Trial@home for children: novel non-invasive methodology for the pediatric clinical trial of the future

Kruizinga, M.D.

CHAPTER 7

Clinical validation of digital biomarkers for pediatric patients with asthma and cystic fibrosis – Potential for clinical trials and clinical care

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Matthijs D. Kruizinga[1,2,3], Esmée Essers[1,2], Frederik E. Stuurman[1,3], Yalçin Yavuz[1], Marieke L de Kam[1], Ahnjili Zhuparris[1], Hettie M. Janssens[4], Iris Groothuis[2], Arwen J. Sprij[2], Marianne Nuijsink[2], Adam F. Cohen[1,3], Gertjan J. A. Driessen[2,5]

1 Centre for Human Drug Research, Leiden, the Netherlands
2 Juliana Children's Hospital, Haga Teaching Hospital, The Hague, the Netherlands
3 Leiden University Medical Center, Leiden, the Netherlands
4 Division of Respiratory Medicine and Allergology, Department of Pediatrics, Erasmus Medical Centre/Sophia Children's Hospital, University Hospital Rotterdam, Rotterdam, The Netherlands
5 Department of pediatrics, Maastricht University Medical Centre, Maastricht, the Netherlands

Abstract

BACKGROUND Digital biomarkers are a promising novel method to capture clinical data in a home-setting. However, clinical validation prior to implementation is of vital importance. The aim of this study was to clinically validate physical activity, heart rate, sleep and FEV1 as digital biomarkers measured by a smartwatch and portable spirometer in children with asthma and cystic fibrosis (CF).

METHODS This was a prospective cohort study including 60 children with asthma and 30 children with CF (age 6-16). Participants wore a smartwatch, performed daily spirometry at home and completed a daily symptom questionnaire for 28-days. Physical activity, heart rate, sleep and FEV1 were considered candidate digital endpoints. Data from 128 healthy children was used for comparison. Reported outcomes were compliance, difference between patients and controls, correlation with disease-activity and potential to detect clinical events. Analysis was performed with linear mixed effect models.

RESULTS Median compliance was 88%. On average, patients exhibited lower physical activity and FEV1 compared to healthy children, whereas the heart rate of children with asthma was higher compared to healthy children. Days with a higher symptom score were associated with lower physical activity for children with uncontrolled asthma and CF. Furthermore, FEV1 was lower and (nocturnal) heart rate was higher for both patient groups on days with more symptoms. Candidate biomarkers and showed a distinct pattern before-and after a pulmonary exacerbation.

CONCLUSION Portable spirometer- and smartwatch-derived digital biomarkers show promise as candidate endpoints for use in clinical trials or clinical care in pediatric lung disease.

Introduction

Clinical follow-up of pulmonary diseases, such as asthma and cystic fibrosis (CF), traditionally relies on both self- and parent-reported symptoms in the outpatient clinic and pulmonary function tests (PFTs). Even though this is considered adequate for pediatric clinical care, both self- and parent-reported symptoms generally suffer from recall bias and are considered subjective, while clinic-based PFTS in children are sometimes associated with challenges in obtaining acceptable and repeatable measurements as well[1,2]. Additionally, new treatments have also led to a slower decline of pulmonary function in CF patients and increasing numbers of patients have pulmonary function in the normal range while still perceiving a significant symptom load[3]. Similarly, pediatric clinical trials, which are difficult to conduct due to ethical and logistical barriers and low inclusion rates[4], either rely on subjective endpoints or rare 'hard' endpoints, such as hospital admission. Rare endpoints lead to unrealistically large sample sizes and long and costly studies, and although subjective symptom reports can be valuable from an investigational point of view, ideally, they should be collected together with additional biomarkers that give a more objective indication of disease control[5]. In pediatrics, such biomarkers are preferably non-invasive, which are scarce. These limitations lead to gaps in knowledge[6,7], and new, objective and non-invasive biomarkers for pediatric pulmonary disease with high clinical and practical utility are needed for use in clinical trials and-care[6,8].

Non-invasive measurements with digital and portable devices for home-use may provide such new biomarkers. Physical activity (PA) has shown to be related to asthma severity[9], and it is plausible that heart rate (HR) and parameters related to sleep also correlate well with an increase in disease-activity[10]. Such parameters can be easily and objectively obtained by consumer devices like a smartwatch[11]. Several PA- and HR-derived digital biomarkers, such as daily step count, step count taken during most active hour per day, and daytime- or nocturnal HR, have been proposed and evaluated in healthy children, and these candidate digital biomarkers exhibited reasonable intra-subject variability[12]. Furthermore, portable spirometers for measurement of complete flow–volume curves have been developed, which can be used in a home-setting[13,14].

Before these digital biomarkers can be included in clinical trials or clinical care, careful selection, technical validation and, most importantly, a rigorous clinical validation process in the target population is necessary[15,16]. A natural next step in the validation of biomarkers derived from PA, HR and FEV1 is clinical validation. A stepwise approach has been

proposed, which is not necessarily comparable to the traditional validation steps for outcome measures[15,17]. This clinical validation should include determination of the tolerability for patients, day-to-day variability in patients, difference between patients and healthy controls, correlation with traditional methods to measure disease activity and potential to detect clinical events to assess the utility of the novel biomarkers[15]. The aim of this study is to initiate the clinical validation process for biomarkers derived from physical activity, HR and sleep and for forced expiratory volume in 1 second (FEV1) measured by a smartwatch and portable spirometer in children with asthma and CF.

Materials and methods

This study was conducted by Juliana Children's Hospital (Haga teaching hospital, the Hague, the Netherlands), Sophia Children's Hospital (Erasmus Medical Centre, Rotterdam, the Netherlands) and the Centre for Human Drug Research (CHDR, Leiden, the Netherlands) from November 2018 to February 2020. The study protocol was reviewed and approved by the Medical Ethics Committee Zuidwest Holland (The Hague, The Netherlands), and conducted according to the Dutch Act on Medical Research Involving Human Subjects (WMO). Written informed consent was obtained from all parents and children aged 12 years and older. The trial was registered at the Dutch Trial Registry (NTR, Trial NL7611).

Subjects and study design

Pediatric patients aged 6-16 with controlled asthma (n=30), uncontrolled asthma (n=30), and CF (n=30) were recruited from the outpatient clinic of the hospitals. In our centers, the diagnosis of asthma is based on clinical symptoms combined with PFTS[18], while the diagnosis of CF patients was confirmed by genetic tests. Asthma control was defined using the Global Initiative for Asthma criteria and Asthma Control Questionnaire (cutoff > 1.5 points). Children used multiple devices as described below and completed a daily symptom questionnaire, together with their parents, for 28 consecutive days. Subjects with asthma were instructed to complete the asthma control diary 6-questions (ACD6), and subjects with CF were instructed to complete a daily respiratory symptom questionnaire adapted from an existing questionnaire (*Supplementary Text S1*)[19,20]. This respiratory symptom questionnaire is not formally validated for children with CF. After 28 days, an end-of-study questionnaire was completed, and the devices were retrieved by the study team.

Subjects were instructed to wear a Steel HR smartwatch (Withings, Issy-les-Molineux, France) during the study period. The watch measures PA with a built-in accelerometer. HR was measured using a photo plethysmography (PPG) sensor on the back of the watch. Furthermore, the watch calculates several sleep-related parameters using the accelerometer and an incorporated temperature sensor, validity of which has been investigated in similar devices[21]. Technical validity of the Steel HR smartwatch was previously investigated (*Supplementary Text S2*). Subjects were instructed to perform daily home-based spirometry using the Air Next spirometry device (NuvoAir, Stockholm, Sweden). This device is validated for use in children and measures FEV1 as well as forced vital capacity (FVC)[13], and the subjects' age, sex and height were used to calculate FEV1 and FVC expressed as z-score based on GLI-2012 equations[22]. All devices used Bluetooth to connect to a smartphone (Motorola G6 (Motorola, Chicago, IL, USA)), which had the Withings Healthmate, and CHDR MORE® (used for data collection and aggregation) applications pre-installed.

Baseline- and environmental data

Parents were instructed to complete the PedsQL 4.0 questionnaire (score 0-100, higher scores represent better quality of life) at the start of the study[23]. Subjects with asthma and their parent(s) completed the asthma control questionnaire (ACQ, score 0-6, higher scores represent worse asthma control) and pediatric asthma quality of life questionnaire (PAQLQ, score 1-7, higher scores represent better quality of life), while subjects with CF and their parent(s) completed the Cystic Fibrosis Questionnaire (CFQ-R, score per subdomain 0-100, with higher scores representing lower disease burden)[24-26]. Other baseline characteristics were collected from the electronic patient file. Prescribed medication at the time of inclusion was registered. Weather (rain duration, temperature) statistics from a local weather station (Hoek van Holland, the Netherlands) were obtained from the Royal Dutch Meteorological Institute (KNMI) and used as covariate in physical activity analyses.

Candidate endpoints

Several physical activity-related candidate endpoints were defined prior to analyses: step count per day (Daily PA), step count during the most active hour (Daily PA^{MAX}, representing daily peak activity) and weekly summarized average-, 10^{TH} centile- and 90^{TH} centile of

physical activity. The last three represents the average-, peak- and trough physical activity[12]. Nocturnal (average HR between 0-5AM) and daytime (average HR between 6AM-22PM) HR were selected as separate endpoints, as well as FEV1 and FVC. Finally, accelerometer-derived sleep parameters total sleep duration, sleep depth (proportion of light sleep) and wakeup count were also selected.

Analysis set

Out of the total dataset (2520 study days), all days with a watch wear time less than 50% between 6AM-10PM were excluded from the analysis (8%, 197 study days). All spirometry curves were graded manually according to ATS criteria[1]. Spirometry sessions graded A, B or C were eligible for statistical analysis (64% of all spirometry sessions, 1165 observations).

Validation criteria

TOLERABILITY Tolerability was assessed by calculating the compliance during the study and the end-of-study questionnaire outcomes. The median and interquartile range (IQR) of the proportion of expected measurements that were performed was calculated for each individual endpoint, as well as for the total amount study activities. For PA and HR, a watch wear time of 50% was required for that day to be included in statistical analyses[12,27,28]. Prior to study initiation, a subject with an overall compliance across all measurements < 70% was considered non-compliant.

VARIABILITY Intrasubject variability was estimated for each condition and candidate biomarker via mixed effect models. For each condition (asthma, CF, healthy) and candidate biomarker, a separate model was fitted with subject as random intercept. The intra-class correlation coefficient (ICC) was calculated by dividing the random intercept variance by the total variance.

DIFFERENCE PATIENTS-CONTROLS To assess the difference between patients and healthy children, data from 128 apparently healthy children aged 6-16 who participated in a separate, comparable trial in parallel to this study[12]. Healthy children from the same geographical area wore the Steel HR smartwatch for 21 days and performed biweekly PFTS. The difference between patient groups and healthy subjects was calculated with a mixed effects model with condition (healthy, controlled asthma, uncontrolled asthma, or CF) as fixed effect and subject as random effect. Additional adjustments for covariates identified in that trial (watch wear time, age, sex, rain duration, temperature, type of day, urbanization for PA-derived biomarkers, age and sex for HR-derived biomarkers) were made if they improved model fit according to the Akaike- and Bayesian Information Criterion (AIC/BIC)[12,29]. Daytime HR was adjusted for physical activity during that day. No adjustment for multiple comparisons was performed. A sensitivity analysis for the choice of wear time threshold was performed by repeating the analysis with varying thresholds.

CORRELATION WITH EXISTING DISEASE METRICS To evaluate whether a change in traditional endpoint, in this case symptom questionnaire scores, corresponds with a change in novel biomarker outcomes, the relationship between candidate endpoints and a symptom questionnaire was analyzed via mixed effects models. A model was fitted for each candidate endpoint, where ACD6 score (asthma) and respiratory symptom score (CF) were included as fixed effect and a random intercept and slope was fitted for each subject. No adjustment for baseline disease activity was performed[30]. Adjustments for baseline symptom score and covariates identified in the previous study were made if they improved model fit as described in the previous paragraph. The estimated marginal effect and the 95% CI was plotted, and significance of the overall effect was assessed with a type III test of fixed effects.

DESCRIPTION OF HEALTH EVENTS Asthma exacerbations were defined according to the ATS/ERS criteria as worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome[31]. Pulmonary CF exacerbations were defined as the need for additional antibiotic treatment as indicated by a recent change in symptoms or decrease in pulmonary function (≥ 10% of predicted FEV1)[32]. In this analysis, the day when corticosteroids or antibiotic treatment was first prescribed, was defined as day 0. Study data from the previous 7 days and the 14 subsequent days were analyzed with a mixed effects model with day as spline covariate and random slope, to allow for nonlinear trajectories[33]. Due to the limited size of the dataset, no adjustments for covariates were made. To assess whether the observed trajectory was not based on random variability, the trajectory over time was also estimated for the group of subjects that did not experience a pulmonary exacerbation during the study.

SOFTWARE AND STATISTICS PySpark version 2.4.6 was used for data aggregation and tabulation. R version 3.5.1 with the lme4, emmeans, rspiro and ggeffects packages was used for statistical analysis. Promasys® software (OmniComm, Ft. Lauderdale, FL, USA) was used for data management. Statistical analysis was performed as described in individual paragraphs above. A p-value < 0.05 was considered statistically significant. Mixed effect model fit was appraised by evaluating the AIC and BIC of each model. Log or square root transformation of the outcome variable was applied during analyses of PA due to heteroscedasticity. A negative binomial distribution was assumed when analyzing wakeup count. A sample size calculation for the difference in PA was performed based on activity data collected in an earlier pilot study[34]. Assuming a significance level of 0.05, a power of 0.8 and the ability to detect a difference between patients and healthy controls of 2750 steps with a standard deviation of 3750 steps in both groups, we calculated a sample size of 30 patients per group.

Results

Baseline characteristics

Baseline characteristics of subjects with controlled asthma (n=30), uncontrolled asthma (n=30) and CF (n=30) were compared with 128 healthy subjects and are displayed in *Table 1*. The mean age of the four groups ranged between 9.7–11.1 years. Subjects with uncontrolled asthma were least likely (67%) to practice any type of sports. Mean quality of life score (PedsQL) was lowest for subjects with uncontrolled asthma (68.7), followed by subjects with cystic fibrosis (79.5), controlled asthma (80.4) and healthy subjects (90.7).

Tolerability

Tolerability was assessed by reviewing the compliance during the study and by a tolerability questionnaire. Median compliance was 88% (IQR[76–95%]) for all subjects (*Table 2*), whereas subjects with uncontrolled asthma had a lower median compliance (79%, IQR[71–95%], *Supplementary Table S1*). Compliance for physical activity and HR was highest for all study groups, followed by sleep, PFT and questionnaire assessments. Children needed a median of 10 minutes per day for study assessments. Eighty-eight percent of respondents of the end-of-study questionnaire reported to be willing to participate in similar studies in the future.

Table 1. Baseline characteristics

	Controlled asthma (n=30)	Uncontrolled asthma (n=30)	Cystic Fibrosis (n=30)	Healthy subjects (n = 128)
Age (mean (SD))	10.5 (2.4)	10.5 (2.9)	9.7 (2.6)	11.1 (3.1)
Sex (% male)	67	67	47	46
Race (% Caucasian)	70	60	100	93
BMI SDS (mean (SD))	0.7 (1.5)	1.2 (1.5)	-0.1 (0.9)	0.3 (1.2)
Plays sports (%)	83	67	80	91
Admissions year prior (mean [range])	0.13 [0–1]	0.37 [0–1]	0.17 [0–1]	-
Atopic asthma (%)	63	83	-	-
Exercise-related symptoms (%)	40	73	-	-
LABA therapy (%)	40	77	17	-
ICS (%)	97	97	17	-
Oral steroids (%)	0	4	-	-
CFTR mutation (%) Class I Class II Class IV	-	-	 3 93 3	-
Pancreatic insufficiency (%)	-	-	93	-
Past pseudomonas infection* (%)	-	-	27	-
PedsQL score (mean (SD))	80.4 (8.6)	68.7 (13.6)	79.5 (11.4)	90.7 (7.4)
ACQ (mean (SD))	0.7 (0.5)	1.9 (0.8)	-	-
PAQLQ (mean (SD))	6.4 (0.4)	5.3 (1.1)	-	-
CFQ respiratory domain (mean (SD))			83.7 (13.9)	
CFQ health perception (mean (SD))	-	-	74.0 (17.1)	-

Abbreviations: SD: standard deviation, BMI: body mass index, SDS: standard deviation score, LABA: long-acting beta agonists, ICS: inhalation corticosteroids, CFTR: Cystic Fibrosis Transmembrane Conductance Regulator, ACQ: asthma control questionnaire, PAQLQ: pediatric asthma quality of life questionnaire, CFQ: cystic fibrosis questionnaire, PedsQL: pediatric quality of life. * Pseudomonas infection was defined as at least one isolate of pseudomonas aeruginosa in sputum in the last 12 months.

Table 2. Median compliance [IQR] during the study period

Assessment	All subjects (n=90)
Step count	100% [100–100]
Heart rate	100% [96–100]
Sleep	85% [74–89]
Pulmonary function test	79% [46–93]
Questionnaire	78% [68–96]
All assessments	88% [76–95]

Variability

ICCS were calculated separately for each group and candidate biomarker and are displayed in *Table 3*. Patient groups exhibited a lower ICC compared to healthy children for PA-related endpoints, HR and sleep while ICC of patient groups was higher for FEV1.

Table 3. Intra-class correlation coefficient (ICC) of candidate biomarkers

Candidate biomarker	Controlled asthma (95% CI)	Uncontrolled asthma (95% CI)	Cystic fibrosis (95% CI)	Healthy 95% CI
PHYSICAL ACTIVITY				
step count per day	0.22 (0.11-0.31)	0.33 (0.21-0.44)	0.16 (0.08-0.24)	0.35 (0.29-0.41)
PA^{MAX}	0.13 (0.06-0.21)	0.21 (0.12-0.31)	0.08 (0.03-0.14)	0.24 (0.19-0.29)
Daytime HR (BPM)	0.48 (0.33-0.60)	0.55 (0.41-0.67)	0.59 (0.42-0.70)	0.65 (0.58-0.70)
Nocturnal HR (BPM)	0.55 (0.40-0.67)	0.50 (0.35-0.61)	0.61 (0.47-0.72)	0.73 (0.66-0.77)
FEV1 (z-score)	0.59 (0.44-0.71)	0.64 (0.48-0.75)	0.63 (0.47-0.74)	0.55 (0.46-0.63)
Sleep duration (hours)	0.26 (0.14-0.37)	0.35 (0.22-0.48)	0.22 (0.12-0.31)	0.31 (0.24-0.36)

Difference patients - controls

Physical activity per day was lower for all three patient groups when compared to healthy children (*Figure 1A*). The largest adjusted difference compared to healthy children was observed for children with uncontrolled asthma (1264 steps, 95% CI 573-1956, p < 0.001), followed by children with CF (847, 95% CI 138-1555, p=0.019) and children with controlled asthma (731, 95% CI 6-1456, p=0.049). PA^{MAX} (*Figure 1B*) of subjects with uncontrolled asthma was lower compared to healthy subjects (adjusted difference 282, 95% CI 134-429, p < 0.001). Average-, peak- and trough physical activity per week showed similar group differences (*Supplementary Figure S1*). Step count per hour of the day (*Figure 1C*) showed that differences in step count between groups were most pronounced during after-school-hours (3PM-7PM). Subsequently, aggregated PA data during after-school-hours was analyzed as exploratory additional biomarker (*Supplementary Figure S2*).

Adjusted average nocturnal HR of subjects with uncontrolled asthma was significantly higher compared to healthy controls and the two other patient groups (*Figure 1D*). Additionally, daytime HR of all patient groups was higher compared to healthy children. Additional adjustment for β-agonist use in patients with asthma showed smaller differences in heart rate between patients and controls (*Supplementary Figure S3*).

CF subjects showed the longest total sleep duration per night (9.1 hours) and slept significantly longer compared to subjects with asthma (*Figure 1E*). There was no statistically significant difference between groups for the parameters sleep depth and wakeup count.

All PFTS performed with adequate technique were included to estimate the difference in pulmonary function between groups. Average FEV1 (expressed as z-score) of patients was lower compared to healthy subjects (*Figure 1F*). There were no differences in FVC between the groups.

Adjusted and unadjusted absolute differences between patients and controls are displayed in *Table 4* for all candidate biomarkers, as well as the standard errors (SE) of the estimate. A sensitivity analysis for the choice of wear time threshold has been included in *Supplementary Figure S4*.

Table 4. Adjusted and unadjusted differences between patient and control groups

Endpoint	Adjustment	Healthy vs. controlled asthma		Healthy vs. uncontrolled asthma		Healthy vs. cystic fibrosis		Adjusted for
		Estimate of the difference (SE)	p-value	Estimate of the difference (SE)	p-value	Estimate of the difference (SE)	p-value	
Daily PA (step count)	Unadjusted	474 (423)	0.26	1097 (406)	0.007	478 (420)	0.25	Wear time, age, rain duration, day type*, sex
	Adjusted	731 (370)	0.048	1264 (353)	< 0.001	847 (361)	0.02	
Daily PA^{MAX} (step count)	Unadjusted	88 (86)	0.31	241 (82)	0.003	30 (87)	0.73	Age, sex, wear time, rain duration, day type*
	Adjusted	150 (79)	0.059	282 (75)	< 0.001	95 (79)	0.23	
Daytime HR (BPM)	Unadjusted	-2.94 (1.45)	0.043	-5.00 (1.45)	< 0.001	-3.76 (1.45)	0.01	Age, sex, physical activity
	Adjusted	-3.24 (1.23)	0.008	-5.71 (1.23)	< 0.001	-2.70 (1.23)	0.03	
Nocturnal HR (BPM)	Unadjusted	-2.97 (1.54)	0.054	-6.82 (1.54)	< 0.001	-2.34 (1.54)	0.13	Age, sex
	Adjusted	-2.92 (1.40)	0.037	-6.77 (1.40)	< 0.001	-0.86 (1.4)	0.54	
Total sleep duration (hr)	Unadjusted	0.14 (0.15)	0.35	0.21 (0.14)	0.14	-0.30 (0.14)	0.04	Age
	Adjusted	0.22 (0.13)	0.08	0.27 (0.12)	0.03	-0.13 (0.13)	0.31	
FEV1 (z-score)	Unadjusted	0.53 (0.24)	0.03	0.8 (0.25)	0.002	0.59 (0.23)	0.01	NA
	Adjusted							
FVC (z-score)	Unadjusted	0.08 (0.26)	0.75	0.32 (0.27)	0.24	0.45 (0.26)	0.08	NA
	Adjusted							

* School day, weekend day or holiday

Figure 1. Difference between patients and control subjects. A: Estimated marginal mean physical activity per day for the four study groups. B: Estimated marginal mean step count during the most active hour on a day. C: Estimated marginal mean physical activity per hour throughout the day. Colors per group are identical as in other panels. D: Estimated marginal mean daytime-and nocturnal heart rate per day. In this estimated average, age is held constant at 12. E: Estimated mean total sleep duration per day, F: Estimated mean FEV1 z-score.

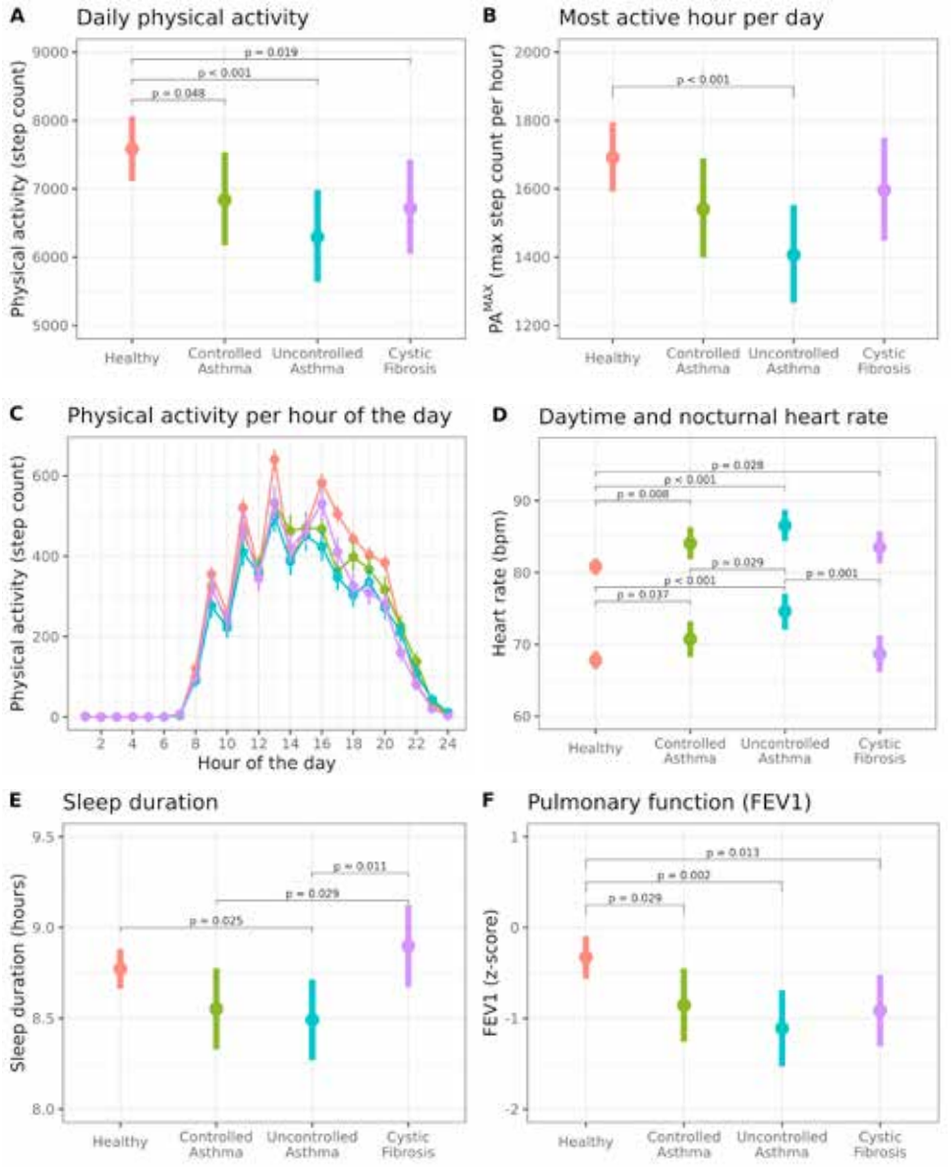


Figure 2. Correlation novel endpoints with traditional endpoints. A-C: Estimated relationship between symptom questionnaire scores and physical activity (step count per day) for subjects with controlled asthma (A), uncontrolled asthma (B) and CF (C). Estimated effects are presented as percentages due to log-transformation of the outcome variable. D-I: Estimated relationship between average daytime HR (D-F) and nocturnal heart rate (G-I) per day and symptom questionnaire scores for subjects with asthma and CF. J-M: Estimated relationship between FEV1 z-score and symptom questionnaire score for subjects with asthma and CF. Bold lines and shaded areas represent the estimated mean and the 95% CI of the relationship. Transparent lines represent individual estimates.

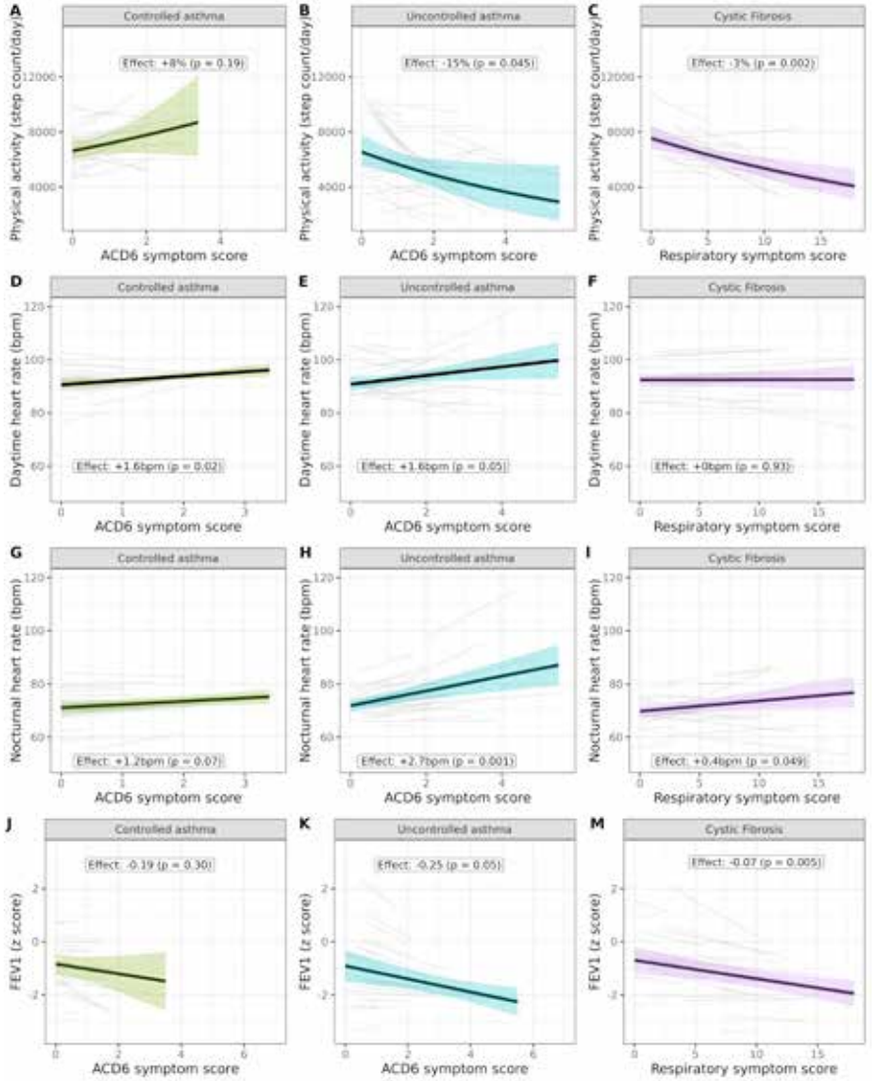
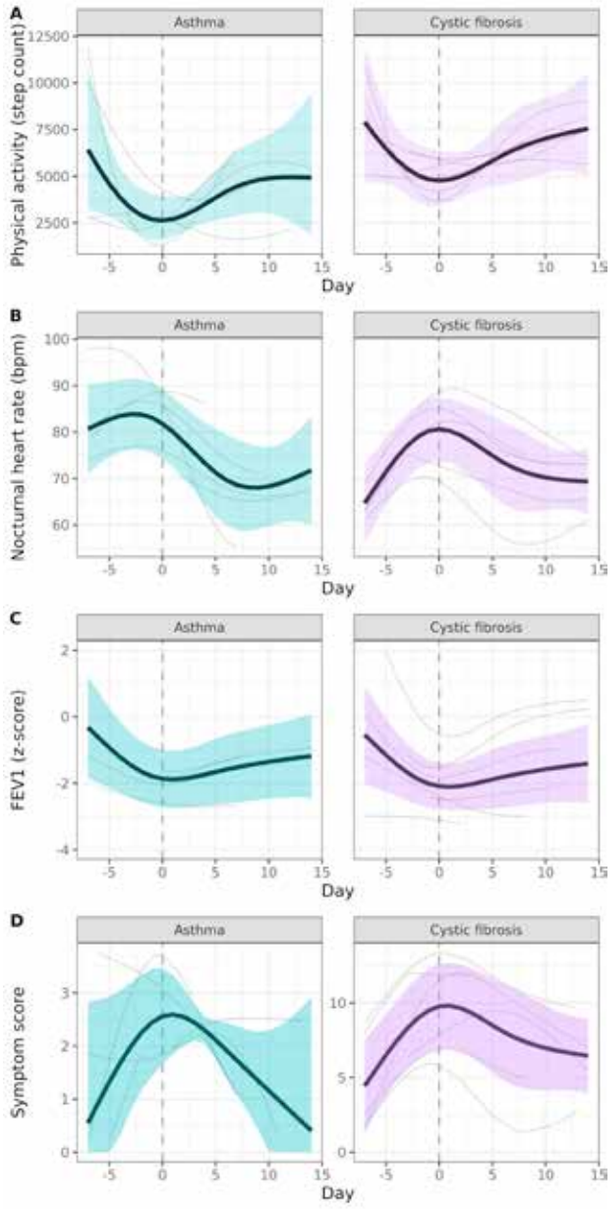


Figure 3. Description of health events. Estimated mean (95% CI) trajectory of physical activity, nocturnal heart rate, FEV1 and symptom score prior-during-and after prescription of rescue therapy (day 0) in the case of exacerbated disease for subjects with asthma (left column) and CF (right column). Bold lines represent the estimated mean. Transparent lines represent individual estimates.



Correlation existing disease metrics

Figure 2 shows the correlation between candidate endpoints and symptom scores. For subjects with uncontrolled asthma, there was a statistically significant relationship between ACD6 score and physical activity per day (15% decrease in step count per point increase in symptom score, 95% CI 0-29% p = 0.045, *Figure 2B*), but not for subjects with controlled asthma (+8% physical activity, 95% CI -5-21%, p=0.19, *Figure 2A*). For subjects with CF, one-point increase in symptom score was associated with a 3% decrease in activity (95% CI 1-5%, p=0.002, *Figure 2C*). Similar effects were found for Daily PA^{MAX} (*Supplementary Figure S5*).

Subjects with controlled asthma had, on average, a daytime HR that was 1.6 BPM higher per point increase in symptom score (95% CI 0.3 - 2.9, p=0.02, *Figure 2D*), and a nocturnal HR that was 1.2. BPM higher (95% CI -0.2 - 2.5, p=0.07) (*Figure 2G*). Daytime HR of subjects with uncontrolled asthma was 1.6 BPM higher per point increase (95% CI 0-3.3, p=0.05, *Figure 2E*), while nocturnal HR was 2.8 BPM higher (95% CI 1.2-4.3, p=0.001, *Figure 2H*). Subjects with CF had a 0.4 BPM higher nocturnal HR per point increase in symptom score (95% CI 0.03-0.75, p=0.049, *Figure 2I*), but no such effect on daytime HR was observed (*Figure 2F*).

Home-measured FEV1 was not correlated to symptom score for subjects with controlled asthma. Uncontrolled asthma subjects had a 0.25 lower FEV1 z-score for each point increase (95% CI 00-0.49, p=0.05 *Figure 2K*), while CF subjects had a 0.07% lower FEV z-score for each point increase (95% CI 0.02-0.12, p=0.005, *Figure 2M*). There was no correlation between FVC and symptom score. PA and FEV1 were correlated for subjects with uncontrolled asthma and CF (*Supplementary Figure S6*).

There was no correlation between ACD6 score and wakeup count, sleep duration or sleep depth. For CF subjects, there was some evidence of an association between wakeup count and respiratory symptom score (RR 1.03, 95% CI 1.00-1.06, p=0.035) but not for sleep duration or sleep depth. Adjustments for baseline disease-activity did not explain additional variance and were not included in the models.

Description of health events

During the study, 5 subjects with asthma and 8 subjects with CF had a case of exacerbated disease and were prescribed systemic corticosteroids and antibiotics, respectively. *Figure 3* displays the estimated mean (95% CI) trajectory of symptom score, physical activity, HR,

and pulmonary function on the 7 days prior to- and the 14 days after the first administration of rescue therapy (day 0). Estimating the same trajectory over time for subjects that did not experience an exacerbation revealed a stable pattern over time (*Supplementary Figure S7*)

Discussion

Innovations in personalized health technology provide a unique opportunity to initiate digital healthcare models and clinical trials that are built around pediatric patients' individual needs[35]. Despite multiple reports on the theoretical promises of wearables and other portable health devices, insufficient research has been performed regarding the clinical application and clinical validation of such measurements[36–38]. This study shows that candidate endpoints physical activity and HR fulfill most of the clinical validation criteria in pediatric patients with asthma and CF[15].

Tolerability and compliance are important predictors of clinical utility[39]. In this study, median overall compliance was 88% for all study assessments, and 100% for HR and physical activity. In addition, subjects found the study enjoyable and 88% of subjects would participate in similar studies. The lower spirometry compliance by subjects with uncontrolled asthma (68%) may be due to the fact that an effort is required for PFTS, leading to lower compliance for children with uncontrolled asthma, who are also generally less adherent to caregiver-instructions regarding their treatment compared to their well-controlled peers[40].

One advantage of monitoring via a wearable device compared to spirometry is the passive nature of data collection. In general, compliance to home-monitoring tasks significantly reduces over time, greatly diminishing the potential benefits[41]. Passive data collection may be less sensitive to this effect. Although spirometry has traditionally been the cornerstone of pulmonary health monitoring, the difficulty of the assessment compared to continuous monitoring by a wearable outside the clinic is a disadvantage in the context of home-monitoring. In this study overall compliance for PFTS was lower, and 36% of PFTS were discarded prior to analysis due to inadequate technique. This significant proportion of missing data impacted the power and generalizability of the analysis, as some subjects were more likely to exhibit bad technique compared to others. Furthermore, this finding raises doubt on the potential of PFTS for home-monitoring purposes. Indeed, previous studies investigating the value of home-based PFTS in pediatrics have reported no- or modest benefits[42–44]. Additionally, the EICE study in adults with CF reported that home-monitoring with PFTS and symptom scores combined with early intervention did not lead to a decrease in decline in pulmonary function compared to standard of care[45]. This study suffered from a similarly low compliance for home-based PFTS, and this indicates that passive monitoring of physical activity may have better value compared to PFT monitoring.

Important validation criteria for digital biomarkers include the difference between patients and controls and a correlation of novel digital endpoints with traditional endpoints, like symptom questionnaires[15]. We found that physical activity was lower in patients compared to controls, which is in agreement with findings that have been reported in the past[9,46], although other studies reported no significant differences in physical activity[47,48]. The differences were especially pronounced between 3PM and 7PM, and future studies may consider using activity during these hours as a separate endpoint (*Supplementary Figure S5*). Furthermore, physical activity was correlated with respiratory symptom scores for both CF and asthma, demonstrating the sensitivity for change in disease-activity. Both the difference in physical activity between asthmatic and healthy children, and the sensitivity of the endpoint to change in disease-activity are supported by Vahlkvist *et al.*, who showed that treatment with inhaled corticosteroids caused a significant increase in physical activity over time for children with recently diagnosed asthma[46]. A limitation of using step count as physical activity endpoint is that it does not capture all types of physical activity, such as cycling or swimming, which may have led to underestimated mean physical activity. The advantages of using a consumer smartwatch are a high compliance and relatively low cost compared to medical-grade devices[49].

For HR, differences between children with asthma and healthy children were observed for nocturnal- and daytime HR, and both were correlated with reported symptom scores. These observations are most likely due to a combination of disease- and pharmacological effects. Children with (uncontrolled) asthma often use (more) β2-agonists, causing elevated HR, which is a positive confounding factor in this analysis and part of the causal pathway between symptoms and heart rate[23,24]. Additional analyses adjusting for this confounder showed lower differences between patients and healthy children (*Supplementary Figure S3*), although the use of a smaller dataset due to questionnaire non-compliance led to increased uncertainty around the estimates. Still, the goal of the current study was to study the association between symptoms and heart rate and to demonstrate that a smartwatch can identify the magnitude of the difference in HR between patients and healthy controls. Considering that there was a difference in HR between healthy

children and patients with asthma and that HR was also responsive to a change in disease activity, we believe that (nocturnal) heart rate is a potential biomarker in real-life settings, irrespective of the underlying physiologic mechanism. Admittedly, digitally monitoring of rescue inhaler use may be a potential biomarker with similar usability[50]. To our knowledge, the application of smartwatch derived heart rate measurements in children with chronic lung disease has not been investigated in the past. In the future, more advanced analyses that integrate heart rate, inhaler use, and physical activity data may be considered to untangle the close relationship of the three variables in patients.

The variability of the investigated candidate biomarkers was assessed previously in healthy children[12], and is an important characteristic for power calculations in future clinical trials planning to utilize the biomarkers as endpoint. We found that ICC was lower for PA- and HR-derived endpoints in patients compared to healthy children, but not for FEV1. We hypothesize the lower ICC for PA and HR, indicating a higher intra-subject variability, is related to fluctuations in disease-activity inherent to the diseases. This is relevant for future clinical trials, since higher intra-subject variability necessitates larger samples sizes to detect clinically significant differences. However, aggregation of daily physical activity in weekly physical activity-related endpoints (*Supplementary Figure S1*) is more stable over time and may be suitable for long-term follow-up studies. A definition of what constitutes a clinically significant improvement is also necessary. Based on the current study, we believe that a change in physical activity or heart rate of 10% could be a reasonable cutoff. However, Future validation studies performed with novel or known (effective) treatments for asthma (e.g., inhalation corticosteroids) and CF should be performed to elucidate the magnitude of improvement in physical activity and other biomarkers that these treatments can elicit.

A final validation criterion is that novel endpoints should be able to discern and describe health events such as pulmonary exacerbations. These events are an important characteristic of severe disease and were defined by the need for rescue therapy during the study. Based on a limited dataset of subjects, physical activity, nocturnal HR and FEV1 appeared to be sensitive to the change in disease activity prior to rescue medication start and showed a distinct recovery curve during the days afterwards. Analysis of the individual trajectories revealed a similar pattern for all subjects throughout the exacerbation period. However, considering the limited sample size and the exploratory nature of this analysis, more research is needed to determine whether prodromal symptoms could provide an early warning sign for subjects and caregivers.

The candidate endpoints included in this study appear to fulfill the predefined clinical validation criteria and may be considered for use in clinical trials- and care. An improvement compared to traditional questionnaire assessments is that the proposed endpoints are objective in nature and less subject to recall bias, and may also assist children who find it difficult to perceive their own asthma-related symptoms[51,52]. Another application in asthma- and CF care that could have value is the prediction of disease control. If a smartphone application with access to the digital measurements predicts an increase in symptoms, it could suggest a specific intervention, which may prevent a pulmonary exacerbation. In the past, researchers have achieved promising results in this respect with asthmatic adults using only peak flow measurements[53], and incorporation of the measurements described in this manuscript may lead to even better predictions. This paper focuses on the necessary preparatory work required, and more longitudinal data of more subjects with more symptom score variability within subjects is needed.

This study has multiple limitations. One of which is that subjects with uncontrolled asthma were included some time after they were seen in the clinic, and an intervention to address the inadequate asthma control may have taken place during that time. Therefore, the true difference between subjects with uncontrolled asthma and subjects with controlled asthma may be more pronounced. Additionally, the smartwatch-derived data obtained is the study was obtained from a single smartwatch model and cannot necessary be extrapolated to smartwatches of other manufacturers. Another limitation is that the daily questionnaire employed for CF patients was not validated in the population. However, no (validated) daily symptom questionnaire was available in pediatric CF patients at the conception of this study.

A major challenge when analyzing datasets is missing data. The mixed effect models use maximum likelihood methods and are robust to randomly missing data, which we believe, based on our exit-interviews with study participants, is the case for the data employed via the smartwatch[54]. However, it is possible that subjects were less likely to perform a spirometry session (with adequate technique) or perform spirometry, on days with a high symptom load. This may have led to an underestimation of the differences between groups. However, the findings in this study may better correspond to the real-world conditions that will apply when the devices will be used in practice.

The sample size for all analyses is limited and future studies should include larger cohorts to increase the generalizability and robustness of the current findings. For example, adjustments for covariates identified in a previous study were performed via mixed

effect models, but only when the previously identified covariates explained additional variance according to prespecified goodness of fit criteria[29]. This was judged to give a good balance between explaining additional variance and risk of overfitting. Future analyses with larger cohorts can adjust for additional covariates with less risk of overfitting.

Strengths of this study include the systematic approach towards clinical validation, which excellently elucidates the characteristics of each individual candidate endpoint. The cohort of healthy children and patients with a wide range of disease-activity is large compared to comparable studies and allowed us to estimate group means representative for the target population. Although the study was not powered to detect many pulmonary exacerbations, the fact that 13 subjects received rescue treatment during the study allowed for a decent description of prodromal indices and recovery after exacerbations. Future research could focus on how to interpret measurements of a single patient in the context of clinical care and on alternative approaches such as fluctuation analyses[55]. Finally, data from a larger cohort with more symptom score variability can give an indication of the predictive capabilities of smartwatch data when monitoring patients with pediatric pulmonary disease.

Conclusion

Remote monitoring with a smartwatch and portable spirometer shows promise as digital biomarkers in pediatric lung disease. Physical activity-, HR-and pulmonary function monitoring is tolerable, can differentiate patients from controls and is correlated to symptom scores.

SUPPLEMENTARY DATA

Sup. Text S1	Respiratory symptom score questionnaire
Sup. Text S2	Technical validation data Steel hr watch
Sup. Table S1	Median compliance [IQR] during the study period for the 4 study groups
Sup. Figure S1	Difference between patients and healthy subjects for physical activity endpoints averaged per week
Sup. Figure S2	Physical activity between 3-7pm as candidate endpoint
Sup. Figure S3	Adjustment for β-agonist use
Sup. Figure S4	Sensitivity analysis
Sup. Figure S5	Correlation symptom score and daily PA^{MAX}
Sup. Figure S6	Correlation between physical activity and pulmonary function
Sup. Figure S7	Trajectory over time of subjects that did not experience pulmonary exacerbation

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