The relation between cough sound characteristics and lung function

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Preface

Before you lies my thesis written to obtain the Masters degree of Technical Medicine at the University of Twente. My thesis started somewhat unconventional, by diving in immediately, when I was given the opportunity to include patients for the WEARCON study. I learned a lot and the WEARCON study was the inspiration for the work that lies before you, the WEARCough study.

After long awaited approval of the Medical Ethics Committee Twente, finally my research could begin! Patients were enrolled in this study, for a home monitoring period of 1 week and to finish the study, an exercise challenge test. Data was obtained afterwards and analysis begun.

I was given the opportunity to start working, whilst finishing my research, at the OCON. This proved challenging, combining two different lines of research, switching between topic every couple of days. As to be expected of such a challenge, I learned so much. Starting with how to carry out the enrolment of patients, conducting exercise challenge tests, learn more on how to work as a medical professional, with both parents and children. I also learned a lot about conducting research, obtaining approval of a study by an ethics committee.

I want to thank my graduation committee for guiding me through this process. First dr. Boony Thio; you welcomed me with open arms to your department, even though I only had been an intern under your supervision in my third bachelor internship, years and years ago. I enjoyed our conversations (work and non-work related) and how your door is always open, even though your work schedule needs you to do at least 10 other things at the same time.

I want to thank dr. Jean Driessen, for learning me how to properly conduct an exercise challenge test and how to interpret them. You made Wednesdays feel like a day off, by always making the day interesting and fun. Speaking of FUN, I also want to thank you for your trust in me to guide one of your projects, the FUN study.

I want to thank dr. Frans de Jongh, for all his advice and referrals to others, to aid me in my research. Additionally, I enjoyed your critical questions, which led to this end result.

I want to thank drs. Paul van Katwijk, for guiding me through my internships. You gave me (un)solicited advice and guidance in understanding my personality traits and how they affect my work in positive and negative ways.

I also want to thank prof. dr. ir. Hermie Hermens, for being the chair of my committee and external supervisor.
Additionally, I want to thank all my fellow students, we were with many and always had fun during work. Especially the two guys who have been at the pediatrics department during my full study; Matièenne and Pascal. You gave me advice when Matlab's documentation wouldn’t suffice, allowed me to blow off steam if I was frustrated, gave me the giggles (scissors come to mind) and serenaded the ‘Carnival Festival’ to ruin each other's day. You’re welcome by the way, if by the time you’re reading this, it’s stuck in your head again.

I want to thank my family; my parents and Nathalie and Gijs for their support during my studies. It’s been a while, but it’s finished! And of course David, who agreed with being a model for pictures in the medical ethics dossier of my study. Finally I want to thank my boyfriend, Vincent, for always supporting me in every decision I make. For putting things into perspective, when my mind is making a mountain out of a molehill. And for having a secret stash of chocolate somewhere around the house.

I hope you all enjoy reading this thesis,

Emilie
Abstract

Rationale
Amongst Dutch children, 7-10% suffers from asthma. Asthma treatment should focus on the control of symptoms and the prevention of exacerbations. Self management is key, however, challenging for children and parents. This is where telemedicine comes in to play. Most telemedicine studies focus on questionnaires or telecommunication, which is dependent on the patients perception of the disease. To obtain an objective measurement of asthma, this study explores the feasibility of measuring coughs as an indication of the Forced Experation Volume in 1 second (FEV$_1$). Different parameters were explored such as the dominant frequency, Welch periodogram, power and kurtosis, in all phases of the cough, as they may contain relevant information.

Objective
To investigate the relation between cough sound characteristics and the Exercise Challenge Test induced changes in the Forced Expiratory Volume in 1 second.

Method
Patients who were scheduled for an exercise challenge test (ECT) were recruited to take part in this study. The patients underwent one week of home monitoring, ending the monitoring with the ECT. During the both periods, coughs were measured with the GENEActiv action accelerometer. Lung function was measured with spirometry. Coughs were measured during the ECT with a smart phone as well, to obtain the full frequency spectrum. Several parameters were derived, such as duration, amplitude, kurtosis and frequency spectrum of the cough.

Results
In this observational pilot study, 16 children were included, of who 5 experienced a decrease in FEV$_1$ during the ECT >10%. A broader interquartile range was found of the higher dominant frequency in the second phase of the cough, measured immediately after exercise. This dominant frequency of the second cough phase at zero minutes after exercise was significantly higher in comparison to the baseline measurement (p <0.05). The maximum power of the Welch periodogram of the first cough phase at 3 minutes after exercise, was lower in all patients in comparison to all other phases. A lower kurtosis was found after salbutamol for the full cough for all patients. All other derived parameters for three phases of cough and the full cough, did not reveal any trends.
Discussion
Measuring more patients could reveal trends in asthmatic patients’ coughs, as in this study only 5 patients had a decrease in FEV$_1$ >10%. Future work should focus on if cough parameters, measured with a standardized protocol during an ECT, are an indication of a decrease in FEV$_1$. If proven valuable, this could be the first step towards a low-cost method for home-monitoring of asthma.

Conclusion
In this study, no relation between cough sound parameters and FEV$_1$ was found.
Acronyms

ACQ  Asthma Control Questionnaire
ADAM Automated Device for Asthma Monitoring
C-ACT Childhood Asthma Control Test
ECG  ElectroCardioGraphy
ECT  Exercise Challenge Test
EIB  Exercise-Induced Bronchoconstriction
fs   Sampling Frequency
FEV₁  Forced Expiratory Volume in 1 second
FVC  Forced Vital Capacity
GINA Global Initiative for Asthma
ICS  Inhaled corticosteroids
IR   Incident Rate
LSA  Lung Sounds Analyzer
METC Medical Ethical Committee (in Dutch; Medisch Ethisch ToetsingsCommissie)
MST  Medical Spectrum Twente
OCON Orthopedisch Centrum Oost Nederland
PA   Physical Activity
PAQ-C Pediatric Activity Questionnaire-Childhood
PAQLQ Pediatric Asthma Quality of Life Questionnaire
PEF  Peak Expiratory Flow
PPG  PhonoPneumoGraph
SABA Short-Acting β₂-Agonist
STG  Stethograph
VAS  Visual Analog Scale
VC   Vital Capacity
VRI  Vibration Response Imaging
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1. Introduction

Asthma is a chronic inflammatory condition of the lungs.[1] Amongst Dutch children with an age of 2-12 years, 7-10 % suffers from asthma, as found by the 'Prevention and Incidence of Asthma and Mite Allergy'-study.[2] Engelkes et al. researched incidence and prevalence of asthma by consulting the Integrated Primary Care Information database, which is used by over 450 general practitioners in the Netherlands for their electronic medical records. They included a study cohort of 176,516 Dutch children who were 5-18 years of age between 2000 and 2012. They reported 23% of the study cohort had specialist confirmed asthma, with an overall incidence rate of 6.7/1000 person-years. The person-years reflect the incidence, expressed in the amount of years subjects are observed. They also found a significant increase in the Incident Rate (IR) of asthma from 2000-2008 and a non-significant decrease from 2008-2012. Nevertheless, in 2008 the Dutch national asthma guidelines were revised, stating that "infants and pre-school children who wheeze are not necessary asthmatics, but may wheeze secondary to viral infections". This change in definition may have caused the downward trend, additional research is needed to confirm whether this actually is a downward trend.[3] The same cohort was studied by Engelkes et al. to retrieve data on the incidence of asthma exacerbations (worsening of symptoms) amongst children. This revealed an overall IR of asthma exacerbations 21/1000 person-years and an IR of 41/1000 person-years for children who were receiving asthma treatment. Asthma treatment was defined as at least 1 prescription for asthma medication.[4] In conclusion, a lot of Dutch children are suffering of asthma, varying from 7-23 %. Additionally, despite asthma treatment, exacerbations of asthma still occur.

Asthma is clinically characterised by airway hyper-responsiveness, inflammation of the airways and airflow obstruction. These can cause various symptoms, such as wheezing, shortness of breath, chest tightness and coughing. Symptoms often worsen at night.[1,5,6] They may also occur or worsen due to exercise, viral infection, weather changes, emotional expressions such as laughing or crying, or by the presence of various irritants. Depending on the individual sensitivity, irritants can be animal fur, house-dust mites, fungi, smoke, pollen and airborne chemicals.[5]

Asthma is diagnosed based upon the occurrence of symptoms, the physical examination, the response to asthma treatment and by measurement of the lung function. The latter can be determined by a spirometry, which is highly recommend by the American Thoracic Society. Spirometry requires a forced expiratory manoeuvre in order to obtain maximal flow-volume loops. The Forced Expiratory Volume in 1 second (FEV$_1$), Forced Vital Capacity (FVC) and the index of both reflects whether a patient suffers from bronchial obstruction. Furthermore, a Short-Acting β$_2$-Agonist (SABA) should be administered after retrieving the baseline spirometry, in order to determine the short term reversibility of the obstruction.[5] To obtain more insight in the condition of the patient, more tests can be employed. One of these tests is the Exercise Challenge Test (ECT), which is designed to reveal the pres-
ence of Exercise-Induced Bronchoconstriction (EIB). The test consists of 6 minutes of Physical Activity (PA), in order to reach a heart rate of 80% of the predicted heart rate (with a predicted heart rate of $220 - \text{age in years}$). This ensures a great enough challenge to provoke bronchial (hyper)reactivity.\textsuperscript{[7]} The effect of the exercise should be measured by regular spirometry, comparing the pulmonary function prior to exercise and post exercise (at t= 1, 3 and 5 minutes).\textsuperscript{[7–9]}

After diagnosis, asthma treatment should focus on the control of symptoms and prevention of exacerbations, according to the Global Initiative for Asthma (GINA). Asthma control can be achieved by medicinal treatment (e.g. Inhaled corticosteroids (ICS) and SABA) and by elimination of symptom triggers, such as previous mentioned irritants. Self-management of asthma is key in order to prevent exacerbations. The GINA advises to monitor Peak Expiratory Flow (PEF) of asthma patients, in order to monitor recovery after an exacerbation or the effect of a change in treatment. Long term monitoring of PEF is advised for patients with a poor perception of asthma, with sudden severe exacerbations or when their asthma is difficult to control. In order to achieve good asthma management, regular contact with a health care provider is advised, in order to review asthma control and treatment issues.\textsuperscript{[6]}

This is where telemedicine comes into play.

An extensive review by McLean et al. included 21 studies, describes multiple tele-healthcare systems designed for asthma patients. The majority of these healthcare systems monitor patients through calls, telecommunication (e.g. Skype or email), questionnaires and telemetry devices. However, telemetry devices have been sparsely used. When these devices are employed for monitoring, most used parameters are the PEF, FEV\textsubscript{1} and FVC. These parameters were combined with several validated questionnaires. McLean et al. came to the conclusion that those who suffer from severe asthma, might benefit from telehealthcare.\textsuperscript{[10]}

A limitation of these studies was that most symptoms were reported through daily questionnaires or through telecommunication. Therefore, these studies still depend mainly on the perception of asthma by the patients. Recording of the symptoms in an objective fashion, such as through telemetry devices, may increase the benefit of telehealthcare. Additionally, the perception of asthma control is difficult to assess when the patient is a small child. This is due to the fact that small children often do not notice, or are able to indicate when their symptoms flare up.
1.1 The WEARCON study

In order to obtain an objective method of monitoring of asthma, the WEARCON study has been initiated by Van der Kamp et al. All patients scheduled for an ECT at the Orthopedisch Centrum Oost Nederland (OCON), with an age between 4-14 years were invited to participate in the WEARCON study. The patients were either previously diagnosed with asthma or suspected to suffer from asthma. Prior to the ECT, patients were monitored off-line for 2 weeks. They were equipped with various telemetry devices, namely:

- the Actigraph wGT3X-BT activity tracker
- the MIR Spirobank II smart spirometer
- the eMotion Faros 180°ElectroCardioGraphy (ECG) device
- the Cohero Health smart inhalers.\cite{11}

Patients’ activity was monitored for the full time span of 2 weeks, by the activity tracker. Besides an accelerometer, the activity tracker also includes a lux (light) sensor, in order to obtain objective information on time spend outside. Patients were instructed to perform a FVC-spirometry before and after PA or when they were experiencing more symptoms then usual. During the two week period, the ECG device has been worn for 2 consecutive days, of which at least one day with intense PA. The smart inhalers were used during the two week period to monitor the use of aerosol inhalers, which counted the amount of doses of ICS and SABA inhaled. Patients were asked to fill in questionnaires with regards to their activity and their asthma on a weekly basis. The questionnaires included the Childhood Asthma Control Test (C-ACT), the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and the Pediatric Activity Questionnaire-Childhood (PAQ-C). After the monitoring period, the patients were separated into controlled and non-controlled asthma groups based upon their ECT results.\cite{11}

The preliminary results of this study (n=25 patients) revealed a significant difference between groups when comparing the recovery time after intense PA of both heart rate recovery time (p=0.05) and respiratory rate recovery time (p<0.01). Both parameters were derived from the ECG. More results are to be expected, as a control group of 30 healthy subjects also were monitored in order to carry out multivariate analysis of the measured parameters.\cite{11}

1.1.1 Sound analysis

Though the WEARCON study monitored the majority of symptoms of asthma, there has not been a focus on either coughing or wheezing. Both are however common in asthma, but, specificity is low.\cite{5,12} Besides an increase in coughing, it is also well known in clinical practice that cough sound changes due to diseases such as asthma.\cite{13,14} Piirilä and Sovjiärvi showed as early as in 1989 that a (statistically significant) difference exists in the duration of a cough sound, when comparing asthma to other lung diseases (bronchitis, tracheobronchial collapse syndrome and pulmonary fibrosis).\cite{15} Korpas et al. illustrated the difference in cough sounds due to different inflammation types. They also illustrated the difference in cough intensity
caused by bronchitis. These differences were however based on case reports.\textsuperscript{[13]} Rietveld et al. evaluated coughing during both challenge tests. They included 30 children (age 7-17 years), with and without asthma, which underwent an ECT. Their results included that the children with asthma coughed significantly more when comparing them to their healthy peers. However, while coughing being fairly sensitive for asthma, the specificity of coughing as a predictor for asthma was low. They also did not take cough features (temporal and spectral) into account and only reviewed the amount of coughs during the challenges in comparison to the lung function.\textsuperscript{[16]} Despite extensive literature research, no articles have been found describing the differences in cough features while performing an ECT.

### 1.2 Research objectives

This introduces the primary objective of this study:

*To investigate the relation between cough sound characteristics and the Exercise Challenge Test induced changes in the Forced Expiratory Volume in 1 second.*

As a final end goal, the measurement device could be implemented in home-monitoring to assess paediatric asthma control. Besides the primary objective, the perception of asthma control and its relation to cough sounds is also a field of interest in this study. This leads to the following secondary objectives of this study;

- To explore the agreement between the wearable device and sound recordings.
- To assess the agreement between the characteristics of voluntary coughs and involuntary coughs, measured in a clinical environment.
- To explore the clinical feasibility of using the wearable device in a non-conventional way.
2. Background

2.1 The cough

Coughs can be divided into two types; laryngeal or tracheobronchial cough. The laryngeal cough is initiated when foreign material has been aspirated. On the contrary, the tracheobronchial cough is initiated distal to the larynx. The latter cough can be voluntary. Each cough consist of three phases, an inspiratory, compressive and expiratory phase. The inspiratory phase allows air to flow into the lungs. Then the compressive phase is initiated, in which the glottis closes. This allows for a high intrathoracic pressure to build up, up to 300 mmHg in adults. Finally, the expiratory phase will start with opening of the glottis. A supramaximal expiratory flow due to the build up of pressure is released. This period of high flow lasts from 30-50 ms. Since the glottis is still open, the residual pressure will result in a lower expiratory flow. This will last for a longer period of time, from 200 to 500 ms. The high expiratory flow allows for clearance of debris in the airways. The mechanical action generated from the cough also results into clearance of the lung periphery.\[17\]

The audible part of the cough, starting at the compressive phase and ending with the expiratory phase, is known to have two or three phases.\[13,18\] Thorpe and colleagues have described these different phases within cough in asthmatic patients:

1. the end of the compressive cough phase, of which the sound is generated from sudden opening of the glottis
2. a continuous, noisy phase
3. the second cough, due to closing of the glottis\[18\]

Korpas et al. measured simultaneously with the cough sound, the air flow and airway pressure as seen in Figure 2.1. In Figure 2.1, the three different phases are clearly distinguishable.

The sound of the cough is dependent on the large airways and laryngeal structures. Turbulent flow through these structures while expiration creates the cough sound. This leads to the idea that coughs are individualised, just like ones voice.\[17\]

It has been shown previously by Olia et al. that dominant frequencies between males and females differ, of which the dominant frequency ranged from 340-450 Hz. They also found different dominant frequencies between the three audible phases of the cough.\[19\]
Figure 2.1: Adapted image and caption from Korpas et al. ‘Representation of glottal activity, time, records of cough sound (recorded by multiscriptor), airflow and oesophageal pressure (inspiration downwards) during one cough effort (indicated with the ↑) in healthy subject. 1: Inspiratory cough phase; 2: compressive cough phase; 3: expulsive cough phase. Time bar = 1 s. ’[13]
2.2 Cough monitors

The registration of coughs per unit of time has been an area of interest for a long time. An up to date review is given of current automated lung sound analysis (such as wheezing, crackles and rhonchi) devices by Pramono et al. in 2017. They included an overview of the following devices:

- the Wheezometer and Wholter (Respiri (former Karmelsonix), Melbourne, Australia),
- the Vibration Response Imaging (VRI) system (Deep Breeze, Or-Akiva, Israel),
- the Lung Sounds Analyzer (LSA)-2000 (Kenz-Medico, Saitama, Japan)
- the LEOSound (Löwenstein Medical GmbH & Co., Bad-Ems, Germany),
- the Stethograph (STG) (Stethographics Inc., Boston, USA).\(^{[20]}\)

The CoughCOUNT\textsuperscript{TM} technology is implemented in both the Wheezometer and Wholter, the LSA-2000 makes use of an electret condenser microphone and the VRI is a device which consists of 40 piezo-elements.\(^{[20–22]}\) The basic principle of the sensor used in the LEOSound was not described in literature, they describe their sensors as 'bioacoustic sensors'.\(^{[23–25]}\) As the name implies, the STG makes use of electronic stethoscopes to capture lung sounds.\(^{[26]}\) None of these are however suitable for home monitoring: Wholter, VRI, LSA-200, LEOSound and STG are all relative large devices, which are not portable or meant to be used by patients. The Wheezometer is a hand-held device which measures for 30 seconds, making it unsuitable for continuous monitoring.\(^{[20,27]}\)

A relatively new device shows more promise for home-monitoring: the Automated Device for Asthma Monitoring (ADAM). The ADAM is a small device, which consist of an iPod in order to store data and a lapel microphone (the specifics of this microphone were not found in literature).\(^{[28,29]}\) The device has been validated for adolescents (\(n=42\), mean age of 15.2 years (1.5)) with asthma. The developed algorithm to detect coughs should be improved, whereas the sensitivity of the detection of coughs yielded 70\%. This translates to two false positive identified coughs per hour.\(^{[28]}\) However, the amount of coughs per day counted by the ADAM still displays a significant correlation with measured FEV\(_1\), FVC and the Asthma Control Questionnaire (ACQ).\(^{[30]}\) The ADAM might be a good solution for home-monitoring for children with asthma, however validation should be expanded including age ranges from 4-13 years. The device is currently not commercially available, but is accessible for clinical trials since March 2017.\(^{[31]}\)
2.3 Sensor selection

As illustrated in Section 2.2, several different sensors have been used to register cough; acoustic microphones, accelerometers and piezoelectric elements. The first is not a sensor of interest to this study as acoustic microphones invade the privacy of patients. Furthermore, they will intercept all auditory signals, such as background noise but also other subjects beside the patient will be recorded. It would require filtering to diminish the background noise. In order to combat the invasion of privacy, a smart system could be developed, which would detect when a patient is speaking prior to start the recording. However, using a different type of sensor was considered more feasible for this study.

In order to be able capture the frequency spectrum of cough sounds, a sensor needs to be chosen with a suitable Sampling Frequency ($f_s$). Olia et al. measured cough of 24 healthy subjects, with a mean age of 30 years. They used a microphone with a frequency response of 20 to 12000 Hz. Subjects were asked to inhale until they reached their Vital Capacity (VC) and then produce a cough. A mean frequency of the obtained coughs of 400 Hz was found. Therefore, to obtain the frequency spectrum of a cough, a sensor should be chosen with a $f_s$ of at least 1000 Hz, to prevent aliasing.

An overview is given in Table 2.1 of accelerometer or piezo-electric based sensors, which have been used previously in literature to detect lung sounds. Earlier described systems, as mentioned in Section 2.2, are included. Other frequently used sensors in lung sound analysis are also enclosed in Table 2.1, such as the Knowles electronic sensors. Furthermore, the sensors used by the group of Pasterkamp and Kraman have been included in the overview, which were one of the first sensors used in lung sound analysis.

The final goal of the system is to be implemented into home monitoring. Therefore, the used sensor should meet a couple requirements:

- the sensor should be piezoelectric or accelerometer based, to secure the patients’ privacy
- the sensor should be wireless, to ensure maximum wearing comfort
- the sensor should have the memory capacity to save data for a long period of time (12 hours)
- the sensor should have a sufficient Sampling Frequency ($\geq 1000$ Hz)
- the sensor should be easy to affix
- the sensor should be safe to wear by children.

The sensors which are described in previous paragraphs and in Table 2.1 do not meet these requirements or are no longer available (such as the Pulmotrack and PhonoPneumoGraph (PPG)). Therefore the available wireless sensors of the WEARCON study were also taken into consideration. Unfortunately the ActiGraph and eMotion Faros ECG device both have an accelerometer with a $f_s$ of 100 Hz (see Table 2.1), which is insufficient to obtain the full frequency spectrum of a cough. After extensive research, the GENEActiv Action has been selected as the measurement device for this study. This device is able to conduct measurements for
Type Sensor Sensitivity range Sample Size (mm)

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<tbody>
<tr>
<td>A</td>
<td>BU-1771 &amp; BU-3173, Knowles Electronics</td>
<td>20 Hz - 10 kHz</td>
<td>-</td>
<td>8 × 6 × 4 *</td>
</tr>
<tr>
<td>A</td>
<td>PPG 201, PPC[36,37]</td>
<td>100 Hz - 4 kHz</td>
<td>-</td>
<td>28 × 8 †</td>
</tr>
<tr>
<td>A</td>
<td>EMT 25C, Siemens[36,37]</td>
<td>100 Hz - 1 kHz</td>
<td>-</td>
<td>28 × 13 †</td>
</tr>
<tr>
<td>A</td>
<td>180° eMotion, Bittium[39,40]</td>
<td>-</td>
<td>100 Hz</td>
<td>48 × 29 × 12</td>
</tr>
<tr>
<td>A</td>
<td>ActiGraph wGT3X- BT, Actigraph[41]</td>
<td>-</td>
<td>100 Hz</td>
<td>46 × 33 × 15</td>
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<tr>
<td>P</td>
<td>21050, Hewlett-Packard[36]</td>
<td>-</td>
<td>-</td>
<td>14 × 26 †</td>
</tr>
<tr>
<td>P</td>
<td>VRIxp, Deep Breeze[22]</td>
<td>50 Hz - 0.4 kHz</td>
<td>-</td>
<td>Covers the full back of the patient</td>
</tr>
<tr>
<td>P</td>
<td>Pulmotrack, KarmelSonix[42]</td>
<td>80 Hz - 2.4 kHz</td>
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Table 2.1: Overview of several sensors used in lung sound analysis.  
A - accelerometer, P - piezoelectric sensor. *length × width × height, †diameter × height.

12 consecutive hours at a $f_s$ of 1000 Hz.[43] The GENEAcentiAction was attached in a non-conventional way. The device needed to be attached as close to the source of the coughs as possible. To be able to achieve this, the straps were removed and edges on the back of the device were melted down. This created a smooth contact surface, as shown in Figure 2.2. After a small trial including 5 healthy adults, the measurement site was selected. This is the sternocleidomastoid region, an in depth overview of the trial can be found in Appendix A. This trial also lead to the method of fixation, which is described into further detail in Appendix B.

The $f_s$ of 100 Hz might however be sufficient in order to function as a cough counter. In 1996, Korpas et al. gave an overview of the analysis of cough sound. They demonstrated that cough also holds frequencies $\leq 100$ Hz.[13] Similar findings are present in the work of Amoh and Odame.[44] The frequency range of other lung sounds are also known, a compact overview is given by Pramono et al. Normal lung sounds, such as vesicular, bronchial, tracheal all have a frequency range with a minimum of a 100 Hz. Abnormal lung sounds, such as wheeze, stridor and crackles are all high frequency sounds, with a pitch $\geq 350$ Hz. Only rhonchi have a low frequency aspect, $<200$ Hz.[20] However, due to the explosive nature of a cough, it is to be expected that a cough would have a greater sound intensity than rhonchi. Therefore, it should be possible to distinguish cough from rhonchi.
Figure 2.2: The GENEActiv Action as employed in this study. Straps of the device were removed, resulting in a wearable with the dimensions of 43mm × 40mm × 13mm and a weight of 16 grams.
3. Method

This study was carried out as a part of the WEARCough study (NTR7329, NL65431.044.18). After receiving approval of the Medical Ethical Committee (in Dutch; Medisch Ethisch ToetsingsCommissie) (METC) (on 31-07-2018) and the board of directors of the Medical Spectrum Twente (MST) (on 29-08-2018), patients who are routinely scheduled for an ECT at the OCON were approached to participate in the study.

3.1 Study population

As stated in Section 1.1, no literature was found regarding the differences in cough features while performing an ECT. Peduzzi et al. illustrated that at least 10 cases per event per group are required if the effect size is unknown.\cite{Footnote1} However, since patients were recruited and monitored prior to the ECT, an uneven distribution was to be expected. Taking this into consideration, the intended sample size of the WEARCough-study was to recruit 30 patients, to have at least 10 patients in both the controlled and uncontrolled group.

3.1.1 Inclusion criteria

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

- Children with paediatrician diagnosed asthma, or children whom are suspected to suffer from asthma, based on reported symptoms, atopy and physical examination performed by a physician.
- Children aged between 4 and 14 years old.
- Children whom will receive an ECT.
3.1.2 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Children who are unable to speak Dutch, or whose legal guardians are unable to speak Dutch.
- Children for whom it is not possible to wear all wearables. For example due to severe skin disease.
- Children with implanted electrical stimulating devices.
- Children with a known band-aid allergy.
- Children with psychomotor retardation.
- Children with chronic diseases (other than asthma).
- Children whom were born prematurely (≤ 37 weeks), since this could lead to underdevelopment of the lungs. This is considered to be a confounder for this study.

3.2 Materials

3.2.1 Telemetric devices

Several telemetric devices were used during the home monitoring period. The majority of the devices were already available due to the previous implementation of the WEARCON-study. The devices were chosen for that study based on several criteria; their availability, their user friendliness, the capacity of their memory (which effects the monitoring time) and the quality of the device and its’ data. The following devices were already made available for this study;

- The ActiGraph wGT3X-BT activity tracker, to monitor PA and sleep pattern.
- The MIR Spirobank ® II smart spirometer, to obtain Flow-Volume loops.
- The Biomation eMotion Faros 180°ECG, to monitor the heart rate.

GENEAActiv Action

To register coughs, the GENEActiv Action has been chosen. This device has been chosen due to it’s high sample frequency and size. It measures continuously for 12 hours with a $f_s$ of 1000 Hz. After removal of the straps, the dimensions of the device yield $43\text{mm} \times 40\text{mm} \times 13\text{mm}$ and it weighs 16 grams. A more in depth description of the selection process of this sensor and the method of attaching the device is described in Section 2.3.
3.2.2 Questionnaires

Subjects were requested to fill in several questionnaires; the C-ACT (Appendix C.3) and PAQLQ (Appendix C.4), which reflect their perception of their asthma. Patients were also requested to fill in a questionnaire with regards to their medication use (Appendix C.1). A new questionnaire was designed to monitor the experience of wearing the GENEActiv Action in a non-conventional way (Appendix C.2).

3.3 Study design

3.3.1 Home Monitoring Period

Subjects received the devices accompanied by an instruction of use, one week prior to the ECT. Subjects and parents were informed how to attach the wearables and how to use the portable spirometer. The devices did not show interpretable data to the subjects.

Patients wore the GENEActiv Action accelerometer to monitor coughs.\textsuperscript{[43]} The monitoring period was divided in 4 periods of 12 hours, of which 2 periods took place during the day when a child will engage in planned sports or PA. The other 2 periods took place during the night, since asthma symptoms are prone to worsen overnight. Patients were instructed to have at least 12 hours between the measurement periods. To fit wearing the device in their daily routine, patients were allowed to wear the device an hour less if this suited their routine better. This way the device could be attached/detached early in the morning after wakening and in the evening when changing into pyjamas.

The Actigraph activity tracker was worn for one week to determine the activity level of the subject and to determine when coughs occurred.\textsuperscript{[41]} The activity tracker was worn in different positions. During the day, the activity tracker was worn at the hips to measure activity. During the night, the tracker was be worn at the wrist to measure sleep. The change of measurement site has been chosen since each parameter (activity and sleep) has a different measurement site which is considered to be the golden standard.\textsuperscript{[48,49]}

PA is considered to be a confounder for this study, since PA is cough provoking. The subjects wore an Actigraph activity tracker to monitor this confounder. Additionally, the activity tracker provides algorithms to determine whether patients were awake or asleep. Synchronization of the GENEActiv Action and the Actigraph to one laptop allowed for determination for when coughs occurred, whilst sleeping or being awake.

During exercise, subjects wore an ECG device in order to determine the intensity of the exercise, to allow for comparison to the intensity of an ECT.\textsuperscript{[40]} A handheld spirometer was used by the patients to obtain flow-volume loops in the morning and evening, pre- and post- exercise and 5 minutes after the use of a SABA whilst wearing the GENEActiv Action. Patients were instructed to perform a voluntary cough after each spirometry. An overview of the monitoring period is given in Figure 3.1.
The monitoring period was chosen prior to the ECT, since the ECT could lead to a step-up in medication. If so, monitoring after the ECT would not reflect the measured asthma status and therefore cause a systematic bias. This also ensures that asthma perception (assessed by the C-ACT and PAQLQ) is not influenced by the results of the ECT.

Figure 3.1: *The set-up of the home monitoring period.*
3.3.2 The Exercise Challenge Test

A thorough medical history was obtained from each patient prior to the ECT, which is carried out at the out-patient clinic at the OCON in Hengelo. Medical history included medication adherence, symptoms, the presence of allergies, if patients were born prematurely and the familiar occurrence of asthma and allergies in the first and second degree. The presence of allergic signs, such as Dannie-Morgan lines and Meyers nasal crease was checked during the physical examination.

The GENEActiv Action was worn during the ECT to register coughs. Additionally, an audio recording was made by using a Samsung S5 mini telephone. The Faros eMotion was worn to determine exercise intensity in retrospect based upon the heart rate. This device also includes an 3D accelerometer with a $f_s$ of 100 Hz, of which its data is analysed for its properties as a cough counter.

The ECT was carried out conform the guidelines of the American Thoracic Society, with an adaptation for children ageing 4-7 (jumping on a bouncing castle to provoke asthma, since running on a treadmill is not feasible for this age group) as described by van Leeuwen et al.\cite{7,8} All involuntary coughs were registered during the ECT, voluntary coughs were implemented in the ECT protocol. The patient was requested to cough prior to the exercise, immediately after exercise, 3 and 6 minutes after exercise and after the administration of SABA. An overview of the ECT protocol including the coughs is given in Figure 3.2. The fall and rise of the FEV$_1$ was monitored during the ECT. The derived cough parameters will be compared to these FEV$_1$ values.

Figure 3.2: The adjusted Exercise Challenge Test protocol with the addition of voluntary coughs on different time instances. Lung function and coughs are monitored prior and post exercise, and post administration of a SABA.
3.4 Data analysis

Prior to analysis, the data of all three devices were synchronised by using different methods. The audio from the telephone and GENEActiv were synchronised by identifying the tapping sounds created prior to the measurement. For precise synchronization, the data of the GENEActiv was up-sampled to the same $f_s$ in both devices. Then, the exact period of tapping was identified. With the xcorr-function in MATLAB, the delay between the two tapping periods was determined. The GENEActiv and the ECG-device were synchronised by instructing the subject to jump up and down 3 times. Since both devices contain a 3D accelerometer, the up and downwards motions of the jumping can be identified. After selection of the period of jumping up and down, the delay between the two devices was also determined by using the xcorr-function in MATLAB. Then, drift was removed from the audio signal from the telephone by a 2nd order highpass Butterworth filter, with a cutoff frequency of 5 Hz. Finally, coughs during the ECT were identified in the telephone data.

Similar to Thorpe et al. and Olia et al., the three different phases of the coughs were identified.\cite{18,19} The identification of the different phases was carried out by using MATLABs changepnts-function, which identifies when a signal changes most significantly. This change was identified by using two different settings, one which returned the points of change based on the root-mean-square of the signal, the other based on the standard deviation of the signal. After calculation of these points, the correct points were confirmed by comparing the placement of the points to the spectrogram of the cough, which visualizes the frequencies within the signal over time. Then, the cough was divided in three or two phases. An example is given in Figure 3.3.

![Cough divided in phases](image)

Figure 3.3: An example of a cough with three phases.
After the selection of the coughs and their phases, the following parameters were derived; the maximal amplitude, duration, kurtosis, skewness, root-mean-square and the power. A normalized version of both the maximal amplitude and duration were calculated, based on the first phase. Skewness and kurtosis are both statistical parameters, both compare the measured data to a normal distribution. Skewness reflects how much the peak of a signal deviates from the centre. Kurtosis reflects the ‘peakedness’ of a signal, whereas a kurtosis of 3 is the amount of kurtosis for a normal distribution.\[50\] Then the Welch periodogram was created with a frequency resolution of 120 Hz. This allowed a sufficient resolution for analysis, without the window being too long for the relative small parts of cough data. Subsequently, the power of the full frequency domain was determined, together with the dominant frequency and it’s corresponding power.

Finally, plots were created of each subject per parameter, to allow for comparison of the development of the parameter during the ECT and within subjects. Furthermore, box plots were also created of each parameter per phase of the ECT, to identify trends.
4. Results

Patients were recruited between September of 2018 - February 2019. A total of 13 patients were included in the WEARcough-study, of whom 6 also participated in the home-monitoring period. One of the subjects dropped out of the study. An additional 6 patients were measured at the OCON, of which 4 displayed hyperresponsiveness to PA during the ECT. The additional patients were registered under the name of ‘Extra’ with a number, in order to prevent confusing their data with the data of the WEARcough-study. This brings the total measured children during the ECT to 16, an overview of patients characteristics is given in Table 4.1.

4.1 Cough sound characteristics and lung function

The FEV\textsubscript{1} measured during the ECT is given in Table 4.2. A total of 5 subjects displayed a FEV\textsubscript{1} decrease larger then 10 %. The development of the FEV\textsubscript{1} during the ECT is depicted in Figure 4.1. The cough sound characteristics were derived from the audio measurements conducted with the telephone. All parameters were first visually inspected per subject, which did not reveal any trends. Then, box-plots were created to assess the development of parameters during the ECT. This revealed a broader interquartile range of the higher dominant frequency in the second phase of the cough, measured immediately after exercise. A Mann-Whitney U test showed that the dominant frequency at t=0 was significantly higher in comparison to the baseline (p<0.05). The dominant frequency at t=3 was not significantly lower in comparison to t=0 (p=0.119). This is shown in Figure 4.2. It was found that the maximum power of the Welch periodogram of the first cough phase at 3 minutes after exercise, was lower in all patients in comparison to all other phases. Differences between the different time periods were however non-significant (Mann-Whitney U test, p>0.05). This is depicted in Figure 4.3. Subsequently, the power of the dominant frequency was lower in all patients in comparison to all other phases. Furthermore, analysis revealed a lower kurtosis after salbutamol for the full cough for all patients, as illustrated in Figure 4.4. The lower kurtosis was non-significant (Mann-Whitney U test, p>0.05) All other derived parameters for the full cough and it’s three phases, did not reveal any trends.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Male/ Female</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>BMI</th>
<th>BMI category</th>
<th>ICS* Inhalation corticosteroids</th>
<th>PAQLQ C-ACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>f</td>
<td>8</td>
<td>44</td>
<td>134</td>
<td>24.5</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>f</td>
<td>10</td>
<td>32</td>
<td>142</td>
<td>15.7</td>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>f</td>
<td>6</td>
<td>19</td>
<td>114</td>
<td>14.6</td>
<td></td>
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<td>No</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>7</td>
<td>27</td>
<td>129</td>
<td>16.2</td>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>m</td>
<td>11</td>
<td>33</td>
<td>146</td>
<td>15.5</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>6</td>
<td>22</td>
<td>124</td>
<td>14.3</td>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>m</td>
<td>13</td>
<td>38</td>
<td>152</td>
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<td>m</td>
<td>9</td>
<td>30</td>
<td>138</td>
<td>15.8</td>
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<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>m</td>
<td>9</td>
<td>32</td>
<td>149</td>
<td>14.4</td>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>m</td>
<td>8</td>
<td>32</td>
<td>138</td>
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<td>m</td>
<td>9</td>
<td>47</td>
<td>145</td>
<td>22.4</td>
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<td>No</td>
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<tr>
<td>12</td>
<td>m</td>
<td>11</td>
<td>48</td>
<td>153</td>
<td>20.5</td>
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<td>No</td>
</tr>
<tr>
<td>13</td>
<td>m</td>
<td>14</td>
<td>48</td>
<td>156</td>
<td>19.7</td>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>f</td>
<td>13</td>
<td>47</td>
<td>158</td>
<td>18.8</td>
<td></td>
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<td>Yes</td>
</tr>
<tr>
<td>15</td>
<td>m</td>
<td>12</td>
<td>53</td>
<td>164</td>
<td>19.7</td>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 4.1: Patients characteristics. Subject 5 dropped out of the study. Patients whom were measured at the OCON but without inclusion in the WEARCough study, were registered as ‘Extra’, with an additional number, determined by order of measuring. The BMI category is based on the age dependent BMI range for children. [51] *Inhalation corticosteroids.
Figure 4.1: The development of the FEV$_1$ during the ECT. The FEV$_1$ is expressed in the percentage of baseline, to be able to compare patients of different sex, age, length and weight.

Figure 4.2: The development of the dominant frequency in the second cough phase, during the ECT. The dominant frequency at $t=0$ was significantly higher in comparison to baseline ($p<0.05$). The dominant frequency at $t=3$ was not significantly lower in comparison to $t=0$ ($p=0.119$).
Development of the power of the Welch periodogram in the first cough-phase, during the ECT

Figure 4.3: The development of the power of the Welch periodogram, of the first cough phase, during the ECT.

Development of the kurtosis of the cough during the ECT

Figure 4.4: The development of the kurtosis of the cough during the ECT.
<table>
<thead>
<tr>
<th>Subject</th>
<th>FEV$_1$ at baseline</th>
<th>Maximum decrease in FEV$_1$</th>
<th>Maximum increase in FEV$_1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>98</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>98</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>-2</td>
<td>*</td>
</tr>
<tr>
<td>4</td>
<td>101</td>
<td>7</td>
<td>-1</td>
</tr>
<tr>
<td>6</td>
<td>89</td>
<td>26</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>76</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>102</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>94</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>101</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>76</td>
<td>-5</td>
<td>14</td>
</tr>
<tr>
<td>12</td>
<td>84</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>13</td>
<td>89</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Extra1</td>
<td>89</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Extra2</td>
<td>91</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Extra3</td>
<td>92</td>
<td>6</td>
<td>-2</td>
</tr>
<tr>
<td>Extra5</td>
<td>100</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Mean(SD)</td>
<td>92.5(8.1)</td>
<td>8.6(8.8)</td>
<td>4.2(4.2)</td>
</tr>
</tbody>
</table>

Table 4.2: The FEV$_1$ during the ECT. The predicted lung function was based on The Quanjer Global Lung Function Initiative-2012 regression equations. *; For this patient it was clinically not relevant to test the response to SABA, this patient had a normal lung function prior to the ECT and an actual lung increase was measured after PA. Subject 11 displayed an abnormal low lung function prior to the ECT, hence the reversibility of this patient was tested despite the increase in lung function after exercise. ☆% of predicted FEV$_1$. §% of baseline.
Table 4.3: Comparison of the parameters derived from both the GENEActiv Action and the telephone, a total of 135 paired coughs were analysed. $p < 0.05$ is statistically significant. * in the frequency domain

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GENEActiv Action data Mean (SD)</th>
<th>Telephone data Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skewness</td>
<td>-0.423 (1.017)</td>
<td>0.200 (0.312)</td>
<td>$p &lt; 0.000$</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>8.005 (7.692)</td>
<td>8.142 (4.316)</td>
<td>$p = 0.061$</td>
</tr>
<tr>
<td>Dominant frequency (Hz)</td>
<td>83 (96)</td>
<td>535 (434)</td>
<td>$p &lt; 0.000$</td>
</tr>
<tr>
<td>Power of dominant frequency (arbitrary units)*</td>
<td>$3.8 \cdot 10^{-4}$ (9.5 $\cdot$ 10^{-4})</td>
<td>$5.0 \cdot 10^{-5}$ (6.3 $\cdot$ 10^{-5})</td>
<td>$p &lt; 0.000$</td>
</tr>
<tr>
<td>Total power in frequency domain</td>
<td>0.015 (0.028)</td>
<td>0.015 (0.016)</td>
<td>$p &lt; 0.005$</td>
</tr>
</tbody>
</table>

4.2 Agreement between devices

After synchronization of the data, several parameters were derived from both the GENEActiv Action and the telephone recordings. The duration of the cough was based solely on the audio recording, therefore, duration of the cough was not compared between devices. Since the data is in different units, m/s$^2$ versus arbitrary units of the telephone, the majority of the data in the time domain was not compared. It was also found that several GENEActiv Action datafiles were corrupt after downloading, leaving a total of 135 paired coughs to analyse. Both voluntary and involuntary coughs were included in this analysis. The parameters that were analysed were the skewness, kurtosis, the dominant frequency and its companying power and the total power of the Welch periodogram. Then, data was analysed by SPSS (IBM Statistics Version 23). First data was visually inspected by creating histograms, then normality of the data was tested by the Shapiro-Wilk test. It was found that all parameters were statistically significant ($p < 0.05$), therefore, all parameters are not normally distributed.

Then, paired parameters were tested by the Wilcoxon signed Rank test, an overview is given in Table 4.3. Skewness, the dominant frequency, the power of the Welch periodogram and subsequently, the power of the dominant frequency in the Welch periodogram differed significantly ($p < 0.05$) between the GENEActiv Action and the telephone recording.
### Table 4.4: Amount of involuntary coughs exerted during the ECT.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Amount of coughs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 6</td>
<td>4</td>
</tr>
<tr>
<td>Subject 9</td>
<td>1</td>
</tr>
<tr>
<td>Subject 12</td>
<td>29</td>
</tr>
<tr>
<td>Extra 1</td>
<td>2</td>
</tr>
<tr>
<td>Extra 2</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 4.4: *Amount of involuntary coughs exerted during the ECT.*

<table>
<thead>
<tr>
<th></th>
<th>Voluntary coughs Mean (SD) (n=144)</th>
<th>Involuntary coughs Mean (SD) (n=39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (ms)</td>
<td>32.296 (10.743)</td>
<td>30.205 (12.049)</td>
<td>p=0.501</td>
</tr>
<tr>
<td>Root-mean-square (arbitrary units)</td>
<td>0.116 (0.052)</td>
<td>0.039 (0.023)</td>
<td>p&lt;0.000</td>
</tr>
<tr>
<td>Total power in time domain (arbitrary units)</td>
<td>0.026 (0.015)</td>
<td>0.009 (0.008)</td>
<td>p&lt;0.000</td>
</tr>
<tr>
<td>Skewness</td>
<td>0.220 (0.277)</td>
<td>0.143 (0.354)</td>
<td>p=0.097</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>8.030 (4.845)</td>
<td>9.760 (3.606)</td>
<td>p&lt;0.000</td>
</tr>
<tr>
<td>Dominant frequency (Hz)</td>
<td>399 (149)</td>
<td>527 (493)</td>
<td>p=0.753</td>
</tr>
<tr>
<td>Power in frequency domain of dominant frequency (arbitrary units)</td>
<td>6.605·10^{-5} (6.307·10^{-5})</td>
<td>9.142·10^{-6} (1.269·10^{-5})</td>
<td>p&lt;0.000</td>
</tr>
<tr>
<td>Total power in frequency domain (arbitrary units)</td>
<td>0.017 (0.014)</td>
<td>0.002 (0.002)</td>
<td>p&lt;0.000</td>
</tr>
</tbody>
</table>

Table 4.5: *Comparison between voluntary and involuntary coughs. p<0.05 is statistically significant.*

### 4.3 Agreement between voluntary and involuntary coughs

For this analysis, only the data from the telephone was used. Of the patient group, 5 patients produced involuntary coughs during the ECT, as seen in Table 4.4. The measured voluntary coughs of all patients were compared to the produced involuntary coughs during the ECT. This gave a total of 183 coughs, of which 144 voluntary and 39 involuntary. Since previously found all data was not normal distributed, the two groups were compared by a Mann-Whitney U test. Results are given in Table 4.5. It was found that the duration, skewness and dominant frequency of the coughs did not differ significantly. All other parameters were statistically significant.
4.4 Clinical feasibility

The patients who wore the GENEActiv Action at home, were asked to fill in a questionnaire with regards to their experience (see Appendix C.2). On average (including the patient who dropped out of the study), patients scored their experience 8/12 points, which was predefined as an acceptable experience. Main complaints were skin irritation caused by the bandages, and on the contrary, bandages which detached from the skin.
5. Discussion

In this study, it was found that the majority of the derived cough sound parameters displayed no relation to the decrease and increase of FEV₁ of children who were suspected to suffer from asthma.

5.1 Cough sound characteristics and lung function

It was hypothesized that the ECT would have an effect on both the frequency components of the cough, and the power of the cough. As previously mentioned, an ECT can induce EIB. Two different pathways describe in literature the working mechanism of EIB. One of the mechanisms proposes that vasoconstriction is induced by airway cooling. The vasoconstriction in turn leads to reactive hyperemia and edema after exercise. In this hypothesis, the bronchoconstriction is a reaction caused by the vascular events. The other hypothesis proposes that dehydration of the airways increases the osmolarity of the airway surface liquid. It is proposed that this hyperosmolarity results in the release of mediators, which in turn induces contraction of the airway smooth muscle cells. This contraction leads to airway narrowing. Furthermore, these mediators could also induce transient edema, which amplifies airway narrowing. Additionally, the increase in osmolarity leads to glandular secretion of mucus, resulting in cough. Since more mucus is produced, it was expected that this would have an effect on the frequency (in Hertz) of the cough. Furthermore, the constricted airways could also influence the frequency of the cough, since the diameter of the airways becomes smaller and the wall tension becomes higher. The induced EIB is measured by a decrease in FEV₁. The decrease in lung function could influence the power of the cough, resulting in a smaller cough amplitude when measured in the time domain. This is in line with what is known in clinical practice.

In this work, the coughs were measured by a holding the phone close to the patients mouth, to obtain the coughs. However, when one assumes that the sound of the cough is in an open area, the intensity decreases by the inverse square of the distance \( I \propto \frac{1}{r^2} \). Therefore, the measurement method used for the WEARCough study introduced an uncertainty when it comes to measuring the intensity of the cough sound, since the distance might not be uniform in all measurements. The measurement protocol was always carried out by one researcher, however, recordings by a lapel microphone versus the telephone would have standardized the measurement.

It was found, as depicted in Figure 4.3, that the power of the Welch periodogram was lower at three minutes after exercise, of the first cough phase. At three minutes after exercise, the majority of the patients also displayed their lowest FEV₁, as shown in Figure 4.1. Therefore the power of the first phase of the cough of the Welch periodogram might reflect the reduced FEV₁. Additionally, a broader frequency range was observed of the dominant frequency of the second phase of the cough,
as seen in Figure 4.2. This dominant frequency at zero minutes after exercise was significantly higher than the baseline measurement \( (p < 0.05) \). It is hypothesized that this is caused by the induced EIB, the airway narrowing and that the amplified mucus production might influence the dominant frequency. The dominant frequency might act as a precursor of the to be expected drop in \( \text{FEV}_1 \). The higher pitch however may be due to a higher respiratory rate after exercise. It is hypothesized that when the respiratory rate goes up, faster vibrations are created by the higher flow in the glottis. This could in turn result in a higher dominant frequency. The pitch however might also be influenced by the age of subjects, which could not be excluded due to the broad variety of the age (see Table 4.1). A sub-analysis could neither dismiss nor confirm whether age is a confounder for the dominant frequency. Additionally, the same sub-analysis was performed to explore if gender is a confounder for the dominant frequency. This sub-analysis also could not confirm if gender plays a role in the dominant frequency. However, literature suggests that the pitch is depended on gender, which contradicts the outcomes of the study.\[54]\] This might be due to the small sample size of the WEARCough-study.

In this work, a lower kurtosis after salbutamol for the full cough duration was found, as shown in Figure 4.4. This is in contrast to the work of Thorpe et al. They compared the kurtosis of the second cough phase from asthmatic to non-asthmatics. They reported a negative kurtosis of -13 for asthmatics versus 50 for healthy subjects \( (p<0.05) \). The trend shown in Figure 4.4 does not correspond to their findings. In contrast to Thorpe et al., the kurtosis of the full cough was given in Figure 4.4. Additionally, the comparison can only be made after salbutamol and not in comparison to healthy subjects. Also, in the work of Thorpe et al, asthmatics displayed a drop in PEF ranging from 17-75% compared to baseline. The included patients in this study displayed a drop in \( \text{FEV}_1 \) ranging from an actual increase in lung function to a maximum of 29%. In conclusion, Thorpe reported cough sound characteristics of patients with a greater drop in lung function.\[18]\]

No trends were found on the duration of the coughs, however, based on the work of Piirilä and Sovjärvi, it was expected that the duration of the cough sound would increase due to the induced bronchoconstriction. Furthermore, they also found that the upper limit of the frequency band was significantly lower in asthma, in comparison to chronic bronchitis and tracheobrochial collapse syndrome.\[15]\] Due to the lack of a control group in the WEARCough study, this comparison could not be made.

More recent work of Abaza et al. created a cough classifier for lung diseases. They compared their cough classifier, which was based upon features of both cough sound and airflow during cough, to the diagnosis of pulmonary physicians. In their study, 3 coughs of 112 subjects were analysed, analysis for males \( (n=58) \) and females \( (n=54) \) were carried out separately. Of the male disease coughs, 94% of the coughs were classified correctly when comparing them to the physicians diagnosis. For females, the system was able to classify 90% of the disease coughs correctly. Though they did report which parameters were derived from the cough sound, they did not report which parameters were most valuable in their model.\[55]\] Additionally, coughs were not obtained while asthma responses were provoked, such as during exercise or during the inhalation of histamines.

As previously stated, Rietveld et al. did find that children with asthma cough significantly more in comparison to their healthy peers during PA. They compared
30 asthmatic children and adolescents to 30 healthy subjects. All children with asthma displayed a decrease in FEV$_1$ of at least 10%. This study only involved involuntary coughing.$^{[16]}$ Therefore it was expected for the WEARCough study that the children who had a decrease in FEV$_1$ of at least 10%, would experience more involuntary coughing. This was not found, when comparing the FEV$_1$ in Table 4.2 with Table 4.4. Only 2 out of 5 subjects who coughed involuntarily had an EIB >10%. The contradiction between this work and the work of Rietveld could be caused by the small sample size of this study. Additionally, there was no healthy control group measured in the WEARCough study.

### 5.2 Agreement between devices

It was found that the GENEActiv Action data was not comparable to the audio recordings, as shown in Table 4.3. Based on the work of Paul et al., it was hypothesized that the GENEActiv Action could be a sufficient device for monitoring of coughs. They compared their accelerometer measurements to video recordings. Two investigators scored the amount of coughs exerted on both recordings, the correlation coefficient was determined per investigator. They found a correlation coefficient between the different recordings of at least 0.918 ($p < 0.05$).$^{[33]}$ Paul et al., and their predecessor Pavesi et al. did however not enclose the used $f_s$ of their accelerometer, which can have a $f_s$ up to 10 kHz, as previously mentioned in Section 2.3.$^{[33,56]}$ Therefore their accelerometer could have been able to measure a broader frequency range. Additionally, they measured their audio recordings at the suprasternal notch, which was not feasible in this study. Finally, Paul et al. did not compare the frequency components between devices, they only compared the amount of coughs measured.$^{[33]}$ Using an accelerometer as cough counter induces only the requirement of being able to distinguish coughs from other sounds. Whereas when an accelerometer is employed to substitute measurements recorded with a microphone, maintaining the majority of the frequency components is considered to be more challenging.

A great advantage of the use of the GENEActiv action was that privacy of the patient was ensured, since the measured acceleration data only reflects a small part of the frequency spectrum of a sound. This also introduces a great disadvantage; due to sound absorption of the body and the relative low $f_s$, the characteristics of the cough are not preserved, as shown in Section 4.2.
5.3 Agreement between voluntary and involuntary coughs

Though Chang describes that the mechanical pathway to exert a cough is identical for voluntary and involuntary coughs, it was found that only the duration, skewness and dominant frequency did not differ (p > 0.05, Table 4.5).\textsuperscript{17} However, since not all patients exerted involuntary coughs, the involuntary coughs only contain coughs of 5 patients. Furthermore, out of the 39 involuntary coughs, 29 coughs were exerted by one patient (see Table 4.4). Matching the involuntary coughs to voluntary coughs, based on when they were exerted, was not deemed feasible. The majority of the coughs exerted by subject 12 occurred after the inhalation of salbutamol. Therefore, matching these coughs to voluntary coughs would imply comparing them to coughs which occurred up to 3 minutes before or 3 minutes after the involuntary cough occurred. This was considered to be too different to be able to make a comparison.

5.4 Clinical feasibility

During the course of this study, it became clear that participation in this study was lower than expected, based on the inclusion rate during the previous WEARCON study. Patients and parents did not feel comfortable to participate in the study since the cough monitoring device was worn visibly in the neck area. This caused resistance to wearing the device in a home environment. An amendment was written; if a patient did not want to participate because of the home monitoring period, they were offered the option to participate in the trial only during the ECT. The amendment was approved by the METC Twente on the 9th of January 2019. Once patients did wear the device at home, the majority of the patients had an acceptable experience, as described in Section 4.4. It was found that the selection of the suitable bandages was dependent on the patients; one bandage might be too rough on the skin for one patient, whereas the same bandage for the other patient would be suitable for keeping the device in place during the full 12 hours. Therefore different bandages were supplied to the patients and patients were instructed to change the used bandage if they experienced discomfort. A solution to this problem could be changing the monitoring device to the ADAM, which is created to capture sound. This device can be attached under clothing, making patients and their surroundings less aware of the device. Additionally, this device comes with a custom bandage to adhere it to the skin.\textsuperscript{31}
5.5 General remarks

During this study, a small amendment in the measurement protocol was made. Instead of asking children to cough immediately when they step off the treadmill or bouncing castle, the children were asked to cough a few seconds later in the office. This change has been carried out to eliminate the background noise which was constantly present in the cold exercise lab, due to the air conditioning.

In Section 3.3.1 a home-monitoring period has been described. This data has not been analysed up to date, since up to this point, it would not be clinically relevant. A small pilot study has been carried out by a student of Technical Medicine for a 10 week internship, defining if the GENEActiv Action was capable of distinguishing between coughs and shouting, spoken words, laughter etcetera. Several parameters were selected to be derived from both measured audio by a telephone and the GENEActiv Action, e.g. duration, signal energy, skewness and root-mean-square. The audio was used to label each sound for automated sound classification. Several machine learning algorithms were evaluated for the automated classification. It was found that subject specific training for the learning algorithm gave an accuracy of 88% for measurements carried out with healthy children. The home-monitoring data could be analysed with a similar method, using the ECT data for the learning part of the model, subsequently classifying the home-monitoring data.

5.6 Future work

Future work should focus on if cough parameters, measured with a standardized protocol whilst provoking EIB, are indicative of bronchoconstriction. Since no comparison in this work could be made to a healthy population, it is yet unknown whether the observed trends (as shown in Section 4.1) are indicative of asthma or if these are healthy behaviour. Additionally, at the moment it is still unclear if patients with a severe drop (>25%) in FEV\textsubscript{1} display different behaviour in comparison to stable asthmatics, since only 2 patients in this study experienced this during the ECT (Table 4.2). Measurement of a larger population of both asthmatic and healthy subjects would also attribute to the quality of the research. When the specific parameters of cough sound indicating severity of FEV\textsubscript{1} decline are identified in a standardised setting, these parameters could be validated in the home situation, enabling parents with easy accessible equipment such as a telephone to monitor their child.
6. Conclusion

In this work, no relation between cough sound parameters and changes in FEV$_1$ was found. Home-monitoring with the GENEActiv action was feasible, however, preliminary analysis reveals that the device was not sufficient to replace sound data captured with a telephone. After the addition of more patients who do display an FEV$_1$ drop during the ECT, the monitoring of coughs might be clinically relevant. The power of a cough could be indicative of FEV$_1$, since the measurement of this parameter in this research was subjective to a confounder.
Bibliography


[27] N. Gavriely and S. Godfrey, “Wheezes, rhonchi and whistles are acoustically distinct, yet all are manifestations of airflow through constricted pulmonary airways,” in Wheezes, Rhonchi And Whistles Are Acoustically Distinct, Yet All Are Manifestations Of Airflow Through Constricted Pulmonary Airways, American Thoracic Society, may 2011.


Appendix A

Measurement site of the GENEActiv Action

Attachment of the GENEActiv Action on the pectoralis major muscle has been explored first. This was the preferred measurement location, since if suitable, the device could be worn underneath clothing. Then the device would be undetectable in their social environment, making patients more willing to wear the device. Unfortunately we found that since the pectoralis is situated above rib cage, it dampened the cough sounds. Then, fixation above the suprasternal notch was opted, similar to Paul et al.[33] During testing, this gave data of good quality, coughs were clearly distinguishable in the frequency domain. The placement however would make the child susceptible for injuries, such as when flexion of the neck takes place. Therefore different placements were compared to the suprasternal notch; the sternocleidomastoid region and the trapezoid region. The data quality at these sites were compared by recording coughs simultaneously, the attachment of the devices is shown in Figure A.1.

Multiple coughs were performed while wearing the devices and the sound was simultaneously recorded with a telephone (Samsung S5 mini). The coughs were performed whilst standing and while jumping up and down. Raw data of all devices was extracted and data was further analysed in Matlab. First the resultant of the x-y- and z-direction ($\sqrt{x^2 + y^2 + z^2} - 1$) was created. This resultant was transferred to the frequency domain by creating a spectrogram. When comparing the data of the sound recording to the data of the GENEActiv Action in the time domain, no obvious similarities were observed. Visual inspection of the spectrogram did reveal similarities in the frequency domain, between the signal of the sternocleidomastoid

![Figure A.1](image_url)

*Figure A.1: Anterior and lateral view of the test configuration for adherence sites. The GENEActiv Action devices are fixated above the suprasternal notch, in the sternocleidomastoid region and the trapezoid region. Due to the curvature of the trapezoid region and the GENEActiv Action, the way this GENEActiv was attached was considered to have the largest contact surface with the skin.*
Figure A.2: Comparison of all locations and the microphone in the frequency domain. Only the z-direction of the GENEActiv Action has been analysed, giving greater distinctions for coughs. The microphone obtained sound has been downsampled from 44100 Hz to 1000 Hz, which enable comparison with the accelerometer, which also has a $f_s$ of 1000 Hz.

region and the sound recording. Visual inspection did reveal agreement between all signals, when only the z-component of the GENEActiv Action accelerometer was compared to the sound recording. This is explained by the fact that movements in the z-plane correspond to movements of the throat in the sagittal plane, which were cancelled out by taking the resultant of all three directions. The comparison between sensors in the frequency domain is shown in Figure A.2. It was found that the trapezoid region dampens sounds too much to be considered as a measurement site, which led to the sternocleidomastoid region as the selected measurement site for this study.
Appendix B

Method of fixation of the GENEActiv Action

In order to maximize comfort and minimize trauma to the skin, the appropriate bandage needed to be selected. First, a test was conducted using Fixomull® Stretch, which has a hypoallergenic polyacrylate adhesive.\[58\] The Fixomull® left the skin, after 12 hours of wear, red and sensitive for both test subjects. The skin irritation lasted for several days, making Fixomull® unsuitable for this trial.

A nurse practitioner of the Wound Expertise Centre in the MST was counselled to determine a more suitable bandage, which resulted in the advice to use the Mepilex® Border Flex. This bandage is lined with the Safetac® technology, which involves the use of soft silicone. This minimizes stripping of the epidermis at removal of the bandage. When using bandages with the Safetac® technology, patients experience smaller peel for ces and a great decrease in pain. The Mepilex bandages are used typically for acute wounds (surgical and traumatic wounds), skin tears, road rashes, burns and skin grafts.\[59\] The Mepilex bandages also has been used for paediatric wounds, e.g. by Morris et al. They compared the Mepilex bandage to traditional bandages. At the first dressing of the wounds a traditional bandage was used, for the subsequent dressings Mepilex band aids were used. The pain during and in-between dressing was assessed by the Visual Analog Scale (VAS) and the Wong-Baker Faces scale. They reported a significant decrease in the mean VAS-scores (p<0.003), with a VAS <1.5 for the removal of the Mepilex dressing.\[60\]

For the second part of the trial, the GENEActiv Action was adhered first with skin closure strips, placing one strip horizontally and one vertically across the device. Then the Mepilex® Border Flex was applied. This reduced redness significantly for the test subjects, with no redness due to the Mepilex® Border Flex and slight redness due to the skin closure strips. Another test subject was included, whom suffered more from more redness due to the skin closure strips. Therefore, the skin closure strips have been replaced by Leukoflex®.\[61\]
The Mepilex® Border Flex bandages were 100mm x 100mm. Since the device is only 43mm x 40mm, the next tests were conducted with the Mepilex® Border Lite of 75 mm x 75 mm to see if a smaller surface area would still be sufficient. This gives more mobility, since the surface area of the bandage was reduced from 100 cm$^2$ to 56.25 cm$^2$. The rim of the bandage which is in contact with the skin was still able to provide a secure fit. The Lite version of this bandage introduced a thinner absorbent pad in the bandage, giving more flexibility in comparison to the regular version. The bandage is given in Figure B.1. Unfortunately no version of the bandage is available without an absorbent pad, due to the intended use of the bandage.

Figure B.1: *The Mepilex border flex bandage. Image from Capes Medical.*[^62]
Appendix C

Questionnaires
C.1 The medication form

In onderstaande lijst kan je bijhouden wanneer je je blauwe pufjes deze week gebruikt.

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De controle medicatie die je gebruikt is ..................., deze gebruik je ........ per dag.
In het onderstaande lijstje kan je opschrijven wanneer je deze hebt gebruikt.

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C.2 The GENEActiv Action questionnaire

Vragenlijst hoestmeter

1. Hoeveel last had je met het dragen van de hoestmeter *s’ nachts*?

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<tr>
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<th>1 punt</th>
<th>2 punten</th>
<th>3 punten</th>
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<td>Ik heb er veel last van en vind het erg vervelend.</td>
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<td>Ik heb er een beetje last en vind het vervelend.</td>
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<td>Ik heb er een beetje last van, maar het gaat wel.</td>
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<tr>
<td>Ik heb er geen last van.</td>
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2. Hoeveel last had je met het dragen van de hoestmeter *tijdens het sporten*?

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3. Hoeveel last had je met het dragen van de hoestmeter *op school*?

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<td>Ik heb er geen last van.</td>
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4. Als je last had van de hoestmeter, waar had je dan last van?

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Een score van 8/12 punten wordt gezien als een accepteerbare ervaring met het dragen van de GENEActiv Action.
C.3 The Childhood Asthma Control Test (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 je astma als je rent, traint of sport?
   - Ik heb er veel last van, ik kan niet doen wat ik wil. □
   - Ik heb er last van, 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 / 13-03-2018
Beantwoord als ouder de volgende vragen:

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

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

7. Hoeveel dagen werd uw kind de afgelopen week ‘s nachts wakker door de astma?
C.4 The Pediatric Asthma Quality of Life Questionnaire (PAQLQ)

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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QOL TECHNOLOGIES Ltd.

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This translation has been made possible through a grant from AEROCRINE AB
Translated by MAPI RESEARCH INSTITUTE
Senior translator: Peter Kramer

© De PAQLQ(S) is auteursrechtelijk beschermd en mag zonder toestemming van Elizabeth Juniper niet worden gewijzigd, verkocht (in print of elektronisch), vertaald of aangepast aan een ander medium.

FEBRUARI 2005
Kwaliteit van leven vragenlijst voor kinderen en jeugdigen met astma (S)

(Dutch version)

Door patiënt zelf in te vullen

Datum

Bladzijde 1 van 4

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

Hoeveel last had je deze week bij/van het volgende:

1. Lichamelijke activiteiten (zoals rennen, zwemmen, sporten, een heuvel/trap oplopen en fietsen)?

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2. Met dieren omgaan (zoals spelen met huisdieren en het verzorgen van dieren)?

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3. Activiteiten met vrienden en familie (zoals spelen tijdens de pauze en dingen doen met vrienden en familie)?

<table>
<thead>
<tr>
<th>Heel erg veel last</th>
<th>Veel last</th>
<th>Nogal wat last</th>
<th>Wel wat last</th>
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4. Hoesten?

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<tr>
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Alles bij elkaar, hoe vaak deze week:

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<thead>
<tr>
<th>Altijd</th>
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5. Voelde je je teleurgesteld, ontmoedigd of kwaad op jezelf door je astma?

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<tr>
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6. Was je moe door je astma?

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</tbody>
</table>

7. Was je ongerust, maakte je je zorgen of zat je te piekeren door je astma?

<table>
<thead>
<tr>
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</tbody>
</table>
Kwaliteit van leven vraaglijst voor kinderen en jeugdigen met astma(s)

(Dutch version)

Door patiënt zelf in te vullen

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**Datum:**

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**Hoeveel last had je deze week van:**

<table>
<thead>
<tr>
<th></th>
<th>Heel erg veel last</th>
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<tbody>
<tr>
<td><strong>8. ASTMA-AANVALLEN?</strong></td>
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**ALLES BIJ ELKAAR, HOE VAAK DEZE WEEK:**

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<tbody>
<tr>
<td><strong>9. was je BOOS vanwege je astma?</strong></td>
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<tbody>
<tr>
<td><strong>10. een PIEPENDEademhaling?</strong></td>
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<tbody>
<tr>
<td><strong>11. was je MOPPERIG of HUMEURIG door je astma?</strong></td>
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</tr>
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<tbody>
<tr>
<td><strong>12. een BENAUVWD GEVOEL IN OF BOVEN IN JE BORSTKAS?</strong></td>
<td>1</td>
<td>2</td>
<td>3</td>
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<th>Nooit</th>
</tr>
</thead>
<tbody>
<tr>
<td>13. had je het gevoel dat jeanders was dananderen of er nietbij hoorde door jeastma?</td>
<td>1</td>
<td>2</td>
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HOEVEEL LAST HAD JE DEZE WEEK VAN:

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</tr>
</thead>
<tbody>
<tr>
<td>14. kortademigheid of datje niet genoeg lucht kon krijgen?</td>
<td>1</td>
<td>2</td>
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<th>Nooit</th>
</tr>
</thead>
<tbody>
<tr>
<td>15. voelde je je teleurgesteld,ontmoedigd ofkwaad op jezelfomdat je deanderen niet bijkon houden?</td>
<td>1</td>
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<td>7</td>
</tr>
<tr>
<td>16. werd je 's nachtswakker door je astma?</td>
<td>1</td>
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<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>17. voelde je je niet op je gemak door je astma?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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</tr>
<tr>
<td>18. was je buiten aademdoor je astma?</td>
<td>1</td>
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<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>19. kon je de anderen niet bijhouden doorje astma?</td>
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<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>20. had je moeite om 's nachts te slapendoor je astma?</td>
<td>1</td>
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<td>7</td>
</tr>
<tr>
<td>21. werd je bang door een astma-aanval?</td>
<td>1</td>
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DENK NU EENS AAN AL DE DINGEN DIE JE DEZE WEEK GEDAAN HEBT:

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<tbody>
<tr>
<td>22. Alles bij elkaar genomen, hoeveel last heb je gehad van je astma bij die dingen?</td>
<td>1</td>
<td>2</td>
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<tbody>
<tr>
<td>23. had je moeite om DIEP ADEM TE HALEN?</td>
<td>1</td>
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**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