduce risk and (b) objective measures that enable early detection of an imminent attack that can be captured by digital sensors[8] (eg, heart rate,[9–11] sleep quality[12] and peak expiratory flow[13]), which can trigger an alert for immediate action to avert further deterioration. However, there has been no research to date that bring together the range of factors. Previous studies have been limited in the application of artificial intelligence (AI) to develop risk prediction models. The studies that have used AI were developed on small data sets with limited validation[14]; few have applied AI to large complex data sets, where AI could be more useful.[13] Exarchos *et al* conducted a systematic review of the application of AI to asthma and concluded that AI in asthma research has still not been exploited to its full potential.[15]

This study 'DIGIPREDICT' proposes to address these limitations by adopting a data-driven approach using multiple data streams to make more timely and realistic inferences about attack risk. This will allow early intervention to reduce asthma-related morbidity and mortality. Data from routinely collected electronic health data, such as previous hospitalisation data, and digital inhaler use have been shown to be predictive of asthma attacks.[7 16–18] Adding diverse data streams that measure physiological, behavioural and environmental parameters to routinely collected health data is likely to improve machine learning predictive model performance and provide insights into an individual's risk of an imminent asthma attack in a timely manner to facilitate near real-time clinical management.[19]

The aim of this study is to prospectively collect real-time data on digital biomarkers and other parameters that are associated with asthma attack risk, using digital technologies and wireless sensors, and combine this information with retrospective data from NZ health and environmental datasets to improve prediction of asthma attack risk.

Specifically, the objectives are to:

i. Eplore the relationship between different physiological, behavioural and environmental factors and the risk of asthma attacks.

ii. Identify digital markers that can be used to detect worsening asthma control.

iii. Develop a risk prediction algorithm for asthma attacks using AI methods with the collected data.

METHODS AND ANALYSIS

Study design

This is a prospective observational cohort study in 300 individuals with asthma, each followed-up for 6 months to generate a longitudinal dataset of factors associated with asthma attacks.

Study population

Individuals will be eligible for inclusion if they meet the following criteria:

i. Aged 12 years or older at the time of enrolment.
ii. Have a physician diagnosis of asthma.
iii. History of a moderate or severe asthma attack in the last 12 months as defined by American Thoracic Society(ATS)/European Respiratory Society (ERS) Statement on Asthma Control and Exacerbations[20] (see study outcomes section).
iv. Currently managing asthma with preventative and/or relief medication delivered via either a pressurised metered dose inhaler (pMDI), Turbuhaler, Ellipta or other device compatible with the study digital inhaler sensors, prescribed by a NZ health practitioner.
v. Residing in Auckland or Waikato, or able to travel to either of these places for the study visits.
vi. Own or be willing to use a smartphone with Bluetooth capability that is compatible with the study devices and can host the study apps;
vii. Available and able to use the technologies for a period of 6 months.
viii. Able to provide written informed consent and to follow study procedures or protocols.

Individuals on treatment with other concomitant asthma medication will be eligible for inclusion. Participants can also change their medication during the study, including starting or stopping new treatments. These changes will be noted by the study investigators and accounted for during data analysis. The lower limit of the inclusion age range was chosen as digital literacy is likely

to be too low for children below 12 years of age to use the study devices independently.

Exclusion criteria will be:

i. A diagnosis of lung disease other than asthma for example, COPD, bronchiectasis, cystic fibrosis, bronchopulmonary dysplasia.
ii. Smoking history (self-reported) of>10 pack years.
iii. Planning to be overseas for more than 28 consecutive days in the next 6 months, unless the participant agrees to extend their period of follow-up to account for time overseas.

Participants will be recruited from two study sites—Auckland and in Waikato. In Auckland, the study sites will be Auckland City Hospital (Te Whatu Ora Te Toka Tumai Auckland) and Papakura Marae Health, located in Central and South Auckland, respectively. In Waikato, the study site will be Waikato Hospital (Te Whatu Ora Waikato). Community recruitment from both regions will be augmented with referrals from Asthma NZ nurses, personal and research networks and social media advertising.

Sample size

The target sample size was selected based on the feasibility of recruiting eligible patients across the funded study timeframe. We will aim to recruit 300 participants who will provide a total of 54 000 daily measurements on average. We will purposively sample for at least 15% Māori and 10% Pacific peoples. Based on the primary outcome of asthma attacks, we expect an estimated 48 individuals to have one or more attacks, based on a mean 20%±5% hypothesised population attack rate based on data from prior work[21 22] at 95% CI, with an estimated 20% dropout rate.[23] This is a conservative estimate with our recent work finding that asthma attack rates have increased significantly in the last 10 years with the most recent data showing a 25% attack rate with an average of 1.7 attacks per patient per year.[24] Based on the events per variable method, the ratio of the number of individuals with the outcome event to the number of candidate predictors should ideally be 10 individuals per a candidate risk factor for the outcome event.[25 26] With our sample size, there is a risk of overfitting as there may not be sufficient events for the number of variables we wish to include in the model. However, the rate of attacks in the population may be higher than our conservative estimate as we are recruiting a population with a history of previous attacks.

Screening and eligibility assessment

Potential participants who meet the inclusion criteria will be identified by the healthcare teams at each respective site, based on prospective appointments and from existing patient lists, and referred to the research team. For Auckland hospital (Te Toka Tumai), participants will be identified by the research team from an electronic report generated by the Business Intelligence Unit. The report captures patients 12 years or older who present with the International Classification of Diseases V.10-AM asthma-related diagnostic codes J45-J46; R05-R06; and J458. Posters informing participants of the study will be posted in ambulatory waiting areas and in the emergency departments.

Recruitment

The research team will assess potential participants to confirm eligibility for inclusion and then invite eligible participants by email for enrolment. Enrolment will not take place until a minimum period of 2 weeks has elapsed since their last hospital admission or presentation to primary care to allow stabilisation of the patient, unless the attendance was for a routine review. All study procedures will be explained to eligible participants by a member of the study team and in-person written informed consent will be obtained. Participants will consent for themselves, depending on their capacity to give valid consent. For children under the age of 16 years, researchers will also get consent from the parents or guardians.

Each participant will be assigned a unique random three-digit participant identifier as they enter the study to ensure data are deidentified. A unique email and password will be created for participants to log into the study-related apps (smartwatch, smart inhaler, cough monitor, food diary and study app), so that no personal emails will need to be used. The participant identifier will be used in all study-related documentation from case record forms to storage of collected data and a key file linking the study ID to the participant will be stored on a university managed secure server.

Follow-up assessments

Participants will be followed up for 6 months, with regular follow-up questionnaires via REDCap for participants to complete every 2 weeks (see figure 1). Participants will also receive a check-in phone call or text message each month to ensure that the participant has no problems with the technologies, though participants can contact researchers at any time if needed.

Participants will be offered a digital retail gift card as a token of appreciation for participation in the study—NZ$50 at the beginning of the study and NZ$50 if the participant attends the final 6-month study visit and engaged with the study throughout (see the Withdrawals section). Participants can keep the smart watch at study end.

End of study definition

The end of the study will be when the last participant has completed their final follow-up, 6 months after their enrolment date.

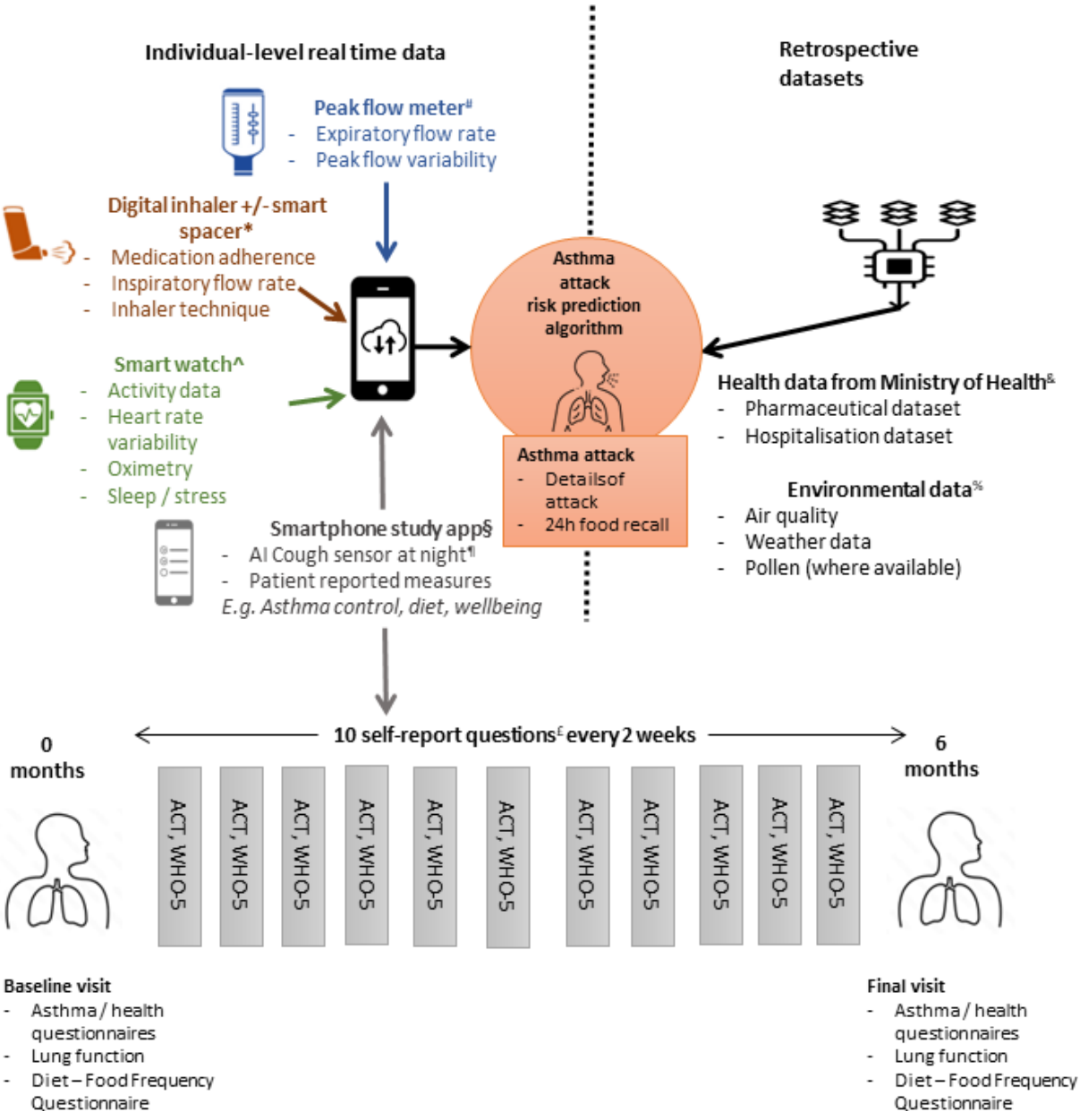

Figure 1 Study overview of study devices, variables and collected measures. ACT, Asthma Control Test.

Withdrawals

Participants may be withdrawn from the study at any time for the following reasons:

- When the participant wishes to be withdrawn from the study.
- If the participant experiences a severe adverse event that may be related to study participation.
- Consistent non-adherence to the study procedures defined as non-engagement with two or more study devices for at least 4 weeks or non-completion of two consecutive follow-up measures with no contact with the research team.
- If continuation in the study causes detriment to a patient's well-being

All withdrawals will be discussed with the study advisory group and fully documented in the participant's file with a record of the date of withdrawal, duration of participation, reasons for withdrawal and any other relevant details. At the point of withdrawal, participants will be offered the option of having the data that have been collected up until the date of withdrawal removed or continue to be analysed and used in the study.

Patient and public involvement

Patients and members of the public, including people involved in the care of people living with asthma, were involved with the planning and conduct of this research. A study advisory group, Māori advisory group and patient and public involvement group will be set up to inform the study design, recruitment and evaluation of the study and dissemination of results. Meetings with these groups

Table 1 Digital biomarkers and retrospective health and environmental data collected during the study

Data source	Parameter(s) collected	Details of data collected and data sources used
Prospective data from devices		
Digital inhaler or spacer*	► Date/time of inhaler doses ► Number of doses ► Inhaler technique parameters (eg, inhalation, inspiratory flow, angle of inhaler, inhaler shaking depending on the inhaler device)	The Hailie sensor records the date and time of each actuation of the inhaler to which the device is attached, and the number of doses used on each occasion. It can also measure inhaler technique by capturing information about device shaking, orientation and inhalation including inspiratory flow rate. The digital or 'smart' spacer is a rechargeable device that uses the same components as an existing CE-marked spacer (Aerochamber), except it incorporates sensing technologies that can monitor inhaler use and inhalation technique.[36 54]
Peak flow meter#	► Date/time of peak flow ► Peak flow readings	Participants will be given a peak flow meter to use to take their personal best (out of three) peak flow rate, which will be recorded on the Hailie app.
Nocturnal cough sensor¶	► Date/time of cough (only if coughing at night) ► Number of coughs ► Type of cough (eg, dry/wet)	The Resmonics nocturnal cough sensor has a cough detection algorithm that can detect and differentiate between different types of coughs, different genders and between adults and children. The cough data are captured passively by the Resmonics app on the participant's smartphone.
Smart watch^	► Resting heart rate ► Instantaneous heart rate ► Activity (step count) ► Activity intensity ► Heart rate variability—during sleep ► Breathing rate – during sleep ► Skin temperature—during sleep ► Oxygen saturation—during sleep ► Sleep Score ► - Stress Score (if available)	The smart watch can capture different physiological measures such as heart rate, respiratory rate, heart rate variability (including raw heart rate information), sleep and physical activity measures such as activity and activity intensity.[55] These readings will be recorded passively and will not require active input from the participant other than requiring the participant to wear their watch including at night, during sleep and charge the device every 2–3 days. These watches will be provided to participants. Data will sync to the commercial FitBit apps via pairing to the participant's phone. Data will also sync to the smart watch cloud on a regular basis and stored for up to 30 days to ensure no data loss when out of internet connectivity for a prolonged period.
Study research app (ie, patient-reported outcomes)§	► Daily log of asthma control and symptoms ► Log of asthma attack events ► Dietary intake via the Research Food Diary ► - Location (GPS) tracking	Participants can rate their asthma control on a 5-point scale from Very Bad[1] to Very Good[5] and log any asthma, cold or rhinitis symptoms. Participants will also record any asthma attacks in the research app. Location tracking on their smartphone will be enabled via the study research app.
Questionnaires via REDCap£	*Baseline and 6 months:* ► Treatment beliefs ► Clinical history (asthma history, asthma severity, medical history including rhinitis or allergies, medication history, asthma management, triggers, smoking/vaping) ► Healthcare utilisation, menstruation, sleep *Two-weekly* ► Asthma control (ACT) ► General well-being (WHO-5)	REDCap will be used to host the online questionnaires which will be administered during the baseline and end of study visits. For ACT and WHO-5, there will be a link out of the study app along with an automated email reminder every 2 weeks for participants to complete.

Continued

Table 1 Continued

Data source	Parameter(s) collected	Details of data collected and data sources used
Retrospective health and environmental data		
Ministry of Health national health datasets[&]	► Sociodemographic information ► Hospitalisation ► - Medication dispensing data	The Ministry of Health maintains a register of all individuals who have had contact with the New Zealand public health system and provides a unique identifier known as the National Health Index (NHI).[56] The NHI dataset will be used to retrieve demographic information and social-economic status.[57] Data on all hospital admissions are captured in the National Minimum Dataset (NMDS).[58] The NMDS includes information on dates of hospital stay; diagnoses, coded according to the International Classification of Diseases 10th edition – Australian modified version (ICD-10-AM) and medical procedures, coded according to the Australasian Classification of Health Interventions (ACHI).[42] Medication dispensing will be obtained from the Pharmaceutical Collection (Pharms) which records all subsidised dispensings.[59]
Environmental datasets[%]	► Air quality ► Meteorological data ► Pollen	Air quality data will be collected from the Ministry for the Environment data service and Stats NZ. Meteorological data such as temperature, humidity, wind speed and rainfall will be retrieved from The National Institute of Water and Atmospheric Research (NIWA) Cliflo database which houses New Zealand's National Climate Database. Data on pollen will be collected from pollen sensors where available near the study sites.

The footnote designators (*, #, ¶, ^, §, £, &, %) correspond to the figure 1 Study Overview symbols.

are scheduled two to three times a year or as needed with a focus on understanding patient experience, ensuring cultural appropriateness of study visits and practices to support study recruitment.

Data collection

Baseline demographic and clinical data

Baseline sociodemographic data such as participant age, gender, ethnicity, usual asthma healthcare provider, insurance, healthcare utilisation and socioeconomic status as per the New Zealand Index of Deprivation; and clinical data such as age at diagnosis, history of asthma attacks and emergency department (ED)/hospitalisation attendance, triggers, medications, allergies, comorbidities, smoking/vaping status will be collected by self-report. The participants' medication history and comorbidities will also be confirmed using data from the national collections from the Ministry of Health and /or clinical records (see the Data on factors related to asthma attacks section).

Information on the participant's treatment beliefs and practical barriers to adherence will be determined using a simple 3-item questionnaire, informed by the Necessity-Concerns Framework.[27] This will be repeated at 6 months. Baseline asthma control will be measured by the Asthma Control Test (ACT)[28] and well-being by WHO-5 index.[29]

Information on diet will be assessed by the Otago Food Frequency Questionnaire (long version) adapted for New Zealand[30] at baseline and at 6 months. The Otago-long form food frequency questionnaires will be administered by a trained interviewer to capture the habitual intake of 154 food items, using seven frequency options on the average consumption of foods over the past 6 months ranging from 'never or less than once per month' to 'two or more every day'. Food records will be analysed using FoodWorks V.10. A nutrient database will be generated and the Dietary Inflammatory Index will be calculated to determine the inflammatory potential of the diet.[31]

Lung function will be collected at the baseline and 6-month study visits. Lung function parameters (Forced Expiratory Volume in 1 second (FEV_1), Forced Vital Capacity (FVC) and Peak Expiratory Flow (PEF)) will be measured using a portable electronic spirometer (Medikro Pro, Kuopio, Finland) by a trained researcher. Predicted normal values for the lung function parameters will be calculated from the dataset from the Stanojevic reference[32] and Growing Lungs software, due to the age range and predicted ethnicity distributions of the study participants.

Data on factors related to asthma attacks

A large set of variables associated with asthma attack risk will be collected prospectively in real-time and combined with data from retrospective data sets (figure 1). Participants will use 'smart' devices—smart inhalers,[33 34] smart watch, cough sensor and a mobile app over 6 months to collect objective, detailed longitudinal data in real time. These smart devices, which have been tested and used before in asthma,[21 35] have sensors that provide real-time data on medication use (adherence and technique), oximetry, heart rate, heart rate variability and physical activity. Data on peak expiratory flow (obtained from a peak flow meter) will be self-reported by patients. Data on medication dispensing, hospitalisation and environmental parameters will be obtained from retrospective data sets. The smart devices, study variables and retrospective data sets are described further in figure 1 and below.

Digital biomarkers collected prospectively by smart technologies

Participants will be provided with several digital technologies to monitor different physiological parameters associated with asthma control and attacks (table 1).

- Digital inhaler or spacer[36] that records the time and date of inhaler use and inhaler technique for use
- Manual peak flow meter
- Resmonics nocturnal cough sensor[12]
- Smart watch—FitBit watch
- Study research app (custom-built for the study)
- Smartphone if the participant does not wish to use their own phone for data collection or if their smartphone is not compatible with the devices

Participants will be able to track their progress through the mobile apps associated with the devices and view the data collected if they wish. If participants have any questions about their collected data or devices, they will be advised to contact the study team who will refer this to the lead investigator and study clinicians if the queries are clinical in nature. Study variables and associated study devices are described below and in table 1 and in more detail in online supplemental table 1.

Medication adherence—digital inhaler sensor

The Hailie sensor (Adherium, August 2023.V—see table 1) is a digital inhaler sensor that records the date and time of each actuation of the inhaler to which the device is attached, and the number of doses used on each occasion. Participants will be provided with a sensor to use with their main reliever and inhaled corticosteroid (ICS)-containing preventer treatments, so each participant will be provided with a maximum of two digital inhalers to use. Participants using multiple inhalers will be assessed on a case-by-case basis to identify which two medications will be monitored.

Participants will be asked to continue to use their inhalers in the usual manner that they were doing prior to study enrolment. No changes will be made to the individual's asthma-inhaled treatment, which will continue as recommended by their usual asthma healthcare provider, though participants who are on separate ICS and long-acting beta-agonists (LABA) treatments may be changed to a combination ICS/LABA inhaler, so to minimise the number of digital inhaler devices they have to use. This will be discussed with the participant to gain consent, and study clinicians to determine appropriateness before referral to the primary healthcare provider to facilitate the change. Participants on salbutamol will be on the Ventolin brand to ensure compatibility with the Hailie sensor.

For participants on a regular preventer, adherence to their recommended treatment plan will be determined using data from the digital inhaler(s). This will be calculated as a percentage to determine the proportion of doses that were used by the patient relative to that which were recommended at the time of taking. The frequency of use of reliever medication will also be calculated from the digital inhalers. A subset of participants using pMDIs will be offered use of a digital spacer (Trudell Medical Ltd) instead of a Hailie sensor, where digital spacer supply is available and feasible for use. Adherence and inhalation technique range from 0% (poor) to 100% (good) and is based on previous research and recommendations on inhalation errors.

Peak expiratory flow—manual peak flow meter

Day-to-day changes in peak expiratory flow may be an indicator of asthma control.[37 38] Participants will be reminded daily to do a daily peak flow at the same time each day by the study app.

Cough—nocturnal cough sensor

Night-time cough has been shown to be a potential marker of overall asthma control.[12] Cough sounds will be captured using a nocturnal respiratory symptom monitor (Resmonics).[12]

Physiological and activity measures—smart watch

The FitBit Inspire V.2 or next available version(s) will be used due to its relatively small size, affordability and acceptability for use in children.[39] The device has been used successfully in several other studies requiring health assessments of patients[40 41] and are considered a valid and reliable tool for monitoring physical activity and sleep.[42 43] Data will be extracted via FitBit Application Programming Interfaces (APIs) to be preprocessed for the data analysis.

Device checks and validation

All devices will be checked on the day of issue to participants to ensure normal functioning of the devices. Any faults or failures of device function will lead to return of

the device to the manufacturer or research team for troubleshooting.

Data from retrospective health and environmental datasets

Health data

Data from participants will be linked with the New Zealand Ministry of Health data sets to obtain information on relevant sociodemographic information, hospitalisations, medication dispensing and /or other clinical or laboratory parameters (table 1). Data will cover the period of enrolment for the individual.

Environmental data

Data on air quality, meteorological data such as temperature, humidity, wind speed and rainfall and pollen will be collected from national and local data sets. These environmental data will be linked to the participant based on the participant's location data, when they are in New Zealand. The location data will be collected via the study app. Participants will not need to provide any input other than having their Global Positioning System (GPS) location enabled. Participants will be notified when location monitoring is on. As these data will be obtained retrospectively, these will not be visible to the participant in real time.

Study outcome measures

Patient-reported outcome measures will be collected via questionnaires hosted either on the custom-built study app or as a link out to REDCap. Participants will be reminded to complete questionnaires when prompted by a push notification and either an email or text message from the research team.

Primary endpoint measures

The primary endpoint is the risk of occurrence of one or more asthma attacks. This will be assessed using two time windows: (a) acute attack risk—risk of an attack within 2 days and (b) medium-term risk—risk of an attack within 14 days. The time window includes the day of measurement of the predictor variable or the following days. The outcome will be measured by self-report.

An attack will be defined as per the criteria in the ATS/ERS definitions for attacks,[20] as either severe or moderate:

Severe asthma attacks:

- The use of systemic corticosteroids (tablets, suspension or injection) or an increase from stable maintenance dose, for at least 3 days
- A hospitalisation or ED visit because of asthma, requiring systemic corticosteroids.[44]

Moderate asthma attacks:

- Deterioration in symptoms, deterioration in lung function or increased rescue bronchodilator use based on digital inhaler data, relative to baseline, for 2 or more days but not severe enough to warrant systemic corticosteroids and/or hospitalisation.
- Use of systemic corticosteroids for less than 3 days.
- ED visits for asthma, not requiring systemic corticosteroids, may be classified as moderate attacks.

Note there is no definition of mild attacks, as recommended by the ATS/ERS task force,[20] as these are likely to represent transient losses of asthma control rather than an attack.

Attack data will be collected by patient self-report at the time of the attack. Participants will be asked to report all attacks via a button on their study app as close to the time of the event as reasonably possible, once the participant is stabilised after their attack. The participant will be asked to provide the following detail:

- Date/time of the attack.
- Help sought (GP/hospital/self-management/other).
- Medicines taken (oral steroids/inhalers/nebulisers/other).
- For women, relationship with menstrual cycle (ie, date of last period).
- Sleep position prior to attack
- 24-hour food recall via the Research Food Diary mobile app (Xyris Software (Australia)). This provides a complete diet record with information on the type, portion and brand of all consumed foods. To minimise inaccurate self-reporting, participants with implausible intakes of <500 or >3500 kcal/day will be excluded.

Each attack will be considered a new event if they are separated by 7 days or more of no systemic corticosteroids.[20] This information will be confirmed by the participant when prompted by the 2 weekly questionnaires, and the hospitalisation information from National Minimum Dataset and from Pharms data sets.

Secondary Endpoint measures

Secondary endpoint measures will be asthma control, well-being, unscheduled healthcare utilisation, productivity loss and activity impairments and participant acceptability. These are described in table 2.

Data management

The study has a data management plan detailing procedures relating to data governance and data management, including what data are collected; where data are stored and who has access to the data. In summary, all participant data will be deidentified (coded) using a unique participant ID. The participant ID is a randomly generated three-digit number and no personal email addresses or passwords will be used in the study. To preserve data privacy, the participant ID will be used to code all the collected data and the key linking the ID with the participant will only be accessible to the few researchers who are immediately working with the data. This key will be stored on the University secure server and will not be accessible by any heterogeneous data sources or APIs. All participant identifying information will also be removed prior to data processing. All other electronic data will be held on

Table 2 Secondary endpoint measures and frequency of assessment

Endpoint measure	Measurement tool	Frequency	Description
Asthma control	Asthma Control Test (ACT)[28]	Baseline and every 2 weeks	The ACT will be self-completed by participants. This scoring system is based on symptoms experienced by the patient over the previous 4 weeks. The five questions ask about the severity of their asthma, restriction of physical activities, frequency of cough and night-time symptoms. Each of these five questions are scored 1–5 to give a composite score of 5–25, with a higher score indicating better asthma control. Participants can also log their asthma control daily on the study app on a 1 (very bad) to 5 (very good) scale, adapted from the eDASTHMA score[60] .
General well-being	WHO-5 index[29]	Baseline and every 2 weeks	The WHO-5 index will be self-completed by participants. The WHO-5 consists of five statements, which respondents rate in relation to the past 2 weeks. The total raw score, ranging from 0 to 25, is multiplied by 4 to give the final score, with 0 representing the worst imaginable well-being and 100 representing the best imaginable well-being.
Unscheduled healthcare utilisation	Self-reported and clinical records of attendance at the emergency department Self-reported unscheduled visits to the participant's general practitioner or to the accident and emergency clinic	Baseline and study end (6 months)	Information on attendance at the emergency department will be obtained by participant self-report, prompted when the fortnightly ACT is administered and from hospital records. Unscheduled visits will be determined from participant self-report, prompted when the fortnightly ACT is completed, and confirmed in the final 6-month study visit.
Productivity loss and activity impairments	Days absent from school or work for participants and/or caregivers using self-report. Information on days absent due to asthma (as per self-report) will also be collected. Work Productivity and Activity Impairment (WPAI) questionnaire[61]	Baseline and study end (6 months)	For days absent from school, this will be recorded as the number of half days attended each term, as per Ministry of Education half-day documentation. The number of days absent from all causes will be used as the end point rather than days absent due to asthma to prevent the risk of misclassification. This may occur, for example, if a child was classified as being absent from school due to a respiratory tract infection, when in fact the cough was secondary to asthma. The validated Work Productivity and Activity Impairment (WPAI) questionnaire will also be used to measure work and activity impairments. The WPAI measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problems during the past 7 days. Participants are asked to score the impact of their asthma on their ability to work, attend classes, and perform regular daily activity during the past week. The questionnaire has been used to assess productivity loss and activity impairment in asthma and correlates well with respiratory symptoms.[62]
Participant acceptability	Adapted version of the System Usability Scale[63] and a questionnaire informed by the Technology Acceptance Model.[64 65]	Baseline and study end (6 months)	The questionnaire will assess the participant's acceptability and views of the devices used in the study at study start and study end.

University of Auckland managed secure research drives. All data access will be password protected and accessible only by study investigators, and the immediate research team, with data management as per The University of Auckland data protection policies in line with FAIR (Findable, Accessible, Interoperable, and Reusable) and CARE (Collective benefit, Authority to control, Responsibility, and Ethics) principles. As data access requires user sign

on, an audit trail for data integrity is available. Physical data (eg, physical copies of consent forms) will be stored in locked cabinets in a secure, access-controlled area of the School of Pharmacy, The University of Auckland.

Statistics and data analysis

The characteristics of the study participants will be summarised using frequencies and percentages for categorical variables and means and SD for continuous variables.

Model development

We will begin by using a traditional statistical approach (regression), which will form the reference analysis. For the regression approach, the primary outcome will be modelled using a mixed effects model to examine the independent associations between each potential risk factor and the outcome of attacks. Medication changes or other factors that may influence the participant's risk of an asthma attack will be considered in the final model. Input variables will be chosen based on statistical and clinical significance. Results will be reported using adjusted rate ratios and 95% CI. A two-sided $p<0.05$ will be designated statistically significant.

Following this, we will explore machine learning (ML) based approaches to investigate whether the performance of the model (see below) can be improved over and above the regression approach. Multiple ML algorithms will be explored because of their intrinsic differences with the overall aim of finding the most accurate model. The following ML-based approaches will be used: Decision Trees, Random Forests and Gradient Boosting Machines such as XGBoost (tree-based). Additionally, as data sets are large and diverse, the use of deep learning-based approaches will also be explored. This will include (1): using artificial neural networks; (2): convolution neural networks and (3): LSTMs (Long Short-Term Memory) [45]—a type of recurrent neural network, which solve the problem of lack of long-term memory in traditional RNN. There is a risk of overfitting and regularisation will be used to address this. A feature engineering process will be conducted to determine the most relevant features for the models.

The data will be randomly divided into three parts: training, validation and evaluation. The training and validation of the ML models will be done with a 'training' set (80% of the data). The 'evaluation' set (20% of the data) will be used for determining the performance of the models. The best combination of parameters for the ML models will be identified through a 10-fold cross-validation using the development cohort. This means that participants in the training set will be randomly divided into 10 mutually exclusive and collectively exhaustive subsets, and the algorithm generated will be trained in 10 distinct repeats. In each repeat, the algorithm will be trained on data from nine of the subsets of the participants. For each algorithm, a final model will be obtained by retraining the algorithm on the entire development cohort (all 10-fold combined) using the best parameters and evaluated on the validation cohort.

To enhance ML accuracy, we will integrate human knowledge to reduce data requirements, increase reliability and understanding of the ML. Embeddings, weight sharing, feature engineering/extraction and incorporating invariance will be used to improve model speed and performance for real-life use.[46] Predictors will be validated by comparing variable importance to coefficients from the regression, depending on if the regression model fits the data well.

Model performance

The area under the curve, area under the precision-recall curve, sensitivity, specificity, positive predictive value and negative predictive value will be used to describe the performance of all the models. Means and 95% CI of the performance measures over the cross-validation and the point estimates of the final models on the validation cohort will be calculated.

We will then test model performance in three groups (if there are sufficient numbers in each group) as an exploratory analysis as sample sizes will be smaller: Māori, Pacific and non-Māori and non-Pacific samples to ensure equal performance by assessing discrimination, calibration and internal validity.[25 47] We will also test performance in young persons (<18 years) vs adults.

Sensitivity analysis

We plan to perform a sensitivity analysis for the prediction window by predicting attacks within 7 and 30 days. This is to determine whether varying the duration of the outcome window will affect model performance.

All analyses will be performed using R and Python and similar software. In cases where items of data are missing for a particular participant, available data for that participant will be included for the relevant data summaries or analyses and a description of the missing data provided, including whether certain groups have greater missing data from certain devices. No estimation or interpolation of missing data will be made. The analyses will be based on the 6-month data. For the patient acceptability outcome, data will be summarised using descriptive statistics, to identify whether certain groups have different acceptability. Free-text data will be summarised thematically.

Assessment of safety

Each participant's health will be evaluated at enrolment via questions about their asthma history, asthma medication, other comorbidities and medications. During the study, the participant will be asked to inform the research team of any changes from baseline in their health or medication. An adverse event describes any sign, symptom or syndrome or illness that newly occurs or worsens during the period of the study and may impair

the well-being of the participant. This covers any changes in the laboratory findings of the patient if relevant as well as the need for any unexpected diagnostic or treatment procedures. Events that occur after enrolment into the study and for 14 days after study end will be considered as an adverse event.

All potential adverse events will be documented in the participant's file, including details of the date of onset, duration, action taken or required, outcome and other relevant details of the event. Identification and documentation of these adverse events do not imply a causal relationship with the study intervention. Participants will provide informed consent at the start of the study to provide permission for the study team to contact the participant's usual health provider if any clinical issues are identified. All adverse events reported will be discussed with the study advisory group, the probability of a causal relationship with the study intervention determined, and any changes to protocol or actions to be taken documented.

Ethics and dissemination

Ethical approval was obtained from the Southern Health and Disability Ethics Committee (2023 FULL 13541). Participants will only be enrolled once written informed consent is provided. The study is registered with the Australian New Zealand Clinical Trials Registry, registration no. ACTRN12623000764639.

Key results will be disseminated via peer-reviewed publications; national and international conferences in respiratory and in digital health; patient organisations; and public engagement events to share findings with the community and key stakeholders.

DISCUSSION

This study is part of a larger programme of planned research that aims to generate a more accurate and comprehensive risk prediction model for asthma attacks by adopting a data-driven approach using multiple data streams collected in real time from digital technologies. The findings will have implications for (a) alerting individuals to their personal risk of an imminent attack that is due to occur in the following days and (b) providing individuals with insights into changes in their medium-term risk of an asthma attack to inform their asthma self-management. Following identification of the key digital markers that are related to asthma attacks, and the development of a robust model of attack prediction, the next steps will be a randomised controlled trial (RCT) of a digital 'alert-based' management of asthma will be compared with standard care.

We hypothesise that there will be clear digital markers that will be associated with asthma attacks, and that their inclusion in a risk prediction model will improve the predictive ability of the models for asthma attacks. As many data sources are being considered in this observational study, the next step will be to select the key digital predictors that can be feasibly and pragmatically assessed on an ongoing basis in routine care. As such, the final prediction model that is evaluated in the RCT may not include all the devices or digital markers that are being assessed in this DIGIPREDICT study. We will use implementation frameworks[48] such as the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM)[49] and non-adoption, abandonment, scale-up, spread, sustainability (NASSS) frameworks[50] to support this intervention development process to ensure that the final intervention has the highest chance of being implemented successfully into routine care.

Potential limitations

Some challenges are expected in supporting patients to use new technologies that they may not be familiar with and ensuring that the technologies do not contribute to any inequities due to differences in digital literacy. There may be issues with participant retention as the study follow-up is intended to be 6 months, and motivation to use these technologies regularly may wane over time. To overcome these potential difficulties, we have planned strategies such as setting up a participant study app to support management of study tasks, keeping in-person visits to a minimum and offering appropriate reimbursement for participant time. There is also a risk that participants may change their behaviour as they can see their own data and gain additional insights into their health, which could inadvertently reduce their risk of a future asthma attack. However, studies have shown that even when participants are aware of being monitored, their behaviour change is not sustained long term.[51] For example, awareness of adherence monitoring by participants has been shown to have some effect on inflating adherence, but the effects are small[52] and may not last beyond 7 days.[33 53] Based on these prior examples, it is unlikely that participant behaviour will change for the full 6 months of follow-up.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement This study is a study protocol so no datasets have been analysed yet for this study. However, at present, the current participant consent does cover the possibility of using the collected data for future research as a fully de-identified dataset, so we plan for the data to be made available in de-identified format upon reasonable request to the Principal Investigator.

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