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Original article

Clinical effect on uncontrolled asthma using a novel digital automated self-management solution: a physician-blinded randomised controlled crossover trial

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Title: Clinical effect on uncontrolled asthma using a novel digital automated self-management solution: a physician-blinded randomised controlled crossover trial

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Abbreviations

ACT	Asthma Control Test
C-ACT	Childhood Asthma Control Test
FEF50l	Forced Expiratory Flow after 50% interval
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
MARS	Medical Adherence Report Scale
RCT	Randomised Controlled Trial

Abstract

Background: AsthmaTuner is a novel self-management system consisting of a patient app, a cloud-based storage solution and a healthcare interface. Patients use Bluetooth spirometers to measure lung function (FEV_1) and can register symptoms. They then receive immediate feedback on asthma control and an image of the correct inhaler(s) to use and the dose. The aim of this pilot study was to evaluate the effect of AsthmaTuner on symptom control and adherence compared with conventional treatment.

Material and Methods: This multi-centre, physician-blinded, crossover trial, randomised patients in two groups that started with 8 weeks of AsthmaTuner or conventional treatment using printed personalised treatment plans, and 2 weeks of wash-out between the crossover treatments. Participants in a primary or paediatric care setting in Sweden with asthma diagnosis, uncontrolled symptoms and Asthma Control Test (ACT) <20 points were included. Symptom control was analysed using t-tests for the difference between the group means of the sums of ACT at each treatment end-visit, with 95% confidence intervals. Medical Adherence Report Scale scores captured differences in adherence (remembering to take asthma medication) between treatment periods.

Results: The study population consisted of 77 patients (60% females). The ACT significantly improved with AsthmaTuner compared with conventional treatment (mean 0.70 [0.06–1.34], p=0.03). Adherence did not improve significantly in all participants, but did improve among those in primary care who used AsthmaTuner an average of once a week or more, compared with conventional treatment (mean 0.45 [0.13-0.77], p=0.01).

Conclusions: AsthmaTuner improved symptom control in patients with uncontrolled asthma.

Sentence summarising the most important findings: AsthmaTuner is an automated electronic clinical decision support system that improves symptom control in patients with uncontrolled asthma.

Introduction

Today's asthma management comprises excellent medications and guidelines, but many patients remain symptomatic [1], suggesting that current management regimens are not optimised or not available for all patients. A further cause of symptoms is suboptimal adherence to prescribed asthma treatment, reported in >50% of all individuals with asthma [2]. Reasons for nonadherence range from conscious decisions to ignore asthma treatments to misunderstanding instructions or forgetting to take the medication.

Digital solutions can encourage greater patient involvement in self-management, thereby improving asthma. Simple and easy digital solutions are promising strategies providing patient and clinical decision support, but they should be developed with patient input and tested for efficacy in patient symptom control and adherence. AsthmaTuner is a cloud-based eHealth solution with a healthcare interface and patient app that enable self-monitoring of asthma symptoms and lung function with a Bluetooth spirometer. The app provides patients with an automated treatment recommendation based on the characteristics of symptom control according to the Global Initiative for Asthma (GINA) [3]. The idea for AsthmaTuner originated from meta-analyses showing that patient education in self-management and self-monitoring of lung function and symptoms, coupled with adjustable treatment plans, are more effective compared with other forms of asthma self-management [4].

The aim of this randomised blinded controlled crossover pilot study was to compare AsthmaTuner to a conventional treatment using a paper individual treatment plan in terms of symptom control and remembering to take prescribed asthma medication.

Material and Methods

Study design

This multicentre randomised controlled physician-blinded crossover pilot trial consisted of two groups who initially received 8 weeks of either AsthmaTuner or a conventional treatment, with a 2–4 week washout period between treatments, Figure 1. The primary outcome of symptom control was assessed with the Asthma Control Test (ACT) or Childhood Asthma Control Test (C-ACT) at baseline and at the end-visit in each treatment period. The secondary outcome of adherence was assessed by the Medical Adherence Report Scale (MARS) based

on how often respondents forgot to take asthma medications. The randomisation was done to each participant at each site by study nurse opening a sealed envelope with the study ID indicating the order of treatments, either AsthmaTuner first and conventional last or the reverse order. The physician was blinded for the randomisation, and individual treatment plans were prescribed for both AsthmaTuner and conventional treatments at study enrolment. Participating centres were endorsed to comply with Swedish national guidelines for treatment and management of asthma [5], which closely resemble with GINA [3]. The regional board of the Ethical Committee in Stockholm (ID: 2015/1527-31/1 and 2016/1546-32) and Swedish Medical Products Agency (ID: 5.1-2016-19829) approved the study. The study was registered at ClinicalTrial.gov ID: NCT02571309.

Intervention

Asthmatuner (Medituner AB, Stockholm, Sweden) is a CE-marked cloud-computing-based system with a healthcare interface and a downloadable patient app (Android or iOS). Asthmatuner was conceptualised and developed in response to the perceived gap between guidelines/treatment recommendations and clinical practice. The primary aims were to facilitate distribution of treatment plans to patients and to improve self-management and education for patients, as the software support patients decide the current state of their asthma. Recently, the term electronical clinical decision support system (eCDSS) has gained acceptance [6, 7]. It is important to achieve a high degree of acceptability to clinicians and patients by focusing on automation, data presentation and design, as well as alignment with professional workflow. To achieve the best results, Asthmatuner was developed in collaboration with the Swedish patient organisation Asthma and Allergy Association and patients by focus groups, and clinicians by interviews with doctors and nurses from public healthcare, as well as private practitioners and on-line clinics. The intended use of Asthmatuner is to automate asthma self-management by letting patients register symptoms and measure forced expiratory volume in one second (FEV1) with a Bluetooth spirometer (MIR, SmartOne), Figure 2. The patient then receives immediate feedback on the status of symptom control (controlled, partly controlled or uncontrolled), and a treatment recommendation, with an image of the correct inhaler or other type of medication and the dose. Symptom control is quantified based on lung function; litre to percentage of personalised best FEV1, using a cut-off ≤80% and symptoms during the last week based on four questions: 1) need for rescue medication more than twice due to asthma symptoms, 2) any daytime symptoms, 3) nocturnal symptoms/awakenings, and 4) limitation in physical

activities [3]. Supplementary table 1 shows the algorithm classifying patient symptom control in AsthmaTuner. Asthmatuner offers patients and health care providers longitudinal data views of assessed symptom control, prescribed treatments and lung function measurements. The back-end data storage of the cloud-based system provided information about participant adherence with AsthmaTuner use.

Conventional treatment

Conventional treatment was defined as non-digital self-management using paper individual treatment plans, which contained treatment adjustments of prescribed medications according to symptoms of controlled, partly controlled or uncontrolled asthma, along with instructions according to national guidelines [5].

Subjects

The study subjects were children from 6 years and adults with at least doctors' diagnoses of asthma, and ACT or C-ACT scores below 20 points from May 2016 to Sept. 2018. Exclusion criteria were presence of comorbidity with significant impact on symptom control, participation in drug trials, and patient/caregiver difficulties in reading Swedish. The study was conducted in Stockholm, Sweden, in the primary health care sector and specialised paediatric health care, at Liljeholmen Health Care Centre, Sophiahemmet Health Care Centre, and Astrid Lindgren Children's Hospital. Supplementary figure 1 shows the total number of randomised patients and drop outs. The study population was all randomised participants with complete ACT or C-ACT information who fulfilled all four visits.

Inhalation technique

Participants inhaler use was assessed at the baseline visit, and if the demonstration was unsuccessful according to criteria of dry powder- and metered dose inhalers [8], they were trained by study nurse to use it correctly.

Questionnaires

Patients or caregivers completed a structured health questionnaire at the first visit, providing information on demographics, asthma, comorbidities and treatment. Symptom control was assessed at baseline and at end-visit in each treatment period with validated ACT in patients older than 12 years [9], and C-ACT in children 6 to 11 years [10]. A mean score $\leq$19

indicated uncontrolled asthma in both tests. The medication adherence score, MARS, captured how often responders forgot to take their asthma medication (1=always, 2=often, 3=sometimes, 4=rarely, 5=never) at baseline and at end-visit for each period.

Lung function

Dynamic spirometry measurements (FVC%, FEV1%, FEV1/FVC and FEF50%) were performed in accordance to guidelines using Hedenström/Soleymar or Zapletal reference values [11].

Data management

The clinical research organisation Karolinska Trial Alliance, Stockholm, conducted the data review and supervised the study according to Good Clinical Practice (GCP) standards and conducted structured data reviews at each study centre.

Statistical analyses

The sample size was estimated assuming that AsthmaTuner would improve the average ACT/C-ACT score by two points compared with conventional treatment (mean standard deviation 3.3). Assuming a dropout rate up to 10%, our power calculation estimated that enrolment of 43 adults and 43 children would be clinically relevant and feasible to attain 80% power at a 5% significance level. The interventional effect of AsthmaTuner on ACT/C-ACT was compared with conventional treatment according to intention-to-treat analyses, including all patients (N=77) assessed with complete information on ACT/C-ACT from each visit. All analyses were stratified by primary health care and paediatric specialist care setting.

The distribution of ACT/C-ACT scores at end-visits 2 and 4 was checked using histograms and quantile-quantile plots and indicated no large deviation from the normal distribution. Examination of the ACT/C-ACT scores revealed that the baseline measurements of period 2 were close to the outcome measurements of period 1, indicating that the baseline measurements of period 2 are not comparable between the randomised groups. Consequently, statistical testing of the carryover effect may be biased, as the carryover effect was observed even when no or negligible carryover effect was present. For this reason, and in line with Fleiss [12], only the ACT/C-ACT measurements at the end-visits were used in the statistical analyses in which carryover and treatment effects were evaluated. Differences in crossover

effects were tested using t-tests for the difference between the group means of the sums of ACT/C-ACT in visits 2 and 4. Differences in treatment effects were tested using t-tests for the difference between the group means of the differences of ACT at visits 2 and 4. When adjusting for adherence and care facility, linear regression was used, with randomization group as explanatory variable of interest, adding number of assessments with AsthmaTuner as the natural logarithm, and an indicator for care facility as additional adjustment variables. The estimate and confidence interval for the randomization group variable was divided by 2 in order to get the estimate for the difference between AsthmaTuner and conventional treatment. Sequence effects of ACT/C-ACT between period 1 and 2 were estimate using t-test. Differences in the MARS question about respondents' forgetfulness to take their asthma medication showed comparable baseline measurements between period 1 and 2; hence, the differences in MARS scores between end and baseline visits were used as outcomes in the analyses. All t-tests were applied using the formulae in section 10.1.2 in Fleiss [12]. P-values <0.05 were considered significant. The software R, version 3.5.0, was used for all statistical analyses.

Results

In total, 77 of 90 (86%) randomised participants fulfilled the study: 37 patients from primary health care and 40 schoolchildren from paediatric specialist care settings (Supplementary figure 1). Some participants were lost to follow up (n=6), withdrew their study consent because of technical mobile phone problems (n=3), or terminated study participation (n=3) for medical conditions other than asthma (severe snake bite reaction, pertussis and another respiratory diagnosis). No severe device deficiencies were observed, but insufficient connection between the Bluetooth spirometer to Android phones was reported, as was inability to use the app after mistaken installation onto a tablet.

Table 1A shows the background characteristics of the study population and Table 1B shows stratification by primary care (n=37) and schoolchildren in paediatric specialist care (n=40). The mean age was 22 years (SD 14.5) for the study population, 33.1 years for the primary care cohort and 11.7 years for the paediatric cohort. The mean daily doses of inhaled corticosteroids (ICS) prescribed in the individual treatment plan for either AsthmaTuner or conventional treatment were 450 µg (budesonide or equivalent) for controlled asthma, 762 µg for partly controlled asthma, and 956 µg for uncontrolled asthma (Table 2A). Allergic

comorbidities of eczema, rhino-conjunctivitis and food allergy were prevalent in 27%, 41% and 35% of the study population, respectively. The number of AsthmaTuner assessments during the treatment period was significantly higher in the paediatric cohort than in the primary care cohort (mean 37.6 vs. 17.6, p=0.006). Supplementary figure 2 demonstrate proportions of participants with uncontrolled, partly controlled and uncontrolled asthma as defined by the AsthmaTuner algorithm across each study week 1-9. The proportion of participants with uncontrolled asthma decreased from 37% to 8% between week 1 and 9. Participants average number of assessments and automated treatment changes by AsthmaTuner at each study week are described in Supplementary table 2.

Table 2 shows the effect size of AsthmaTuner compared with a conventional treatment with printed treatment plans on ACT/C-ACT. The ACT/C-ACT end-visit scores were significantly better with AsthmaTuner than with conventional treatment (mean difference 0.7 [95% CI, 0.06–1.34], p=0.03, Figure 3A). However, AsthmaTuner showed no statistically significant effect on ACT/C-ACT, stratified by primary care cohort, compared with conventional treatment, Figure 3B. The paediatric specialist care cohort alone showed significantly improved ACT/C-ACT scores with AsthmaTuner compared with conventional treatment (mean difference 0.97 [95% CI, 0.13–1.81], p=0.02, Figure 3C). Tests of differences in crossover effects were all far from significant (p-values = 0.63, 0.49, and 0.23) for all participants, and stratified by primary care or paediatric specialist care cohort.

Linear regression in Table 3 estimate crude and adjusted effect on ACT/C-ACT between AsthmaTuner and conventional treatment. No additional effect of AsthmaTuner on ACT/C-ACT was found when adjusting for either number of assessments with AsthmaTuner or care facility (primary- or paediatric care), or both, compared with crude analysis. Significant sequence effects on ACT/C-ACT of both AsthmaTuner and conventional treatment were observed between period 1 and 2; AsthmaTuner: period 1 vs. period 2, mean 4.28 (SD 3.70) vs. 0.67 (SD 2.09), $p < 0.001$; Conventional: mean 2.61 (SD 3.25) vs. -0.08 (SD 2.80), $p < 0.001$.

The participant adherence to remember to take asthma medication was assessed with the MARS questionnaire, Table 4. Adherence was not improved with AsthmaTuner compared with conventional treatment. However, adherence was increased in 27 participants using

AsthmaTuner once a week or more, based on derived data from the cloud-based back-end, compared with conventional treatment in the primary care setting (mean difference 0.45 [95% CI, 0.13–0.77] p=0.01). No similar effect was detected in 35 schoolchildren that used AsthmaTuner once a week or more in the paediatric cohort. The p-values for the tests of differences in crossover effects were all far from significant (p-values = 0.37, 0.40 and 0.65), for both cohorts, primary care cohort, and paediatric specialist care cohort, respectively; hence, differences in carryover effects were ruled out.

Discussion

This crossover pilot RCT showed significantly better symptom scores of ACT/C-ACT with AsthmaTuner than with conventional treatment using a printed personalised treatment plan. Our assessment of the effect on adherence, i.e. remembering to take asthma medication, in the overall study population revealed no significant effect compared with conventional treatment. However, adherence was enhanced in 27 participants of the primary care cohort that used AsthmaTuner an average of once a week or more compared with conventional treatment. Overall, the novel digital AsthmaTuner system seems to be an easy and effective strategy for managing uncontrolled asthma.

In this intention-to-treat study, the primary outcome of validated ACT/C-ACT was significantly improved (mean score increase 0.7) in patients with uncontrolled asthma using AsthmaTuner compared with conventional treatment. The effect on ACT/C-ACT was most prominent in schoolchildren of the paediatric specialist care cohort. The findings imply that AsthmaTuner can be recommended for patients with uncontrolled asthma. Empowering patients by linking self-monitored data to an adjustable individual treatment plan is a promising strategy for self-management, however, only a few studies are available and most are small in scale with conflicting evidence. The RCT by Ryan et al. on 288 adults and children with poorly controlled asthma found no significant effect on symptom control comparing a mobile phone-based transmission of symptoms, medication and feedback prompting patient an action plan versus printed self-management [13]. However, after 6 months the symptom control did improve significantly in both study arms. The RCT by Perry et al. on 34 adolescents with persistent asthma found no significant effect on ACT scores using smartphone versus print-based treatment plans [14]. However, Burbank et al. found a significant improvement in symptom control in 20 adolescents in one of the arms in the study,

suggesting that personalised treatments with mobile-based asthma action plans are feasible for communicating individual treatments and improving symptom control [15]. These trials have functions related to web based systems where patients can simply access, and submit, their data. Having access to a treatment plan on a web based system, instead of a traditional paper treatment plan, does not seem to improve asthma control. Instead, it seems, an adjustable treatment plan stored on the smart phone allows for more effective control. In our study, almost all participants were prescribed ICS control medication at each symptom control level, and this could also explain some of the differences in efficacy in symptom control. Ryan demonstrated that ICS first was prescribed at step 2 of a total of 4 treatment steps, while neither Perry nor Burbank clearly indicated the ICS level or dose given. The Asthmatuner system has advantages of a minimum need for manual input. This may contribute to ease of use and acceptance, for example there was no need for manual input from the wireless spirometer. Also, the result with a clear presentation of treatment recommendation as an image of the inhaler/medicine and number of inhalations required may help the user. Assessment of different digital solutions requires an understanding of how the targeted patient groups perceive and use a specific digital tool. In this study, the number of assessments with AsthmaTuner were significantly higher in the paediatric cohort than in the primary care cohort, indicating that schoolchildren were motivated to use AsthmaTuner more frequently. Patient involvement with the first available prototype of AsthmaTuner was established by in-depth interviews of patients and children's caregivers. These interviews gave important feedback on the functionality and usability of AsthmaTuner and on whether testing pulmonary function with wireless spirometers to assess possible bronchial obstruction encouraged patients to take control of their self-management. The interviews also clarified that answering symptom questions on a regular basis was tiring and that automated feedback on asthma status was more desirable. The historic view of collected data, shared with the health care provider, was an appreciated reminder of previous health status and aided health care providers in monitoring and prioritising patients in most need of care. The AsthmaTuner system is currently being implemented in European countries.

Overall, AsthmaTuner did not show a clear benefit on reminding participants to take their medication over conventional treatment. Stratified analysis of participants using AsthmaTuner at least once a week or more indicated improved adherence in the primary care cohort. Studies using an electronic monitoring device with an audio-visual reminder showed significant improvements in adherence to inhaled corticosteroids in school-aged children [16] and in

adults with asthma [17]. The evaluated version of AsthmaTuner lacked electronic monitoring devices with audio-visual reminders, but an upgraded, currently available version of AsthmaTuner has settings for self-monitoring and medication reminders. One limitation of our study is our failure to assess adherence in caregivers to children because they typically supervise medication.

Strengths and limitations

Regarding the generalisability of this study is the multi-centre design and the inclusion of participants from two different settings: primary health care and paediatric specialist care a strength. Most asthma cases in Sweden are managed in these two settings. L. Araújo et al. successfully assessed the clinical feasibility of web-based versus standard asthma self-management in a small crossover study [18]. The crossover RCT design has strengths by adding sensitivity and power when compared with parallel arms [19] and reduces the influence of confounding factors because each crossover participant serves as their own control. The four follow-up visits in our study are in line with Swedish guidelines that recommend at least two follow-up visits per year for managing uncontrolled asthma. The use of printed personalised treatment plan in the conventional group is promoted in Swedish national asthma programs [5], nevertheless, few patients receive treatment plans and that is an evidence-based care gap [20].

There are reports of improved learned behaviour using internet-based asthma self-management solution [21, 22]. A possible limitation of this study is its crossover design, which carries an obvious risk that the effect of the first period treatment is carried over into the next period. The use of AsthmaTuner may lead to behavioural changes that are difficult to extinguish with a washout period between treatment periods. However, in this study, we saw no significant difference in ACT/C-ACT scores between management periods one and two, indicating that our imposed washout period prevented crossover effects and that differences in carryover effects could be ruled out. Instead, we saw that the baseline measurements of period two were close to the outcome measurements of period one, indicating that the baseline measurements of period two are not comparable between the randomised groups. Consequently, the statistical analysis of the carryover effect may be biased, as the carryover effect could be seen even when no or a negligible carryover effect exists. We overcame this problem, in line with Fleiss [12], by using only the ACT/C-ACT measurements at the end-visits in the statistical analyses where carryover and treatment effects were evaluated.

Furthermore, significant sequence effect of period 1 was observed for both AsthmaTuner and conventional treatment on uncontrolled asthma, which underlines how effective improved self-management is on symptoms control [23], and that AsthmaTuner is a digital modification of evidence-based conventional treatment.

Asthma diagnosis needs to be regularly verified in both adults and children [24]. A limitation of this real-life study is the used criterion of doctor's asthma diagnose. We did not confirm participants asthma objectively before enrolment. However, a great potential of eCDSS is providing patients with wireless spirometer and health care information on lung function to objectively verify diagnosis based on variability and treatment response.

The scope for future studies will be to assess AsthmaTuner in a larger population with unselected symptom control. The main outcomes will be evaluation of the effects on symptom control and adherence, as well as characterisation of specific phenotypes based on time-serial measurements of lung function in relation to symptoms and exacerbation. The goal will be to develop mathematical algorithms for generating individual prescribed action plans to prevent exacerbations.

Conclusions

This study indicates significant improvements in symptom scores of ACT/C-ACT in patients with uncontrolled asthma using AsthmaTuner compared to conventional treatment with printed personalised treatment plans. The effect on adherence to remember to take asthma medication was not significantly improved in the overall study population compared with conventional treatment. Adherence was only improved in participants of the primary care cohort that used AsthmaTuner on average once a week or more compared with conventional treatment. The novel digital self-management system AsthmaTuner is a simple and easy solution that can be recommended for management of uncontrolled asthma in schoolchildren and adults.

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BIO, Stockholm County Council Innovation Foundation, Capio Research Foundation, Sweden's Innovation Agency and Medituner AB.

Conflict of Interest

H. Ljungberg and B. Nordlund have founded the company Medituner AB that owns AsthmaTuner.

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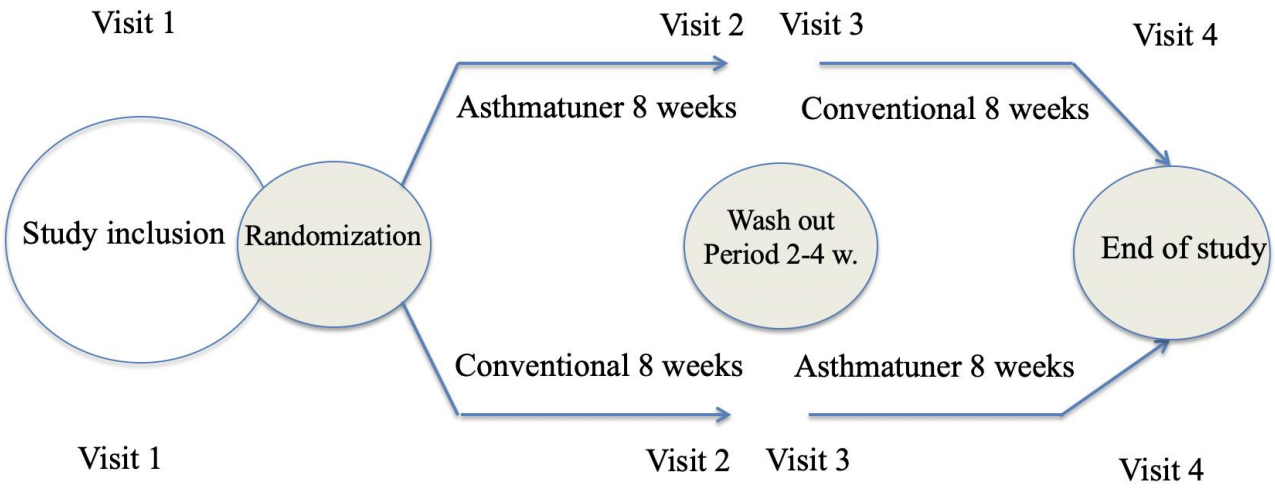

Figure 1. Study design of randomized controlled physician blinded crossover study assessing the effect of treatment with AsthmaTuner on asthma control test compared with conventional treatment using paper personalized treatment plan.

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Figure 2. Asthmatuner is a CE-marked electronic clinical decision support system with a cloud-based data-storage with a healthcare interface and a downloadable patient app (Android or iOS). The intended use of Asthmatuner is to automate asthma self-management by letting health care prescribe treatment and patients register symptoms and measure forced expiratory volume in one second (FEV1) with a Bluetooth spirometer. Patient then receive immediate feedback on asthma control and an image of the correct inhaler(s) to use and the dose. The healthcare can simultaneously monitor patient's asthma control.

Table 1A. Characteristics of the study population at study baseline.

	n	Median (IQR; min-max)	Mean (SD)
Age (years)	77	16.0 (12-30; 6-72)	22.0 (14.5)
ACT	77	16.0 (13.8-18.0; 8-19)	15.6 (3.1)
MARS – forget asthma medication	77	4.0 (3.0-5.0; 2-5)	3.6 (0.9)
FVC%	75	88.0 (80.0-98.0; 60.0-118.0)	88.9 (12.4)
FEV_1%	76	85.3 (76.0-96.9; 55.0-137.0)	86.4 (14.2)
FEV1/FVC	77	0.84 (0.78-0.87; 0.52-0.98)	0.82 (0.09)
FEV50%	76	74.8 (61.0-88.0; 24-144)	74.6 (22.3)
Prescribed treatment plan:			
Controlled Asthma, ICS µg	77	400 (320-640; 0-1472)	450 (259)
Partly Controlled Asthma, ICS µg	77	800 (480-960; 0-1600)	762 (386)
Uncontrolled Asthma, ICS µg	77	960 (750-1200; 0-2080)	956 (423)
Assessments with AsthmaThuner	77	18.5 (11-34; 1-217)	28.0 (32.5)
	n	%	
Female	46	59.7%	
ICS	74	96.1%	
Montelukast	32	41.6%	
Long-Acting Beta-2 Agonist	72	93.5%	
Allergic self-reported comorbidities:			
Eczema	21	27.3%	
Rhino-conjunctivitis	32	41.6%	
Food Allergy	27	35.1%	
Randomization AsthmaTuner first	38	49.4%	

ACT – Asthma Control Test or Childhood Asthma Control Test

MARS - Medical Adherence Report Scale; 1=always, 2=often, 3=sometimes, 4=rarely, 5=never

ICS – Inhaled corticosteroids, daily dose of budesonide or equivalent

Table 1B. Characteristics of study participants stratified by primary care and paediatric specialist care at study baseline.

	Primary care, n=37			Paediatric specialist care, n=40		
	n	Median (IQR; min-max)	Mean (SD)	n	Median (IQR; min-max)	Mean (SD)
Age (years)	37	32.0 (23.0-40.0; 13-72)	33.1 (13.7)	40	12.5 (9-14; 6-17)	11.7 (3.2)
ACT	37	16.0 (13.0-17.0; 8-19)	15.1 (2.9)	40	17.0 (15.0-18.0; 8-19)	15.9 (3.2)
MARS – forget asthma medication	37	4.0 (3.0-4.0; 2.0-5.0)	3.6 (0.8)	40	4.0 (3.0-5.0; 2.0-5.0)	3.7 (1.0)
FVC%	36	85.0 (78.0-93.6; 60.0-109.0)	84.6 (11.0)	39	94.0 (82.0-103.0; 71.0-118.0)	93.0 (12.3)
FEV_1%	37	83.7 (75.5-94.9; 55.0-115.3)	84.2 (12.8)	39	89.0 (76.0-100; 62.0-137)	88.5 (15.3)
FEV1/FVC	37	0.82 (0.78-0.86; 0.52-0.98)	0.81 (0.08)	40	0.84 (0.79-0.91; 0.52-0.98)	0.83 (0.09)
FEV50%	36	74.7 (59.0-85.0; 35.0-110)	72.7 (17.9)	39	75.0 (61.0-95.0; 24.0-144)	76.3 (25.8)
Prescribed treatment plan:						
Controlled Asthma, ICS µg	37	320 (400-710; 0-1472)	537 (285)	40	320 (267-500; 0-800)	370 (205)
Partly Controlled Asthma, ICS µg	37	800 (800-1240; 0-1600)	923 (436)	40	640 (400-800; 0-1280)	612 (258)
Uncontrolled Asthma, ICS µg	37	1200 (800-1600; 0-2080)	969 (498)	40	800 (640-960; 0-1280)	791 (249)
Assessments with AsthmaThuner	37	15.0 (9.5-24; 1.0-46.0)	17.6 (11.1)	40	26.0 (13.0-48.3; 4.0-217)	37.7 (42.0)
	n	%		n	%	
Female	28	75.7%		18	45%	
ICS	35	94.6%		39	97.5%	
Montelukast	9	24.3%		23	57.5%	
Long-Acting Beta-2 Agonist	36	97.3%		36	90.0%	
Allergic self-reported comorbidities:						
Eczema	9	24.3%		12	30%	
Rhino-conjunctivitis	17	45.9%		15	37.5%	
Food Allergy	11	29.7%		16	40%	
Randomization AsthmaTuner First	16	43.2%		23	57.5%	

ACT – Asthma Control Test or Childhood Asthma Control Test

MARS - Medical Adherence Report Scale; 1=always, 2=often, 3=sometimes, 4=rarely, 5=never

ICS – Inhaled corticosteroids, budesonide or equivalent

Table 2. The effect on Asthma Control Test at end visit after treatment with AsthmaTuner or Conventional treatment in all participants, and stratified by cohort in primary care and paediatric specialist care.

	ACT end values AsthmaTuner	ACT end values Conventional	ACT difference AsthmaTuner vs. Conventional
	Mean (95% CI; p-values)	Mean (95% CI; p-values)	Mean (95% CI; p-values)
All participants, n=77	19.45 (18.70-20.21)	18.75 (17.97-19.53)	0.70 (0.06-1.34; 0.03)
Primary Care, n=37	19.14 (18.08-20.19)	18.78 (17.63-19.94)	0.33 (-0.68-1.35; 0.51)
Paediatric Care, n=40	19.75 (18.65-20.85)	18.73 (17.61-19.84)	0.97 (0.13-1.81; 0.02)

Differences in crossover effect between study period 1 and 2 were non-significant in all participants (p=0.62), primary care (p=0.49); paediatric care (0.23).

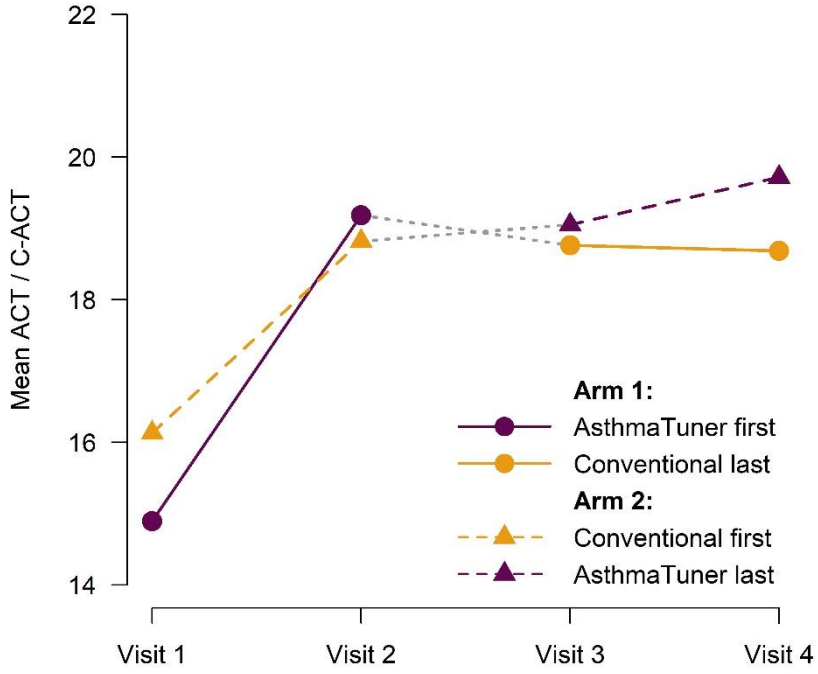


Figure 3A. The mean ACT/C-ACT scores at baseline and at the end-visits after AsthmaTuner or Conventional treatment in all participants (n=77).

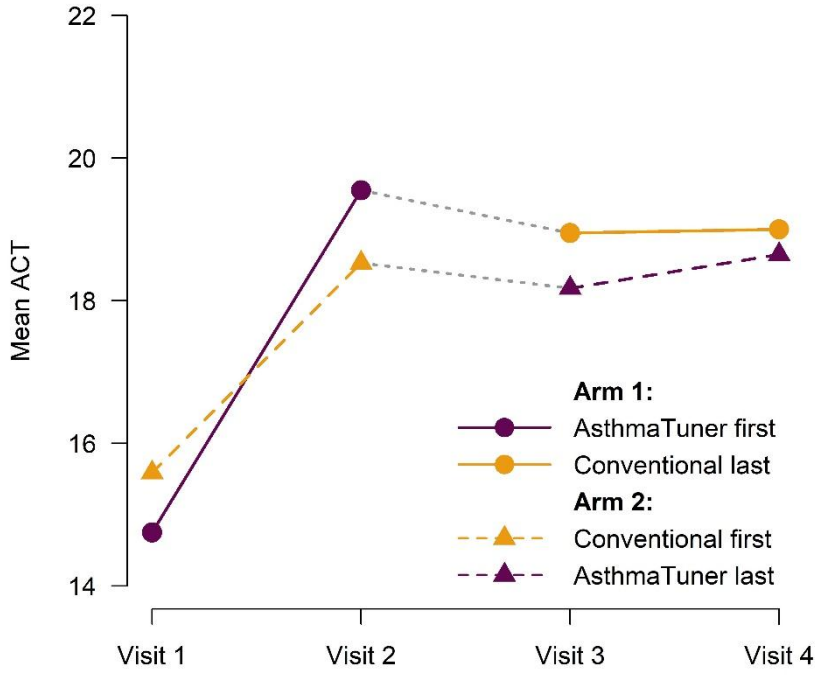


Figure 3B. The mean Asthma Control Test scores at baseline and at end-visit after AsthmaThuner or Conventional treatment in primary care cohort (n=37).

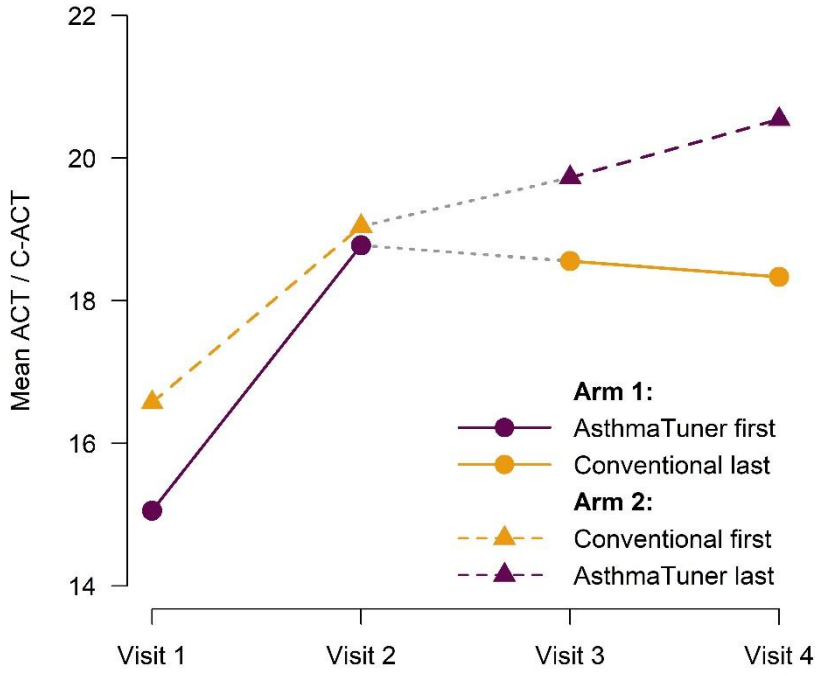


Figure 3C. Mean ACT/C-ACT scores at baseline and at the end visit after AsthmaTuner and Conventional treatment in the paediatric specialist care cohort (n=40).

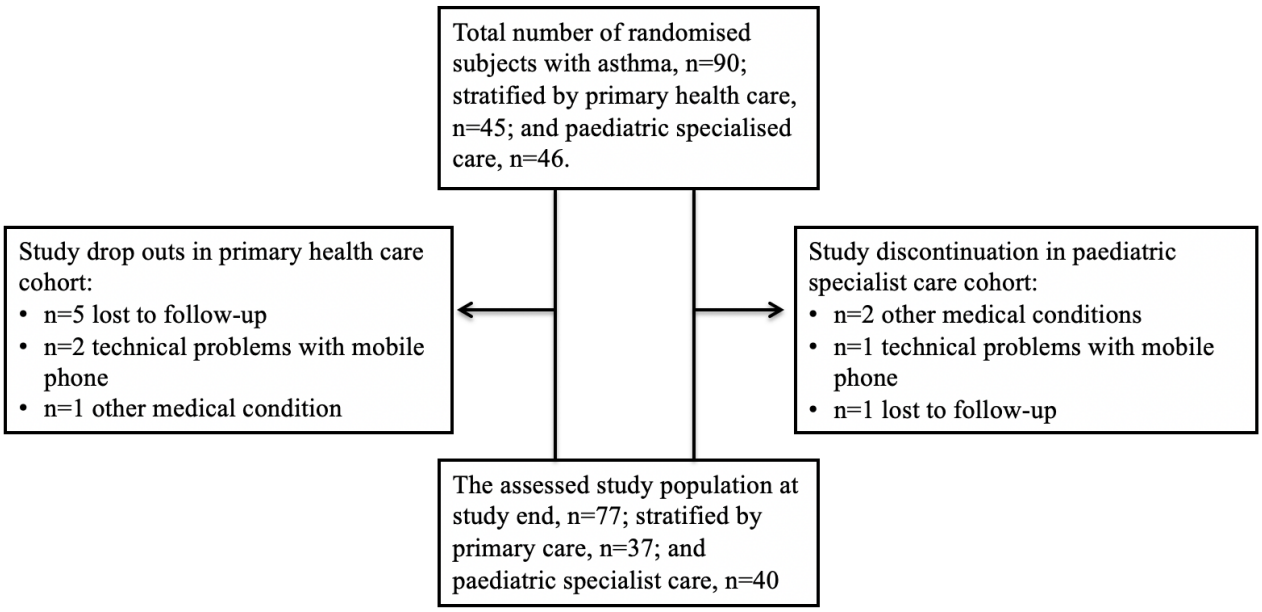
Table 3. Linear regression estimating the effect on Asthma Control Test (ACT) between AsthmaTuner and Conventional treatment adjusted for number of assessments with AsthmaTuner and primary- or paediatric care facility, n=77.

	Difference in ACT between AsthmaTuner and conventional treatment
	ß coefficient (95% CI; p-values)
Unadjusted	0.70 (0.06-1.34; 0.03)
Adjusted for number AsthmaTuner assessments (log)	0.70 (0.03-1.36; 0.04)
Adjusted for care facility (primary or paediatric)	0.66 (0.02-1.31; 0.04)
Adjusted for AsthmaTuner assessments (log) and care facility	0.62 (-0.05-1.30; 0.07)

Table 4. The effect on MARS, difference in participants' forgetfulness to take their asthma medication, within and between treatment with AsthmaTuner or Conventional treatment in all study participants, and stratified by cohorts in primary care, paediatric specialist care and weekly average use of AsthmaTuner at least.

	MARS difference AsthmaTuner	MARS difference Conventional	Mean MARS difference AsthmaTuner vs. Conventional	Difference in crossover effect
	Mean (95% CI; p-values)	Mean (95% CI; p-values)	Mean (95% CI; p-values)	P-values
All participants, n=77	0.06 (-0.11-0.24; 0.47)	-0.06 (-0.23-0.10; 0.43)	0.13 (-0.11-0.38; 0.29)	0.64
Primary care, n=37	0.11 (-0.14-0.35; 0.38)	-0.14 (-0.35-0.08; 0.20)	0.23 (-0.11-0.57; 0.17)	0.39
Paediatric care, n=40	0.03 (-0.24-0.29; 0.85)	0.00 (-0.25-0.25; 1.00)	0.08 (-0.29-0.45; 0.67)	0.87
AsthmaTuner used on average once weekly or more:				
Primary & Paediatric cohort, n=62	0.19 (0.01-0.38; 0.04)	-0.08 (-0.27-0.11; 0.40)	0.27 (0.00-0.55; 0.05)	0.37
Primary care, n=27	0.26 (0.02-0.49; 0.03)	-0.19 (-0.43-0.06; 0.13)	0.45 (0.13-0.77; 0.01)	0.40
Paediatric care, n=35	0.14 (-0.14-0.42; 0.30)	0.00 (-0.29-0.29; 1.00)	0.16 (-0.26-0.57; 0.45)	0.65

Medical Adherence Report Scale (MARS); 1=always, 2=often, 3=sometimes, 4=rarely, 5=never

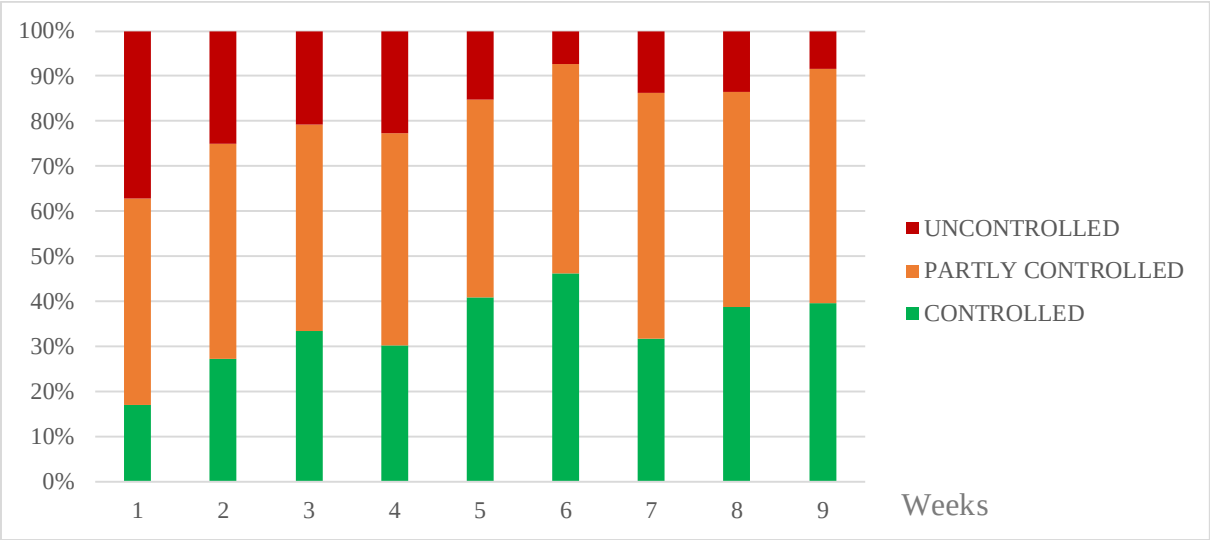


Supplementary figure 1. Flow chart of all participants that were randomised and the assessed study population at study end.

Supplementary table 1. AsthmaTuner algorithm classifying automated adjustable treatment and symptoms control based on symptom questions and lung function (FEV_1).

None of the following:	**One or two of the following:**	**Three or more of the following**:
1. Lung function < 80% of personal best (FEV_1) Last week any of following: 2. Twice need for reliever/rescue inhaler due to asthma symptoms 3. Daytime symptoms 4. Nocturnal symptoms/awaking 5. Limitation in physical activities		

FEV_1 – forced expiratory volume in one second



Supplementary figure 2. The proportion of participants with uncontrolled, partly controlled and uncontrolled asthma defined by AsthmaTuner algorithm across each study week, n=77.

Supplementary table 2. Classification of study participants symptom control by the AsthmaTuner algorithm, and the average number of assessment and automated treatment changes with AsthmaTuner at each study week, n=77.

Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Diff week 1 to 9**
Uncontrolled, %	37	25	21	23	15	7	14	13	8	-29
Partly controlled, %	46	48	46	47	44	46	55	48	52	+6
Controlled, %	17	27	33	30	41	46	32	39	40	+23
Assessments with AsthmaTuner, mean	4.7	2.6	2.5	2.0	2.0	1.8	2.0	1.8	1.3	
Automated treatment changes, mean	1.2	0.7	0.5	0.6	0.4	0.4	0.5	0.5	0.3	

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