UNIVERSITY OF TWENTE

MASTER THESIS TECHNICAL MEDICINE

WEARCON

Wearable home-monitoring in asthmatic children

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Preface

This thesis has been written to fulfill the graduation requirements of the Technical Medicine master program at the University of Twente (UT). I was engaged in researching and writing this thesis from September 2016 till September 2017.

This graduation year had started of with an extensive literature research on the monitoring of asthmatic children. Throughout this process a lot of ideas were gathered and evaluated, resulting in a plan of action for this study.

The plan of action included patient measurements, so a precise protocol had to be written and judged by the Medical Ethical Commission. Fortunately, this approval did not let us wait for long.

At that point, the study could start and the first patients were recruited. This required a lot of organizing skills; selecting the right children, informing parents by phone, sending information letters, giving instructions to the children and their parents, keeping in contact with them during the monitoring period and collecting data at the exercise challenge test in the OCON. Afterwards, the data of all wearables, questionnaires and tests had to be stored, preprocessed and analyzed.

Despite the hard work, I liked to be closely engaged in the asthma care of these patients and this boosted my motivation for this project. Furthermore, I am happy to see that the results of this study give new insights into the best way to home monitor asthmatic children.

At the end of this graduation year, I can conclude that I have learned a lot about the asthma care, the handling of children, clinical research, Matlab and wearable home-monitoring. However, there is still more to learn and I hope that I can proceed with that.

I hope you enjoy reading this thesis.

Mattiènne van der Kamp

Enschede, August 31, 2017

Acknowledgements

I would like to gratefully acknowledge various people who have journeyed with me in the past year as I worked on this thesis.

I would first like to thank my colleagues at the pediatric department of the MST for their hospitality during this year. I would particularly like to single out my supervisor dr. Boony Thio. Boony, I want to thank you for your inspiration and extensive supervision during this year. Besides all the medical related discussions, there was always room for general conversations about for example sports, which made sharing a working-room very pleasant.

In addition, I would like to thank dr. Jean Driessen. You learned me everything there is to learn about asthma in children. I always looked forwards to the Wednesdays, because I knew this clinical day would be fun and interesting.

I would like to thank dr. Frans de Jongh for his advise when I needed it the most. You always knew someone who could help me with a certain problem. Furthermore, you always had some hard questions for me which contributed to the quality of this thesis.

Besides my medical and technical supervisors, I would like to thank the rest of my graduation committee: Prof. H. Hermens and drs. P. van Katwijk for their supervision, encouragement and insightful comments.

I thank my fellow Technical Medicine students for their help and advise in carrying out this study. Other than the serious discussions about our studies, we had a lot of fun, which kept the spirit good. Even when the mess in our small workroom was spread out across the whole desk. I am still sorry for that guys.

I would also like to thank all subjects for their participation in this study. Especially the subjects living in Haaksbergen and beyond, you made my physical fitness level increase substantially as I cycled to every wearable instruction at your place.

Finally, I must express my very profound gratitude to my girlfriend for providing me with unfailing support and continuous encouragement throughout the process of researching and writing this thesis. This accomplishment would not have been possible without her. Thank you.

Abstract

Rationale Pediatric asthma is the most common chronic disease in childhood. Treatment is focused on the control of asthma symptoms, enabling patients to fully participate in daily life. However, children's expression of asthma symptoms is often difficult to assess and interpret. Additionally, accurate monitoring of pediatric asthma is challenging as symptoms are episodic and therefore often absent during clinical visitation. Home-monitoring of asthma symptoms can provide the physician more insight into the current asthma status and offer an opportunity to anticipate into the waves of asthma. Therefore, this research focused on home-monitoring of asthmatic children using wearable technology.

Objective The objective was to find the most effective combination of wearable devices accurately reflecting pediatric asthma control in a home-monitoring situation, by studying the relation of the home-measured signals to the currently used exercise challenge test (ECT) for assessment of asthma control in children. It is hypothesized that combining wearable home-monitoring devices can provide a reliable tool for assessing asthma control.

Methods In this observational pilot study 25 children were included and categorized in controlled (n=16) and non-controlled asthma (n=9) based on the outcome of an ECT. The study consisted of a home-monitoring period of two weeks. During this period lung function, physical activity (PA), sleep, heart rate (HR), respiratory rate (RR) and medication use were monitored.

Results Univariate analysis showed significant larger maximal differences between multiple baseline FEV_1 (p=0.03), higher amounts of used reliever medication (p=0.01) and an increased respiratory rate recovery time (HRRT) ($p<0.01$) in the non-controlled asthma group.

Discussion Including more subjects would allow multiple regression analyses, which might lead to additional relevant parameters for home-monitoring of pediatric asthma. Future research should focus on implementing home-monitoring into the outpatients care, by creating a straightforward interface to analyze and display the home-monitoring signals. Randomized controlled trials (RCTs) can be used to test whether home-monitoring results in better asthma control and less hospital admissions.

Conclusion This study suggests that wearable devices can be used for home-monitoring of pediatric asthma. Wearable home-monitoring is feasible and provides the pediatrician with clinical information, which might be missed during regular pediatric asthma management.

List of abbreviations

BHR	Bronchial Hyperreactivity
BMI	Body Mass Index
(C)-ACQ	(Childhood)-Asthma Control Questionnaire
C-ACT	Childhood Asthma Control Test
CRF	Cardio Respiratory Fitness
ECG	Electro Cardiogram
ECT	Exercise Challenge Test
EIA	Exercise Induced Asthma
EIB	Exercise Induced Bronchoconstriction
EMG	Electro Myogram
FEF_{25-75}	Forced Expiratory Flow between 25 and 75 percent of the FVC.
FEV_1	Forced Expiratory Volume in 1 second
FOT	Forced Oscillation Technique
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
HR	Heart Rate
HRRT	Heart Rate Recovery Time
ICS	Inhalation Corticosteroids
KNMI	Koninklijk Nederlands Meteorologisch Instituut
LABA	Long-Acting Beta-adrenoceptor Agonist
LF	Lung Function
MST	Medisch Spectrum Twente
OCON	Orthopedisch Centrum Oost-Nederland
PA	Physical Activity
PAQ-C	Physical Activity Questionnaire Children
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
PEF	Peak Expiratory Flow
PWC-170	Physical Working Capacity-170
RCT	Randomized Controlled Trial
RR	Respiratory Rate
RRRT	Respiratory Rate Recovery Time
SABA	Short-Acting Beta-adrenoceptor Agonist
Vm	Vector Magnitude
$VO2_{max}$	Maximal Oxygen Uptake

Contents

1 Introduction

Asthma is a chronic inflammatory disease of the airways, which is characterized by bronchial hyper-responsiveness to various stimuli. This results in symptoms, such as chest tightness, shortness of breath, coughing and wheezing. [1]

The prevalence of asthma in the Netherlands has been rising for decades, with a year-prevalence of 200.000 for children (0-14 years old) in 2015 [2]. Therefore, asthma is the most common chronic disease in childhood. Furthermore, incidence and prevalence of asthma in boys (<14 years old) is higher then in girls [2]. Recent publications show that asthma prevalence seems to stabilize the last years, however the coming years will have to show whether there really is stabilization of prevalence [3].

1.1 Phenotypes of asthma

A division in observable properties within asthma can be identified. These so called phenotypes can give guidance in the different etiologic, physiological and clinical characteristics of the group population. [4–6] The phenotypes can be divided into two groups, based on the amount of inflammatory response; the T-helper-2-associated phenotypes and the non-T-helper-2-associated phenotypes. The emphasis of pediatric asthma lays on the T-helper-2-associated phenotypes; allergic asthma, viral induced asthma and exercise induced asthma (EIA) [7, 8]. Obese asthma, which is defined as an adult phenotype, is suggested to confound asthma in childhood. [7] Figure 1 shows an indication of the phenotype prevalence over the age of the child.

Virus induced asthma

Viruses are common acute triggers for exacerbations, especially in young children [8, 9]. The most common virus is the rhinovirus. The viruses cause both acute airway inflammation and chronic airway remodelling, which could result in a hyper-reactivity phenotype. Virus induced asthma is characterized with viral infections and therefore have additional specific symptoms, such as fever, headache, loud dry cough and sneezing [8].

Allergic asthma

Early onset allergic asthma is a phenotype in children. This group of asthmatic patients develops their symptoms in childhood and often maintains their symptoms into adulthood. Children with a family history of atopy, sensitization and allergic dermatitis are almost all expected to develop asthma. [10] Allergic asthma can be detected with positive skin prick tests, specific IgE antibodies in serum and eosinophilia in peripheral blood or sputum. [10, 11]

Exercise induced asthma

EIA is a condition which occurs in 80 to 90% of individuals (both adults and children) with asthma [12]. EIA is characterized with airway obstruction during and/or after exercise. It can be diagnosed with exercise provocation tests with lung function (LF) analysis [13]. Furthermore EIA is associated with lower amounts of activity in children [14]. Participation in daily physical activities (PA) is paramount for a child's development. The non full participation can compromise their quality of life, cardio respiratory fitness (CRF) and motor development. For this reason one of the goals in pediatric asthma management is that patients are able to participate in every day PA. [15]

Despite the best efforts to define asthma phenotypes, it is still not helpful in individual guiding therapy, due to variations in the course of the disease. Additionally, asthma phenotypes can shift or interfere during childhood resulting in the fact that pediatric asthma phenotypes cannot be seen as separate entities. Figure 2 shows a case example of the interference of the asthma triggers.

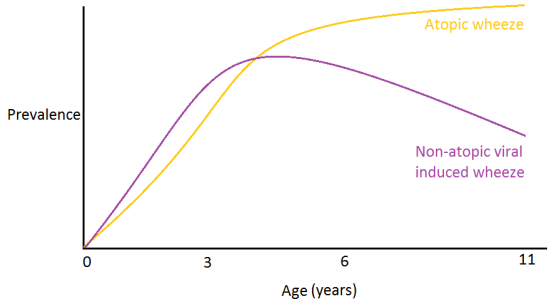


Figure 1: Phenotypes of asthma by the age of the child: The occurrence of non-atopic viral induced wheezers peaks around the age of 4. The amount of atopic wheezers gradually increases at young age and stabilizes around the age of 11 [7].

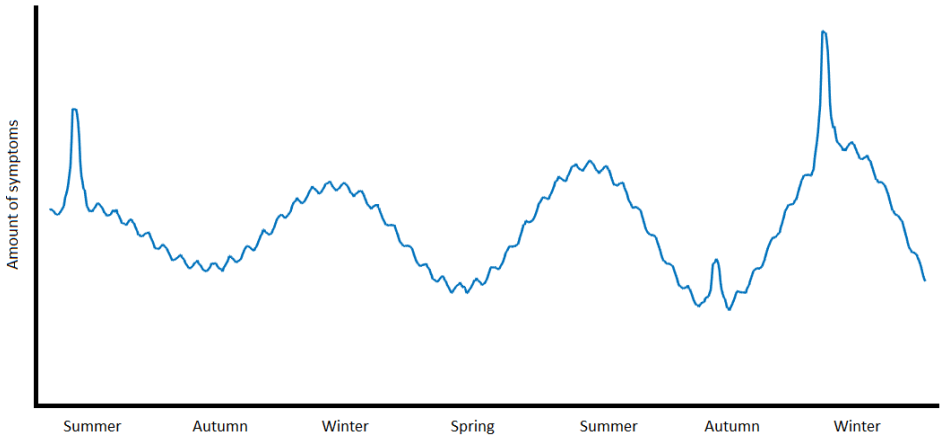


Figure 2: Case example of the waves of asthma: This graph shows the course of the amount of symptoms of a 6 year old child with severe allergies for house dust mite and grass pollen. His allergies are predominant in the course of his symptoms. A slow decrease of asthma control can be seen in the transition periods between spring and summer (grass pollen) and autumn and winter (house dust mite). Additionally, events of viral infections can be seen as bursts in the wave of asthma symptoms. A higher increase in symptoms, due to a viral infection, can be seen in periods with low asthma control.

1.2 Pediatric asthma management and the importance of home-monitoring

Pediatric asthma management is focused on controlling asthma symptoms, enabling patients to fully participate in daily life. However, children's expression of asthma symptoms is often difficult to assess and interpret. Additionally, monitoring pediatric asthma is challenging as symptoms are episodic and therefore often absent during clinical visitation.

A LF test with reversibility to adrenergic $\beta 2$ receptor agonists is a standard test for asthma [16]. A significant rise in LF is diagnostic for asthma. However, a negative test result does not exclude the presence of asthma.

A bronchoprovocation test can give a more reliable insight in the current asthma status. A common stimulus of bronchial hyperreactivity in the daily life of children is exercise. Exercise induced Bronchoconstriction (EIB) occurs in 80 to 90% of the children with asthma and is highly specific for asthma in childhood [17]. However, exercise provocation tests are labour intensive and require specialized knowledge and facilities. For this reason, the use of these test is limited in daily clinical practice.

1.3 Home-monitoring of asthma control

Home-monitoring of asthma symptoms could be used to provide the physician with more objective insight into the current asthma status. Over the past decade, asthma control as distinct from asthma symptom severity has been defined by the Global Initiative for Asthma (GINA) [16,18]. Questionnaires are often used to access the symptom severity in the home-situation. Some of these questionnaires are validated for children such as the childhood asthma control test (C-ACT) [19] and the childhood asthma control questionnaire (C-ACQ) [20]. However, still questionnaires are limited objective and prone to the perception of the child or parents. Therefore, it is expected that asthma questionnaires provide mostly information about the trends of individual symptoms and are therefore sensitive for floor/ceiling effects. Furthermore, questionnaires, especially in children, are often affected with recall bias [21]. Madhuban et al. [22] showed a positive predictive value, of the ACQ for EIB in children, of 51% and a negative predictive value of 59%. This emphasizes the limited usefulness of questionnaires for the purpose of asthma control in children.

For this reason, more objective methods of monitoring asthma control were investigated. The most used monitoring device is peak expiratory flow monitoring. Kotses et al. [18] concluded that peak flow only gives a small increment in effectiveness beyond that afforded by symptom monitoring. Other home-monitoring methods involve measurements of activity [23], inflammation markers [24], respiratory distress [25,26] or coughing/wheezing [27]. All parameters show potential in monitoring asthma. However, one by one they could not provide sufficient correlation with asthma control for all asthmatic children. Therefore, proper randomized controlled trials (RCTs) or large longitudinal studies will be needed to establish the exact relevance of these parameters. [28]

Another note that should be made is the inconsistency by which asthmatic children are defined in home-monitoring literature. Some uses questionnaire scores to define asthmatic children, others use LF criteria, while some only state to that clinical diagnosed asthmatic children were included. This makes it hard to interpret and compare the results found in literature. An exercise challenge test (ECT) according the American Thoracic Society (ATS) criteria should be used as gold standard for defining asthma control [15,29].

In conclusion, it can be said that no perfect home-measurement of asthma control is currently available. This research focuses on combining relevant monitoring parameters to accurately assess asthma control in children. This could facilitate early detection of deterioration of asthma control, which could lead to early intervention or even prevention of the loss of asthma control.

1.4 Research objective

This brings us to the primary objective of this study, which is:

Linking information of different wearable devices together to create an effective tool for home-monitoring of pediatric asthma control, as assessed by an exercise challenge test.

A secondary objective is to assess the feasibility of collecting data from wearables worn by asthmatic children, acquired in the home-situation and create an overview image of relevant wearable data.

2 Background

2.1 Wearable home-monitoring

Wearable technology has been introduced into the healthcare and offers new tools to connect patients with care providers at any time from all places. This causes not only improvement in patient monitoring but also enhances patient experience and reduces healthcare expenses [30]. Furthermore, wearable technology steers healthcare more and more to self-management of chronic diseases. With the right tools this could reduce the ever rising healthcare costs, which poses a burden on healthcare resources. [31]

Still, wearable technology has some deficiencies to deal with. Consumers are sceptical of sharing healthcare information and cybercrime is a potential risk for medical devices [32]. Nowadays, the wearable technology is a trending research topic. Therefore, the wearable market is expected to increase rapidly in a few years (figure 3), due to more affordable products which offer greater value for users and healthcare partners. [33]

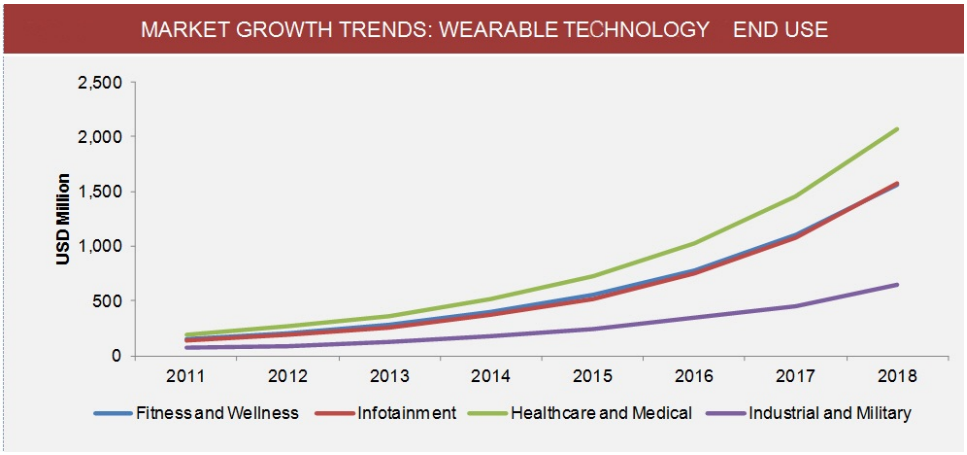


Figure 3: Global market growth prediction of wearable technology [34].

The challenge of the wearable industry is to combine the right sensors and hardware for various different medical purposes and develop software which is in line with this purpose, so that analysis reveals clinical relevant parameters. Furthermore, validation of the wearables with gold standard medical equipment is required to facilitate the clinical use of wearable devices.

2.2 Asthma parameters to monitor

Wearable home-monitoring of asthma could focus on many different aspects. Literature study provided many symptoms and confounders for asthma and information about how to monitor these. The schematic overview of this is shown in appendix A.1.

2.2.1 Symptoms

Asthma symptoms can be categorized into the umbrella groups: bronchoconstriction, hyperinflation, respiratory distress, inflammation, respiratory sounds and PA.

Bronchoconstriction An asthma exacerbation causes airway smooth muscle spasm, airway wall inflammation and mucus production. All resulting in a decrease of bronchial lumen. Several studies showed with radiological images that bronchial lumen decreases and the bronchial wall thickens in asthma patients [35].

CT-images can therefore be used to assess bronchoconstriction, but there are other measures to detect the amount of bronchoconstriction. The decreased lumen of the bronchioles results in a higher airway resistance and therefore a decreased expiratory airflow when exhaled with maximal effort. This decreased expiratory flow can be measured with spirometry or peakflow measurements.

Spirometry is an often used and validated measure of LF [28]. Spirometry provides the volume and flow of air that can be inhaled and exhaled. Currently, spirometry is the most used monitoring tool of asthma in the clinic.

Peakflow measurements are often used for monitoring respiratory diseases at home, because peakflow meters are inexpensive and portable. Peakflow meters can provide the patient and clinician objective data upon which they can base therapeutic decisions. Studies demonstrated that daily monitoring peakflow decreased healthcare utilization and improved quality of life [28, 36]. However, peakflow measurements provide less information than spirometry.

Unfortunately, in both spirometry and peakflow measurements, maximal effort and maximal patient cooperation is required to have an accurate outcome measure. In children, especially young children (below 6 years) maximal cooperation is only achievable with professional guidance. Non-maximal cooperation may result in underestimation of the forced LF parameters [37, 38].

Airway resistance can further be measured with body-plethysmography, interrupter technique or forced oscillatory technique (FOT). As these techniques can be carried out relatively independently of active collaboration they are suitable for preschool children. However, this equipment is not yet available for wearable home-monitoring in children. [39, 40]

Hyperinflation An obstructive disease like asthma will show increased functional residual capacity, due to the air trapping after bronchoconstriction. 49% Of the children with airflow obstruction ($FEV_1/FVC < 80\%$) showed significant hyperinflation (defined as a residual volume of $>120\%$ of predicted) [41]. Therefore, hyperinflation measurements (i.e. body-plethysmography or dilution techniques) may be of interest in the management of asthma.

Respiratory distress An asthma exacerbation is characterized by respiratory distress. An exacerbation usually starts with bronchoconstriction that causes a compromised airflow in the lower airways, especially during expiration. This could result in air trapping and reduced oxygen and carbon dioxide (CO2) exchange in the peripheral lung tissues, which causes the amount of CO2 in the blood to rise and blood oxygen to drop (defined as respiratory acidosis). [42]

This induces physiologic stress on the body. The body will react by enhancing circulation and ventilation with an increased heart rate (HR), increased ventilation rate and an increased work of breathing due to accessory respiratory muscle use. This lowers the blood CO2 levels and stabilizes the drop in blood oxygen levels. However, when bronchoconstriction remains or worsens over time, the body will be subject to fatigue (respiratory lactate acidosis) and blood oxygen levels continue to gradually decrease. [42]

Useful parameters to objectively measure respiratory distress would therefore be; HR and respiratory rate (RR) [43], blood oxygen levels (saturation), blood CO2, the end-tidal CO2 measures of capnography [44–46] or the activity of (accessory) respiratory muscles (EMG) [25, 26].

Airway inflammation In children with asthma bronchioles react to chronic triggers, such as allergens, by inflammation. These triggers set off a whole cascade of inflammatory cell recruitment, activation and mediator release [47]. Figure 4 shows an example of the inflammatory cascade of allergic asthma.

Airway inflammation can be monitored by measuring the presence of these mediator particles. For this purpose laboratory blood tests, breath analyzers and sputum tests can be used.

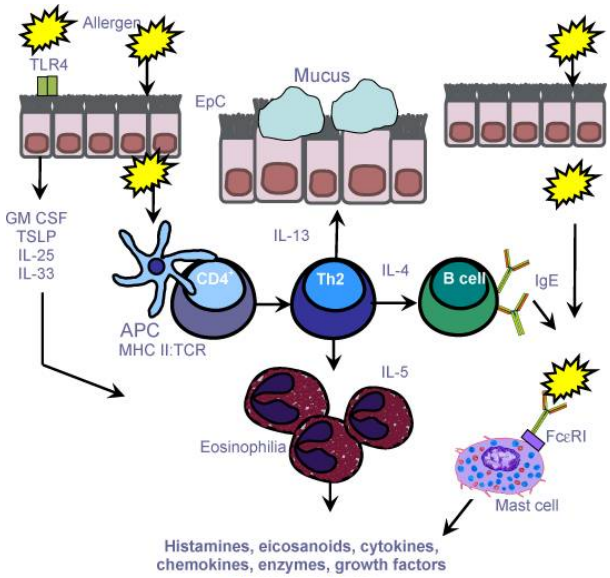


Figure 4: Inflammatory cascade of allergic asthma [47].

Respiratory sounds Expiratory wheezing is associated with lower airway obstruction. Wheezing is believed to be generated by oscillations of constricted airways. During expiration air passing through the narrowed airway at high velocity produces decreased gas pressure and flow in the constricted region (according to Bernoulli's principle). The airway pressure in the small airways will increase. The transition between open and nearly closed airway produces an oscillation of the airway walls and a continuous sound, which is called wheezing. [48]

Rietveld et al. [49] showed that sound patterns of wheezing children are sensitive and specific predictors of airway obstruction. Besides wheezing, coughing is also associated with asthma. However, coughing is far less specific as wheezing. Research showed that acoustic analyses of coughing could identify several respiratory pathologies [50]. Own research of Technical Medicine student J. Stoks showed that, especially in the time domain intensity distribution histogram of the cough sound, differences in signal characteristics can be observed between controlled and non-controlled asthmatic children. [51]

Activity changes Being physical active brings extra benefits to asthmatic children as it reduces airway inflammation [52]. Additionally, PA mediates the relation between asthma and obesity which could positively influence asthma control [53]. Figure 5 shows a summary of the activity relation with body composition, CRF and asthma. It is extremely important that children are physically active at young age, as it is suggested that PA habits acquired in childhood are likely to be kept in adulthood [54].

Asthma and the impact on PA has been a frequently investigated topic of research. Vahlkvist et al. [23] found that improvements in asthma control are related to significant improvements in moderate to vigorous activity. This implicates that poorly controlled asthma has a negative effect on the ability of children to perform physically and that this effect can be reversed by the right treatment. Sousa et al. [55] showed that children with good asthma control, independent of disease severity, had similar PA levels to children without asthma. Previous research performed at the pediatric department of the Medisch Spectrum Twente (MST) Enschede showed several interesting outcomes regarding the activity patterns of asthmatic children [56]:

- Children with asthma have less total activity;
- Children with asthma tend to have less moderate to vigorous activity;
- Children with mild asthma try to compensate the decreased intense activities with more light activities, where children with severe asthma do not compensate;
- Children with asthma have shorter activity bouts.

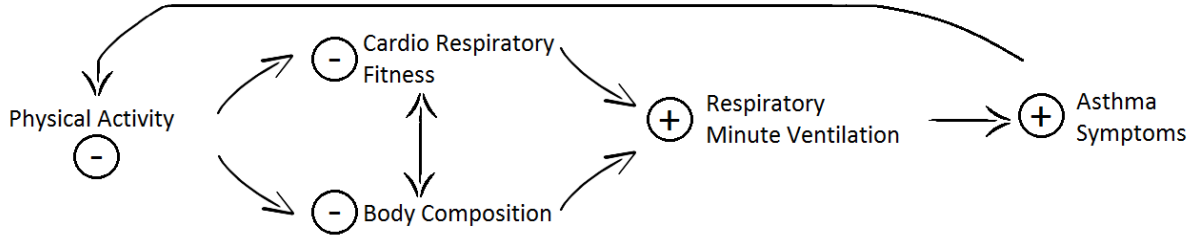


Figure 5: The dependency flowchart of physical activity, cardiorespiratory fitness, body composition and asthma symptoms: Less physical activity causes cardiorespiratory fitness and body composition to deteriorate, which results in an increase of oxygen use of the body. This is compensated with an increased respiratory minute ventilation, which causes more air to pass along the bronchial wall and therefore increase the susceptibility for asthma triggers. Consequently, this leads to more asthma symptoms which may have a negative effect on the physical activity. This makes the vicious downwards circle round.

PA is difficult to measure in children because children's activity is characteristically intermittent, consisting of frequent, short burst. [57,58] Therefore, accelerometers seem to be the best choice for capturing PA patterns in children. [57, 59, 60]

Accelerometer based activity tracking also provides information about activity during sleep [61, 62]. Asthmatic children often have nocturnal symptoms, due to the fluctuating daily response of asthma mediators like histamine and cortisol [63,64]. Sleep analyses could therefore be of great value to monitor nocturnal awakenings and sleep times [65, 66]. It is expected that children with difficulties sleeping are shifting their sleep rhythm to later bedtimes, often have more awakenings per night and therefore have less total sleep time.

Medication use Asthma medication can play a key role in the control of asthma. Roughly, all medications can be divided into two groups, controlling medication and reliever medication.

Short-acting beta-adrenoceptor agonists (SABAs), such as salbutamol, are reliever medications which induce bronchodilatation. They are the first line of treatment for asthma [67]. It can be administered whenever asthma symptoms are present or preventive just before a provocative event such as for example exercise.

There are several controller medications. Corticosteroids are used to reduce bronchial inflammation and mucus production. Long-acting beta-adrenoceptor agonists (LABAs) are used to reduce bronchoconstriction over a longer period. This is the reason this medicine was promoted as control therapy, but it is not. In contrast, LABAs actually seem to promote bronchial inflammation and asthma sensitivity. Therefore, it is advised to use LABAs in combination with corticosteroids [16]. Other regular used medications are leukotriene receptor antagonists, such as montelukast. They are preferred as an add-on therapy supplementary to corticosteroids in children [67].

A systemic review of Engelkes et al. [68] states that poor adherence to asthma medication results in more frequent asthma exacerbations and therefore decreased asthma control.

Medication usage can be monitored with smart inhalers. The smart inhaler sensor can register the dosage and the time of inhalation for research purposes. In this way the adherence to the controller medication and the use of reliever medication can be monitored.

2.2.2 Confounders

There are numerous factors which have an influence on the origin of asthma symptoms. The most important ones are explained below.

Intense exercise (Continuous sub-maximal) Exercise is a common trigger of bronchial hyperreactivity (BHR). This is the reason the ECT is used to diagnose asthma in children [29, 69]. This also implies that asthmatic children who are fully committed to exercise, will experience more symptoms, due to the repeated provocation. This is the reason PA is a confounder when monitoring asthma.

Viral infection A respiratory infection is another frequent trigger of BHR. The cold viruses affect the nose, throat and sometimes even the bronchial wall. In that case the viral infection can mediate the BHR pathway resulting in asthmatic symptoms [8,9]. Children who have a cold during the monitoring period could therefore have more symptoms. Viral infections can be monitored with blood tests or body temperature. Exhaled breath samples could give an indication of viral airway infection as well [70].

Cardiorespiratory fitness CRF is a confounder in measuring activity. In 2013 McNarry et al. [71] published a study regarding the relationship between body mass index (BMI), aerobic performance and asthma performed in a population-level cohort containing 20.577 pre-pubertal children. About 11% of the children in the population had asthma. They found that children with asthma were relatively more overweight and that CRF (independently of BMI) is significantly influenced by asthma. Wanrooij et al. [72] showed in a systemic review that physical exercise training increases pulmonary function and can be recommended in children with asthma.

The gold standard for measuring CRF is the maximal aerobic power test ($VO2_{max}$-test), but the most commonly used field tests involve distance-timed runs of varying length and graded-pace runs (i.e. the shuttle run test). [73] Furthermore, CRF can be estimated after performing submaximal exercise with HR monitoring [73]. The Physical Working Capacity-170 (PWC-170) test is the best known and most widely used test for this purpose [74]. The PWC-170 is often validated, with moderate to strong correlation to the $VO2_{max}$-test. Another widely known test for testing CRF is the Astrand-Rhyming test, making use of the Astrand Nomogram, which is also validated for children of 10-18 years old [75].

However, for the estimation of CRF in children no consensus was found. Rowland et al. [76] and Mahony et al. [77] showed that the PWC-170 only provides a crude estimate of maximal oxygen uptake ($VO2_{max}$) and should not be used to predict individual maximal aerobic power. Boreham et al. [78] also found that the PWC-170 is not significantly correlated to the $VO2_{max}$ in children. Other studies showed that PWC-170 is a valid method for assessing CRF, however it is only valid for children over the age of 11. [76,78,79]

Body composition Body composition is a confounder in measuring PA. Children with asthma are associated with a higher incidence of overweight than their healthy peers [14]. The causality question is hard to answer. It is not clear yet whether childhood asthma causes overweight (due to their reduced PA) or the other way around [80]. The prevailing hypothesis is that obese children are more prone to develop asthma, therefore body composition is a confounding variable.

In terms of obesity, the amount of visceral fat is an often used parameter. Measurements of visceral fat represent an important tool in assessing risk for the metabolic syndrome. Sideleva et al. showed that airway reactivity significantly relates to visceral fat expression in adults. [81]

Body composition can be assessed with multiple methods. The 4-side skinfold measurement is one of them. It is used to measure subcutaneous fat thickness at 4 sides of the body (biceps, triceps, subscapular and suprailiac), which strongly correlates with the total body fat [82,83]. The skinfold measurement is more a measure of excess body fat rather than excess weight therefore it does provide a more accurate assessment of body composition than BMI [83]. Another way to measure body composition is with a bio-impedance scale. This technique makes use of a small alternating current, which can measure extracellular resistance. Most researchers showed that the extracellular resistances correlate well with the 4-side skinfold measurement [84,85].

Allergen exposure Allergen exposure is also confounding the asthma symptoms. Children with for example an allergy for house dust mite often have more symptoms during the winter, where children with pollen-allergy often have more symptoms during spring or summer. The measurement period is therefore confounding the primary outcome of asthma control.

Allergen sensitivity can be tested with skin prick tests or IgE specific blood tests. [86] Furthermore, pollen-quantities in the air can be assessed.

Weather conditions One of the functions of the lung epithelium is conditioning the inhaled air. Therefore, cold and dry weather conditions induce an increased heat and water loss of the lungs, especially during PA due to the increased ventilation rate.

Evaporation of surfactant water on the respiratory mucosa is the way in which the lungs give the inspired air humidity. But this evaporation causes the mucosa to dry out, which results in an increased osmolarity of airway surfactant, which on his turn causes mast cell degranulation and subsequent releases of inflammatory mediators. These mediators interact with the smooth muscles of the bronchioles and vessels and causes them to contract (osmotic hypothesis) [69, 87]. In contrast to dry air, humid weather conditions could also trigger asthma symptoms by the inverse effect, resulting in bronchoconstriction due to stimulation by hypo-osmolar deposits in the airway. [88, 89]

Another mechanism which induces bronchoconstriction is stated as 'the thermal hypothesis'. It is stated that a rapid warming of the airways, after exercise in cold air, induces reactive hyperaemia. This leads to vascular engorgement and therefore a narrowing of the airways and vascular leakage. This hypothesis is confirmed by the fact that EIB often occurs after exercise. [69, 90, 91] Both theories are summarized in figure 6.

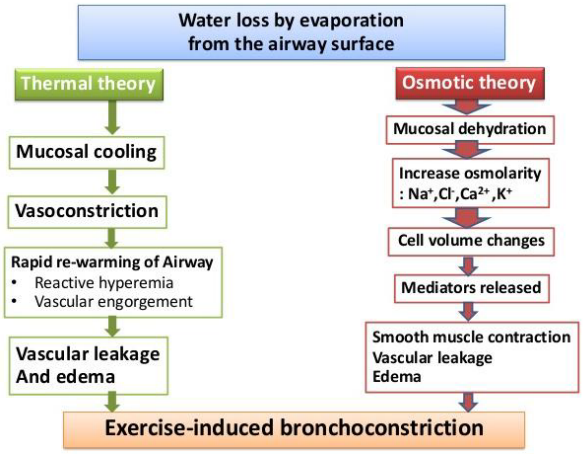


Figure 6: Pathogenic response during exercise induced bronchoconstriction. [92]

Makra et al. [93] shows that among all meteorological elements, temperature and relative humidity are most concerned in exacerbating asthma attacks. These weather conditions can be monitored with temperature and moisture sensors or assessed by meteorology institutes.

3 Methods

This study is part of the umbrella study: WEARCON. WEARCON (P16-27) was approved January 2017 by the Medical Ethical Committee of Twente (METC).

3.1 Study design

This study was described as a pilot study to determine which wearable devices would be the most useful for assessing asthma control. Several wearables were tested for their clinical usability and for the agreement in assessing asthma control with the currently used ECT test. A time overview of this research is given in figure 7.

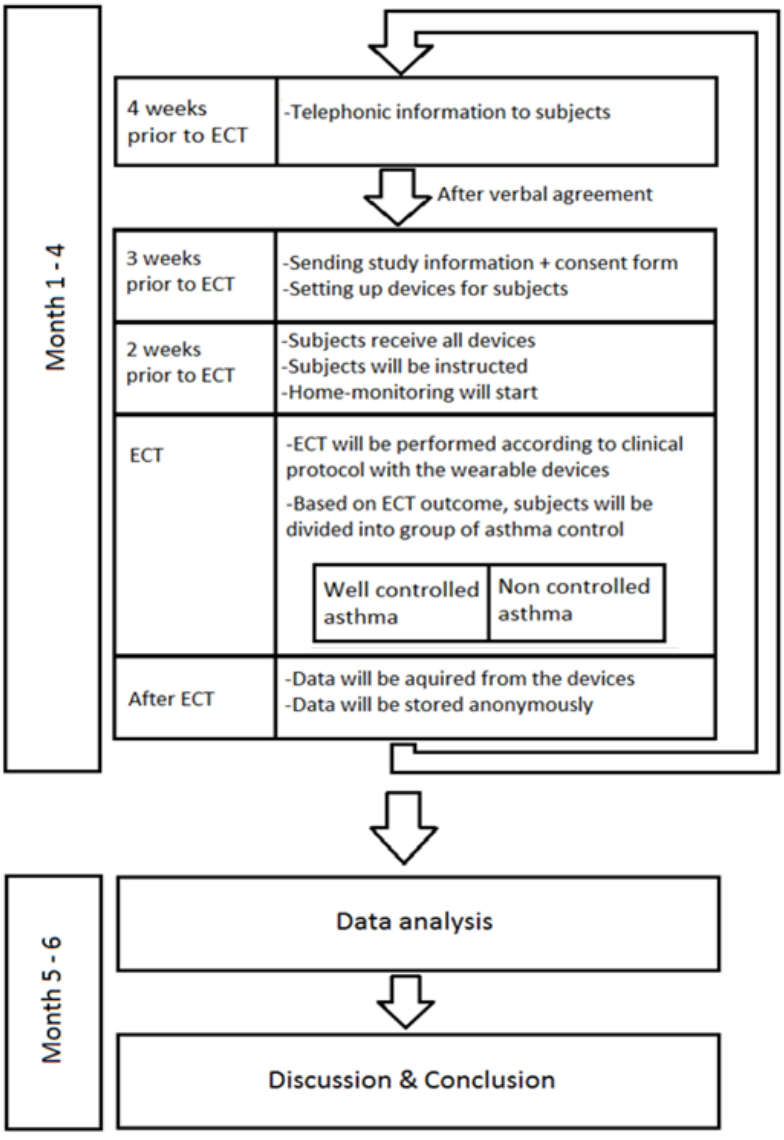


Figure 7: Study overview of the WEARCON study.

3.1.1 Inclusion

This study had a prospective observational design, in which 25 children, aging from 4 to 14 years old, with pediatrician diagnosed asthma, scheduled for an ECT, were asked to participate. The children and their parents were informed by telephone 4 weeks prior to the ECT. After verbal agreement, subjects received a study information letter (for both themselves and their parents) and a (parental) consent form (Appendix A.2).

3.1.2 Home-monitoring period

Two weeks prior to the ECT, subjects received all study devices, see figure 8. The children and their parents were instructed orally on how to attach the wearables and on how to use the portable spirometer. All wearables did not show interpretable data to the children to minimize the Hawthorne effect [60]. Furthermore, children and parents received instruction materials, so they could also access instructions at later times.

Figure 8: All the wearable devices: MIR Spirobank II smart spirometer (top left), Actigraph wGT3X-BT activity tracker (top right), Cohero Health smart inhalers (bottom left) and eMotion Faros 180° (bottom right).

The children were asked to continuously wear an Actigraph activity tracker during two weeks, including day and night and week- and weekend-days. Besides, an ECG device was used for two days within the monitoring period. A portable hand-held spirometer was occasionally used in case the patient experienced symptoms and pre- and post-PA. The children had to write down for which cause they used the spirometer. Furthermore, asthma controller and reliever medication were monitored with smart inhalers.

Besides, several confounding parameters were monitored. Weather and allergen conditions in the environment were assessed with hourly data of the KNMI and pollen-data of pollennieuws.nl.

Additionally, children were asked to fill in a questionnaire at the end of each week, containing about 40 questions about their asthma symptoms (C-ACT), quality of life (Pediatric Asthma Quality of Life Questionnaire (PAQLQ)) and their activity (Pediatric Activity Questionnaire-Childhood (PAQ-C)), see appendix A.5.

The home-monitoring period was chosen to be executed before the ECT, because the results of the ECT could lead to a change in medication. So, monitoring after the ECT could influence asthma control and therefore cause a systematic bias. Furthermore, a period of two weeks monitoring was expected to be sufficient for reliable asthma symptom monitoring and activity monitoring [94, 95].

3.1.3 Exercise challenge test

During an out-patient visit at the OCON in Hengelo, the ECT was performed according to international guidelines of the ATS [29]. Children below the age of eight were challenged with six minutes of jumping on a jumping-castle according to the described protocol of J. Driessen [15].

A thorough medical history was performed for medication adherence, PA and familiar occurrence of asthma in the first or second degree. During physical examination, attention was paid to the presence of allergic signs, such as Dannie-Morgan lines and Meyers' nasal crease. Furthermore, body composition was assessed with the four-side skinfold and CRF was assessed based on the results of the submaximal ECT test. The clinical research form that was used to capture the medical history, physical examination and other ECT data can be seen in appendix A.3.

Based on the outcome of the ECT test, subjects were categorized as controlled asthma versus non-controlled asthma groups. The children were categorized based on the judgment of the physician and based on LF data during the ECT. Figure 9 shows a graphical example of the LF parameters used to determine the outcome of the ECT. Non-controlled asthma was defined with having one of the following criteria:

- A subject with a FEV_1 decrease $> 13\%$ after exercise provocation, whilst on inhaled corticosteroids (ICS) or $> 20\%$ after exercise provocation without ICS;
- A subject with a FEV_1 lability $> 20\%$ after exercise provocation and subsequent reliever medication;
- Spirometer induced asthma [96]. Defined as a subject with a baseline decrease of $> 10\%$.

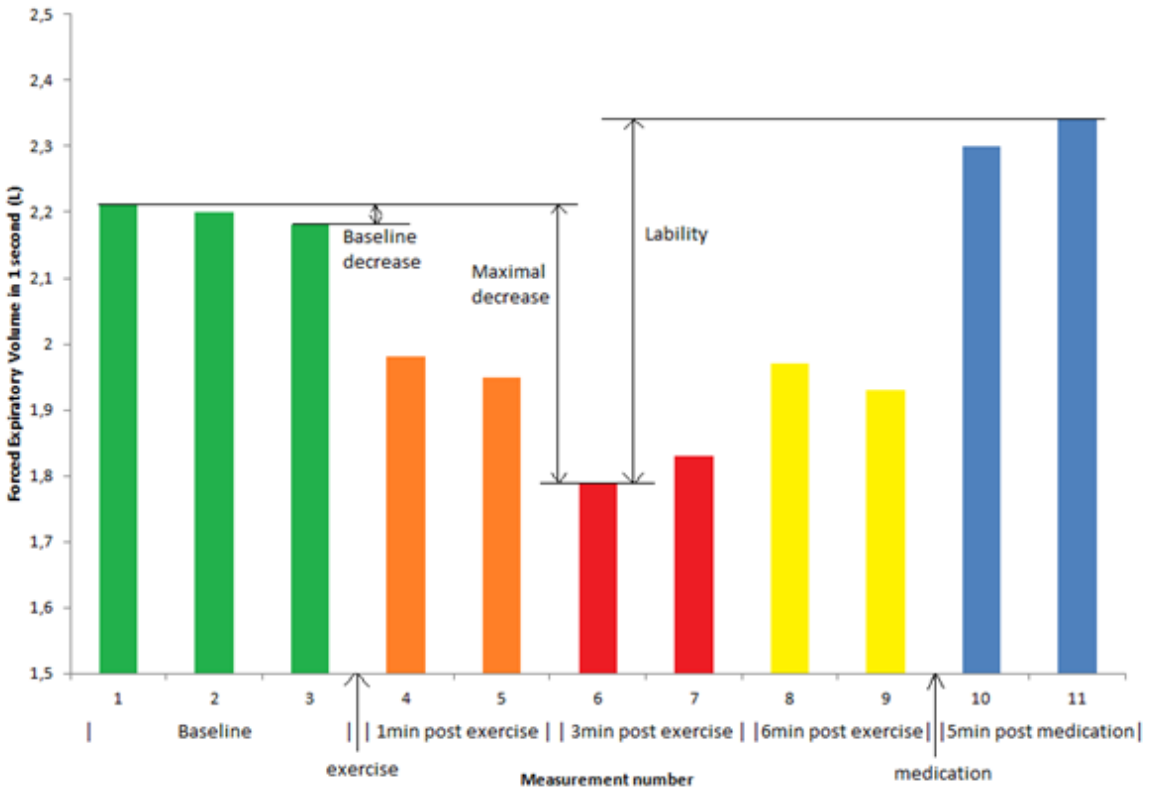


Figure 9: Overview of the lung function parameters: FEV_1 decrease and lability.

After the ECT all devices and questionnaires were collected. Data was acquired from the devices and stored anonymously for later data-analysis.

3.2 Study population

The population of this study consisted of all children with pediatric diagnosed asthma. In 2015 there were over 200.000 Dutch children between 0 and 14 years old with asthma [2]. From this population children (of all ethnicities and sexes) between the age of 4 and 14 years old, who were already scheduled for a clinical ECT, were approached. This age range contained a complete subset of schoolchildren, without the children aged 15 years or older. These older children were excluded because of the presence of pubertal changes regarding physiology, PA and behaviour in this early adolescent phase of life [97].

3.2.1 Inclusion criteria

In order to be eligible to participate in this study, a subject had to meet all of the following criteria:

- Children with pediatric based asthma;
- Children aged between 4 and 14 years old;
- Children that undergo an ECT.

3.2.2 Exclusion criteria

A potential subject who met any of the following criteria was excluded from participation in this study:

- Children with the inability to understand or speak Dutch. This also applies for the parents of all children below the age of 12;
- Children with a pacemaker, implantable cardioverter-defibrillator (ICD) or other electrical stimulation device;
- Children for whom it was not possible to wear all wearables. For example due to severe skin diseases or amputation of the arms etc.;
- Children with psychomotor retardation;
- Children with chronic diseases (other than asthma).

3.2.3 Sample size calculation

To find the best combination of wearables for the assessment of asthma control, a logistic multiple regression had to be used with the dependent categorical variable asthma control. It was tested whether asthma control can be described with the measured wearable parameters (determinants) and the contributing confounders. A. Agresti [98] and P. Peduzzi [99] suggested ten cases per event per group. This indicated that for a three parameter multiple regression 60 (30/30) subjects were required. Taking into account that an equal distribution between the controlled and non-controlled asthma groups was expected.

Including more subjects might led to a better estimation of asthma control, due to the fact that extra parameters could be included into the regression model. It was expected that three parameters would be sufficient to correlate well with asthma control. This was based on the already reasonable correlation of single parameters of spirometry [28], or activity patterns [23], with asthma control.

3.3 Materials

3.3.1 Wearables

For home-monitoring purposes several wearable devices were used (figure 8). These wearables were mainly chosen based on the availability, patient comfort and the quality of the product. Moreover, the devices had to be able to sample and store two weeks of data and to extract raw data. Extensive information reports of all wearable devices can be found in appendix A.4.

Spirobank spirometer To monitor bronchoconstriction interrupter and FOT were considered, as they do not require maximal effort of the patient. However, availability for home-monitoring purposes of these techniques fell short, therefore spirometry was selected. The MIR Spirobank II was chosen because of its small size and the reliability and accuracy of the MIR spirometers [100]. Furthermore, this device was able to measure $FEV_{0.5}$, extract raw flow-volume data and store more than 2 weeks of spirometer data.

Actigraph activity tracker Accelerometer based monitoring of activity is the predominant choice for objective activity assessment [57, 59, 60]. Multiple activity trackers of the consumer market (i.e. Fitbit, Polar, Garmin) were evaluated. However, these devices were often not intended to be used for research purposes, because of the lacking specifications (low sample frequency, not able export raw data, battery time of only days). The Actigraph was chosen because this device is made for research purposes only. The device is very suitable for home-monitoring as everything can be set-up before the monitoring period. It is an often used and validated device in literature (for both laboratory and clinical settings) [80, 101–108]. The device can store enough continuous data with a sample frequency of 100 Hz for two weeks of monitoring and the battery is sufficient for that period too. Furthermore, the Actigraph can be set-up for children. Finally, the device and software analyzes of the extra included sensors are able to monitor light intensity, sleep registration, position and weartime, which made this the most suitable device, available on the market, for this study. [109]

eMotion Faros ECG Respiratory distress could be assessed by various techniques. EMG was considered first because of the promising literature results on monitoring nocturnal asthma with chest wall electromyography [25] and detection of asthma exacerbations with surface EMG of the sterno cleido mastoid muscle [26]. However, EMG wearables that were available on the market could often not continuously record for a long period of time and needed to be in constant connection to a receiver device or PC. Additionally, many EMG devices are large and uncomfortable for children. Saturation and CO2 content devices were also evaluated, but these physiological effects are a late response to more severe asthma exacerbations and were therefore seen as less favorable in a home-monitoring setting of asthma. Therefore, HR and RR, which are seen as the primary parameters of physiological distress, were monitored. To minimize the burden of the children the choice was made to use one ECG device, from which the RR could be derived with ECG-derived respiration algorithms. Several ECG patches (i.e. Health patch, Zio Patch, PADSY Live ECG) were evaluated, but did not meet the required 1000 Hz sample frequency or raw data could not be exported. The eMotion Faros 180 was chosen because of its small size, feasibility and usefulness for research purposes.

Cohero Health smart inhalers Medication use was tracked with the Cohero Health smart inhaler. This device stores the timestamps of medication use [110]. The smart inhaler was favorable because of its design, which made it possible to pull the device over all sorts of doses aerosol inhalers, so that no medication had to be changed, while other devices (i.e. Adherium, 3M) require specific brands of asthma medication.

3.3.2 Questionnaires

Several questionnaires were used to monitor the patients perception of their asthma (C-ACT & PAQLQ) and their activity level (PAQ-C) and to investigate whether these questionnaires did have a predicting value to the actual measured asthma control or activity level. The questionnaires can be found in appendix A.5.

C-ACT The C-ACT is a simple questionnaire with the purpose to determine whether the child's asthma symptoms are well controlled. The C-ACT test is validated for children. [19] It consists of 4 questions for the child (scored 0 to 3) and 3 for the parents (scored 0 to 5). The scores were added up. A score below 19 was classified as non-controlled asthma, a score equal or above 20 was classified as controlled asthma.

PAQLQ The PAQLQ was developed to measure the functional problems (physical, emotional and social) that are most troublesome to children with asthma. The PAQLQ proved to detect quality of life changes in asthmatic children with strong significance [20]. An average PAQLQ-score and separated symptom, activity and social scores were calculated for the PAQLQ.

PAQ-C The PAQ-C was used to recall PA of the last 7 days. It was developed to assess general levels of PA throughout the elementary school till 14 years of age. The PAQ-C provided a summary of PA score derived from nine items, each scored on a 5-point scale. The average PAQ-C score was used as a marker for PA levels. Evidence was provided that supported the PAQ-C as a reliable and valid measure of general PA levels in children during the school year [111].

3.4 Statistical analysis

All continuously measured signals had to be at least 75% complete. Otherwise, the parameter(s) calculated from this signal were registered as missing data. Furthermore, calculated cumulative parameters, such as total active minutes, were corrected for the amount of missing signal (only when it is more than 75% complete).

Missing data techniques such as expectation maximization were not used, due to the introduction of biased estimates [112]. Therefore, missing data was handled with pairwise deletion.

3.4.1 Wearable parameters

The primary endpoint of this study is asthma control. An univariate analysis was performed with SPSS statistics (IBM Corp. Released 2013, Version 22.0) to find significant differences of parameter values between the asthma control groups. First, normality of the distribution was verified with the Shapiro-Wilks test. The Levene's test for equality of variances was used to determine if the variables had equal variances. If not the Mann-Whitney U test was used for the univariate analysis, otherwise a statistic unpaired T-test was used. A Chi-square test was used for ordinal variables and Fisher's exact test for binary variables. Variables with a p-value$<$0.10 are taken into consideration for the future analysis in the WEARCON study. A p-value$<$0.05 was considered as significant different. The wearable parameters for the univariate analyses are shown in table 1 and described below.

Spirometry The most used spirometer parameter for obstructive lung diseases is the forced expiratory volume in 1 second (FEV_1) [113]. The average, minimal and difference between the maximal and minimal FEV_1 were chosen as parameters to resemble the baseline variation in LF. Furthermore, FEV_1 values after exercise and during symptoms were used to resemble bronchial hyperresponsiveness. The Tiffaneau index (FEV_1/FVC) is another index of obstruction, however this parameter requires both a maximal effort in the first part of the blow and full expiration to resemble the forced vital capacity (FVC), which makes this parameter prone to measurement errors. Therefore, FEV_1 was chosen as the primary outcome measure. The amount of symptom LFs might also be a parameter which could indicate the level of asthma control. Additionally, the forced expiratory flow between 25 and 75 percent of the FVC (FEF_{25-75}) is a parameter that provides information about the reaction in the small airways [114, 115]. An advantage of this parameter is that it is less dependent of the maximal peak effort, however it is dependent on the volume of the forced spirometer test [115]. Finally, the peak expiratory flow (PEF) was used as LF parameter, because peakflow measurements are often used for both clinical and home-monitoring purposes [36].

Activity The activity pattern in children can be described with a variety of parameters. Often used parameters are the total amount of activities (subdivided by the intensity level) and the average duration of activity bouts [57, 60]. Previous research showed that next to these parameters the boutlength distribution also showed significant differences between different severities of asthma [56]. Besides these proven activity parameters, the amount of prolonged activities was used as a parameter. Because it was hypothesized that asthmatic children tend to avoid long lasting activities. The Actigraph has extra sensors which made it possible to also investigate the time being outside and the body position. These parameters could provide information whether non-controlled asthmatic children tend to be less outside and show for example less time in standing position.

Sleep The Actigraph was able to measure sleep parameters as well [61]. Previous studies showed with the use of actigraphy that asthmatic children have less sleep time, less sleep quality and an increased sleep latency [65, 66]. Therefore, the sleep efficiency and the minutes awake per night were used to test sleep quality. The total sleep time and the total time in bed were used to describe sleep time. The average time to bed was used as an indirect measure of sleep latency, because reliable direct sleep latency values for children could not be provided by the used version of Actigraph analysis software.

Heart rate and respiratory rate An increased HR and RR are important parameters in acute asthma care in children [95]. In a home-monitoring situation average day and nighttime HR and RR may provide an indication of long term respiratory distress. Minimal heart rate reserve and the percentage of time in vigorous activity were used as parameters to investigate whether non-controlled asthmatic

children tend to avoid intense PA. Finally, the recovery time of the HR and RR after intense PA were used as parameters. It was hypothesized that these parameters will be increased in non-controlled asthmatic children, due to the physiological distress after exercise provocation of their asthma. Heart rate recovery is a parameter which is described in literature for evaluation of physical fitness [116] and can also be used to identify parasympathetic recovery effects [117]. Therefore, this parameter may be used to differentiate between normal parasympathetic recovery and sympathetic recovery in times of respiratory distress [118].

Medication use Medication use is one of the key questions used in pediatric asthma consultation. GINA states that high SABA use is a risk factor for non-controlled asthma [16]. Therefore, the amount of SABA inhalations is used as a test parameter. A systemic review of Engelkes et al. [68] states that poor adherence to asthma medication results in more frequent asthma exacerbations and therefore decreased asthma control. This is the reason why the amount of controller medication and the medication adherence are used as parameters.

Combined parameters Besides all the single-device derived parameters, additional multi-device parameters may be used to differentiate between controlled and non-controlled asthma. The combination of activity data and medication use could provide information of activity induced reliever use and protective reliever use. Both are hypothesized to be increased in non-controlled asthma. Medication data can also be combined with ECG data, to monitor the effect of reliever medication on the RR, because asthma patients use reliever medication in periods of respiratory distress. Reliever medication reverses the bronchoconstricted effect of an asthma response and therefore a decrease in RR was expected [67]. Furthermore, sleep and activity data could provide information of the sleep restlessness in the early morning, which is expected to be increased in non-controlled asthma based on the altered circadian rhythm of asthma mediators [63, 64, 119]. Activity data combined with ECG data provides opportunities for new parameters as well. The average RR in periods without any activity was used as a parameter to indicate the respiratory effort required in non-active periods, which may correlate to the chronic inflammation of the airways in non-controlled asthma patients. Lastly, the amount of physiological distress moments was thought to correlate to the level of asthma control [42].

3.4.2 Questionnaires

The patients perception of asthma control was scored with questionnaires. The C-ACT and PAQLQ scores were tested with an unpaired statistical T-test (or in case of non-normal distribution a Mann-Whitney U test) for differences between the controlled asthma group and the non-controlled asthma group. A p-value$<$0.05 was considered as significant different.

The patients perception of their activity level was scored with the PAQ-C questionnaire. The PAQ-C score was tested with simple linear regression for the correlation with the measured activity levels of the Actigraph. A R^2 larger than 0.8 was considered as well-correlated [120].

3.4.3 Confounders

CRF, body composition, medication adherence and allergen & weather exposure were taken into account as confounders of asthma control. Descriptive statistics, non-parametric Mann-Whitney U tests and univariate linear regression were used to describe the difference between the asthma groups or the correlation to other variables.

Table 1: The wearable parameters.

Spirometry
• FEV_1 baseline • Minimal FEV_1 baseline • Maximal difference in baseline FEV_1 • FEV_1 decrease after exercise • FEV_1 decrease during symptoms • Amount of symptom lung functions • PEF baseline • FEF_{25-75} baseline
Activity
• Time outside • Percentage of standing time • Sedentary activity • Light activity • Moderate activity • Vigorous activity • Total activity • Average boutlength • Amount of prolonged activities • Boutlength distribution
Sleep
• Average time to bed • Minutes awake per night • Sleep efficiency • Total time in bed • Total sleep time
Heart rate and respiratory rate
• Average heart rate during daytime • Average heart rate during nighttime • Average respiratory rate during daytime • Average respiratory rate during nighttime • Percentage of vigorous heart rate • Heart rate recovery time • Respiratory rate recovery time • Heart rate reserve
Medication use
• Amount of used reliever medication • Amount of used controller medication • Medication adherence
Combined parameters
• Restlessness in the early morning • Effect of reliever medication on the respiratory rate • Average respiratory rate during non-active periods • Amount of physiological distress • Amount of activity induced reliever medication use • Amount of protective reliever medication use

3.5 Data acquisition and preprocessing

In general the acquired data of the wearables was extracted from the devices with the associated software, preprocessed in the software and finally analyzed in MATLAB (The MathWorks Inc, version R2016a).

Spirobank spirometer All spirometer blows were classified as test, symptom, before exercise or after exercise, based on a list the children kept updated during the measurement period.

All non-correct spirometer measurements were excluded, by first using a self-made MATLAB algorithm to exclude spirometer data that did not met the below described flow-volume criteria, which were based on the European Respiratory Society (ERS) criteria [113]:

1. Extrapolated volume (EV) $<$150 mL and $<$5% of the FVC;
2. Forced expiratory time (FET) at least 1 second;
3. No cough, max 5% of the peakflow deviation of peaks;
4. First peak in the flow-volume curve is the maximal peak;
5. No more than 10 oscillations were seen;
6. No premature ending (steep fall at end of the flow/volume curve). No more than 10% of peakflow decrease of the last samples before crossing zero flow line.

Afterwards, all spirometer blows were manually checked for realistic curve shapes and FEV_1 values.

Actigraph activity tracker The Actigraph data was measured with an one second epoch at the wrist location. This location was chosen because it takes all kind of activities into account which is useful for child activities.
During preprocessing the following steps were performed:

- Defining non-wear periods: The weartime was based on an internal wearsensor. A metallic plate at the back of the watch detects skin contact. Furthermore, Troiane (2007) weartime validation algorithms were used to confirm non-weartime periods [109]. Settings of this algorithm were; a minimum length of 20 minutes, the use of vector magnitude (Vm) and mark sleep period as weartime. The wearsensor data was decisive in determining the periods of non-wear.
- Activity scoring: All non-wear periods were excluded from the activity scoring. Raw accelerometry data was converted to counts. The counts contain information about the frequency and amplitude of the accelerometry data. Activity Vm counts (a combination of the counts of all 3 axis) were stored per epoch. The Vm was chosen because at the wrist location it is considered as the most accurate estimation of activity levels. Furthermore, children are not only very active in straight-lining direction walking/running, but also in other activities dancing, jumping and playing, which made the Vm the superior choice of activity monitoring.
- Sleep scoring: All sleep parameters were derived with the Cole-Kripke sleep algorithm [61]. This algorithm used 60 second epochs. Therefore, the activity data had to be reintegrated only for this analyses.

eMotion Faros ECG ECG data (1000 Hz) was acquired from the eMotion Faros device. The ECG signal was preprocessed to get a continuous HR and respiratory signal. This preprocessing was performed with MATLAB scripts made in collaboration with Technical Medicine student M. Boonstra [121]. This ECG-derived respiration script showed an average correlation coefficient of 69% with a reference flow method and a sensitivity of at least 76% during high intensity exercise. The framework of this algorithm is displayed in figure 10.

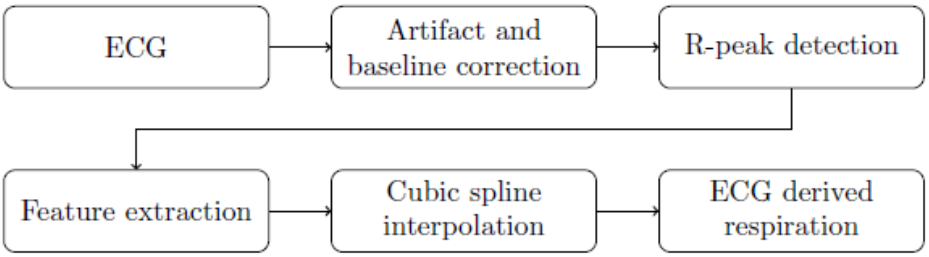


Figure 10: Framework ECG preprocessing.

Artifact and baseline correction: First, artifacts and baseline wanders were removed by filtering the signal with a FIR filter with a Kaiser window using cutoff frequencies of 0.45 and 39 Hz. This filter-setting is based on the standard ECG monitoring bandpass filter from 0.5 to 40 Hz. [122]

R-peak detection: Thereafter, R-peaks were detected using the squared second derivative signal to detect fast large amplitude changes in the ECG. A threshold of 40% of the 99th quantile of the squared second derivative was used for the determination of R-peaks, assuming that the amount of error with fast fluctuations in the recording is 1%. Thereafter, a sliding window of 6.4 seconds was used to distinguish noisy intervals from regular heart beats, by using the mean peak amplitude and interval to estimate the location of the next peak. In the last step, a small window around the detected QRS complexes was used to determine the precise location and amplitude of the R- and S-peak. As a final control measure, all R- and S-peaks with considerable deviation from the median amplitude of the ECG were excluded. The HR was derived of the R-peak locations.

Feature extraction: The RS amplitude has been determined by subtracting the S-amplitude from the R-amplitude of the same QRS complex.

Cubic spline interpolation: The respiratory curve based on the RS-amplitude was established by using cubic spline interpolation (MATLAB function spline). This function interpolated the signal to construct a respiratory signal with 50 Hz. This sampling rate was chosen because of the best trade off between enough data points per respiration (max. 0.5 Hz) but excluding small fluctuations in the respiratory signal, so that the respiratory signal resulted in a smooth curve. More RR monitors use this sample frequency to present the respiratory signal [123].

Cohero Health smart inhalers Data of the smart inhalers was stored in the BreathSmart application. The data was acquired from the Cohero Health server and stored with date and time stamps.

3.6 Data analysis

After preprocessing the data, self-made MATLAB scripts were used to analyze the data in a way that previous described parameters (table 1) could be calculated.

3.6.1 Wearable parameters

Spirometry Average baseline FEV_1 (% of predicted) was calculated by averaging all test and before exercise FEV_1 measurements. From the same measurements the minimal FEV_1 was taken to get the minimal baseline FEV_1 (% of predicted). The maximal difference in baseline FEV_1 was calculated by subtracting the minimal FEV_1 baseline of the maximal FEV_1 baseline. For this parameter at least two baseline spirometer measurements had to be available.

The FEV_1 decrease after exercise was calculated by averaging all percentages decrease between pre- and post-exercise measurements. When a pre- or post-measurement was missing this specific measurement was not taken into account. The same method was used to calculate the decrease in FEV_1 during symptoms. The decrease was then calculated from the average baseline FEV_1.

Furthermore, the amount of spirometer blows which were classified as symptom LFs were added to get the amount of symptom LFs. The PEF and FEF_{25-75} of all baseline LFs were averaged to calculate the last spirometer parameters.

Activity The time being outside was derived from the lux sensor of the Actigraph. All epochs with a lux intensity of 500 or more were classified as outside. This cut-off was chosen to include cloudy days and exclude bright light at school or in house [124]. From here a percentage of the outsidetime in respect to the total weartime was calculated.

The Actigraph uses an internal algorithm to analyze wearposition. When activity exceeds six counts per second, the user is assumed to be standing due to the activity values and thus the inclination angles are ignored. Otherwise, an angle smaller than 17° is considered standing, an angle between 17° and 65° is considered sitting, and an angle of more than 65° is considered lying. This algorithm is based on hip placement. Wrist placement is therefore less accurate, especially in the sitting and lying position, due to the variability in wrist position during sitting/lying. Therefore, it was chosen to only analyze standing position. The Actigraph analyzed all epochs. From here a percentage of the total weartime was calculated to get the percentage of standing time.

By preprocessing the activity data every epoch was scored with an amount of counts. Ten one-second-epochs were averaged to resemble small activity bouts. If the average counts were less than 61 counts per second of the Vm this bout was classified as sedentary activity, between 61-164 counts per second as light activity, between 164-394 counts per second as moderate activity and above 394 counts per second as vigorous activity. All activities from at least light intensity were summed to get the total activity. [125]

The average activity boutlength of moderate to vigorous activities was calculated by temporarily setting all epochs below 164 to 0. A consecutive serie of at least five 0-epochs (5 seconds) was seen as an interruption of the moderate to vigorous activity. Thereafter, the length of all moderate to vigorous activity series were averaged.

The activity length distribution is a parameter that differs between the amount of short activities and the amount of long activities. This type of distribution is very well comprised by the Weibull scale parameter, see figure 11. Evering et al. [126] used the distribution of the amounts of the activity bouts lengths as an outcome parameter in patients with chronic fatigue syndrome. Therefore, for this study the Weibull distribution scale parameter was calculated in MATLAB [127].

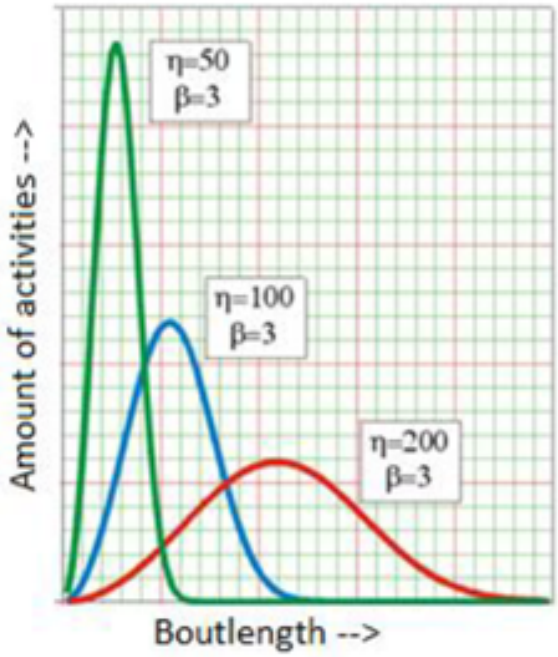


Figure 11: Example of several activity distributions and its effect on the Weibull distribution: a higher scale parameter (η) results in a stretched and shrinked distribution graph. The shape parameter (β) is constant in this graph. It has an effect on the shape of the distribution, for example the skewness and kurtosis.

Sleep The sleep parameters were derived with the Cole-Kripke sleep algorithm. The algorithm provided all sleep parameters (average time to bed, minutes awake per night, sleep efficiency, total time in bed and total sleep time per night) [61]. All these parameters were averaged over the two weeks of measurement.

Heart rate and respiratory rate The HR signal over the 2 days of weartime was analyzed manually. The continuous HR and RR (derived by preprocessing the ECG data) were plotted. Thereafter, a serie of daytime and nighttime signal of at least 4 hours was selected to calculate the average day and nighttime HR and RR.

Furthermore, the end of an intense activity was selected and the graph was zoomed in at this point. Thereafter, the point where the HR and RR were stabilized was selected as can be seen in figure 12. The time between the end of the activity and this point resulted in the heart rate recovery time (HRRT) and the respiratory rate recovery time (RRRT).

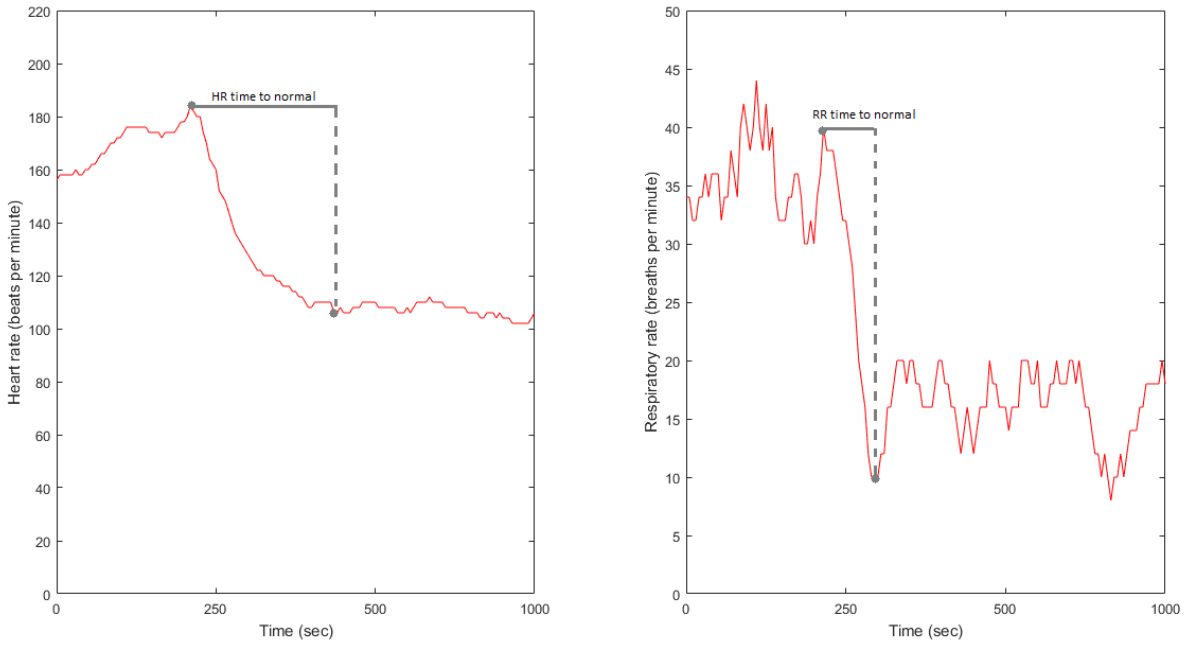


Figure 12: Selection example of the heart rate and respiratory rate recovery times: These parameters were calculated by selecting the end of an activity and the moment that the heart rate or respiratory rate reached its normal value. The difference in time between these points were described as the recovery times.

Besides, the percentage of vigorous HR was calculated by summing all HR values above 70% of the maximal HR of the child and divide it by the total weartime of the ECG device. The HR reserve was calculated by taking the maximal reached HR and subtract it together with the age of 220.

Medication use For the medication parameters all reliever puffs and controller puffs were simply added to get the total amount of reliever and controller medication used. The medication adherence was calculated by dividing the used controller puffs by the expected controller use, based on the prescribed medication by the pediatrician.

Combined parameters The restlessness in the early morning was defined as the average activity level (Vm) in a period 3 hours prior to the average outbedtime till 2 hours prior to the average outbedtime. The average outbedtime is rounded downwards to the whole hour. The 2 hours space between the end of the endnight period and the average outsidetime is used as a security window, so that during mornings where the child is standing up early no activity was taken into account. Furthermore, this timeframe was based on the optimal nighttime response of asthma mediators like histamine and cortisol [119,128]. There was chosen for a personal average outbedtime (instead of a daily varying outbedtime) because this parameter is expected to show differences between asthma control based on the nighttime

response of the asthma mediator levels. These asthma mediators are dependent on the person specific day-night rhythm and therefore not fluctuating daily.

The effect of reliever medication on the RR was assessed by taking the difference of the RR between after and before reliever medication usage. The RR was averaged in a period of 5 minutes before and after reliever medication use.

The average RR during non-active periods was assessed by averaging all RR samples wherein no activity was seen. No activity was defined as less than 61 counts per second over a 5 second average. So that incidental movements were not recognized as activity. Each non-active period of more than 3 minutes, in the period of ECG measurements, was used for analysis. This choice was made to only exclude periods which were influenced by surrounding activity. The first 2 minutes of each non-active period were not taken into account, due to the possible confounding effect of previous activity. The mean RR was acquired from the remaining non-active periods. The mean was taken as a mean of all non-wear periods, not as the mean of all bouts. This choice was made because in this way the effect of a non-active-but-high-breathing-rate period on the outcome is increased.

The amount of physiological stress periods was defined as the number of 5-second-periods wherein the HR and RR were above the upper-bound of the normal ranges (from the reference guidelines of PALS 2015 [129]), without moderate to vigorous activity. All HR and RR points were analyzed, resulting in a data set of only sample points wherein physiological stress occurs. The activity level (Vm) was averaged over 30 seconds prior to these sample point. When this average activity was more than 82 counts/sec, it was defined as an active period and not taken into account as physiological stress. 82 Counts/sec was chosen to resemble a moderate to vigorous activity during half of the period. A time window of 30 seconds was chosen to be an optimum between the long lasting effect of long activities and the immediate effect of short intense activities just seconds before the sample points. Finally, only sample periods of at least 1 minute were taken into account to exclude short rises in HR and RR, measurement errors, etc. To prevent the exclusion of physiological stress periods, which have a few samples that do not fit within the pre-described criteria, the periods were moving averaged over 1 minute. This moving average parameter had to consist of at least 2/3 of physiological distress periods, otherwise these periods were excluded. All remaining sample points were added to the total number of 5-second periods of physiological distress over the total ECG measurement period.

The amount of activity induced reliever medication use was defined as all reliever medication usages after an active period. The amount of preventive reliever medication use was defined as all reliever medication usages before an active period. An active period was defined as a 30 minutes period with on average at least 109 counts per second, resembling 2/3 of the time at least moderate activity.

3.6.2 Confounders

Body composition Body composition was assessed with the sum of the 4-side skinfolds (thickness of skinfold in mm on the biceps, triceps, subscapular and supra-iliac location) [82, 83].

To assess an estimation of the amount of visceral fat the relative proportion of truncal fat (subscapular and supra-iliac) to total fat (sum of skinfolds) was used [130].

Cardio respiratory fitness CRF was estimated with the modification of the Astrand-Rhyming test. This modification of the predicting equation for maximal oxygen uptake ($VO2_{max}$) was made by Buono et al. [75] and can be seen in equation 3.1. The power of the running exercise is calculated with a physics approach of the running power (equation 3.2) and the influence of the slope (equation 3.3).

$$VO2_{max} = 100 * \frac{(0.00212 * power * 6.12 + 0.299)}{(0.769 * HR - 48.5)} * 0.66 - 0.028 * age + 0.026 * weight + 0.166 \quad (3.1)$$

$$Runningpower(watt) = 981(watt/kg/km) * \frac{speed(km/h)}{3600} * weight(kg) \quad (3.2)$$

$$Inclinationpower(watt) = \frac{Inclination(\%)}{100} * \frac{speed(km/h)}{3.6} * 9.81(m/s^2) * weight(kg) \quad (3.3)$$

Allergen and weather exposure Local weather data was assessed from the data centre of the KNMI. Hourly data of relative humidity (%) and temperature (° Celcius) were used. Daily pollen-symptom scores were assessed from pollennieuws.nl. Both datasets were compared with the outsidetime, measured with the Actigraph (LUX>500).

The cold exposure was calculated by multiplying the percentage of outsidetime by the temperature score. The temperature score was calculated by (1-temp/15), where all scores below 0 were set to zero. In this way temperatures below 15° Celcius were taken into account as cold exposure.

In order to assess the dry air exposure the percentage of outsidetime is multiplied by the average air humidity for every hour. Thirdly, pollen-exposure is calculated by multiplying the average daily pollen-symptom score (1 to 10) by the percentage of outsidetime each day.

4 Results

4.1 Overview of a single patient

Figure 13 shows an overview of all wearable data of a single child. The upper graph contains information about the LF and the inhaler use over time. The FEV_1 of all performed spirometer measurements is plotted. The background color reveals the interpretation of those measurements. Green indicates a FEV_1 of more than 90% of predicted, yellow between 70% and 90% and red a FEV_1 of less than 70%. The inhaler use is plotted with the colored squares. Blue squares indicate a reliever inhaler was used. The purple squares indicate a controller inhaler was used.

The second graph contains activity, HR, RR and sleep data. The black line shows the accelerometer derived activity counts. The black dotted horizontal lines indicate, from bottom to top, the transition of sedentary to light, light to moderate and moderate to vigorous activity. The blue and red line indicate respectively HR and RR per minute. Lastly, the green lines at the bottom of the graph indicate the periods when the subject is asleep.

The third graph is an overview-graph of the conditions the subject encountered. The dark blue graph is the daily pollen-score. The light blue and purple lines are respectively the outside humidity and temperature. The yellow bars at the bottom of the graph indicate whether the patient was outside.

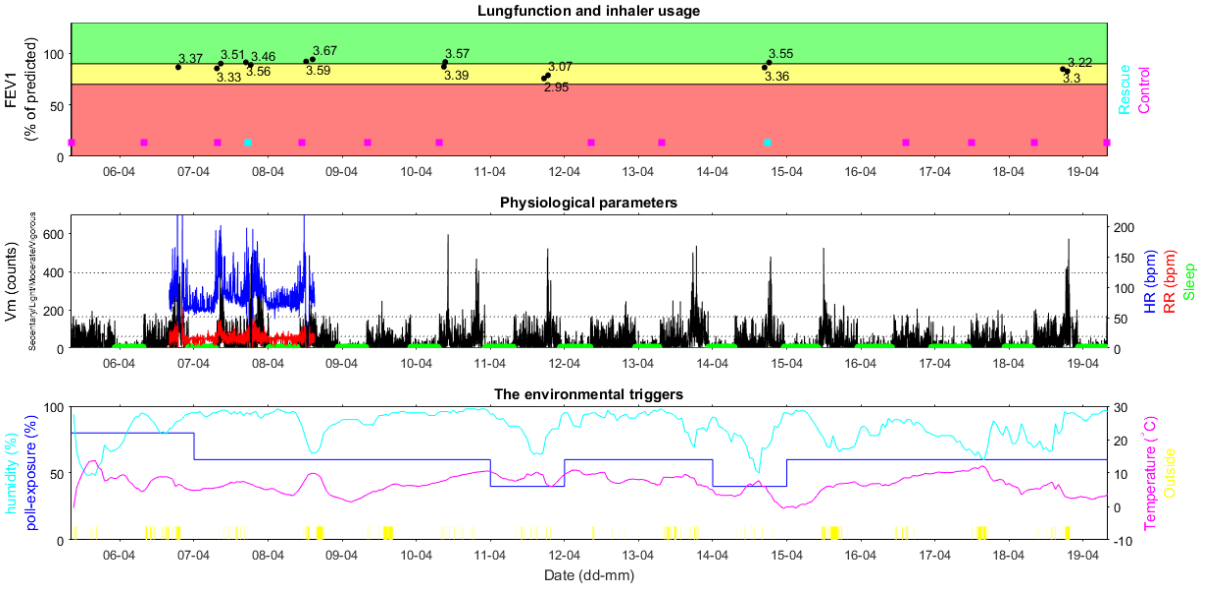


Figure 13: Overview plot of the 2 weeks monitoring data of all wearable devices worn by subject 11.

4.2 Baseline characteristics

Table 2 shows an overview of the baseline characteristics of all 25 subjects. A quick view reveals that most of the subjects were boys (84%), 80% of the subjects used controller medication and that 15 of the 22 patients, with a previously executed allergy test, have one or more inhalation allergies.

*Table 2: Baseline characteristics per subject: *BMI category is based on the age dependent BMI range for children [131], #Missing data.*

Subject	Gender	Age (years)	Weight (kg)	Length (cm)	BMI (kg/m^2)	BMI category*	Control medication	Inhalation allergies
1	m	6	24	127	14.9	2	no	yes
2	m	6	21	117	15.3	2	yes	#
3	m	11	38	161	14.7	1	yes	no
4	m	5	20	112	15.9	2	yes	yes
5	m	6	24	116	17.8	3	no	yes
6	m	9	35	139	18.1	2	yes	yes
7	m	12	48	144	23.1	3	yes	yes
8	m	11	40	152	17.3	2	yes	yes
9	m	12	53	163	19.9	2	yes	#
10	f	9	36	133	20.4	3	yes	yes
11	m	13	75	177	23.9	3	yes	yes
12	m	10	39	151	17.1	2	yes	yes
13	m	10	35	130	20.7	3	no	no
14	m	12	43	146	20.2	2	yes	yes
15	m	5	22	116	16.3	2	yes	yes
16	m	5	23	117	16.8	2	yes	no
17	f	10	43	141	21.6	3	yes	yes
18	m	10	37	150	16.4	2	yes	yes
19	m	11	46	145	21.9	3	no	no
20	m	9	38	142	18.8	2	yes	yes
21	f	6	25	123	16.5	2	yes	no
22	m	9	30	137	16.0	2	yes	no
23	f	13	44	158	17.6	2	no	no
24	m	10	37	147	17.1	2	yes	#
25	m	5	18	112	14.3	2	yes	yes
Mean (SD)	**0.84**	**9.0 (2.6)**	**36 (12)**	**138 (17)**	**18.1 (2.6)**	**2.2 (0.5)**	**0.8**	**0.68**

Table 3 shows the baseline characteristics of the control group versus the non-control group. The physician based definition of asthma control results in significant differences of age, weight and length between the control groups. The mean age difference between the groups is 2.8 years (p=0.02).

Table 3: Physician based baseline characteristics of the control group versus the non-control group. One subject (nr.15) was not tested with an ECT, therefore he could not be classified as controlled or non-controlled.

	Control (n = 15)		Non-control (n = 9)		
	Mean	**SD**	**Mean**	**SD**	**p-value**
Age	10.2	2.3	7.4	2.2	0.02
Gender	0.93	0.26	0.67	0.50	0.11
Weight	40.6	12.6	29.2	9.5	0.03
Length	145.1	16.5	129.2	14.7	0.04
BMI	18.9	2.7	17.0	2.5	0.07
BMI category	2.3	0.6	2.2	0.4	0.80
Control medication	0.73	0.46	0.89	0.33	0.40
Atopy (n=14 vs n=7)	0.57	0.51	0.75	0.46	0.44

4.3 Wearable parameters

4.3.1 Spirometry

The spirometer at home was used by 21 of the 25 (84%) children. The other four stated that they forgot to use the spirometer and were excluded from the spirometer results. On average 66% of those spirometer measurements were classified as correctly blown according to the previous described quality criteria [113].

Figure 14 shows the percentage of correctly blown spirometer curves versus the age of the children. An average increase of 13% in correctly blown curves can be seen over the age range from 5 to 13 years old. However, this linear regression has a R^2 of 0.02 and showed no significant relation (p=0.53).

Figure 16 illustrates the relation of the home-measured baseline FEV_1 and the baseline FEV_1 at the start of the ECT at the OCON. This correlation has a substantial coefficient of determination (R^2) of 0.67.

The distribution of all spirometer parameters within the asthma groups are displayed in box plots, which can be seen in figure 15. The figure shows lower median values of all LF parameters in the non-controlled asthma group, except the amount of symptom LFs and the FEV_1 decrease during symptoms. Significant inequality between the physician based asthma groups can be seen in the maximal difference in baseline FEV_1 (p=0.03).

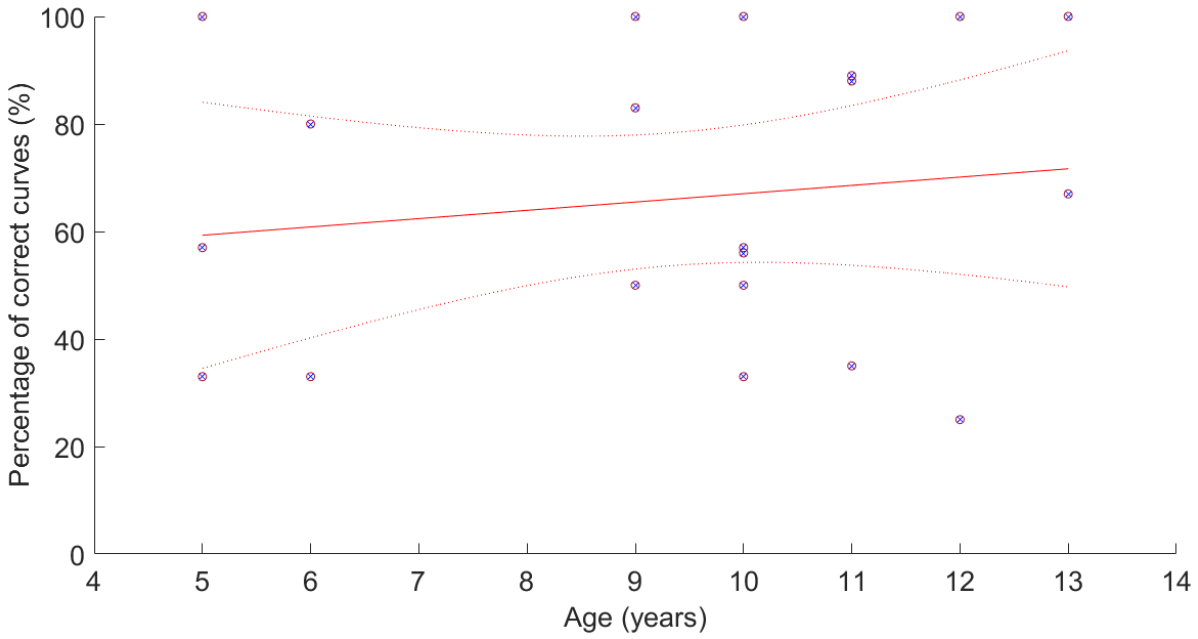
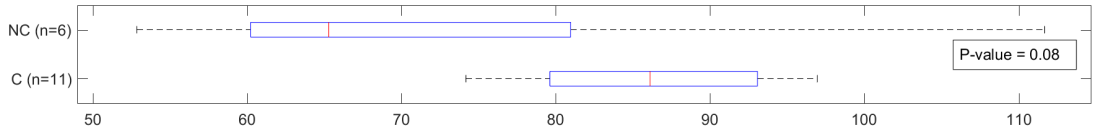
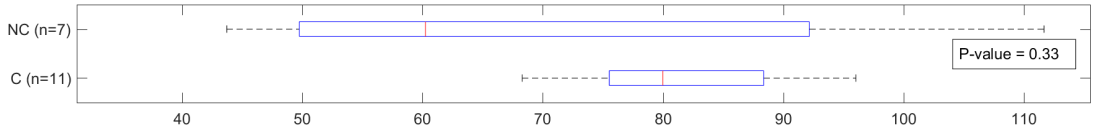


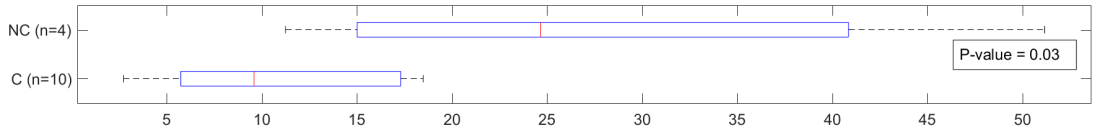
Figure 14: Percentage of correctly blown spirometer curves versus the age of the children with a linear regression fit and its 95% confidence bounds (R^2=0.02).



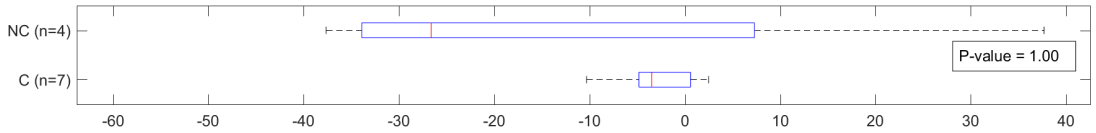
(a) FEV_1 baseline (% of predicted)



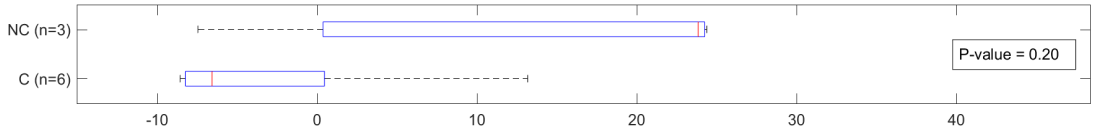
(b) Minimal FEV_1 baseline (% of predicted)



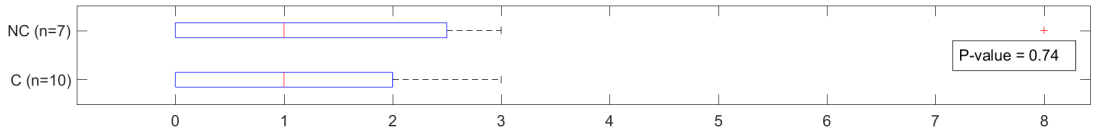
(c) Maximal difference in baseline FEV_1 (% of predicted)



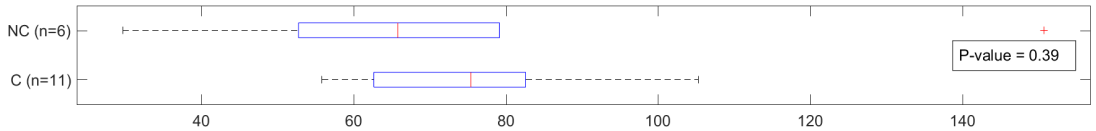
(d) FEV_1 decrease after exercise (%)



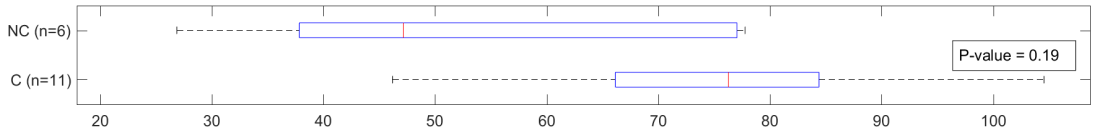
(e) FEV_1 decrease during symptoms (%)



(f) Amount of symptom lung functions



(g) PEF baseline (% of predicted)



(h) FEF_{25-75} baseline (% of predicted)

Figure 15: Spirometry results: Box plots with medians (red line), interquartile ranges (blue box), extremes (striped line), outliers (red plus sign).

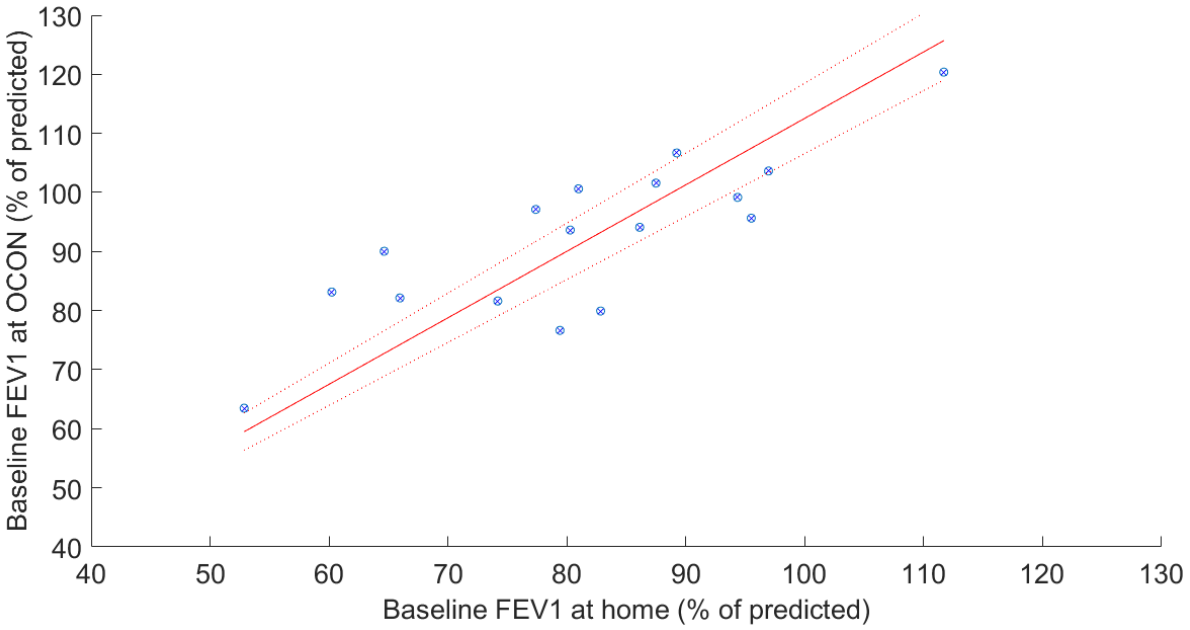


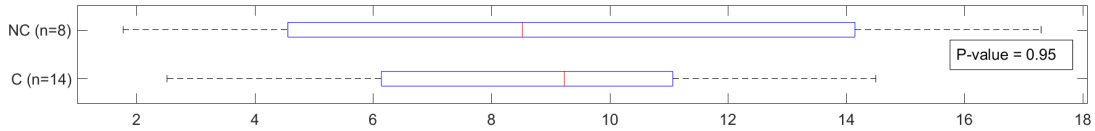
Figure 16: Baseline FEV_1 measured at home versus the baseline FEV_1 measured during the ECT at the OCON, with a linear regression line (fit through the origin) and it 95% confidence bounds (R^2=0.67).

4.3.2 Activity

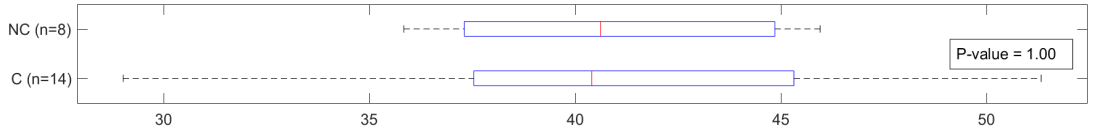
24 of the 25 (96%) children did wear the Actigraph for at least 75% of the wearperiod. Besides, one measurement was incorrectly set-up and one child lost an Actigraph. Therefore, the activity data of 22 subjects remained for analysis.

The distribution of all activity parameters within the asthma groups are displayed in box plots, which can be seen in figure 17. These box plots show no significant differences between the controlled and non-controlled asthma group.

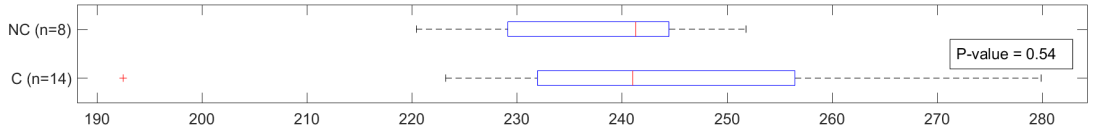
Whether or not subjects stated to have symptoms during activities does not differ between the asthma groups (p=1.00). Doing sports (at least 2 hours a week) does differentiate between controlled asthma (80%) and non-controlled asthma (33%) with a significance level of p=0.03. Doing sports or stating to have symptoms during activities does not show a significant difference in total activity, p-values are respectively 0.51 and 0.38.



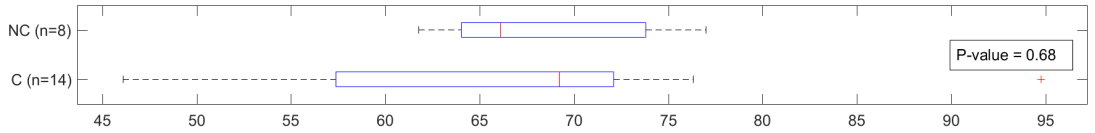
(a) Percentage of time outside (%)



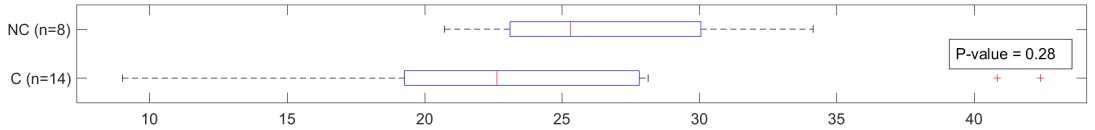
(b) Percentage of standing position (%)



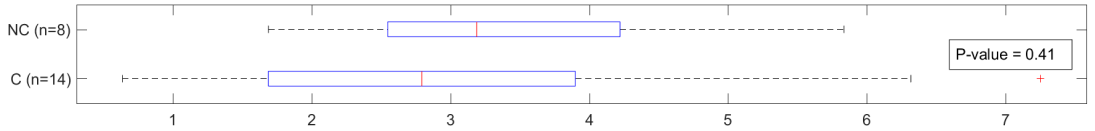
(c) Sedentary activity (hours)



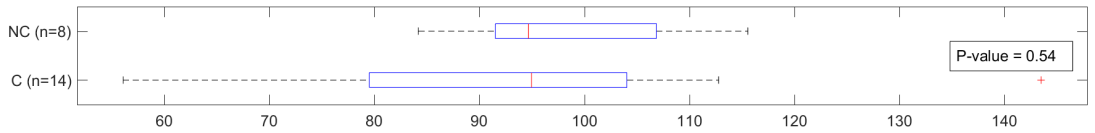
(d) Light activity (hours)



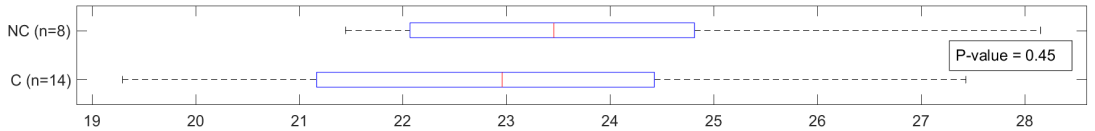
(e) Moderate activity (hours)



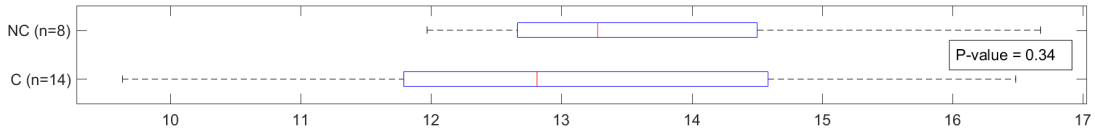
(f) Vigorous activity (hours)



(g) Total activity (hours)



(h) Average activity length (seconds)



(i) Weibull scale parameter

Figure 17: Activity results: Box plots with medians (red line), interquartile ranges (blue box), extremes (striped line), outliers (red plus sign).

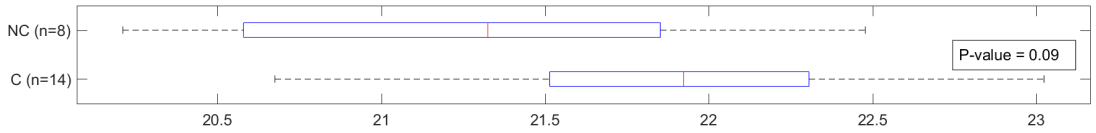
4.3.3 Sleep

The sleep parameters were based on the activity data, so also 22 subjects were included in the sleep analysis. The distribution of all sleep parameters within the asthma groups are displayed in box plots, which can be seen in figure 18.

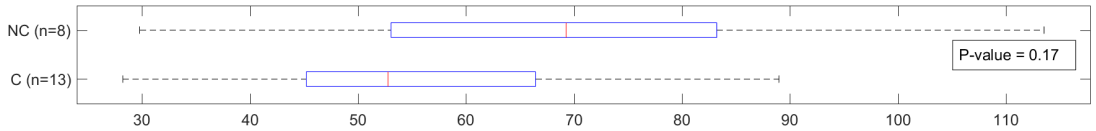
No significant sleep parameters were found. The non-controlled asthma children seem to go to bed earlier (p=0.09). Furthermore, the non-controlled asthma children seem to be more awake during the night (p=0.17), have a lower sleep efficiency (p=0.31), stay longer in bed (p=0.45) and sleep more (p=0.72).

During the ECT, 67% of the non-controlled subjects stated to have nighttime symptoms. Within the controlled asthma group 40% stated to have nighttime symptoms. This difference is not statistically significant (p=0.40).

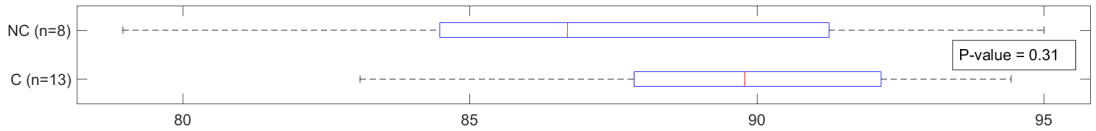
The subjects that stated to have nighttime symptoms show more awake minutes during the night (p=0.03). Other parameters do not significantly differ.



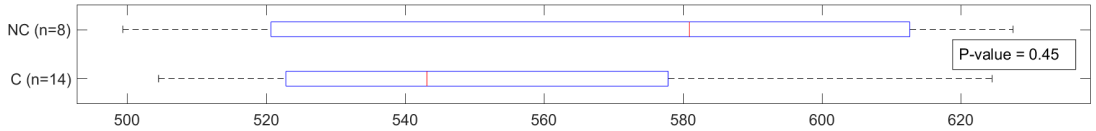
(a) Average time to bed (hour of the day)



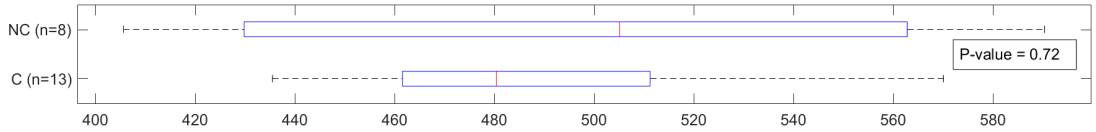
(b) Minutes awake per night (min)



(c) Sleep efficiency (%)



(d) Total time in bed (min)



(e) Total sleep time (min)

Figure 18: Sleep results: Box plots with medians (red line), interquartile ranges (blue box), extremes (striped line), outliers (red plus sign).

4.3.4 Heart rate and respiratory rate

21 of the 25 (84%) children did wear the Faros ECG correctly during the wearperiod of 2 days and nights. 2 nighttime, 1 daytime and 2 during activity ECG parts were excluded due to poor skin-contact (resulting in artifacts) or an interrupted measurement period.

The distribution of all HR and RR parameters within the asthma groups are displayed in box plots (figure 20). This figure shows that all respiratory parameters show significant or almost significant differences between controlled and non-controlled asthma. The average day and night RR were higher in the non-controlled asthma group with p-values of respectively p=0.08 en p=0.05 and the RRRT was higher with $p<0.01$.

Heart rate parameters show less conclusive differences. The average day and night HR were higher in the non-controlled asthma group with p-values of respectively p=0.16 en p=0.22. The HRRT was higher in the non-controlled group (p=0.05).

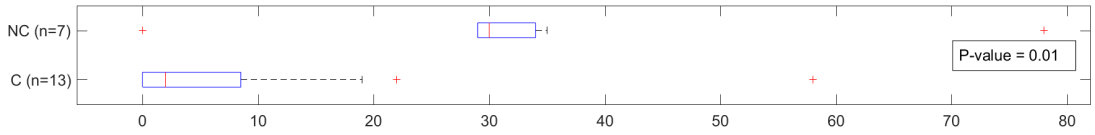
The agreement of the home-measured HRRT and RRRT showed good correlation with the recovery times measured at the ECT. The HRRT correlation has a R^2 of 0.68 ($p<0.01$) and the RRRT correlation has a R^2 of 0.72 ($p<0.01$).

4.3.5 Medication use

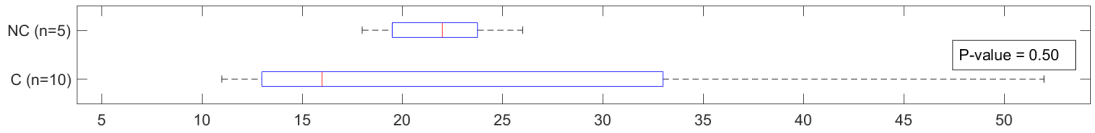
Reliever medication use could be tracked in 20 children, from which 13 were defined as controlled and 7 as non-controlled. The median reliever use of the controlled asthma group is 2. The median reliever use of the non-controlled asthma group is 30.

Medication adherence could be tracked in 15 children, from which 10 were defined as controlled and 5 as non-controlled. The median adherence of the controlled asthma group is 93%. The median adherence of the non-controlled asthma group is 80%.

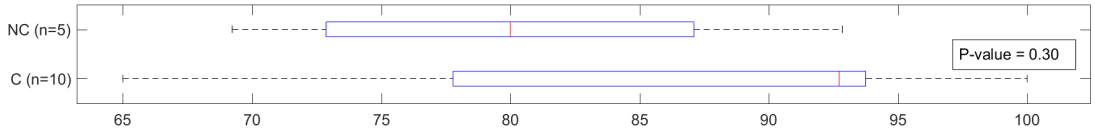
The distribution of all medication parameters within the asthma groups are displayed in box plots, which can be seen in figure 19. It shows a significant higher reliever medication use in the non-controlled group (p=0.01). The amount of controller medication or the adherence to controller medication does not significantly differ. The adherence seems to be lower in the non-controlled asthma group (p=0.30).



(a) Amount of used reliever medication

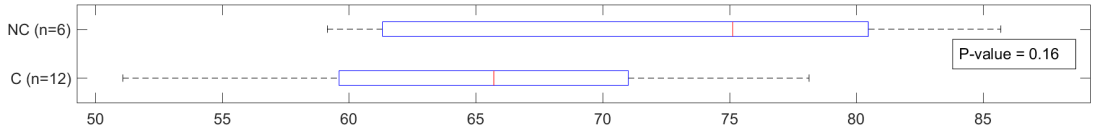


(b) Amount of used controller medication

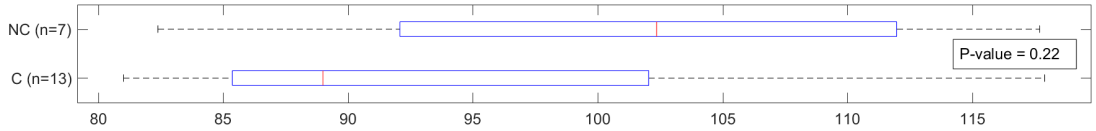


(c) Medication adherence (%)

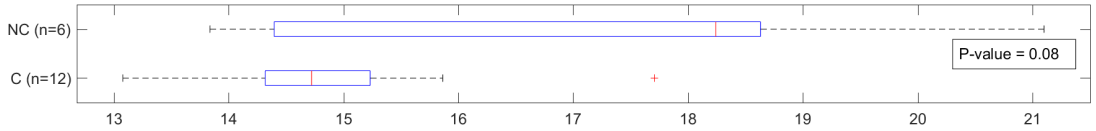
Figure 19: Medicine results: Box plots with medians (red line), interquartile ranges (blue box), extremes (striped line), outliers (red plus sign).



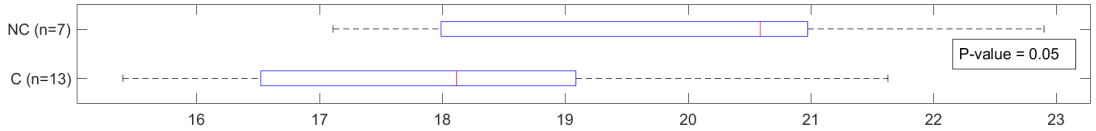
(a) Average heart rate during daytime (beats per minute)



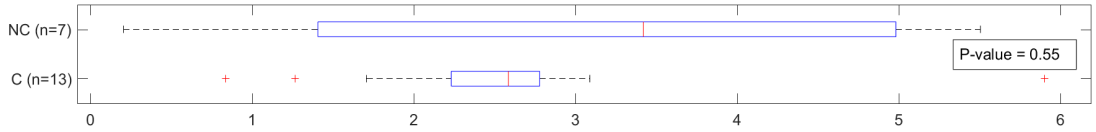
(b) Average heart rate during nighttime (beats per minute)



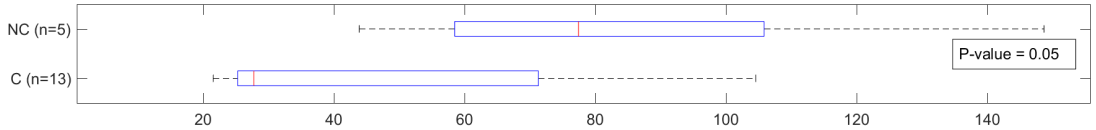
(c) Average respiratory rate during daytime (breaths per minute)



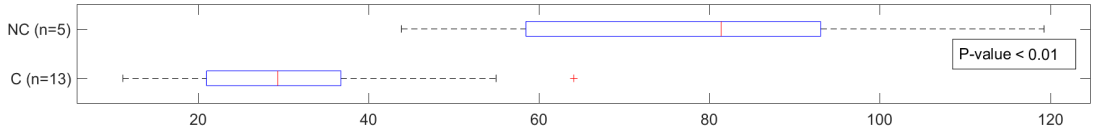
(d) Average respiratory rate during nighttime (breaths per minute)



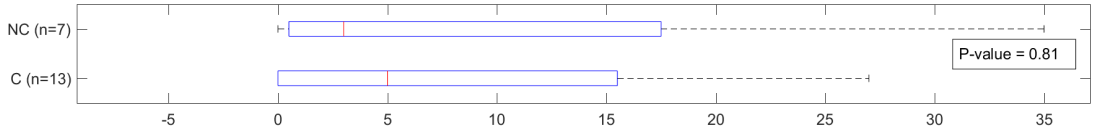
(e) Percentage of vigorous heart rate (%)



(f) Heart rate recovery time (sec)



(g) Respiratory rate recovery time (sec)



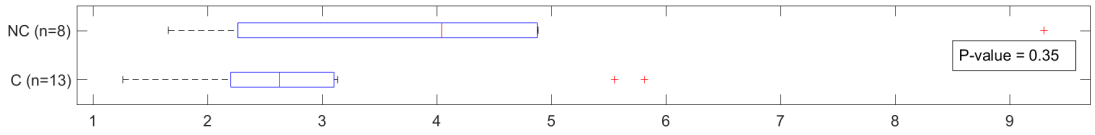
(h) Heart rate reserve (beats per minute)

Figure 20: Heart rate and respiratory rate results: Box plots with medians (red line), interquartile ranges (blue box), extremes (striped line), outliers (red plus sign).

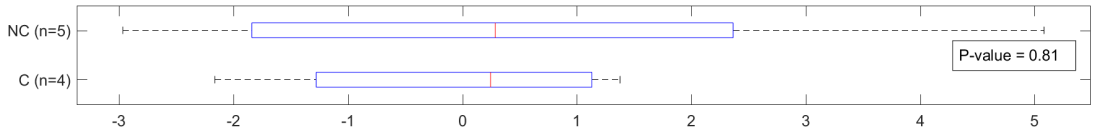
4.3.6 Combined parameters

The distribution of all parameters, which were acquired from multiple device signals, can be seen in figure 21. This figure shows a significant higher average RR during non-active periods (p=0.03) in the non-controlled asthma group. Furthermore, both the amount of activity induced (p<0.01) and protective (p=0.01) reliever medication use are significant higher in the non-controlled asthma group.

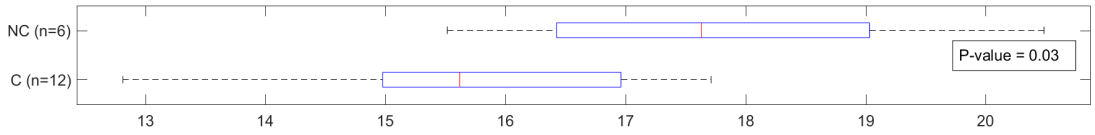
The median sleep restlessness in the early morning is higher in the non-controlled asthma group (4.0 versus 2.6), however this difference is not statistical significant (p=0.35). The median scores of the effect of reliever medication on the RR do not show any difference, resulting in a not significant p-value of 0.81. The amount of physiological distress is higher in the controlled asthma group, with a significance level of p=0.10.



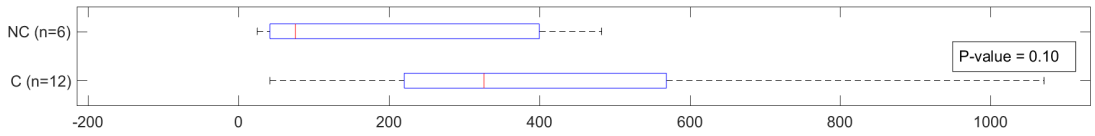
(a) Sleep restlessness in the early morning (counts/sec)



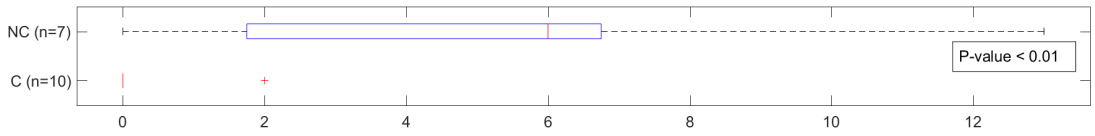
(b) Effect reliever medication on the respiratory rate (breaths per minute)



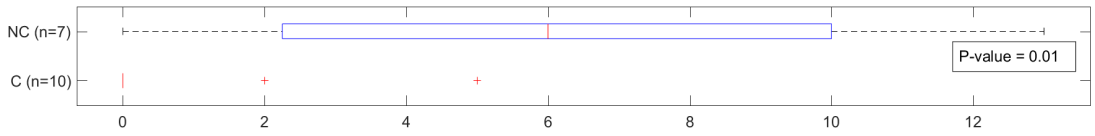
(c) Average respiratory rate during non-active periods (breaths per minute)



(d) Amount of physiological distress



(e) Amount of activity induced reliever medication use

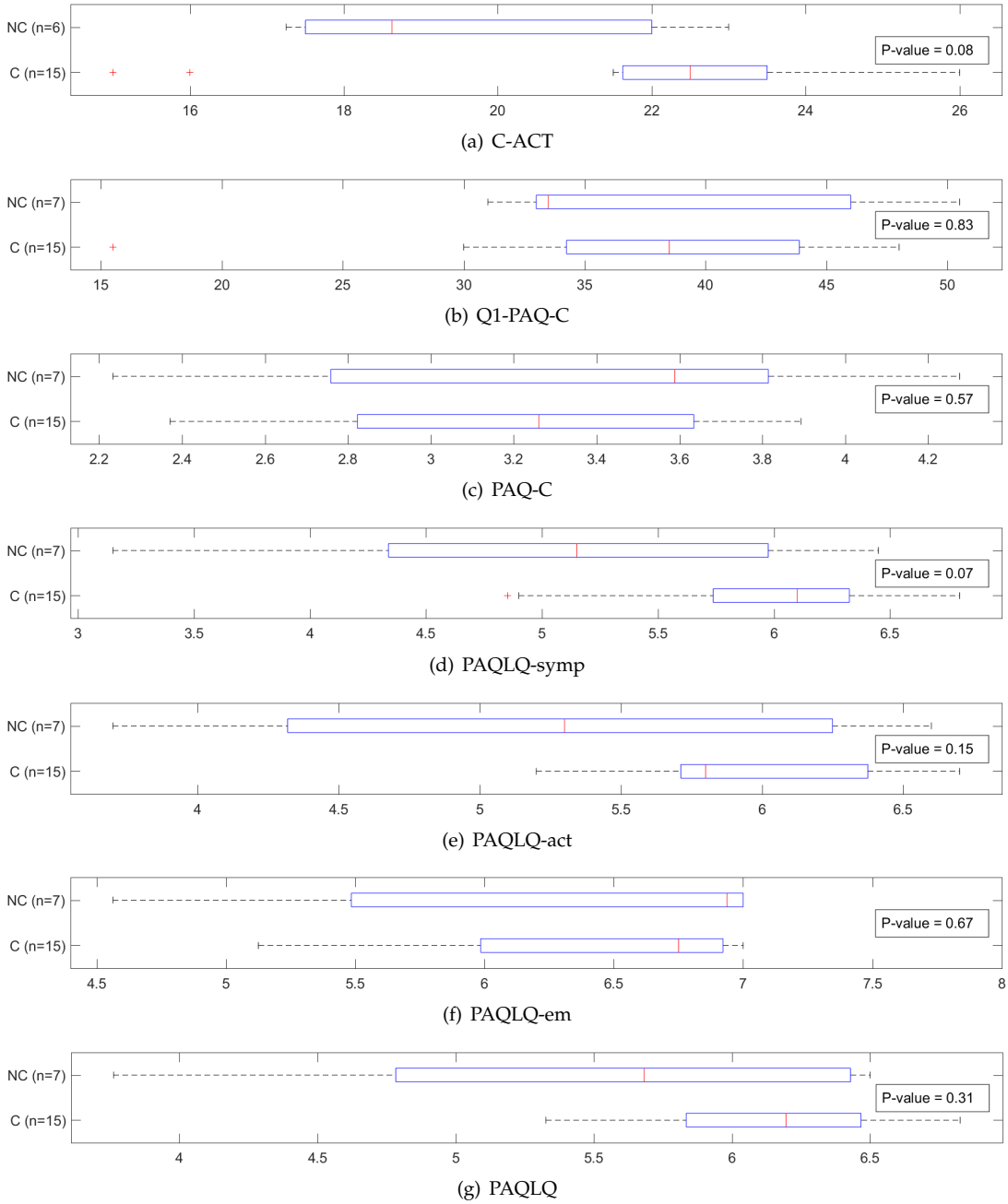


(f) Amount of protective reliever medication use

Figure 21: Combined parameter results: Box plots with medians (red line), interquartile ranges (blue box), extremes (striped line), outliers (red plus sign).

4.4 Questionnaires

The distribution of all questionnaire parameters within the asthma groups are displayed in box plots, which can be seen in figure 22. The C-ACT and PAQLQ symptom scores seem to be the best questionnaire predictors for asthma control. The non-controlled asthma group shows lower C-ACT (p=0.08) and PAQLQ symptom (p=0.07) scores.



(a) C-ACT

(b) Q1-PAQ-C

(c) PAQ-C

(d) PAQLQ-symp

(e) PAQLQ-act

(f) PAQLQ-em

(g) PAQLQ

Figure 22: Questionnaire results: Box plots with medians (red line), interquartile ranges (blue box), extremes (striped line), outliers (red plus sign).

4.4.1 C-ACT

21 Children and parents filled up at least one C-ACT test (15 controlled and 6 non-controlled asthma children). The median C-ACT score of the non-controlled group is 18.7 and the median C-ACT score of the controlled asthma group is 22.5. Those median scores do not significantly differ from each other (p=0.08). When making the C-ACT score a binary variable <20 (non-controlled) and >=20 (controlled) there is a significant difference (p=0.03) between the controlled and non-controlled group with the Fisher's exact test. Table 4 shows the cross-table of the binary C-ACT score and the physician based asthma control, from which a sensitivity of 67% and a specificity of 87% were calculated.

Table 4: Cross-table C-ACT versus asthma control.

	Non-controlled asthma	**controlled asthma**	**Total**
C-ACT <=20	4	2	15
C-ACT >20	2	13	6
Total	6	15	21

Figure 23 shows the amount of FEV_1 decrease during the ECT test (as a continuous measure of EIB) versus the C-ACT score. It can be seen that a C-ACT score <20 is 60% sensitive for a LF decrease of >13%. Therefore, the positive predictive value of the C-ACT is 60%. The C-ACT test has a negative predictive value of 75%. The overall sensitivity of the C-ACT for LF decrease at the ECT is 65%.

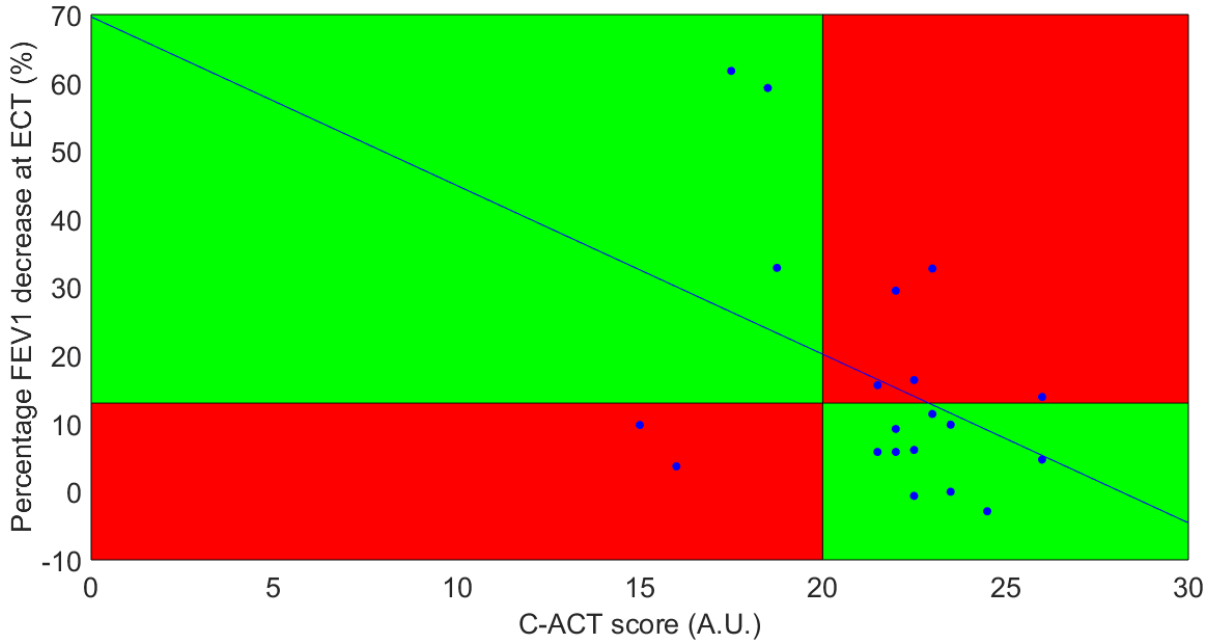


Figure 23: C-ACT score versus the lung function decrease in FEV_1: The red area indicates incorrectly classified children by the C-ACT scores. The green area indicates the correctly classified children. The blue line is the linear regression line with R^2=0.13.

4.4.2 PAQLQ

22 Children filled up at least one PAQLQ test (15 controlled and 7 non-controlled asthma children). The PAQLQ score does not significantly differ (p=0.31) between the controlled (median 6.20) and the non-controlled group (median 6.05). The specific symptom score (p=0.07), activity score (p=0.15) and emotional score (p=0.67) of the PAQLQ do not show a significant difference either. The specific activity score is not significantly correlated (R^2=0.12) with the total amount of activity (p=0.07).

4.4.3 PAQ-C

22 Children filled up at least one PAQ-C questionnaire. 20 of those children also completed the 2 weeks of activity monitoring. The PAQ-C score does not significantly differ (p=0.57) between the controlled (median 3.20) and the non-controlled group (median 3.33). The activity questionnaire does not significantly (R^2=0.07 with p=0.39) correlate to the total activity (figure 24). Table 5 shows that the best correlation is found with the amount of vigorous activity (R^2=0.12 with p=0.13). Question 1 of the PAQ-C showed no correlation with the total activity (negative linear correlation of R^2=0.06).

Table 5: R^2 value and p-value of the linear regression between the PAQ-C score and the amount of active hours in each intensity level.

	Activity			
	Light	**Moderate**	**Vigorous**	**Total**
R^2	0.01	0.04	0.12	0.07
P-value	0.66	0.30	0.13	0.39

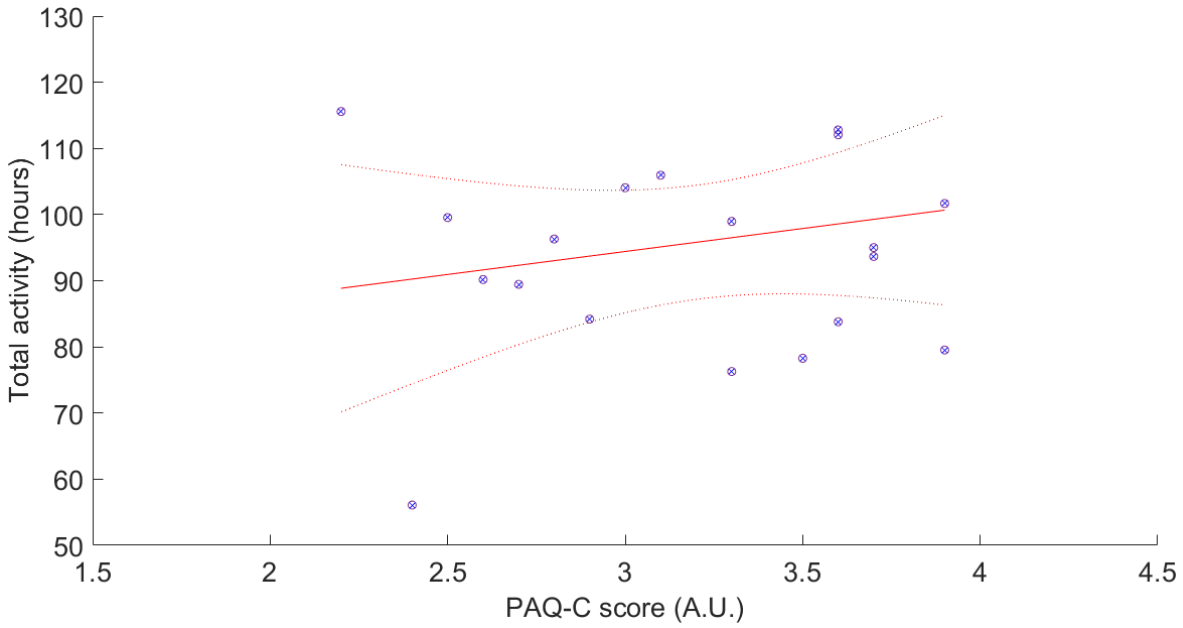


Figure 24: PAQ-C score versus the total activity with a linear regression line and its confidence bounds (R^2=0.07).

4.5 Confounders

4.5.1 Body composition

Body composition could be assessed in 24 children. The controlled asthma group shows larger 4-side skinfold scores than the non-controlled asthma group, respectively a median of 42.6 versus 25.7. This is not a significant difference (p=0.13). The relative portion of truncal fat in respect to the total body fat did not show a significant difference either (p=0.40). The body composition does show a significant correlation (p<0.01) with the estimated CRF. The resulting regression function can be seen in equation 4.1

$$EstimatedCRF = 73.079 - 0.153 * SumOfSkinfolds \tag{4.1}$$

4.5.2 Cardiorespiratory fitness

CRF could be assessed in 17 children who performed the ECT on the treadmill. 13 in the control group and 4 in the non-controlled group. The estimated CRF does not significantly differ (p=0.65) between the control (median 64.8) and non-controlled (median 67.5) asthma group.

4.5.3 Allergen and weather exposure

Allergen and weather exposure could be assessed in 22 of the 25 children. The other three could not be used because activity data was missing. Therefore, no estimation of the time being outside could be made.

Median cold exposure is higher (5.4 vs. 4.0) in the controlled asthma group. However, cold exposure, dry-air-exposure and pollen-exposure do not show a significant difference between the controlled and non-controlled asthma group, respectively p=0.33, p=0.95 and p=0.73.

The children with a pollen-allergy do show a lower median pollen-exposure (52.2) than the children without a pollen-allergy (60.3). However this difference is not significant either (p=0.46).

Figure 25 shows the daily pollen-symptom scores versus the reliever medication use. This figure does not show a significant relation between the reliever medication use and the pollen-symptom score of those days (R^2<0.01, p=0.50).

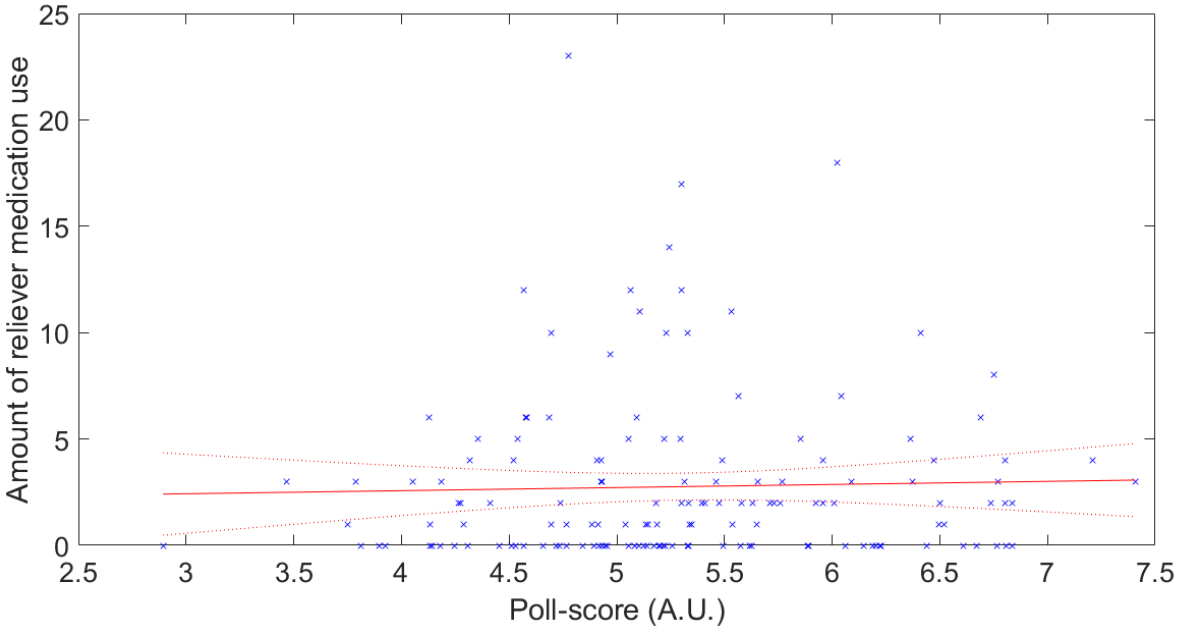


Figure 25: Daily pollen-symptom scores versus reliever medication use those days, with a linear regression line and its confidence bounds (R^2 <0.01).

Table 6 shows the cross-table of having Meyers nasal crease and/or Dannie Morgan lines versus having allergies. Having both allergic signs is 88% sensitive and 46% specific for having allergies (p=0.11).

Table 6: Cross-table with having the allergic signs (Meyers nasal crease & Dannie Morgan lines) versus having allergies.

	No allergies	**Allergies**	**Total**
No allergic signs	3	2	5
Meyers nasal crease	2	3	5
Dannie Morgan lines	1	2	3
Both allergic signs	1	7	8
Total	7	14	21

5 Discussion

In this study we evaluated parameters of asthma control in the home-situation and under laboratory conditions with an ECT. Since multiple parameters have been investigated, we will discuss the results per parameter category.

5.1 Interpretation of the results

5.1.1 Wearable parameters

Spirometry A significant difference was found in the maximal difference in baseline FEV_1. So, non-controlled asthmatics show a wider range of baseline LFs at several moments in time. This implies that their airways are not stable and that BHR causes the baseline LF to vary throughout the monitoring period [28]. Brouwer et al. [132] concluded that the contribution of FEV_1 variation to diagnosing asthma in children is limited. However, in this study the variation in baseline LF seems to be a relevant parameter for identifying asthma control. It could further be discussed whether FEV_1 baseline variance would be a better parameter than the maximal difference in baseline LFs. An advantage of choosing variance is that single incorrect measurements that slip through the preprocessing have less influence on the parameter. On the other hand a variance averages instable LFs with other LFs and therefore can underestimate LF differences. The variance was not taken into account for this study because there was a large variance in the amount of blown LFs.

An almost significant (p=0.06) difference could be seen in baseline FEV_1 (% of predicted). The non-controlled group shows lower baseline LF which corresponds to the long-term chronic inflammation and hyper responsiveness of the small airways.

One spirometer parameter stands out of the results, due to the fact that is does not correspond to our expectations. This parameter is the FEV_1 decrease during symptoms. The non-controlled asthma group shows in two of the three cases an average increase $>$20% of FEV_1 relative to the average baseline LF. The fact that these two exceptions were seen in a group of only three subjects, explains the unexpected difference between the non-controlled and controlled asthma group. The reason that these two children show an increased FEV_1 during symptoms could be the effect of multiple factors. First of all one of these children has only one symptom and one baseline LF, therefore an error in one of the spirometer tests has a direct effect on this parameter. Secondly, the effect of reliever medication could have influenced the result. Although, the patients were instructed to use the spirometer before taking their reliever medication. It is speculated that some symptom LFs where done under the effect of a reliever medication, due to a substantial increase in FEV_1 in respect to the average baseline FEV_1.

Besides the parameter results, the adherence to the home used spirometer can be discussed. 84% Of the children did use the spirometer at home. Only 66% of those measurements were technically correctly blown, despite the fact that all patients where thoroughly instructed on how to use the device and correctly blow a LF. Moreover, 92% of the subjects showed to be able to perform correct spirometry at the ECT. So there can still be gained a lot on the correct spirometry technique at home. In addition, a lot of children had limited amounts of tests (only 2 or 3), while they were instructed to use the device every time before and after an intense activity and when they were experiencing symptoms. Therefore, for future research more attention should be given to the children's devotion to use the spirometer and to the individual technique of blowing.

The percentages of the correct spirometer tests vary from 25 to 100% between subjects and seems not to be age related. The average improvement of the percentage of correctly spirometer curves with the age of the child is small and not significant, due to the large inter-individual variation. This is in contrast to the international guidelines, which states that above the age of 6 most children are able to perform spirometry and that this level increases with age. Pelkonen et al. [38] showed corresponding results to this study; children aged 5-10 years could perform reproducible spirometer tests during home-monitoring, although there was a wide individual variation. So it can be hypothesized that age is not a crucial factor in performing spirometry, but that it mainly depends on other factors.

Activity This study does not show any significant difference in activity patterns. Previous research at the MST showed that activity levels of children with asthma were altered [56]. Children with severe asthma had less total activity, less intense activity and shorter activities. Children with mild asthma show less time of vigorous activities and seems to compensate that with more light activity [56]. Other studies are not decisive in the influence of asthma on the activity patterns in daily life [55, 80, 133–136]. Anthracopoulos et al. [136] investigated the association between PA and EIB. They showed that decreased levels of PA are associated with EIB. EIB was assessed by a standardized free running ECT. Therefore, their classification of asthma control resembles our used method the most. However, their assessment tool for PA was a physical activity questionnaire. Cassim et al. [137] performed a systematic review on activity patterns in children with asthma and concluded that there was no evidence supporting the change in amount of activities in children with asthma. A strength of this review is that only accelerometer based activity levels were included. However, the grouping of asthma control was not strictly defined. This means that asthma categorization of the included studies was based on questionnaire results, physician judgments or other criteria. No published studies were found that use both an ECT to classify asthma control and accelerometry to measure activity patterns, despite the fact that both are the gold standard in their measurement domain [29, 60]. Therefore, ideally, future research should have explicit emphasis on this grouping of asthma subgroups by ECT and accelerometry based activity monitoring. It is further recommended to repeat a thorough systematic review on this subject when multiple of these studies are performed.

The fact that this study does not show any difference in activity patterns, between the asthma control groups, can be explained with the age difference of both groups. The non-controlled asthma group based on the physician's opinion is significantly younger than the controlled asthma group (on average 7.4 instead of 10.2 years old). The non-controlled asthma group does not contain any children above the age of 10. Literature shows that activity patterns change with the age of the children [138]. Cooper at al. [138] showed a decrease in total activity with increasing age and showed that maximal moderate to vigorous activity was reached around the age of 7 to 8. This study showed similar age dependent activity graphs, see figure 26. Therefore, this study is still inconclusive whether activity patterns are relevant to monitor asthma control. More patients should be included in the study to match the baseline characteristics of both groups. When the difference in age is still present after completion of the WEARCON study, all activity parameters should be corrected for age. It is recommended to correct based on the age dependent graphs for all activity parameters in stead of using linear correction. In this study this correction could not yet be realized, due to the low amount of subjects.

The children showed on average 120 moderate to vigorous minutes per day. In relation to the international guidelines this is well above the minimal required 60 active minutes a day [139]. However, accelerometry does take all short burst activities into account, where the guidelines were established based on longer lasting activities like cycling, walking and doing sports. Therefore, it is assumed that the accelerometer overestimates the active minutes when comparing it to the guidelines.

Sleep The non-controlled asthma children go to bed earlier and have more sleep time, although those differences were not significant. The increased total sleep time does not agree with the results that were shown by a polysomnography study of Ramagopal et al. [140] and an actigraphy based study of Kieckhefer et al. [141]. This disagreement might be explained by the age difference between the groups. The non-controlled asthmatic children is significantly younger and therefore go to bed earlier and have more sleep time.

Furthermore, the non-controlled asthma children seem to be more awake during the night ($p=0.17$) and have a lower sleep efficiency ($p=0.31$). These results do agree with polysomnographic and activity based sleep monitoring studies in asthmatic children [140, 141]. Although these results are not significant, it could explain the effect that more non-controlled asthmatic children state to have nighttime symptoms and corresponds with the fact that asthma can induce nighttime symptoms [63, 64].

Sleep latency (time to fall asleep) would be an interesting parameter to monitor. Jensen et al. [65] showed that asthmatic girls had an increased sleep latency of 46 minutes compared to 33 minutes of the non-asthmatic group. The Cole-Kripke sleep analyses of the Actigraph was used to calculate this parameter. However, the sleep latency was 0 in more than 90% of the cases, which could not be true. Maybe the first transition from awake to asleep is different in children than in adults causing this unexpected values, due to incorrect sleep latency calculations. Literature showed that the Cole-Kripke sleep

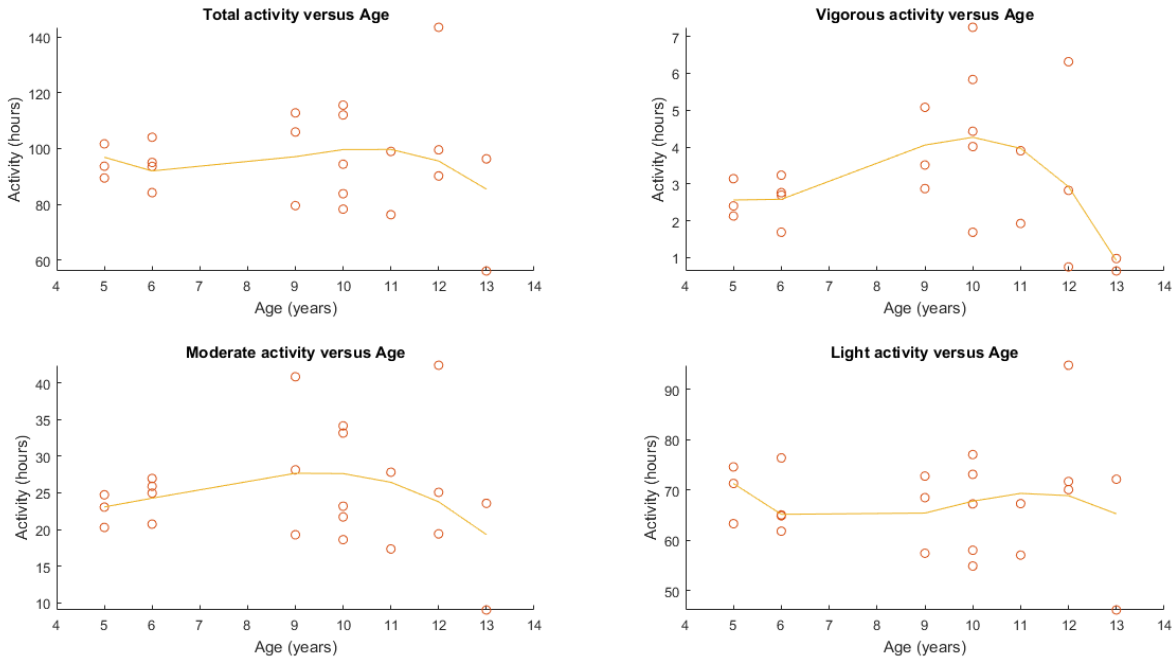


Figure 26: Activity versus the age of the children.

analysis highly underestimates sleep latency in respect to polysomnography [142]. Therefore, this parameter was not included in the sleep analysis yet. However, other methods for assessing sleep latency might be considered for future research as sleep latency seems to be differentiating asthma control from non-controlled asthma [65].

Finally, an interesting result is that subjects who stated to have nighttime symptoms show indeed more awake minutes during the night ($p=0.03$). Apparently, this question in the medical history is reliable in determining sleep awakening.

Heart rate and respiratory rate HR and RR are important parameters in acute asthma care in children [95]. Therefore, it was expected that these physiological parameters show another course in non-controlled asthmatic children. The univariate analysis of all ECG derived parameters strongly suggests that respiratory parameters are the most effective for identifying non-controlled asthmatic children. This complies with the fact that RR is used in home-monitoring of adult asthma [43].

RR during day and RR during nighttime are higher in the non-controlled group. However, again a note has to made that the children in that group are younger and therefore have a higher HR and RR [129]. It is expected that this fully describes the increased HR and RR of the non-controlled group, due to the median difference of only two breath per minutes. Besides, it could be said that a difference of only two breaths per minute is not clinically relevant. Both groups fall within the normal age dependent reference range of the RR [129].

On the other hand, the RRRT after exercise does show clinical relevant differences. The RRRT is about 50 seconds larger in the non-controlled group, with a strong significance level of $p<0.01$. This suggests that subjects with non-controlled asthma develop respiratory distress after exercise. It is not clear whether the effect of the age difference of the asthma groups also influences the RRRT. It might be that younger children need longer recovery times because their oxygen debt after exercise can only mainly be restored by an increased RR, where older children could also use larger tidal volumes [143]. However, on the other hand it can be suggested that older children have larger oxygen debts. Nevertheless, the difference in RRRT is large (200% increase in median RRRT) and the difference between the asthma groups is strongly significant ($p<0.01$). Therefore, it is assumed that asthma control is an important factor on the RRRT. For analysis of the RRRT the most intense exercise within the ECG monitoring period was chosen. It can be discussed that this parameter should be averaged for all activities above a certain intensity level. Additionally, an activity with a cooling down is an influencing factor on this parameter,

those kind of samples should be automatically excluded because in this way HR and RR do decrease slower. Comparing the home-measured ECG signal and the ECG measurement at the ECT shows that the recovery times, for both the HR and the RR at home, is significantly correlated ($p<0.01$) with that measured at the ECT. During the ECT there is one single activity and therefore manual assessment of the data is simple. The fact that it correlates significantly with the home-measured parameters indicates that those activity selections were done correctly in this study. This strengthens the expectation that home-measured ECG derived RRRT could be useful in determining asthma control.

In addition to these parameters the percentage of vigorous HR does not show a difference between the asthma groups. The interquartile bars of this parameter's box plot indicate a wide variation among the non-controlled children. This could be described by the fact that there are two ways to cope with uncontrolled asthma; 1) to avoid any kind of activity or other triggers 2) to go beyond the limit with the consequence of having symptoms more often. The first strategy results in less moments with a HR above 70% of the maximal HR, while the second strategy results in more periods of having symptoms on top of the normal moments of a vigorous HR. Therefore, the mix of children with different strategies in the non-controlled asthma group could explain the larger variation in this parameter. Additional to this strategies, it can also be discussed that experiencing dyspnea drives up the HR, which contributes to an even higher percentage of vigorous HR in the non-controlled asthmatic children that cope by going beyond the limit.

The HR reserve does not show any differences between the asthma groups. Indicating that both groups equally challenge themselves at least once in the two days of ECG monitoring.

Combined parameters The thought that an increased reliever medication use is associated with non-controlled asthma is strengthened by the fact that both activity induced and protective SABA use is significantly higher in the non-controlled asthma group, respectively $p<0.01$ and $p=0.01$. This corresponds with the fact that the GINA states that high SABA use is a risk factor for non-controlled asthma [16]. Additionally, Butz et al. [144] showed that children with high SABA use are five times more likely to be hospitalized as a result of asthma. Therefore, SABA use is an important parameter for monitoring asthma control. Furthermore, a note should be made that current recommendations in asthma care state that as-needed therapy of SABA can be used as a measure of asthma control [145]. However, this study showed that the amount of protective SABA use can also discriminate asthma control ($p=0.01$).

The average RR during non-active periods is found to be significantly different between the asthma groups as well. However, it is suggested that this difference results from the baseline discrepancy in the age of the asthma groups. Furthermore, the difference of 2 breaths per minute is not seen as a clinical relevant difference, because both groups fall within the age dependent reference range of RR [129].

Previous studies showed that the circadian rhythms of asthma mediators like cortisol and histamine in asthmatic children are related with sleep restlessness in the early morning [63,64]. Median values of the asthma groups show indeed a higher sleep restlessness in the non-controlled asthma group. However, this result is not statistically significant ($p=0.35$).

The effect of reliever medication on the RR is almost null, which complies with the effect of bronchodialators in healthy subjects [146]. Furthermore, the effect of reliever medication on the RR did not show any difference between the asthma groups ($p=0.81$). This might by explained by the fact that only a part of the reliever medication is actually used in times of respiratory distress. Therefore, this parameter seems not useful for future asthma monitoring.

5.1.2 Questionnaires

The questionnaires had an average adherence of 87%. All questionnaires showed approximately the same adherence. Therefore, they seem suitable for home-monitoring purposes.

The C-ACT questionnaire is often used for the assessment of asthma control throughout the world. Therefore, it was tested whether this questionnaire does match asthma control and show a relation with the FEV_1 decrease, after the ECT. In this study the C-ACT test shows to be a moderate to good predictor of asthma control with a sensitivity of 87% and a specificity of 67%. This corresponds with the results of Chinellato [147]. However, when the C-ACT scores are plotted against the LF decrease after exercise at the ECT, it can be seen that the linear correlation is poor. This corresponds with the published work of Lee et al. [148] and the poor relation between EIB and the asthma control questionnaire [22].

This indicates that the C-ACT has its main value when using it as a binary outcome measure for asthma control. However, one must be careful interpreting this score, because it does not relate to the proportion of EIB and can therefore underestimate children with severe non-controlled asthma [149].

The total PAQLQ score does not differentiate between controlled and non-controlled asthma. This is in contrast with for example the study of Poachanukoon et al. [150], which validated the PAQLQ for 51 children aged from 7 to 17 years old. It can be explained by the fact that the emotional score of this questionnaire is not different between the asthma groups. This indicates that asthmatic children (and their parents) state that symptoms do not effect the emotional wellbeing of the child. A contributing factor to this could be the local mentality in the region Twente, which means that children do not complain quickly. It could be concluded that the PAQLQ symptom score is the best measure of the PAQLQ to differentiate between controlled and non-controlled asthma (p=0.07).

The PAQ-C questionnaire does not significantly differ (p=0.57) between the controlled and non-controlled group. Besides, it does not correlate to the total activity (p=0.39) either. Therefore, this questionnaire is not expected to provide a correct estimate of the PA of a child. Additionally, the first question of the questionnaire (which is a summary of all activities last week) does not correlate with the total activity. Considering the fact that the PAQ-C is the best questionnaire available for activity monitoring in children, it could be concluded that questionnaire based activity monitoring is not accurate and accelerometry based activity measurements are preferred and advised.

5.1.3 Confounders

4-side skinfold scores were higher in the controlled group even as the relative portion of truncal fat. Although, these differences were not significant (p=0.13 and p=0.40). This could be explained by the fact that the non-controlled group contains a lot of very young children, which are less vulnerable for overweight [151]. Still, these results are in contrast to other studies, which indicated that non-controlled asthma is related to changes in body composition [14]. More subjects will have to show whether this trend continues.

CRF is non-significantly higher in the non-controlled asthma group (p=0.65). This may indicate that the CRF is not altered in non-controlled asthma patients. A note should be made that the included children were already diagnosed with asthma and therefore CRF and keeping up with their peers were already monitored and stimulated by the pediatrician. Additionally, CRF and body composition did show a significant correlation ($p<0.01$), which is also described in other literature [135]. The lower skinfold scores therefore explain the lower CRF in the controlled asthma group. Furthermore, it could be discussed whether the CRF estimation is correct. The estimated $VO2_{max}$ of the children is on average 65.8 (ml O2/kg). Young children often have a relative high oxygen uptake per kilogram weight because of their low weight and other physique as adults. However, 65.8 on average is a to high estimate compared to the reference $VO2_{max}$ of 48.5 in 6-7 year old boys, provided by Eiberg et al. [152]. This could be explained by an overestimation of the running power in the estimation or by an inadequate correction for children.

Poll, allergen and weather exposure did not differ significantly between controlled and non-controlled asthma. Therefore, children with non-controlled asthma not seem to avoid those condition. Multivariate analysis has to reveal whether there is a confounding effect of these types of exposures with primary study parameters. It is still expected that children who are more exposed to those triggers will show more asthma related symptoms.

5.2 Strengths and limitations

5.2.1 The complete WEARCON-study

Due to the limited amount of time and resources the WEARCON study is not completed yet. The protocol states that 60 asthmatic children and 30 healthy children have to be included. Till this report, 25 asthmatic children were included and the results were used for an interim analysis.

Sample size calculation showed that 30 subjects per group were needed to perform a logistic multivariate analysis with 3 determinants. Due to the limited amount of subjects multivariate analysis was not assessed yet. With the currently known univariate results a hypothesis of well correlating multivariate regression models can be made.

5.2.2 Determining asthma control

The WEARCON study protocol stated that the asthmatic children would be categorized in a non-controlled or a controlled asthma group based on their LF results at the ECT. During this study the correctness of this method was doubted. Literature is not decisive in the best way to classify asthma control. GINA [16] states that asthma control can be classified based on symptoms, medication use and activity limitation. However, this classification has not been validated from the clinical point of view [153]. More often, asthma control is based on LF measurements or questionnaire outcomes [28, 153, 154].

During this study, a couple of children were classified as non-controlled asthma by their LF, due to the fact that one LF parameter was just exceeding the criteria level. For this reason the main results of this study were based on the physicians judgment of asthma control (which is based on the complete package of LF results (both FOT and spirometry), medical history, allergic signs and physical examination). There could be discussed whether this more subjective method is correct to use. In this research 75% of the children were categorized the same by the physicians judgment as with the criteria based method. Six children were classified as controlled asthma based on the physicians judgment, but had just one criteria that slightly exceeded the criteria cut of point (a lability of 21%, 23% and 23% with 20% as criterium or a decrease in LF after exercise of 14%, 16% and 16% with 13% as criterium). These values are in absolute contrast to the average lability (40%) and LF decrease (37%) of the other non-controlled asthmatic children. Therefore, even besides the physicians judgment, these cases seem to fit better in the controlled group. It further can be argued whether all subjects with LF values close to the criteria should be classified based on the physicians judgment, because these outcomes may be within the uncertainty level of the reproducibility of the ECT test.

Furthermore, it should be tested what impact other definitions of asthma control have on the distribution of all outcome parameters. When finding a marginal influence the most suitable definition should be chosen. However, if the outcome parameters do change, future research should focus on an objective measure to classify asthma control, which takes all relevant parameters into account.

5.2.3 Baseline characteristics

The significant difference in age between asthma groups is a bias for several parameters. This could not be corrected, due to the design of the study as every patient who met the criteria was included. Furthermore, inclusion took place before knowing whether the subject would be placed in the controlled or non-controlled asthma group.

Length and BMI were also significantly different, but that could be explained by the difference in age. BMI was normalized by making it a categorical variable, which classified BMI as very low, low, normal, high, very high. This was based on the pediatric age dependent BMI tables of voedingscentrum.nl [131].

When the WEARCON study is completed and the difference in age is still present, the age should be included in the regression model. This extra parameter has as consequence that an additional 20 subjects would be needed to still test a 3 parameter multiple regression.

5.2.4 Overview single patient

Plotting all wearable data in an overview plot (figure 13) provides the pediatrician with relevant inside information on asthma symptoms over time. At one glance the physician could see the course of spirometry results over time. This information reveals inside into the amount and severity of periods of dyspnea. Furthermore, the physician could anticipate on a LF trend deviation, by for example adjusting treatment. In that case, the physician could also review the effect of a new treatment on the LF and simultaneously check the adherence to the new prescribed medication, by checking used medication data.

Besides just recording LF deviations, this information could also be used to investigate which triggers have an effect on the LF of the child. For example vigorous activity just before a LF decrease or before a SABA puff, could indicate an exercise triggered reaction. Furthermore, outside temperature and pollen-exposure could be taken into account.

Plotting the activity levels together with the HR reveals dynamic information about the trends in PA of the child. As exercise and good CRF are relevant in asthma management, this information could provide the physician handles to redirect the child's lifestyle. It would then also be very interesting to monitor activity several times a year to observe the progression that is made.

Finally, the amount of sleep can be easily read out of the graph. Sleep is very important in the development of the child. Besides its relevance for the regular pediatric care, some asthmatic children have difficulty sleeping. With this plot sleep problems can be objectified and detected early.

In summary, this plot gives a complete overview of several relevant asthma signals. The plot can be fine-tuned on the needs of the physician or be adjusted to every individual patient. So that clinical decline of asthma control can be identified and pediatricians can anticipate on these clinical trends. Additional to the graph, an application can be build which automatically provides parameter values and scales them across a reference bar.

5.2.5 Clinical feasibility

One goal of this research was to investigate the feasibility of wearable devices into the current outpatient care. The results show that not all wearable devices were used to their full capacity, especially the portable spirometer and the smart inhalers were not always used properly. This has two underlying causes; the devices were not as simple to use as the others and they are not continuous measured signals. So subjects have to remind themselves to use the device, instead of installing the device ones and do not have to worry about it anymore. For spirometry these deficiencies cannot be overcome. However, there could be made an environment wherein the children will be reminded when they have to use the spirometer. In contrast to spirometry, the medication trackers can overcome the deficiencies. So there has to be searched for devices that do not require a lot of input from the subject. New devices like the Amiko Automatic Inhaled Medication Tracker could be used. These devices do not require regularly synchronization or other subject inputs. Additionally, these devices could also review the inhalation technique with which the puff is taken.

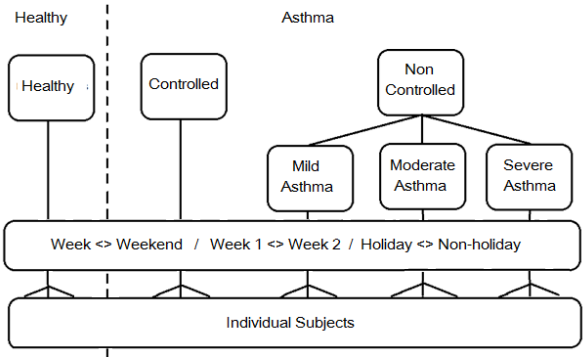


Figure 27: An example of a multilevel analysis set-up: The primary level divides the population in healthy, controlled and non-controlled children. The secondary level distinguishes between asthma severities. A third level might be used to investigate differences within the 14 days of measurement (i.e. week versus weekend, holiday versus non-holiday). The final level consists of individual analyses.

5.3 Research opportunities

This research produced a lot of relevant data. Despite the extensively performed analyses more parameters can be investigated, for example the heart rate variability. Including more subjects (both asthmatic and healthy) also opens a lot of opportunities for new analyses. For instance to investigate the difference between healthy and asthmatic children and the use of multiple regression analysis. Besides, a multi-level analysis set-up may provide additional information. Figure 27 shows an example of such an analysis. Although many more parameters can be analyzed, this pilot study was focused on the most relevant parameters. The results on those parameters give leads for new research opportunities.

First of all, a lot of parameters were defined by various (filter)-settings, cut-of points, restrictions and mathematic formulas, as can be seen in the methods section. It is plausible to belief, that some of these parameters did not show a difference between the asthma control groups yet. However, when systematically varying the method by which the parameter is defined, it could result in a difference between the asthma groups. Therefore, future research should focus on optimizing algorithms (i.e. fmincon (MATLAB inc.)), which maximizes the discriminative effect of a parameter by systematically testing parameter settings [155].

Secondly, the significant difference of the RRRT could be further investigated. It will be interesting to measure this parameter during the ECT at the OCON in well controlled circumstances. Furthermore, this parameter should be analyzed automatically to prevent biased results.

Thirdly, more attention need to be given to the children's devotion to use the spirometer and to the individual technique of blowing, because a lot of data was missing or not technically correctly blown. First of all children need an additional stimulus, for example an app which reminds them and shows an incentive during blowing (i.e. blowing bubbles) to maximize effort. Furthermore, spirometer results have to be assessed in real-time to be able to intervene during the measurement period when necessary. This kind of improvement might also be used in the other wearables to prevent incomplete data of those devices as well.

Additionally, future research should focus on an objective measure to classify asthma control. This research showed that when the LFs of the children during the ECT are close to the pre-defined criteria for asthma control, physician based and criteria based asthma control differ quite often. Therefore, especially these cases need an additional objective tool that includes other measures of asthma control other than LF alone. Asthma control criteria of the GINA, such as activity limitation or SABA use might be useful for this purpose.

Furthermore, when the overview plot is fully developed to the needs of the physician and the patient, a RCT can be performed, which consists of one group of asthmatic children that should receive wearable home-monitoring additional to the conventional asthma care and a control group that only receives conventional care. The main question of this research should be: Can home-monitoring of asthmatic children result in better asthma control?

Finally, the focus of new research should lay on combining wearables. Sensors can be combined to minimize the burden for the children. Integration of the wearables into a mobile app allows real-time monitoring, makes it possible to steer children towards asthma control and prevent data loss. Furthermore, it provides the fundament towards a self-regulation app for asthma control in children, as in the asthma monitoring study of Honkoop et al. [43]

6 Conclusion

This report showed and discussed the preliminary results of the WEARCON study. In this study activity, medication use, cardiac function and respiratory function were monitored with wearables and questionnaires. The study showed that these wearable devices can be used for home-monitoring purposes.

Univariate analysis showed significant differences between controlled and non-controlled asthma, with as most important outcomes; the maximal difference in baseline FEV_1, the amount of used reliever medication and the RRRT.

The way of home-monitoring used in this study delivers relevant information for the physician, especially about trends and relationships of different wearable data. Therefore, future research should focus on implementing home-monitoring into the outpatients care, by creating a straightforward interface to analyze and display the home-monitoring signals. RCTs can be used to test whether home-monitoring results in better asthma control and less hospital admissions. Furthermore, some wearable devices or measurements should be adjusted to increase the adherence. Besides, new research should also focus on how to incorporate self-management of the asthmatic children and their parents in the home-monitoring of asthma.

When these research steps are made, wearable monitoring can aid management of childhood asthma in several ways. It might assist self-management of asthma, individualize asthma care, reduce healthcare expenses and increase the quality of care.

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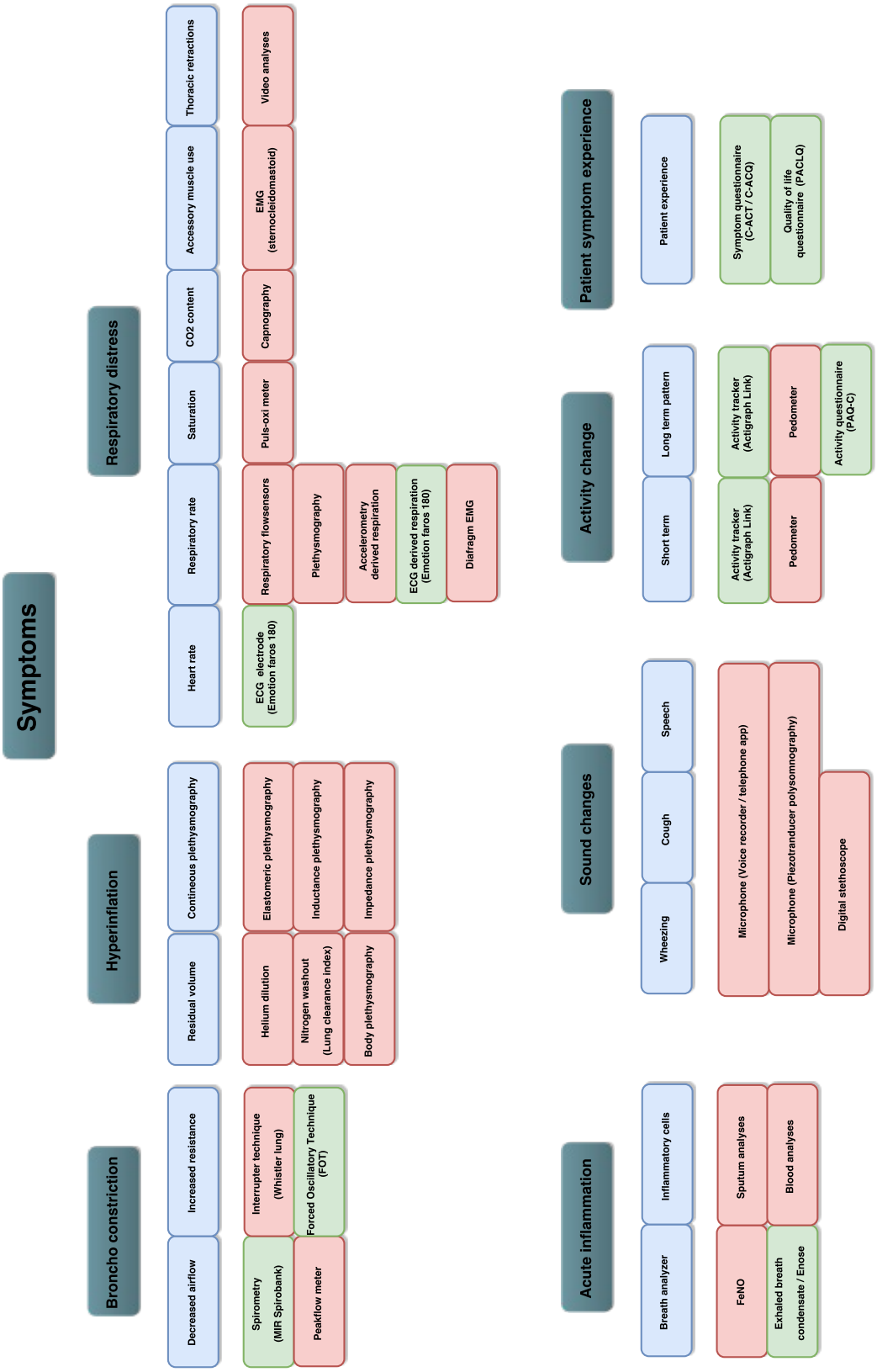
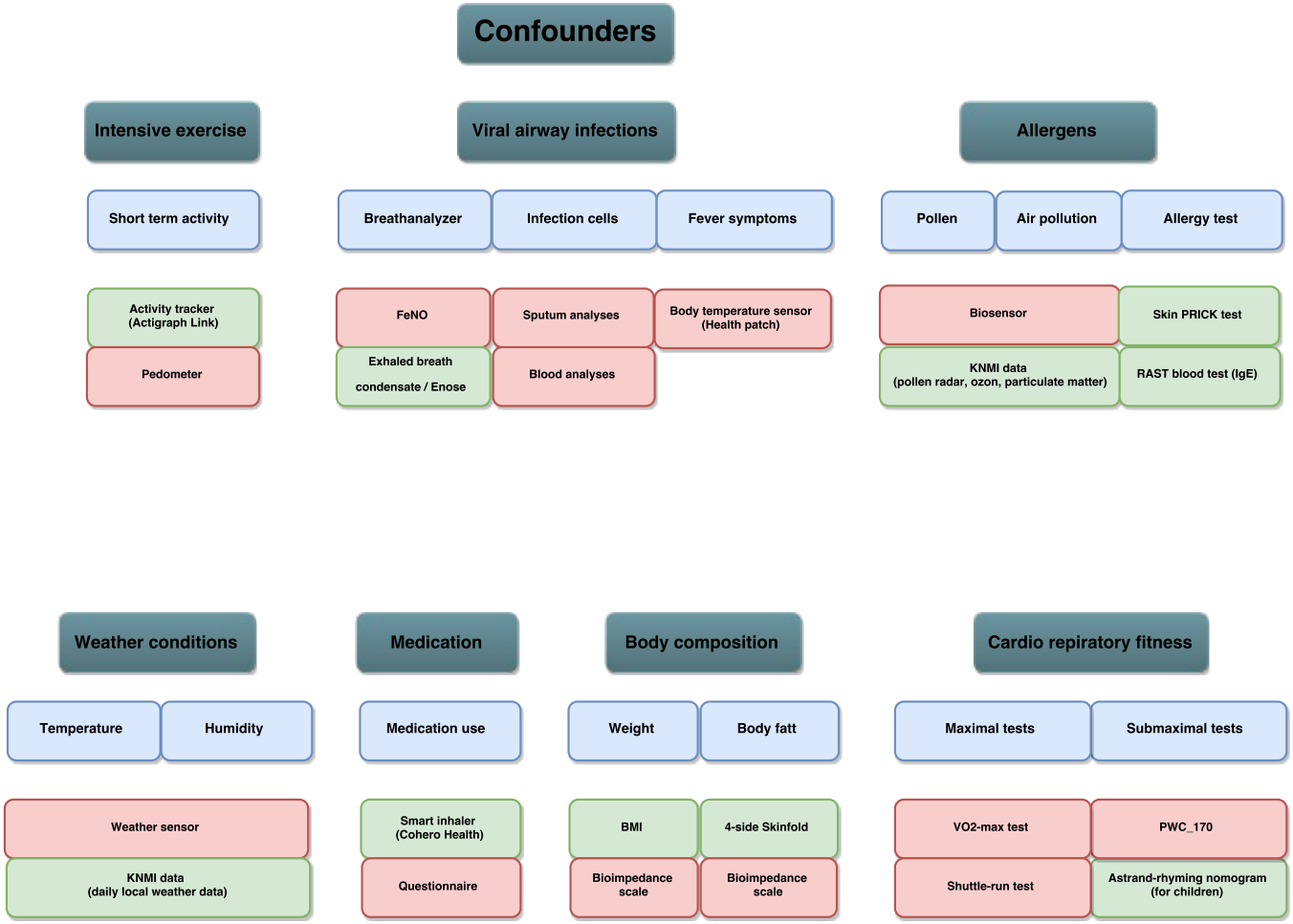
A Appendices

A.1 Parameter overview




Confounders
Intensive exercise
Short term activity
Activity tracker (Actigraph Link)
Pedometer
Viral airway infections
Breathanalyzer
Infection cells
Fever symptoms
FeNO
Sputum analyses
Body temperature sensor (Health patch)
Exhaled breath condensate / Enose
Blood analyses
Allergens
Pollen
Air pollution
Allergy test
Biosensor
Skin PRICK test
KNMI data (pollen radar, ozon, particulate matter)
RAST blood test (IgE)
Weather conditions
Temperature
Humidity
Weather sensor
KNMI data (daily local weather data)
Medication
Medication use
Smart inhaler (Cohero Health)
Questionnaire
Body composition
Weight
Body fatt
BMI
4-side Skinfold
Bioimpedance scale
Bioimpedance scale
Cardio repiratory fitness
Maximal tests
Submaximal tests
VO2-max test
PWC_170
Shuttle-run test
Astrand-rhyming nomogram (for children)

A.2 Study information letter and consent form

A.2.1 Parental information letter

ToetsingOnline nr: NL59878.044.16, de WEARCON studie

INFORMATIE OVER DEELNAME AAN EEN WETENSCHAPPELIJK ONDERZOEK

Wearable thuis-monitoring om astma controle, de WEARCON studie

ONDERZOEKERS: *dr. B.J. Thio, Kinderarts / M.R. van der Kamp, master student Technische Geneeskunde*

Geachte heer/mevrouw,

U heeft aangegeven geïnteresseerd te zijn in deelname van uw kind aan het bovengenoemde medisch-wetenschappelijk onderzoek. Dit onderzoek is opgezet in het MST om te testen of kleine draagbare meetapparaten (wearables) de mate van astma controle thuis kunnen vaststellen.

Voordat u en uw kind de beslissing nemen, is het belangrijk om meer te weten over het onderzoek. Lees deze informatiebrief rustig door. Bespreek het met elkaar, vrienden of familie. Verdere algemene informatie over meedoen aan zo'n onderzoek staat in de bijgevoegde brochure 'Medisch-wetenschappelijk onderzoek'.

Hebben u of uw kind na het lezen van de informatie nog vragen? Dan kunt u terecht bij de onderzoekers. Ook kunt u het bespreken met de onafhankelijke arts, die veel weet van het onderzoek. Op bladzijde 3 vindt u de contactgegevens (vraag 13).

1. Wat is het doel van het onderzoek?
Astma is een veel voorkomende chronische ziekte waar kinderen veel klachten, zoals benauwdheid, van kunnen hebben. Op dit moment is het voor kinderartsen, ouders en kinderen soms lastig om een goed beeld te krijgen van de oorzaken en klachten van het kind met astma. Iedere kind is immers anders. Om deze klachten beter te begrijpen vraagt de kinderarts een inspanningstest aan. Hierbij wordt er longfunctie onderzoek gedaan voor inspanning, na inspanning en na salbutamol (blauwe puf). Zo'n test vergt specialistische zorg en kan daarom maar beperkt uitgevoerd worden. Daarom wordt er nu onderzoek gedaan of thuis-monitoring, met behulp van wearables, een goede inschatting kan maken van de astma controle.

2. Welke wearables worden onderzocht?
Tijdens de studie worden verschillende wearables getest om te kijken welke meters nou het beste zijn om astma thuis te monitoren. Alle apparaten zijn voor kinderen veilig en makkelijk in gebruik. U kunt afbeeldingen van de wearables zien in de bijlage op pagina 4.

Onderzoek heeft uitgewezen dat kinderen met astma een ander activiteitenpatroon kunnen hebben. Daarom gebruiken we onder andere een activiteitsmeter om dit te meten. Deze geavanceerde meter meet niet alleen het aantal stappen maar ook heel nauwkeurig de duur en intensiteit van activiteit. De activiteitsmeter wordt met een bandje om de pols bevestigd.

Ook is het belangrijk voor het onderzoek dat we informatie hebben over hart- en longfunctie. Daarom wordt de hartslag en ademhaling gemeten met een hartslagmeter (ECG-patch) en zal ten tijde van benauwdheid en voor en na inspanning een longfunctie meting gedaan worden.

Verder wordt met een smartinhaler bijgehouden hoevaak inhalatie medicijnen genomen wordt. Deze meter wordt om de inhalator geklikt en registreert alle genomen puffen.

3. Hoe wordt het onderzoek uitgevoerd?
Voor de start van het onderzoek zullen u en uw kind een instructie krijgen van circa 30 minuten over het gebruik van de wearables voor dit onderzoek. Deze instructie kan bij u thuis of in ziekenhuis uitgevoerd worden, afhankelijk van uw voorkeur.

Vervolgens kan uw kind twee weken voor de inspanningstest beginnen met het dragen van wearables. Het is belangrijk dat de activiteiten meter altijd gedragen wordt. De enige uitzondering hierop zijn zwemactiviteiten. Ook is het belangrijk dat de hartslagmeter gedurende 2 dagen gedragen wordt om een sport-/gymactiviteit heen. Tijdens de instructie bespreken we welke 2 dagen de meter gedragen zal worden. Verder is het belangrijk dat uw kind de spirometer en de puffer met smart inhaler altijd bij zich heeft en gebruikt wanneer nodig. Verder vragen we van uw kind om aan het eind van elke week een vragenlijst van ongeveer 40 vragen in te vullen.

De inspanningstest waarvoor uw kind ingepland is, zal de afsluiting van het onderzoek zijn. Deze test zal verlopen volgens normaal protocol, zoals u daarvoor door de kinderarts bent ingelicht. De enige toevoegingen hierop zijn dat uw kind tijdens de test de wearables draagt, het gewicht van uw kind gemeten wordt met een geavanceerde weegschaal en de adem van uw kind geanalyseerd wordt met een apparaat dat de elektronische neus genoemd wordt. Na de test worden de wearables weer afgehaald en kunt u en uw kind naar huis. De inspanningstest zal niet langer duren dan normaal.

4. Wat wordt er van u en uw kind verwacht?
Er wordt van uw kind verwacht dat hij/zij de wearables draagt tijdens de twee weken monitoring en de geplande inspanningstest doet.

5. Wat zijn mogelijke voor- en nadelen van deelname aan dit onderzoek?
Uw kind heeft zelf geen direct voordeel van deelname aan dit onderzoek. Wel geeft de inspanningstest een inzicht in zijn/haar astma. Ook is het mogelijk dat het onderzoek tot nieuwe inzichten kan leiden die de diagnose/behandeling van astma in het algemeen zou kunnen verbeteren. Een nadeel van deelname kan zijn dat u en uw kind regelmatig moeten opletten of de wearables bijgedragen worden. De belasting van het onderzoek is zo klein mogelijk gehouden en er worden geen extra medicijnen toegediend. Er zijn dan ook geen risico's verbonden aan deelname aan dit onderzoek.

6. Wat gebeurt er als u of uw kind niet wenst deel te nemen aan dit onderzoek?
U en uw kind beslissen zelf of uw kind aan het onderzoek deelneemt. Deelname is vrijwillig. Als u of uw kind besluit niet mee te doen, hoeft u verder niets te doen. U hoeft niets te tekenen. U hoeft ook niet te zeggen waarom uw kind niet wilt meedoen. Als uw kind wel meedoet, kunt u of uw kind zich altijd bedenken en toch stoppen. Ook tijdens het onderzoek, mag uw kind op elk moment stoppen. Als uw kind zich tijdens het onderzoek verzet – denk hierbij aan sterke angst, verdriet of boosheid – dan wordt het onderzoek gestopt.

7. Wat gebeurt er als het onderzoek is afgelopen?
Na twee weken thuismonitoring zal de inspanningstest plaatsvinden. Na deze test is het onderzoek afgerond.

8. Is uw kind verzekerd wanneer hij/zij aan het onderzoek meedoet?
Deelname aan dit onderzoek heeft een dermate laag risico dat ontheffing van verzekering is verkregen. Meer informatie over de algemene verzekering kunt u vinden in de Algemene Brochure.

9. Worden u en uw kind geïnformeerd als er tussentijds voor u relevante informatie over de studie bekend wordt?
Als blijkt dat tussendoor relevante informatie bekend wordt, bespreken we dat direct met u. U en uw kind beslissen dan zelf of uw kind met het onderzoek wil stoppen of doorgaan. Als uw kind zijn/haar veiligheid of welbevinden in gevaar is, stoppen we direct met het onderzoek.

10. Wat gebeurt er met de gegevens van uw kind?
Al uw kind zijn/haar gegevens blijven vertrouwelijk. De meetresultaten worden gecodeerd opgeslagen, nooit met naam. De sleutel voor de code blijft bij de onderzoekers van de Kindergeneeskunde. Ook in rapporten over het onderzoek wordt alleen die code gebruikt.
Sommige mensen mogen uw medische en persoonsgegevens inzien. Dit is om te controleren of het onderzoek goed en betrouwbaar uitgevoerd is. Algemene informatie hierover vindt u in de brochure 'Medisch-wetenschappelijk onderzoek'.
Mensen die de gecodeerde meetresultaten mogen inzien zijn: De onderzoekers van de kindergeneeskunde en de onderzoekers van de ademanalyse, de Medisch Ethische Toetsingscommissie Twente (METC Twente), een controleur die door de Raad van Bestuur MST is ingehuurd en de Inspectie voor de Gezondheidszorg. Zij houden uw kind zijn/haar gegevens geheim.
De gegevens van de smart inhaler worden in eerste instantie opgeslagen op een online platform van de fabrikant zelf. Het bedrijf mag deze data gebruiken om de app te kunnen verbeteren. Het bedrijf mag echter geen data verkopen, delen, verhuren of verhandelen. De data wordt direct na de studie van het online platform verwijderd.
De gecodeerde onderzoeksgegevens worden na afloop van het onderzoek 15 jaar bewaard. Misschien kunnen we daar later een ander onderzoek mee uitvoeren binnen hetzelfde onderzoeksgebied. Als u of uw kind dat niet wilt, kunt u dit aangeven op het Toestemmingsformulier. Als u of uw kind aan het einde van de studie de resultaten via e-mail willen ontvangen, dan kunt u dat aangeven op het Toestemmingsformulier.

11. Is er een vergoeding wanneer u besluit aan dit onderzoek mee te doen?
Voor deelname aan het onderzoek wordt geen vergoeding uitgekeerd. Uw kind zal wel een kleine attentie krijgen als dank voor deelname.

12.Welke medisch-ethische toetsingscommissie heeft dit onderzoek goedgekeurd?
Voor dit onderzoek is toestemming verkregen van de Raad van Bestuur van het MST Enschede na een positief oordeel van de Medisch Ethische Toetsingscommissie Twente (METC Twente). Meer informatie over de goedkeuring vindt u in de Algemene brochure (Bijlage 1).

13. Wilt u of uw kind verder nog iets weten?
U en uw kind heeft minimaal vijf werkdagen bedenktijd voor deelname aan dit onderzoek. Als u of uw kind nog vragen heeft over het onderzoek, kunt u contact opnemen met uitvoerend onderzoeker dhr. M.R. van der Kamp (tel. 06-36200803 en mail *m.vanderkamp@mst.nl)* of de behandelend kinderarts via telefoonnummer 053-4872310. Als u of uw kind vragen heeft voor of tijdens het onderzoek, die u liever niet aan de onderzoekers stelt, kunt u contact opnemen met de onafhankelijke arts dhr. Eijsvogel via telefoonnummer 053-4872610.

14. Hoe te handelen bij klachten?
Als u of uw kind klachten heeft kunt u dit melden aan de onderzoeker of aan uw behandelend arts.

Met vriendelijke groet,

Dr. Boony Thio, Hoofdonderzoeker en Kinderarts
Mattienne van der Kamp, uitvoerend onderzoeker en student Technische Geneeskunde

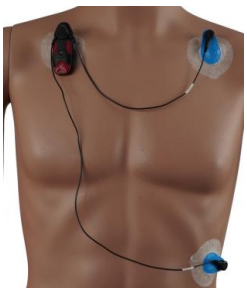
Bijlagen
- Algemene brochure medisch-wetenschappelijk onderzoek met mensen
- Voorbeelden wearables
- Toestemmingsformulier

Bijlage: voorbeelden van de wearables

Smartinhaler

Activiteitsmeter

Spirometer



Hartslagmeter

Toestemmingsformulier

Titel van het onderzoek:
Wearable thuis-monitoring om astma controle bij kinderen vast te stellen, de WEARCON studie

ToetsingOnline nr: NL59878.044.16
Versie 3, 17-01-2017

Ik ben gevraagd om toestemming te geven voor deelname van mijn kind aan dit medisch-wetenschappelijke onderzoek:

Naam proefpersoon (kind): ..... Geboortedatum: .... /.... / .....

Ik heb de informatiebrief (versie 3) voor de proefpersoon gelezen. Ik kon aanvullende vragen stellen. Mijn vragen zijn naar tevredenheid beantwoord. Ik had genoeg tijd om te beslissen of mijn kind mag meedoen.

Ik weet dat meedoen helemaal vrijwillig is. Ik weet dat mijn kind op ieder moment kan beslissen om toch niet mee te doen. Daarvoor hoeft mijn kind geen reden op te geven.

Ik weet dat sommige mensen de gegevens van mijn kind kunnen zien. Die mensen staan vermeld in de informatiebrief.

Ik geef toestemming om de gegevens van mijn kind te gebruiken, voor de doelen die in de informatiebrief staan.

Ik geef toestemming om de onderzoeksgegevens van mijn kind 15 jaar na afloop van dit onderzoek te bewaren.

Ik geef toestemming om mij en mijn kind in de toekomst opnieuw te benaderen voor deelname aan nieuw onderzoek.

☐ Ja

☐ Nee

Ik wil de uitslag van het onderzoek via de mail ontvangen:

☐ Ja , graag op het volgende e-mail adres: ……..

☐ Nee

Ik wil mijn kind laten meedoen aan dit onderzoek.

Naam ouder/verzorger*: Naam ouder/verzorger*:

Datum : __ / __ / __ Datum : __ / __ / __

Handtekening: …… Handtekening: ……..

Ik verklaar hierbij dat ik de ouders van deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Een kopie van de informatiebrief en ondertekende verklaring wordt meegegeven aan de proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger):

Handtekening: Datum: __ / __ / __

Aanvullende informatie is gegeven door (indien van toepassing):

Naam:

Functie:

Handtekening: Datum: __ / __ / __

---

* Doorhalen wat niet van toepassing is.

A.2.2 Children information letter

INFORMATIE OVER HET MEEDOEN AAN EEN ONDERZOEK

Het meten van astma controle met wearables, de WEARCON studie

ONDERZOEKERS: *Dokter Thio, Kinderarts en Mattienne van der Kamp, student Technische Geneeskunde*

Beste ..... ,

Leuk dat je misschien wilt meedoen aan dit onderzoek. Voordat je definitief de beslissing neemt, is het belangrijk om meer te weten over het onderzoek. Lees deze informatiebrief rustig door en praat erover met je ouders, vrienden of familie. Heb je na het lezen van de informatie nog vragen? Dan kun je altijd contact opnemen met ons.

Waarom doen we dit onderzoek?
Astma is een veel voorkomende ziekte waar kinderen heel veel last van kunnen hebben. Om dat te voorkomen geeft de arts medicijnen, zoals bijvoorbeeld puffjes. Maar het is voor een arts en ook voor jou of je ouders soms moeilijk om in te schatten hoe het nu eigenlijk gaat met je astma. Daarom is het dus ook lastig om te weten welke medicijnen nodig zijn. Met dit onderzoek willen we kijken of we met een aantal kleine apparaten ("wearables") kunnen meten hoe je astma ervoor staat, zodat de arts beter weet hoe je het beste behandeld kan worden.

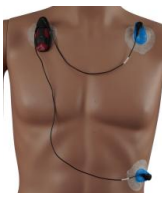
Wat houdt het onderzoek in?
Voor dit onderzoek vragen we je om 2 weken verschillende "wearables" te dragen. Hieronder staan de apparaten op een rijtje:

1. *Een activiteiten meter*

Dit apparaat doe je om de pols en meet hoe lang je actief bent en hoe zwaar die activiteiten zijn.

2. *Een hartslag meter*

Deze hartslag meter bestaat uit 3 plakkers voor op de borst. Hiermee kunnen we de hartslag en de ademhaling meten. Deze wordt onder de kleding gedragen. De meter wordt door jou voor het douchen of zwemmen los gehaald en daarna weer vastgeklikt, de plakkers kunnen dan blijven zitten.



3. *Een spirometer*

Een spirometer is een apparaat waarmee je longen worden opgemeten. Het apparaat meet hoe hard je blaast. Het is de bedoeling dat je het apparaat altijd bij je hebt. De meting doe je wanneer je je benauwd voelt en voor en na een sporttraining of wedstrijd.

4. *Een smart inhaler*

Een smart inhaler is een apparaat dat je om je puffer zet. Het apparaat onthoudt wanneer jij een puff neemt.

Wat moet ik verder nog doen in die 2 weken?
Het onderzoek zal starten met een uitleg van de "wearables". Deze uitleg kan bij jou thuis of in het ziekenhuis gegeven worden en duurt ongeveer 30 minuten. Het is belangrijk dat je de activiteiten meter altijd om je pols draagt, behalve als je gaat zwemmen. Ook is het belangrijk dat je de hartslagmeter 2 dagen draagt. Tijdens de uitleg bespreken we met jou en je ouders welke 2 dagen dat zijn. Verder is het belangrijk dat je de spirometer en de puffer met smart inhaler altijd bij je hebt en gebruikt wanneer nodig. Naast deze metingen vragen we je aan het einde van elke week een vragenlijst van ongeveer 40 vragen in te vullen over je activiteiten en astma.

Wat gebeurt er als de 2 weken meten erop zitten?
Nadat je 2 weken de wearables gedragen hebt, zal er een inspanningstest zijn. Deze test is aangevraagd door jouw kinderarts en je zult hierover per brief informatie krijgen. Bij deze test wordt gekeken hoe je ademhaalt voor en na inspanning. Zo kunnen we zien hoe je astma ervoor staat en of de puffjes die je gebruikt werken.

Voor dit onderzoek zullen we tijdens de inspanningstest twee metingen extra doen.

We gaan namelijk je gewicht meten met een speciale weegschaal (zie het plaatje hiernaast). Deze meet niet alleen je gewicht maar ook hoeveel van dit gewicht spier, vet of bot is. Het apparaat meet door de handen en je voeten en zal geen pijn doen.

Ook gaan we je adem meten in een ander apparaat die we de "elektronische neus" noemen. Je wordt gevraagd om uit te blazen in het apparaat. De "elektronische neus" meet dan je adem. Zo kunnen we onderzoeken of bij astma je adem verandert.

Wat als ik niet meer mee wil doen aan dit onderzoek?
Je beslist samen met je ouders of je mee wilt doen aan het onderzoek. Als je niet mee wilt doen hoef je verder niks te doen. Ook kun je op elk moment tijdens het onderzoek zonder reden stoppen met het onderzoek als je dat wilt.

Wil je verder nog iets weten?
Als je nog vragen hebt over het onderzoek, kunnen jij of je ouders altijd contact opnemen met Mattienne van der Kamp (tel. 06-36200803 en mail *m.vanderkamp@mst.nl)*

A.3 Clinical research form

Proefpersoon nummer:
Leeftijd:

Ocon Invullijst:

Anamnese:

Klachten: Benauwd / Hoesten / Piepen / Kortademig /...../.....

Frequentie klachten: .....per week **'s nachts?:** Ja / Nee **Bij inspanning:** Ja / Nee

Sport: ..... **Aantal uur per week:** .....

Astma medicatie: .....(...dd....) .....(....dd.....)

..... (...dd....) .....(....dd.....)

Therapie trouw?: Ja / Nee .....

Allergisch?: Ja / Nee > zoja wat, ... **All.Test**: Ja/Nee Bloed/Prik

Familie: Ja / Nee > zoja wie, ...

Prematuur?: Ja / Nee **Roken:** Roken/Ouders binnen/Ouders buiten/Niet roken **Koffie:** Ja / Nee

Zwemdiploma, probleem gat?: Ja / Nee .....

LO:

Meyers: Ja / Nee **Dannie-Morgan lines:** Ja / Nee

Lengte: ..... cm **Gewicht:** ..... kg

Auscultatie: .....

Skinfold

Biceps: ..... Subscapular: .....

Triceps: ..... Suprailiac: .....

Breath free sampler:

Opmerkingen: .....

De Test:

Springkussen / Loopband

Indien loopband

	Band snelheid (km/h)	**HR (bpm)**	*Opmerkingen*
T=1			
T=3			
T=5			

Indien Springkussen

Opmerkingen:

Longfunctie

Tijdstip	**FEV1**			*FEV0.5*	*Opmerkingen*
Baseline					
Inspanning (2min)					
Inspanning (4min)					
T=1					
T=3					
T=6					
(T=9)					
Na salbutamol					

FOT

Tijdstip	**R5**	**X5**	**Fres**	*Opmerkingen*
Baseline				
T=5				
Na salbutamol				

A.4 Wearable information

A.4.1 MIR Spirobank II smart spirometer

MIR is a global medical device company founded in 1993 and is a recognized name in the market areas; spirometry, oximetry and telemedicine. The latest version of their portable spirometry is the Spirobank II smart.

Name and description The Spirobank II is a medical device in which a turbine flow sensor measures respiratory flow. It is a hand-held device with Bluetooth connectivity, which makes real-time monitoring possible. Besides, the device is simple to operate. With only three buttons a spirometry test can be started. All these features make this device suitable for home-monitoring purposes.

Measurement principles The turbine of the Spirobank has a rotor which rotates with a speed, which is dependent on the delivered respiratory flow. An infra-red sensor detects the amount of rotations, which thus is a measure of respiratory flow. Flow can be measured with an accuracy of $\pm$5% or 200 ml/s. Volume parameters are extracted from integrating the flow-time signal, resulting in an accuracy of $\pm$3% or 50ml.

The device further has a build-in temperature sensor for Body Temperature Pressure Satured (BTPS) correction for flow and volume [156].

Measurement parameters The Spirobank smart is able to measure a complete set of spirometry parameters, such as the forced vital capacity (FVC), vital capacity (VC), forced expiratory volume in one second (FEV_1), peak expiratory flow (PEF), mean expiratory flow between 25 and 75% of the maximal flow (FEF_{25-75}). Furthermore, $FEV_{0.5}$ can be measured, which is relevant for assessing lung function of young children with asthma [149, 157].

Spirobank software (Winspiropro) aligns the measured lung function parameters to the international standards reference set of the GLI (Global Lung Function Initiative). These equations refer to multi-ethnic reference values for spirometry for the 3 to 95 year age range [158].

Certifications The MIR company is certificated with an ISO 9001, insuring quality management system of the organization. The MIR Spirobank is provided with CE certification.

Summary of findings from non-clinical studies The Spirobank spirometer received the label "meets American Thoracic Society (ATS) recommendations" [159]. This label supposes that the spirometers were checked by a series of predetermined flow-volume curves via a computer-driven piston pump [113].

G. Liistro et al. [159] performed a comparison study of multiple office spirometers. They were compared to standard diagnostic spirometers (Sensormedics and Morgan medical). The Spirobank showed similar limits of precision to the standard spirometers. In addition, a Bland-Altman analysis was performed. This showed a non significant proportional difference of the Spirobank, indicating comparable agreement.

Degryse et al. [100] showed in another laboratory study that the Spirobank spirometer performed very well, displaying an underestimation of the FEV_1 and FEV_1/FVC of 2-5%. High correlations were found for all pulmonary function parameters, varying from 0.864 to 0.949. Therefore they concluded; "The Spirobank device seems to be appropriate for research purposes if the standardized protocol is used correctly and the acceptability criteria are respected."

Summary of findings from clinical studies According to the NAEPP expert panel, history and physical examination alone are not reliable to accurately diagnose asthma [95]. Global Initiative for Asthma (GINA) experts recommend spirometry to be performed on children five years of age and older. Spirometry with maximal expiratory flow–volume curves is considered to be the gold standard for the assessment of lung function in children with asthma [28, 160].

M. Wördemann et al. [161] performed a cross-sectional study of 1320 children, aged 4–14 years, to examine the relationship of intestinal Helminth infections with asthma, allergic rhinoconjunctivitis, atopic

dermatitis and atopy. In this study Spirobank spirometry was used to demonstrate asthma after an exercise challenge test, conform ATS guidelines.

The MIR Spirobank is further an often used spirometer in clinical trials with children [162, 163].

Summary of known and potential risks and benefits No potential risks of using spirometry are known or expected. However, in young children forced spirometry maneuvers are difficult to perform correctly, which could lead to misinterpretation of the results by patients/parents themselves. Therefore, all children and parents are instructed to not watch and act on the results of the spirometry. Benefits of this device are the small size and the reliability and accuracy of the MIR spirometers. Furthermore, this device has Bluetooth connection which makes it usable for future real-time monitoring.

Several spirometers and other lung function devices (such as FOT and interrupter techniques) were evaluated. For example the Whistler lung, Piko 6 or the microDiary. There was chosen for the MIR spirobank II, because of its suitability for home-monitoring, due to its size and user-friendliness. Additionally, the device can store enough measurements and has enough battery capacity for 2 weeks of monitoring. Besides, the reliability of the MIR company for lung function devices was taken into account. One other decisive criteria was the ability of the MIR's Spirobank to measure $FEV_{0.5}$, because this parameter is useful for lung function in young children.

A.4.2 Actigraph wGT3X-BT activity tracker

The company of Actigraph was founded in 2004, after several years of technical refinements and scientific validation of the "Actigraph" device. Since then, Actigraph has become internationally recognized for ambulatory activity monitoring systems.

Name and description The wGT3X-BT is ActiGraph's latest activity monitor. It uses 3-axis accelerometer and digital filtering technology for activity assessment. In addition, it includes integrated wear time and ambient light sensors. This device can be worn on the wrist and is equipped with a Bluetooth connector.

Measurement principles The wGT3X-BT activity tracker makes use of a 3-axis MEMS accelerometer. This sensor converts mechanical acceleration into an electrical signal. An electrical signal is generated by a change in capacitance, which is caused by an increase in distance between the electrodes. The device can measure up to an acceleration of 8 G. The sample frequency of acceleration can be set from 30 to 100 Hz and battery life is at least 20 days, depending on the chosen sample frequency and Bluetooth settings.

A wear time sensor on the back of the monitor uses capacitive touch technology to automatically detect when a wrist worn device has been removed. This technology is also used in the touchscreen of mobile phones.

Light intensity is measured with a lux sensor in the device. It measures light intensity with a photodetector in the unit lux (lumen per square meter).

Measurement parameters Activity will be measured and stored in the so called "Counts". These counts are a result of summing post-filtered accelerometer values into blocks of a certain time period (epochs). The count value will vary based on the frequency and intensity of the raw acceleration. Further analysis on these counts versus time data can provide parameters such as, the total amount of activity (steps and minutes of activity), the intensity of activity (sedentary, light moderate or vigorous) and the duration of activity bouts [164]. Furthermore, the Actigraph could measure the body position based on the accelerometry data. This could be a relevant parameter to measure sedentary time in a sitting or laying down position, outside school times. This parameter could be an indication of television/tablet screentime, which was showed to be increased in children with asthma [165].

Sleep detection can be measured based on the activity. Sleep-wake scoring algorithms of Sadeh [166] and Cole-Kripke [61] are used to analyze the accelerometer data.

Light intensity is measured with a lux sensor in the device. It measures light intensity in amount of lux, also; lumen per square meter. With this parameter a division can be made between outdoor activities (1000+ LUX) and indoor activities (500- LUX) [104].

Certifications The Actigraph is provided with CE certification.

Summary of findings from non-clinical studies The Actigraph activity trackers are widely used for research purposes and most frequently referred to in literature [106].

Activity recognition has mostly been studied in supervised laboratory settings. M. Ermes et al. showed that activity trackers also have to be validated in a non-controlled out-the-laboratory setting [105]. The Actigraph is validated for assessment of activity in children, in both laboratory and outdoor environments [106, 107]. For example, Trost et al. [108] showed that the Actigraph accelerometer can provide useful estimates of moderate to vigorous physical activity in toddlers.

Activity analysis of the activity trackers are performed with data processing algorithms. An example of such a children based processing algorithm is that of Freedson et al. [164]. New research of Ellingson et al. [167] is even focusing on machine learning processing algorithms for activity tracking, which had an overall classification agreement of 79%.

Summary of findings from clinical studies Over the last decades, wearable activity trackers are of interest to monitor patients their physical activity and energy expenditure. Devices are used in many different areas of research and medicine, for example in cardiology, revalidation medicine, geriatrics, sports medicine, sleep medicine and particularly in the pediatric department. [109]

In the asthmatic population several clinical trials were performed with Actigraph activity trackers and showed that the Actigraph is a clinical feasible activity tracker in children. For example, Eijkemans et al. [80] tested the hypothesis that children with asthmatic symptoms are less physically active. Dunton et al. [101] used the Actigraph to measure physical activity in asthmatic children to determine the relation with psychological stress.

Clinical studies with the Actigraph reported that the agreement rate between polysomnography and actigraphy for sleep/wake state determination is in the range of 85% to 96% [102]. Therefore, actigraphy provides an alternative for assessing bedtime and wake time with diary data [103].

A report of Flynn et al. [104] showed that the Actigraph light sensor is able to detect outdoor and indoor activity, of children, during a school-day validation, with 97% accuracy. The lux threshold was determined to be 240 lux.

Summary of known and potential risks and benefits No potential risks of wearing the wGT3X-BT Actigraph are known or expected. Benefits of this device are the small size, the water resistance and the diversity of parameters, besides activity, which can be measured with this device, such as sleep, light intensity or body position. Furthermore this device has Bluetooth connection which makes it usable for future real-time monitoring. This combined with the fact that it is one of the most used activity trackers for research purposes made use choose for this device.

There are many activity trackers for the consumer market. However, these activity trackers are often focused on showing interpretable results to the user and not to extract raw data from. Additionally, the devices often show lesser specifications. Therefore, these devices are not suited for this research purpose. There was chosen for the Actigraph because this device is made for research purposes only. The device is very suitable for home monitoring and is an often used and validated device in literature. The device could store enough continuous data with epochs of 1 second for 2 weeks of monitoring and the battery is sufficient for that period too. Furthermore, the Actigraph could be set-up before the children receive the device and be read out afterwards. So that the children or their parents do not have to sync, set-up or do anything with the device except wearing it. The extra sensors and analyses of the device/software (light intensity, sleep registration, position and wear sensor) made this the best suitable device, available on the market, for this study. After inquiry, the device was also recommended by researchers from the Roessingh Research and Development for this study purpose.

A.4.3 Cohero Health smart inhaler

Cohero Health is a company with the goal to be able to track how patients are using their respiratory medication and how they are responding to their medication, in real-time.

Name and description The smart medication inhalers of Cohero Health track adherence for both asthma controller medication and rescue medication. The device works with a push sensor at the top of the device, so that the medication use is registered when a inhalator puff is used. The dates and times of usage are stored internally, with a data capacity of 30. To empty the storage it can be synchronized with the mobile Breathesmart^{TM} app, using Bluetooth connection.

The investigator can real-time monitor medication usage in the accompanied online platform of Cohero Health. This platform is secured with a user-account which is only accessible by the investigator.

Summary of known and potential risks and benefits No potential risks of the smart inhalers are known or expected. A disadvantage of the device is the storage limit of 30 measurements. In the most controlled asthma patients this is sufficient for a 2 week monitoring period. However, severe asthma patients often use more puffs and therefore have to sync the device with a smart phone after several days. A benefit of this device is its design, which makes it possible to add the device to the medication inhaler of the child. Another benefit is that the device does not directly show the amount of puffs so that behavior of the child cannot adapt based on the results of the measurements. Furthermore, this device has Bluetooth connection which makes it usable for future real-time monitoring.

Multiple smart inhalers were considered, such as the smart inhalers of Adherium or 3M. However, they require specific brands of asthma medication. The Cohero Health smart inhaler is a device which could be placed around various dosis-aerosols, due to its flexible design. Therefore, children could remain using the same dosis-aerosol as they did before the study. Furthermore the device does not directly show medication adherence to the patient and the device does only have to be synced with a smartphone when more than 30 puffs were taken.

A.4.4 eMotion Faros 180° ECG patch

Name and description The eMotion Faros 180° is a small, low weight ECG monitor. Due to this compact design the Faros is applicable for ambulatory ECG recording even in child's play. The device has an internal storage of at least 60 days and a rechargeable battery that lasts around 3 days. This makes it very useful for home-monitoring. The eMotion Faros Sensor can be used for the purpose of health monitoring, biofeedback and scientific research.

Measurement principles The electrodes of the device register small electrical voltages, originating from the heart. Voltage differences over the electrodes (leads) are then amplified and displayed. This ECG signal contains information about the heart rhythm.

Measurement parameters: Based on the raw ECG signal, heart rate can be analyzed. Furthermore, respiration rate can be extracted from the ECG signal. There are two common used methods for extracting respiratory rate of the ECG signal; respiratory sinus arrhythmia (RSA) and the QRS amplitude change. RSA is based on the physiological principle that heart rate increases with inspiration (R-R interval decreases) and decreases with expiration (R-R interval increases). Therefore, the R-R interval series can be used to extract a respiration signal. Another method is the QRS amplitude change. During inspiration the voltage of the QRS peak is higher, due to the changing distance between heart and electrodes. This variation of these voltages over time can therefore be used to distinguish between fully inspired and fully exhaled states and thus be used as a measure of respiratory rate. [168] However, several other ECG-derived respiration methods were also described [169, 170].

Certifications The eMotion ECG patch is provided with CE certification for medical electrical equipment (EN60601-1) and ambulatory electrocardiograph (EN60601-2-25).

Summary of findings from non-clinical studies Kalhoudi et al. [171] published an European Commission funded project, which thoroughly categorized sensors in terms of observables/conditions monitored, detailed technical specifications and the application modality. This project recommended the Faros 180° and 90° for ECG recording at home.

Furthermore, several articles were published on the technical details of this type of ECG monitoring patches [172–174]. Accuracy of this device was tested and approved according to standard (EN60601-2-25).

Summary of findings from clinical studies No clinical studies using the eMotion Faros 180° could be found. However, other small wireless ECG devices are often used in clinical studies [175].

Summary of known and potential risks and benefits No potential risks of the ECG-patch are known or expected. However, this device uses a bio-impedance measurement to check if the electrodes are still in place. Therefore, all patients with electrical stimulating device are excluded. It is not expected that this very small current could influence electrical stimulating devices, because no events were known with this kind of devices and the device has a CE mark for ambulatory electrocardiograph. However, still precaution is taken.

The main benefit of this device is its feasibility, the compatibility with MATLAB for data analysis and the fact that it has a event button for if the subject gets an asthma exacerbation. This patch is yet suitable for real-time monitoring (it already has a Bluetooth connection). It is not completely waterproof. The device was chosen because it is the most feasible non-invasive ECG monitor that is available at this moment and its accuracy is tested and approved [171]. Furthermore the Faros 180° has a sampling frequency of 1000 Hz, which makes it very suitable for research purposes.

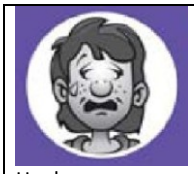
Data-analysis of these ECG signals is expected to reveal accurate continuous heart rates. However, a critical note must be made that the continuous respiratory rate derived indirectly with purely ECG-derived respiration algorithms is not the most accurate type of respiration measurements [169]. However, given the poor availability of suitable devices this method was chosen. The investigator will test the Faros 180° and the algorithm in a clinical validation environment on himself, so that accuracy of the respiration signal could be taking into account when reviewing the results of the study.

A.5 Questionnaires

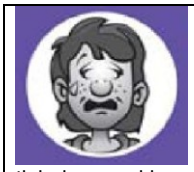
A.5.1 C-ACT

Vragenlijst astma klachten

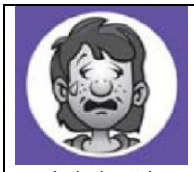
1. Hoe was het afgelopen week met je astma?

 Heel erg. ☐	 Erg. ☐	 Goed. ☐	 Heel goed. ☐

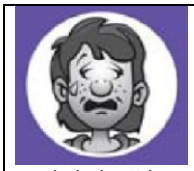
2. Hoeveel last heb je van astma als rent, traint of sport?

 Ik heb er veel last van, ik kan niet doen wat ik wil. ☐	 Ik heb er last van en vind het vervelend. ☐	 Ik heb er een beetje last van, maar het gaat wel. ☐	 Ik heb er geen last van. ☐

3. Moet je hoesten door je astma?

 Ja, de hele tijd. ☐	 Ja, meestal. ☐	 Ja, soms wel. ☐	 Nee, nooit. ☐

4. Word je 's nachts wakker door je astma?

 Ja, de hele tijd. ☐	 Ja, meestal. ☐	 Ja, soms wel. ☐	 Nee, nooit. ☐

Versie 1: C-ACT vragenlijst / datum 25-11-2016

Beantwoord als ouder de volgende vragen:

5. Hoeveel dagen had uw kind de afgelopen week overdag astma klachten?

Helemaal niet	1 dag	2 dagen	3-4 dagen	5-6 dagen	Elke dag
☐	☐	☐	☐	☐	☐

6. Hoeveel dagen had uw kind de afgelopen week overdag last van piepende ademhaling door de astma?

Helemaal niet	1 dag	2 dagen	3-4 dagen	5-6 dagen	Elke dag
☐	☐	☐	☐	☐	☐

7. Hoeveel dagen werd uw kind de afgelopen week ’s nachts wakker door de astma?

Helemaal niet	1 dag	2 dagen	3-4 dagen	5-6 dagen	Elke dag
☐	☐	☐	☐	☐	☐

A.5.2 PAQ-C

Versie 2: PAQ-C vragenlijst / datum 20-12-2016

Activiteiten Vragenlijst

Geslacht: Jongen / Meisje

Leeftijd: ……. Groep/Klas: ……

Deze vragenlijst gaat over je activiteiten van de afgelopen 7 dagen (de afgelopen week). Hieronder vallen alle (sport)activiteiten die je hebben laten zweten of die je benen moe hebben laten voelen of activiteiten die je sneller hebben doen ademen (bijvoorbeeld touwtje springen, rennen, klimmen).

Deze vragenlijst is geen toets. Dus er zijn geen goede of foute antwoorden. Vul de vragen naar waarheid en zo nauwkeurig mogelijk in.

---

1. Activiteit in je vrije tijd: Heb je één van de volgende activiteiten in de afgelopen 7 dagen (vorige week) gedaan? Zo ja, hoe vaak? (vul slechts één cirkel per rij in)

Activiteit	**Niet**	**1-2 keer**	**3-4 keer**	**5-6 keer**	**7 of meer keren**
Tikkertje	○	○	○	○	○
Touwtje springen	○	○	○	○	○
Rennen	○	○	○	○	○
Klimmen	○	○	○	○	○
Fietsen	○	○	○	○	○
Wandelen (intensief)	○	○	○	○	○
Skateboarden	○	○	○	○	○
Skeeleren	○	○	○	○	○
Gymnastiek/turnen	○	○	○	○	○
Zwemmen	○	○	○	○	○
Dansen	○	○	○	○	○
Voetbal	○	○	○	○	○
Hockey	○	○	○	○	○
Basketbal	○	○	○	○	○
Volleybal	○	○	○	○	○
Schaatsen	○	○	○	○	○
Tennis	○	○	○	○	○
Badminton	○	○	○	○	○
Judo	○	○	○	○	○
Atletiek	○	○	○	○	○
Handbal	○	○	○	○	○
Honkbal/Softbal	○	○	○	○	○
Fitness	○	○	○	○	○
Anders:					
……	○	○	○	○	○
……	○	○	○	○	○

Versie 2: PAQ-C vragenlijst / datum 20-12-2016

2. Hoe vaak was je tijdens de gymles afgelopen week erg actief (tikkertje, rennen, springen, etc.)? (1 antwoord invullen)

Ik doe niet mee met de gym.	○
Bijna nooit	○
Af en toe	○
Vaak	○
Altijd	○

3. Wat heb je voornamelijk de afgelopen 7 dagen in je pauzes (op school) gedaan? (1 antwoord invullen)

Zitten (praten, lezen, huiswerk)	○
Gestaan en rond gelopen	○
Een beetje gerend en gespeeld	○
Redelijk veel gerend en gespeeld	○
Bijna alleen maar gerend en gespeeld	○

4. Wat heb je de afgelopen 7 dagen tijdens lunchtijd gedaan (behalve het eten van de lunch)? (1 antwoord invullen)

Zitten (praten, lezen, huiswerk)	○
Gestaan en rond gelopen	○
Een beetje gerend en gespeeld	○
Redelijk veel gerend en gespeeld	○
Bijna alleen maar gerend en gespeeld	○

5. Hoe vaak heb je de afgelopen 7 dagen actief gesport, gedanst of gespeeld nadat je thuis kwam uit school? (1 antwoord invullen)

Niet	○
1 keer	○
2-3 keer	○
4-5 keer	○
6 keer of meer	○

6. Hoe vaak heb je de afgelopen 7 dagen actief gesport, gedanst of gespeeld in de avonden? (1 antwoord invullen)

Niet	○
1 keer	○
2-3 keer	○
4-5 keer	○
6 keer of meer	○

7. Hoe vaak heb je het afgelopen weekend actief gesport, gedanst of gespeeld? (1 antwoord invullen)

Niet	○
1 keer	○
2-3 keer	○
4-5 keer	○
6 keer of meer	○

8. Welke van de onderstaande zinnen beschrijft jou het beste als je kijkt naar de afgelopen 7 dagen? Lees alle 5 zinnen voordat je er één uitkiest.

A. Ik heb bijna al mijn vrije besteed tijd aan zaken waarbij lichte activiteit komt kijken.	○
B. Ik heb af en toe (1-2 keer) activiteit vertoond in mijn vrije tijd (bijv. sporten, rennen, zwemmen, fietsen, etc.).	○
C. Ik heb regelmatig (3-4 keer) activiteit vertoond in mijn vrije tijd.	○
D. Ik heb vrij vaak (5-6 keer) activiteit vertoond in mijn vrije tijd.	○
E. Ik heb zeer veel (7 keer of meer) activiteit vertoond in mijn vrije tijd.	○

9. Geef aan hoeveel activiteit je onderging per dag van afgelopen week.

	Niet	Weinig	Gemiddeld	Veel	Zeer veel
Maandag	○	○	○	○	○
Dinsdag	○	○	○	○	○
Woensdag	○	○	○	○	○
Donderdag	○	○	○	○	○
Vrijdag	○	○	○	○	○
Zaterdag	○	○	○	○	○
Zondag					

10. Was je afgelopen week ziek, of was er iets anders dat er voor zorgde dat je je normale fysieke activiteiten niet hebt kunnen uitvoeren?

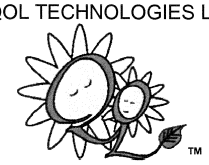
Ja	○
Nee	○

Zo ja, waardoor kwam dit?

……

KWALITEIT VAN LEVEN VRAGENLIJST VOOR KINDEREN EN JEUGDIGEN MET ASTMA - MET GESTANDAARDISEERDE BEZIGHEDEN (PAQLQ(S))

IN TE VULLEN DOOR DE PATIËNT (SELF-ADMINISTERED) DUTCH VERSION



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Senior translator: Peter Kramer

FEBRUARI 2005

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KWALITEIT VAN LEVEN VRAGENLIJST VOOR KINDEREN EN JEUGDIGEN MET ASTMA (S)

(DUTCH VERSION)
DOOR PATIËNT ZELF IN TE VULLEN

[redacted]

DATUM_____

Beantwoord **alle** vragen door het getal te omcirkelen dat het beste omschrijft hoe je je **deze week als gevolg van je astma** hebt gevoeld.

HOEVEEL **LAST** HAD JE DEZE WEEK BIJ/VAN HET VOLGENDE:

	Heel erg veel last	Veel last	Nogal wat last	Wel wat last	Een beetje last	Bijna geen last	Helemaal geen last
1. LICHAMELIJKE ACTIVITEITEN (zoals rennen, zwemmen, sporten, een heuvel/trap oplopen en fietsen)?	1	2	3	4	5	6	7
2. MET DIEREN OMGAAN (zoals spelen met huisdieren en het verzorgen van dieren)?	1	2	3	4	5	6	7
3. ACTIVITEITEN MET VRIENDEN EN FAMILIE (zoals spelen tijdens de pauze en dingen doen met vrienden en familie)?	1	2	3	4	5	6	7
4. HOESTEN?	1	2	3	4	5	6	7

ALLES BIJ ELKAAR, **HOE VAAK** DEZE WEEK:

	Altijd	Meestal	Vrij vaak	Geregeld	Af en toe	Bijna nooit	Nooit
5. voelde je je TELEURGESTELD, ONTMOEDIGD OF KWAAD OP JEZELF door je astma?	1	2	3	4	5	6	7
6. was je MOE door je astma?	1	2	3	4	5	6	7
7. was je ONGERUST, MAAKTE JE JE ZORGEN OF ZAT JE TE PIEKEREN door je astma?	1	2	3	4	5	6	7

KWALITEIT VAN LEVEN VRAGENLIJST VOOR KINDEREN EN JEUGDIGEN MET ASTMA (S)

(DUTCH VERSION)
DOOR PATIËNT ZELF IN TE VULLEN

[redacted]_____

DATUM_____

HOEVEEL **LAST** HAD JE DEZE WEEK VAN:

	Heel erg veel last	Veel last	Nogal wat last	Wel wat last	Een beetje last	Bijna geen last	Helemaal geen last
8. ASTMA-AANVALLEN?	1	2	3	4	5	6	7

ALLES BIJ ELKAAR, **HOE VAAK** DEZE WEEK:

	Altijd	Meestal	Vrij vaak	Geregeld	Af en toe	Bijna nooit	Nooit
9. was je BOOS vanwege je astma?	1	2	3	4	5	6	7

HOEVEEL **LAST** HAD JE DEZE WEEK VAN:

	Heel erg veel last	Veel last	Nogal wat last	Wel wat last	Een beetje last	Bijna geen last	Helemaal geen last
10. een PIEPENDE ADEMHALING ?	1	2	3	4	5	6	7

ALLES BIJ ELKAAR, **HOE VAAK** DEZE WEEK:

	Altijd	Meestal	Vrij vaak	Geregeld	Af en toe	Bijna nooit	Nooit
11. was je MOPPERIG of HUMEURIG door je astma ?	1	2	3	4	5	6	7

HOEVEEL **LAST** HAD JE DEZE WEEK VAN:

	Heel erg veel last	Veel last	Nogal wat last	Wel wat Last	Een beetje last	Bijna geen last	Helemaal geen last
12. een BENAUWD GEVOEL IN OF BOVEN IN JE BORSTKAS?	1	2	3	4	5	6	7

KWALITEIT VAN LEVEN VRAGENLIJST VOOR KINDEREN EN JEUGDIGEN MET ASTMA (S)

(DUTCH VERSION)
DOOR PATIËNT ZELF IN TE VULLEN

[redacted]_____

DATUM_____

ALLES BIJ ELKAAR, **HOE VAAK** DEZE WEEK:

	Altijd	Meestal	Vrij vaak	Geregeld	Af en toe	Bijna nooit	Nooit
13. had je het gevoel dat je ANDERS WAS DAN ANDEREN of ER NIET BIJ HOORDE door je astma?	1	2	3	4	5	6	7

HOEVEEL **LAST** HAD JE DEZE WEEK VAN:

	Heel erg veel last	Veel last	Nogal wat last	Wel wat Last	Een beetje last	Bijna geen last	Helemaal geen last
14. KORTADEMIGHEID of dat je NIET GENOEG LUCHT KON KRIJGEN?	1	2	3	4	5	6	7

ALLES BIJ ELKAAR, **HOE VAAK** DEZE WEEK:

	Altijd	Meestal	Vrij vaak	Geregeld	Af en toe	Bijna nooit	Nooit
15. voelde je je TELEURGESTELD, ONTMOEDIGD of KWAAD OP JEZELF OMDAT JE DE ANDEREN NIET BIJ KON HOUDEN?	1	2	3	4	5	6	7
16. werd je 'S NACHTS WAKKER door je astma?	1	2	3	4	5	6	7
17. voelde je je NIET OP JE GEMAK door je astma?	1	2	3	4	5	6	7
18. was je BUITEN ADEM door je astma?	1	2	3	4	5	6	7
19. kon JE DE ANDEREN NIET BIJHOUDEN door je astma?	1	2	3	4	5	6	7
20. had je moeite om 'S NACHTS TE SLAPEN door je astma?	1	2	3	4	5	6	7
21. werd je BANG DOOR EEN ASTMA-AANVAL?	1	2	3	4	5	6	7

KWALITEIT VAN LEVEN VRAGENLIJST VOOR KINDEREN EN JEUGDIGEN MET ASTMA (S)

[redacted]

(DUTCH VERSION)
DOOR PATIËNT ZELF IN TE VULLEN

DATUM_____

DENK NU EENS AAN AL DE DINGEN DIE JE DEZE WEEK GEDAAN HEBT:

	Heel erg veel last	Veel last	Nogal wat last	Wel wat last	Een beetje last	Bijna geen last	Helemaal geen last
22. Alles bij elkaar genomen, hoeveel last heb je gehad van je astma bij die dingen?	1	2	3	4	5	6	7

ALLES BIJ ELKAAR, **HOE VAAK** DEZE WEEK:

	Altijd	Meestal	Vrij vaak	Geregeld	Af en toe	Bijna nooit	Nooit
23. had je moeite om DIEP ADEM TE HALEN?	1	2	3	4	5	6	7

DOMEIN CODE:

Symptomen: 4, 6, 8, 10, 12, 14, 16, 18, 20, 23

Activiteitsbeperking: 1, 2, 3, 19, 22

Emotionele Functie: 5, 7, 9, 11, 13, 15, 17, 21