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PhD thesis
Karen Hjerrild Andreasson

Patients with incomplete asthma control – effectiveness of breathing exercises and associations with asthma-specific quality of life

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PhD Thesis
Karen Hjerrild Andreasson, PT MSc

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Abbreviations

6MWT	6-minutes' Walk Test
ACQ6	6-item Asthma Control Questionnaire
AE	Adverse events
BEAT DB	Breathing Exercises in Asthma Targeting Dysfunctional Breathing
BMI	body mass index
Borg CR10	amount of breathlessness in rest using
BrEX	Breathing Exercises
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials statement
COPD	Chronic Obstructive Pulmonary Disease
EIB	Exercise-induced bronchoconstriction
EuroQoL-5D-5L	European Quality of Life Questionnaire, 5 dimensions, 5 levels
FEV_1%pred	predicted forced expiratory volume in first second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GLI2012	Global Lung Functions Initiative (GLI) 2012
GPE	Global Perceived Effect
HADS-A	Hospital Anxiety and Depression Scale (anxiety)
HADS-D	Hospital Anxiety and Depression Scale (depression)
ICS	Inhaled corticosteroids
IQR	Inter quartile range
IRR	Incidence rate ratio
ITT	Intention-to-treat
MID	Minimal important difference
MiniAQLQ	Mini-Asthma Quality of Life Questionnaire
NNT	Number-needed-to-treat
NQ	Nijmegen Questionnaire
OCS	Oral corticosteroids
PEFR	Peak Flow Rate
QoL	Quality of Life
RCT	Randomised Controlled Trial
RR	Respiratory Rate
SAP	Statistical Analyses Plan
SD	Standard deviation
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
STROPE	Strengthening the Reporting of Observational Studies in Epidemiology
TIDieR	Template for Intervention Description and Replication statement
UC	Usual Care
UC+BrEX	Add-on breathing exercises to usual care.

List of papers

Paper I

Protocol for a multicentre randomised controlled trial to investigate the effect on asthma-related quality of life from breathing retraining in patients with incomplete asthma control attending specialist care in Denmark

Karen Hjerrild Andreasson, Søren Thorgaard Skou, Charlotte Suppli Ulrik, Hanne Madsen, Kirsten Sidenius, Jannie Søndergaard Jacobsen, Karin Dahl Assing, Kirsten Brændholt Rasmussen, Celeste Porsbjerg, Mike Thomas, Uffe Bodtger

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Study 2

Factors associated with asthma-specific quality of life: a cross sectional analysis of 193 patients with moderate-to-severe asthma

Karen Hjerrild Andreasson, Søren T. Skou, Charlotte Suppli Ulrik, Hanne Madsen, Kirsten Sidenius, Karin Dahl Assing, Celeste Porsbjerg, Jannie Rhod Bloch-Nielsen, Mike Thomas, Uffe Bodtger

Status: pre-submission

Study 3

Breathing exercises for asthma patients in specialist care - a multicentre randomised trial

Karen Hjerrild Andreasson, Søren T. Skou, Charlotte Suppli Ulrik, Hanne Madsen, Kirsten Sidenius, Karin Dahl Assing, Celeste Porsbjerg, Jannie Bloch-Nielsen, Mike Thomas, Uffe Bodtger

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Thesis at a glance

This thesis presents research conducted in a population of 193 patients with incompletely controlled, moderate-to-severe asthma. Patients were prospectively recruited from one of eight participating centres, and consented to participate in a multicentre randomised controlled trial (RCT) called BEAT-DB.

Breathing Exercises in Asthma Targeting Dysfunctional Breathing (BEAT-DB) was the original name of the Ph.D. project. However, very early we realised that the absence of a valid way to diagnose dysfunctional breathing made it impossible to recruit participants. Instead, we used dysfunctional breathing as a pragmatic approach, focusing our interest on breathing exercises in patients with asthma.

The trial aimed at investigating the effect of *breathing exercises* on asthma-specific quality of life assessed by the validated questionnaire "Mini Asthma Quality of Life".

The methodological design of the multicentre RCT is described in a protocol paper (Paper I).

Next, I present the associations between the primary RCT outcome and demographical, asthma-related, comorbidity-related and respiratory/physical factors that were investigated in the baseline data of the participants, using univariable and multivariable regression analyses (Study 2).

Finally, the results of the multicentre RCT are presented, investigating the effect of add-on *breathing exercises* to usual care in patients with incompletely controlled moderate-to-severe asthma on asthma-specific quality of life and pre-specified secondary end-points (Study 3).

The thesis opens with a background section on asthma including diagnosis and assessment, asthma-specific quality of life, *treatable traits*, comorbidities including dysfunctional breathing, the challenges in diagnosis of dysfunctional breathing, and the role of physiotherapists in asthma.
I present a summary of the contemporary evidence on the relevant topics, and then follows the overall and specific aims with the thesis.

The studies are presented in Methods, Results, and Discussion sections.

Finally, I present my conclusion and recommendations for clinical practise and future research.

It is my hope that you will find my thesis informative and of sufficient quality, and I'm looking forward to hear your comments.

With kind regards,
Karen Hjerrild Andreasson

English summary

Asthma is a common, chronic, heterogeneous, and treatable disease affecting >300 million patients worldwide. Asthma is characterized by airway inflammation and bronchial hyperreactivity resulting in variable airflow obstruction and symptoms of breathlessness, cough, chest tightness and wheezing. Asthma treatment consists of behavioural changes such as asthma trigger avoidance, and inhaled drugs, primarily inhaled corticosteroids. Asthma is classified according to level of symptoms control (controlled, partly incomplete control, uncontrolled), and asthma severity based on the amount of medication to achieve control (mild, moderate, severe asthma).

Uncontrolled asthma affects 40% of patients, who should be referred from general practitioners to pulmonologist for optimization, as uncontrolled asthma is a risk factor for hospital admissions, sick leave, loss of income and poor quality of life (QoL). However, a subgroup remains uncontrolled despite intense medical treatment. Many factors are involved including comorbidities that can worsen or mimic asthma. A common such is *dysfunctional breathing* (DB), which is an alteration of the breathing pattern that results in symptoms such as breathlessness or chest tightness. DB is observed in ~50% of patients with moderate-to-severe asthma.

Asthma-specific QoL describes how living with asthma is perceived. It is well-known that asthma control explains a lot (39-50%) but not all of asthma-specific QoL. Factors related to the individual's disease or situation, which are changeable, are so-called *treatable traits.* Identifying factors that affect asthma-specific QoL could potentially improve the types of interventions used to improve the life of patients with asthma. In patients with mild-to-moderate asthma, physiotherapy (*breathing exercises*) has been shown to improve QoL.

This thesis aimed to find factors that relates to asthma-specific QoL and to investigate the effect on asthma-specific QoL from physiotherapist-delivered breathing exercises in patients with moderate-to-severe asthma.

The first study explored factors affecting asthma-specific QoL in 193 patients with moderate-to-severe asthma. The results confirmed a strong and negative association with asthma control, but also with anxiety and DB, all being potential *treatable traits*. A protective aspect was having a high income, whereas neither sex, age, educational level, employment status, asthma severity, body mass

index, depression, chronic rhinosinusitis, number of chronic diseases, lung function, level of breathlessness, walking speed, nor respiratory rate was associated with asthma-specific QoL.

These 193 patients were treated by specialists in one of eight asthma care centres (seven hospitals and one private lung clinic) due to poor asthma control, and accepted to participate in a trial, in which one half of all participants were randomized to receive supplementary breathing exercises in addition to the usual care delivered in the department. The other half received their usual care. Participants in the breathing exercises group had three sessions during 12 weeks with a physiotherapist: participants received introduction to the exercises program, were treated, did the program, received progression and corrections. Additionally, these participants were encouraged to do home exercise ten minutes twice daily. The breathing exercises program is thoroughly described in a study protocol presented as Paper 1 in this thesis.

The results showed that breathing exercises improved asthma-specific QoL both 3 and 6 months after onset, and was safe, well-tolerated and easy to perform. Asthma-specific QoL was measured using a validated questionnaire, MiniAQLQ. Both groups improved MiniAQLQ but the group receiving breathing exercises improved significantly more: 0.35 units (95%CI 0.07 to 0.62) which is corresponding to the impact of add-on medications. This effect size corresponds to a low number (7.6) of patients needed to treat before one patient improves markedly in MiniAQLQ.
The group receiving breathing exercises also improved more in level of depression (-0.9; 95%CI -1.67 to -0.14), whereas no differences were observed in use of medication or in number of unwarranted events like worsening of asthma.

In conclusion, this thesis concludes that anxiety and dysfunctional breathing are important *treatable traits* in patients with poorly controlled moderate-to-severe asthma, and breathing exercises is a safe, and easy intervention that improves asthma-specific QoL in this patient group. Contemporary asthma care should include access to breathing exercises.

Dansk resumé (Danish summary)

Astma er en almindelig og kronisk luftvejssygdom, og en sygdom, som kan behandles. Globalt set, har flere end 300 millioner mennesker astma. Astma skyldes inflammation i luftvejenes slimhinde med forøget følsomhed overfor irritanter (husstøvmider, dyrehår, røg, halsbrand m.fl.) som giver forsnævring af de små luftveje. Patienten oplever da varierende symptomer som åndenød, trykken for brystet, pibende vejrtrækning og hoste. Astma behandles ved at undgå irritanter og med medicin, især inhaleret binyrebarkhormon (glukokortikoid) for at opnå kontrol med inflammationen og dermed symptomerne på astma. Astma klassificeres i forhold til graden af symptomer (kaldet kontrolleret, delvis kontrolleret, ukontrolleret astma) og i forhold til sværhedsgrad (mild-moderat-svær astma) alt efter hvor meget medicin der skal til for at kontrollere symptomerne.

Ca. 40% af patienterne oplever ukontrolleret astma og denne gruppe bør henvises fra egen læge til udredning og behandling hos lungemedicinsk speciallæge på hospital eller i speciallæge praksis, fordi denne gruppe er i risiko for hospitalsindlæggelse, sygefravær og forringet livskvalitet.
Men nogle patienter oplever fortsatte symptomer trods optimal medicinsk behandling. Mange forskellige faktorer kan være årsag til det, blandt dem at have andre kroniske sygdomme, som kan forværre eller ligne astma. En hyppig årsag til åndenød hos astmatikere er dysfunktionel vejrtrækning (*Dysfunctional breathing*, DB), som er en tilstand, hvor man har et ikke-hensigtsmæssigt vejrtrækningsmønster. DB ses hos omtrent hver anden patient med moderat til svær astma.

Astma-relateret livskvalitet (herefter kaldet astma-livskvalitet) beskriver, hvordan det opleves at have astma. Man ved, at der er en association mellem astma-livskvalitet og kontrol af astma-symptomer, således at 39-50% af astma-livskvaliteten kan forklares ved graden af astma-kontrol. Faktorer, som har sammenhæng med individets sygdom eller livssituation og som er potentielt kan behandles/ændres, kan kaldes behandlelige faktorer (*treatable traits*). Identifikation af faktorer som påvirker astma-livskvaliteten, er derfor skridt på vejen til at finde nye behandlingsmetoder, som vil forbedre livskvaliteten for patienter med astma.
Tidligere studier har vist, at patienter med mild til moderat astma oplever forbedret astma-livskvalitet ved at få vejrtrækningsgenoptræning hos fysioterapeut.

Denne afhandling havde til formål at finde faktorer, der er associerede med astma-livskvalitet samt at undersøge effekten af vejrtrækningsgenoptræning ved fysioterapeut på astma-livskvalitet hos patienter med moderat eller svær astma.

Det første studie (artikel 2 i denne PhD) undersøgte hvilke faktorer, der har betydning for niveau af astma-livskvalitet hos 193 patienter med moderat eller svær astma. Studiet fandt, at der er en stærk og negativ association mellem astma-livskvalitet og niveau af astma-kontrol, angst og dysfunktionel vejrtrækning, som derfor er potentielle *treatable traits*, og ligeledes en stærk, men beskyttende effekt på astma-livskvalitet ved at have 'høj indkomst'. Derimod var der ingen sammenhæng mellem astma-livskvalitet og følgende faktorer: køn, alder, uddannelsesniveau, erhvervsstatus, astma sværhedsgrad, body mass index, depression, kronisk næseirritation, antallet af andre kroniske sygdomme, lungefunktion, åndenødsoplevelse, ganghastighed eller vejrtrækningsfrekvens.

Det andet studie var et stort multicenter-forsøg, med 193 patienter fra 7 hospitaler og 1 privat lungeklinik. Alle deltagerne havde et igangværende behandlingsforløb i lungeambulatoriet/ lungeklinikken på grund af vedvarende astma-symptomer. Halvdelen af deltagerne fik i tillæg behandling med vejrtrækningsgenoptræning hos fysioterapeut (behandlingsgruppe). Resten af deltagerne var kontrolgruppe, som fortsatte et almindelig behandlingsforløb. Deltagerne i behandlingsgruppen var hos fysioterapeut til behandling 3 gange, hvor metoderne blev introduceret, trænet, progredieret og korrigeret. Derudover skulle disse deltagere træne hjemme to gange 10 minutter dagligt. Forløbet varede 12 uger. Metoden til vejrtrækningsgenoptræning er grundigt beskrevet i protokollen til forsøget (artikel 1 i denne PhD).

Resultatet af forsøget viste (artikel 3 i denne PhD), at vejrtrækningsgenoptræning er en sikker og virksom metode til at forbedre astma-livskvalitet efter både 3 og 6 måneder fra forsøgsstart målt med det validerede sygdomsspecifikke *Mini-Asthma Quality of Life Questionnaire* (MiniAQLQ). Begge grupper forbedrede deres MiniAQLQ score, dvs. oplevede forbedret livskvalitet, men forbedringen var signifikant større i behandlingsgruppen: 0,35 enheder (95%CI 0,07 til 0,62), hvilket svarer til den forbedring, man finder i studier med tillægs-medicin, kaldet *second controllers*. Forbedringen svarer desuden til, at der skal behandles få (7,6) patienter for at opnå en klinisk betydende effekt hos én patient. Forsøget fandt også, at behandlingsgruppens niveau af depression faldt en smule mere end kontrolgruppens niveau (-0,9; 95%CI -1,67 til -0,14). Der var

ikke forskel mellem grupperne i ændring af forbrug af astma-medicin eller i antal af bivirkninger, såsom astma-forværringer.

Konklusionen af denne afhandling er, at angst og dysfunktionel vejrtrækning er betydningsfulde tilstande, som begge potentielt kan behandles, hos patienter, som har ukontrolleret, moderat til svær astma, samt at tilføjelsen med vejrtrækningsgenoptræning er en sikker og let behandlingsmetode til at forbedre astma-livskvalitet i denne gruppe af patienter. Mulighed for at give vejrtrækningsgenoptræning bør indgå i behandlingen af astma.

BACKGROUND

Asthma and asthma care in Denmark

Asthma and the burden of asthma

Asthma is a common, chronic, heterogeneous, and treatable disease. Asthma is characterized by airway inflammation and bronchial hyperreactivity resulting in variable airflow obstruction.[1,2] Globally, asthma affects around 334 million individuals, and in Denmark around 300,000 individuals are estimated to have asthma. The prevalence is high and stable in developed countries whereas in less developed countries, asthma prevalence is lower (and probably underestimated) but increasing.[1–4] Onset of asthma can occur at all stages in life but with a peak in early childhood and at around age 40-50 years.[2]

The most typical symptom of asthma is dyspnoea, which significantly restricts physical activity and quality of life (QoL) for the patient.[2,3] Chest tightness, coughing and wheezing are other main symptoms causing exhaustion especially in severe asthma.[3,5]

Besides the individual burden of having asthma, the societal burden of asthma is high due to both use of health care resources, lost days at work or education, and early retirements.[3,6,7]

Asthma diagnosis

A gold standard for diagnosing asthma does not exist, however symptoms and variable expiratory airflow limitation are cornerstones.[3] Guidelines suggest to objectively verify asthma diagnosis, but due to the variable airflow limitation, many patients are asymptomatic when scheduled for diagnostic work-up.[3] A lung function test is mandatory, and the expiratory airflow is measured using spirometry using the ratio of forced expiratory volume in first second (FEV_1) to forced vital capacity (FVC). A subgroup of patients present with the classical *positive reversibility test* showing improvement in FEV_1 of ≥12% or ≥200ml after either inhaled bronchodilators (usually short-acting ß2-agonist) or a course of inhaled or systemic corticosteroid.[3,8] However, other asthma phenotypes are dominated by inflammation with sparse airflow limitation, and in specialist care settings, only a minority present with a positive reversibility test.[9]

A patient with asthma is characterized according to phenotype (e.g. allergy-driven or not, eosinophil-driven or not, early- or late-onset, presence of specific comorbidities such as nasal polyps, reflux, obesity), asthma control and asthma severity.[3]

Clarification of exposure to triggers (smoke, allergens, or other airborne particles) and presence of comorbidities (obesity, reflux, allergy, heart failure etc) is essential, as these usually worsen – or in some patients - cause the asthma.[3]

Asthma control

Asthma control is defined as the absence of symptoms (e.g. dyspnoea, coughing during night-time or exercise), and reduces risk of exacerbations and emergency health care usage.[3] However, across cultures and generations only about 40% of an asthma population achieve asthma control, with the remainder achieving either incomplete (30-40%) or uncontrolled asthma (20-30%).[10,11] Several tools have been developed to measure asthma control.[12–14] One of the most commonly used is the, Asthma Control Questionnaire (ACQ), which has been validated in more versions including 5, 6 or 7 items.[12,13] The original 7-item version (ACQ7) has six self-reported items to be scored concerning the experiences of following during previous seven days: frequency of waking up by symptoms at night, severity of symptoms in the morning, limitation during activities, amount of shortness of breath, time with wheezing, number of puffs of short-acting ß2-agonist, and further an assessment of level of airway limitation (forced expiratory volume in first second, FEV_1).[12]

A 7-point Likert scale is used (e.g. 0= no symptoms to 6= extreme symptoms, and for reliever medication use: 0= No use; 6= >16 puffs most days) with the mean score of items used, 0= fully controlled to 6= severely uncontrolled.[12,13]

Definition of cut-off levels of asthma control are suggested by the authors in the original version: ACQ7<0.75 denoting well-controlled asthma, ACQ7 ≥1.5 denoting uncontrolled asthma, whereas ACQ7 from 0.75 - 1.5 denoting incomplete controlled asthma.[15]

The 6-item version (ACQ6) is convenient as it can be completed without involvement of clinical staff, as FEV_1 measurement is omitted, and ACQ6 is validated and recommendable in clinical trials.[13] (See Appendix A-1)

Asthma severity – pharmacological treatment

Asthma severity is defined according to the amount of pharmacological treatment needed to obtain asthma control.[2,16] Global Initiative for Asthma (GINA) advocates for use of treatment steps 1-5 to define asthma severity. (**Figure 1**) According to this, the medical doctor' choice of pharmacotherapy is supported by step-up and step-down guidelines increasing daily dose of inhaled corticosteroids (ICS) and second controllers until asthma control is achieved.[2]

The target of the pharmacological treatment is always (except in very mild asthma) airway inflammation and often bronchoconstriction. ICS is the treatment-of-choice in both adult and children.[2]

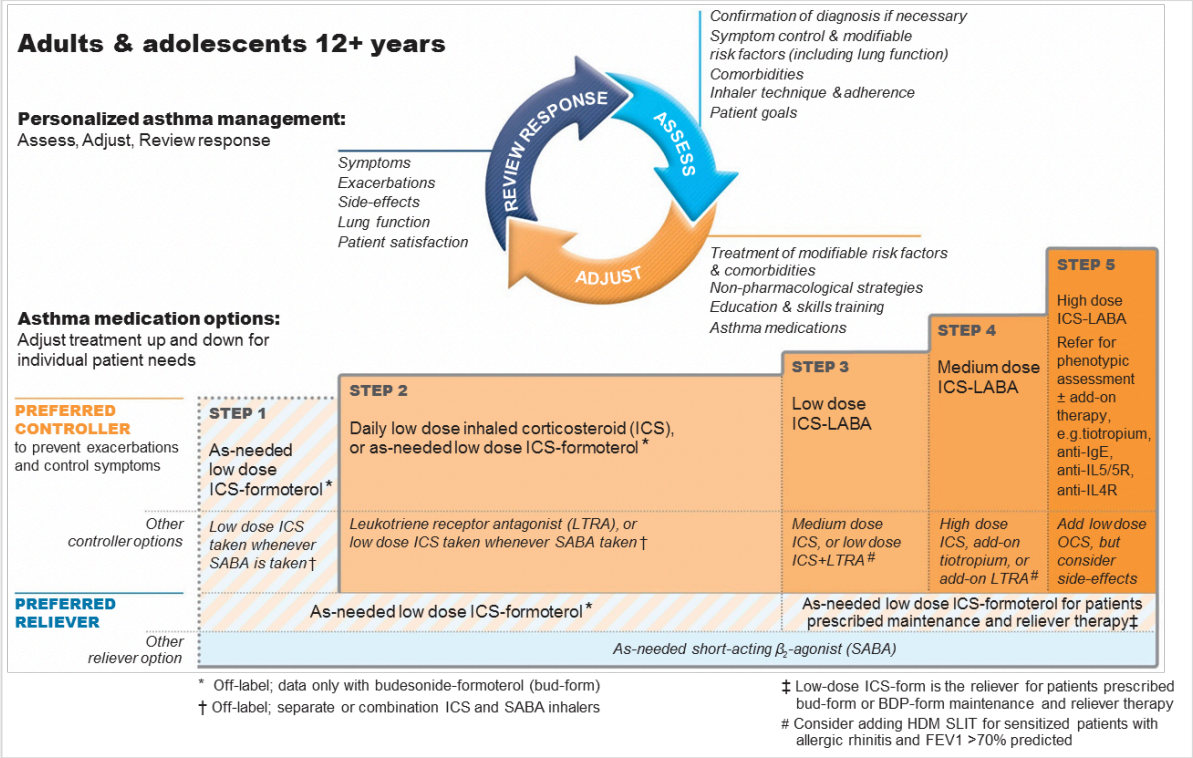

Figure 1. Personalized management for adults and adolescents to control symptoms and minimize future risk (Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019 Box 3-5A. p 47) (Use of figure approved September 29th 2020, permission attached after References)

At least 10% of patients with asthma suffer from so-called difficult-to-treat asthma, characterized by uncontrolled asthma despite intense pharmacological treatment corresponding to GINA steps 4-5.[17] Some patients do have truly severe asthma, but the majority have other causes for the apparent inadequate asthma control, thus careful and systemic evaluation is warranted to offer the patient optimal treatment.[18] Some patients turn out to have no or mild asthma with a high disease burden due to non-asthma disease.[19]

Poor treatment adherence (intended or unintended such as poor inhaler technique), trigger exposure, comorbidities (e.g. non-asthma respiratory disease, obesity, rhinosinusitis, cardiovascular diseases, dysfunctional breathing, neuromuscular disease, poor cardiorespiratory fitness), and poor patient education and insufficient patient–doctor relationship are the typical causes of difficult-to-treat asthma.[1,2,20–24]

Asthma-specific Quality of Life

Asthma-specific Quality of Life (QoL) describes the extent the asthma impairs an individual' life and is a key self-reported information reflecting the patient's experience and perspective of her/his condition.[3,7]

Asthma-specific QoL is currently not included in the assessment of asthma, but is impaired in most patients with asthma.[3,5] Poor asthma-specific QoL is associated with poor symptom control in moderate-to-severe asthma, although it does not entirely explain asthma-specific QoL.[4]

Numerous factors affect asthma-specific QoL including asthma-specific (such as asthma phenotype, disease severity, airflow limitation, symptom control, exacerbations, and hospitalisation), asthma-related (such as triggers, comorbidities, treatment side effects) and 'patient-related' /psychosocial factors, such as health literacy, emotional stability, overall stamina, education, and income.[19,25–27]

Several tools have been developed to measure asthma-specific QoL.[28–32] A very commonly used is the validated questionnaire Mini-Asthma Quality of Life Questionnaire (MiniAQLQ).[29]

MiniAQLQ is a disease-specific outcome measure. It has 15 items concerning domains of symptoms, emotions, environment, and activity limitation experienced in previous two weeks. A 7-point Likert scale (1=extremely impaired to 7=not impaired) is used, and MiniAQLQ score is the mean score of the items.[29,33] (Appendix A-2)

Danish asthma care setting

The Danish health-care system includes free health service for all citizens, and is organized as five administrative regions, each providing health care to 0.7 to 1.2 million inhabitants (total population 5.6 million inhabitants). Primary health-care includes self-employed general practitioners, and secondary health-care includes public hospital service and private specialized clinics. Each region has at the most one multidisciplinary clinic for difficult-to-control asthma.

Every citizen has a general practitioner who is the gatekeeper to secondary care. The general practitioners have responsibility for treatment of mild-to-moderate asthma (GINA steps 1-3), and can refer to the local hospital's Respiratory Service in case of diagnostic uncertainty, lack of asthma control, or GINA steps 4-5.

At time for this thesis' project design and study initiation, no tradition of staffing for physiotherapy in asthma care existed in Denmark, neither in primary, nor in secondary health-care. In 2016, we

did a survey among 20 Danish asthma care centres including all health care regions of Denmark (75% response rate) showing that treatment by physiotherapist only was given in five centres.[34] However, one highly specialized clinic, Bispebjerg University Hospital, has had physiotherapists treating patients with difficult-to-treat asthma during the last 5-6 years.

Treatable traits

"*A treatable trait can be defined as a therapeutic target identified by phenotypes or endotypes through a validated biomarker*." (*Treatable traits in acute exacerbations of chronic airway diseases,* p.4, VM. McDonald, CR. Osadnik, PG. Gibson. 2019, Chronic Respiratory Disease Volume 16).[35]

Recently, the *treatable traits approach* has been launched to recognise the need for personalized or precision medicine in patients with chronic airway diseases.[36] This approach addresses the limitations of the conventional diagnostic labels, and identifies pulmonary, non-pulmonary and behavioural *treatable traits*, thus aspects that are potentially changeable and can alleviate the patient's disease burden and thus improve QoL.[36]

Therefore, *treatable traits* include the *individual* genetic, phenotypic, immunological, pulmonary, non-pulmonary, comorbidity, psychosocial, lifestyle (e.g., physical activity level, diet, smoking habits), and/or environmental factors that are association with impaired control of asthma or other respiratory conditions.[36,37] Ideally, a candidate trait must fulfil three characteristics: be clinically relevant, identifiable/measurable, and treatable.[35] However, it is possible for traits to exist that are not treatable (e.g., age, sex), and it is possible for treatable traits to exists without a reliable biomarker to identify them.[35,37–40]

The prevalence of comorbidities in asthma is high, and increases with asthma severity.[38] As described for difficult-to-treat asthma, many comorbidities may impair asthma control besides raising the individual's total disease burden.[38,41]

Anxiety is an example of a treatable trait in asthma.[3,38,42] The odds ratio for anxiety in asthma is 1.5 compared to patients without asthma in a global WHO study.[43] Anxiety may be the consequence of

living with a chronic disease, and may affect asthma control, as anxiety often causes dyspnoea, hyperventilation, and coughs thus mimicking asthma symptoms.[3]

The identification of possible treatable traits affecting asthma-specific QoL are stepping stones to targeted interventions to improve QoL in individuals with asthma.[36] It is of relevance to explore associations in different aspects e.g., individual, disease-related, comorbidity-related, and functional performance. Evidence from high-quality trials in patients with moderate-to-severe asthma attending specialist care is sparse.[25,44]

Dysfunctional breathing in asthma

A common comorbidity and *treatable trait* in asthma is considered to be dysfunctional breathing (DB).[36]

A definition of DB was proposed by Barker and Everard in 2015: '*An alteration in the normal biomechanical patterns of breathing that result in intermittent or chronic symptoms which may be respiratory and/or non-respiratory'*. (*Getting to grips with 'dysfunctional breathing'* p.54, N. Barker, ML. Everard, 2015, Paediatric Respiratory Reviews 16).[22]

They proposed a perceptual model to help diagnosing and managing the condition, depending on where the alteration was: thoracic or outside thorax (e.g., breathing pattern disorder versus vocal cord disorder), and whether it was a consequence of a function (e.g., movement pattern) or an anatomic structure (e.g., phrenic nerve lesion).[22]

In this thesis, as the pragmatic approach, I understand DB as being a functional, thoracic condition, usually characterized by irregularities in the breathing pattern including route, rhythm, speed, inhaled volume, or extent of thoracic and/or diaphragmatic movement and that this is associated with symptoms that include persistent or intermittent dyspnoea, chest tightness, coughing, sighing, yawning, loss of voice, sensation of lump in the throat, anxiety, fatigue, and bloating of stomach.[2,20,22,45,46] Further, that symptoms improve with normalisation of the breathing pattern.[22,47–49]

This clearly differs from exercise-induced bronchoconstriction (EIB), which presents with exercise related dyspnoea due to transient airway obstruction and increased respiration rate.[50] EIB may occur as a specific phenotype in asthma or in asthma patients in whom pharmacotherapy is not optimized,

e.g., inadequate inhaled steroid treatment. EIB is typically observed 5-8 minutes after initiation of vigorous exercise or after exercise termination, contrary to DB, in which symptoms (e.g., dyspnoea, hyperventilation, sighing) may occur in rest, in settings unrelated to exercise, or immediately after exercise initiation.[23,50]

It is estimated that approximately every second asthma patient has DB, but unevenly distributed as the prevalence appears to increase with increasing asthma severity.[19,51,52] Lesser control of asthma is seen in patients with DB than in those without DB.[41] DB can occur as an isolated problem without underlying respiratory disease.[22,45,46]
DB is a well-recognised entity, yet there is still neither consensus on diagnostic criteria, nor an International Classification of Diseases (ICD-10) code given.[22,45,53,54]
Several DB patterns exists, e.g. the *thoracic breathing pattern* (fast, shallow breathing of 20-40/minute; equals the hyperventilation syndrome) and the *diaphragmatic and whole thorax breathing pattern* (slow rate of 5-8/minute with large tidal volumes close to total lung capacity).[22,55,56] Both of these patterns result in an increased minute ventilation volume potentially causing hypocapnia.[57] At normal breathing, the functional residual capacity (FRC) is at the end of expiration when relaxation pressure of lungs and chest wall equals the atmospheric pressure.[55,57]
DB is often associated with over-inflation due to elevated tidal volume, and patients with DB may sigh frequently to compensate for over-inflation and to achieve FRC.[53,58]

The alterations of the disordered breathing pattern is similar to normal responses observed during emotional or mental stress or severe somatic disease,[22] and Barker and Everard proposed "*DB can be seen as an unconsciously learnt, habitual change in the normal patterns of breathing, which may become apparent at rest or only when stressed*". (*ibid.* page 55)[22] Thus, DB could be seen as a "bad habit", and can appear delayed from the episode(s) or the 'triggers' that initiated the condition. The pathophysiology is poorly understood.[45]
See a proposed explanation of triggers and their action, **figure 2.**

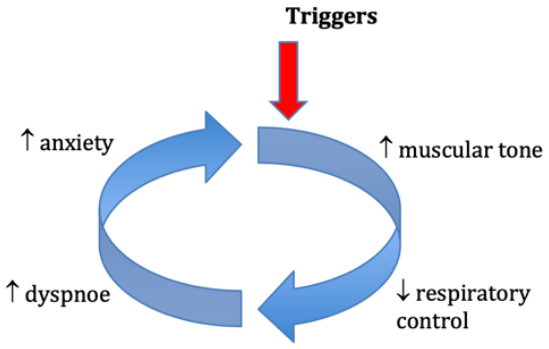

Figure 2; Triggers can alter the respiratory pattern and cause symptoms. Triggers can be stress factors like anxiety, pulmonary disease, other somatic disease, and mental or emotional stress. Symptoms may in turn accelerate negatively. Triggers can have their origin in the past.

Graphics: Karen Hjerrild Andreasson

Episodes of DB may mimic asthma or asthma attacks with breathlessness, coughing, chest tightness and escalated rate of breathing, thus DB confers a risk of overtreatment.[19,45,52,59]
It has been proposed that during episodes of hyperventilation in asthma, the high ventilation in itself may dehydrate the bronchial airways and facilitate/increase bronchoconstriction, thereby accelerate the asthma attack.[45]

The dilemma of absent diagnostic criteria for a well-known condition has led researchers and clinicians to diagnose or measure DB using the Nijmegen Questionnaire (NQ).[49,60,61] The authors describe that NQ measures *functional respiratory complaints*.[49] This self-reported 16-item questionnaire asks about symptoms related to respiration (i.e., breathing movements, ventilation, dyspnoea) and function (i.e., relationship to stress and anxiety) experienced during the previous week.[49] (Appendix A-3) The sum of scores from a 5-point Likert scale (0=never to 4=very often) is used. NQ was originally validated against the Hyperventilation Provocation test.[62]
The original intention of NQ was a tool that was able to detect whether patients with a high score would improve by normalisation of breathing pattern, e.g., by breathing exercises.[49]
There is an ongoing debate of the validity of NQ in DB using different cut-offs for DB (≥23 versus >23 versus continuous outcome measure).[49,61–63] The latter is supported by the observation that improvement in NQ after breathing exercises were observed even in patients with baseline NQ <23.[49,61]

In 2018, a novel tool - *The Brompton Breathing Pattern Assessment Tool* (BPAT) - was developed to investigate and define DB severity, and the first research papers have been published.[52,64] BPAT is completed by the clinician during one minutes observation of the sitting patient and includes seven elements of breathing: movement, route, rhythm, rate, sounds (in-/expiration), and signs of breathlessness (i.e., yawn, sigh), each to be scored 0-2 (0=normal/expected to 2=severe signs of DB).[64] The BPAT has been validated in asthma and dysfunctional breathing patients, showing that score ≥4 corresponds to having breathing pattern disorder (sensitivity 0.92 , specificity 0.75), and it relates – however weakly - with NQ and AQLQ.[64]

The term 'dysfunctional breathing' is frequently used in clinical practice and in the communication between a physiotherapist and a patient, but usually without the formal diagnostic criteria outline above being met. Although, without use of a tool that reliably identify and quantify an abnormal breathing pattern, physiotherapists do make clinical assessments of the spontaneous (resting and exercising) breathing pattern as a part of their treatment.

Physiotherapy in asthma

Historical background

For decades, the main focus of physiotherapy in respiratory diseases including asthma was interventions to improve sputum drainage.[65] In 1979 in New England Journal of Medicine, medical doctor John F Murray pointed to the first research papers concerning chest physiotherapy, and discussed the very limited evidence for sputum clearance methods in respiratory diseases, stating that more research was needed.[65] And with the Evidence Based Medicine, the recommendations have changed as the effect of airway clearance methods in asthma cannot be confirmed.[66,67]
Murray continued: "*The scanty evidence for and against the retraining of breathing was reviewed in 1974 and will not be considered here because virtually nothing new has been added since then*" (*The Ketchup-Bottle Method*, p.1155, JF Murray 1979, N Engl J Med).[65]
Reviews since 2013 have explored the role of physiotherapy in asthma.[67–70] The review from 2013 identified 21 papers on RCTs.[67] They report that inspiratory muscle training (IMT), physical training, and *breathing retraining* (breathing exercises) may improve QoL, inspiratory muscle strength, and cardiopulmonary fitness, reduce dyspnoea and other symptoms, and reduce need for medication, however evidence is still sparse.[67]
In the following, I will present breathing exercises in details.

Breathing exercises

Background and terminology

In the literature, both terms - *breathing retraining* and *breathing exercises* - are used frequently.[53,70,71] During design and conduct of the BEAT DB-trial, we have used the expression *breathing exercises*, therefore this term is used in rest of the thesis.

Breathing exercises aims at modifying route, rhythm, and coordination of muscles used in the breathing pattern.[48,72] In the last decades, *breathing exercises* has gained attention as a treatment in asthma care as many patients with asthma show signs of DB.[34,47,48,60,71–74]

Methods

Breathing exercises are combined of a) *Papworth method* that includes breathing modifications (diaphragmatic breathing using nasal inhalation, rhythmic respiration, at rate 12-16 per minute), relaxation, and use of methods in physical active situations,[72] b) *Buteyko technique* that also includes nasal breathing, and additionally decrease of ventilation, resistance of urge to overbreathe, and breath holding at FRC to increase tolerance at low lung volume,[75,76] and c) suppression of tendency to sigh, yawn or cough,[77] which can be expressions of hyperventilation,[78] see **Figures 3**.

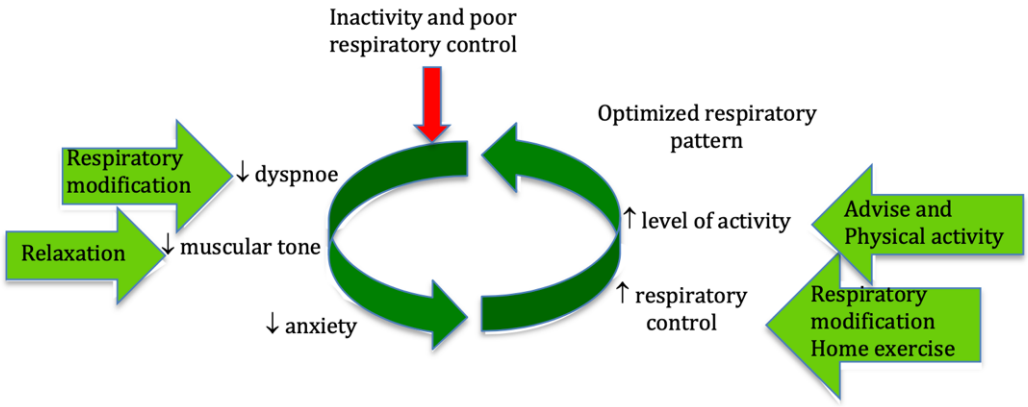

Figure 3; Improvements from breathing exercises on the way to an optimized respiratory pattern
The different elements of the intervention are shown in the light-green arrows.

Graphics: Karen Hjerrild Andreasson

Evidence

Breathing exercises provided by trained physiotherapists is an inexpensive and safe intervention.[74,60,73,71,79]

Further, *breathing exercises* is well-received by patients, when delivered either as face-to-face from a physiotherapist or digitally (a DVD).[80] A qualitative study found that participants who received *breathing exercises* face-to-face expressed increased motivation by meeting the physiotherapist and appreciated receiving tailored treatment according to their needs. Participants receiving *breathing exercises* in either form of delivery found the method useful with an impact on their awareness of the breathing and helping them to develop better breathing habits.[80] A quantitative investigation of the difference between the two forms showed that participants who received the face-to-face form practiced significantly more and were more likely to use nasal inhalation and diaphragmatic breathing than participants receiving DVD-form.[81]

The use of *breathing exercises* in participants with mild-to-moderate asthma improved asthma-specific QoL and asthma control, and lowered the breathing rate,[72] however did not change airway inflammation or lung function parameters.[34,47,60,82,83] Adding manual therapy (e.g., techniques manipulating muscles, facies and joints in the neck shoulder, thorax, and spine regions) to *breathing exercises* in non-asthma patients showed no significantly between groups improvement in dysfunctional breathing related symptoms (NQ score).[84]

Two systematic reviews on *breathing exercises* in moderate-to-severe asthma conclude that the methodological quality leave *"insufficient evidence for a firm recommendation"*.[69,74] The recently updated Cochrane review investigated QoL (primary outcome) and included 22 trials, in total 2880 participants, treated in general practice or in an outpatient department.[70] Considerable heterogeneity of the included trials was found, concerning sample sizes (ranged 17 to 655 participants), type of breathing exercises (yoga, Papworth, Buteyko, pranayama, or 'breathing exercises'), type of comparator (usual care, asthma education, or inactive control), duration and number of sessions, and outcomes (e.g., AQLQ, MiniAQLQ, or St. George's Respiratory Questionnaire). The review did not report whether anti-asthmatic medication was optimized in the included trials.[70] Of included trials, the majority investigated yoga (n=14), and only five trials investigated *breathing exercises* as described above.[47,60,70,72,73,82]

This review concluded that evidence of improvement of asthma-specific QoL from breathing exercises in mild-to-moderate asthma populations exists, however no trial investigating moderate-to-severe asthma populations was found.[70]

Relevance of this thesis

Asthma is a common and heterogeneous airway disease that is associated with reduced QoL due to symptoms burden, risk of worsening, and restrictions in daily life activities. Poor asthma-specific QoL is a unique and patient-oriented descriptor of living with asthma, and is not fully explained by asthma control or asthma severity.

Despite efficacious pharmacological treatment, a vast number of patients do not achieve asthma control. Many factors – both relating to asthma but also to comorbidities and behaviour – contribute to this. The identification of *treatable traits* associated with asthma-specific QoL is less investigated, but exploring this would help providing patients and clinicians with interventions that potentially improve the patient's life with asthma, ideally also improving asthma control.

Dysfunctional breathing (DB) is suggested to be a common comorbidity in asthma, and to be associated with impaired asthma-specific QoL and with increasing prevalence with increasing asthma severity. However, DB is still a condition without consensus on diagnostic criteria, and has no ICD-10 code. Furthermore, existing DB screening tools such as Nijmegen Questionnaire have so far not been shown to reliably identify patients who were more likely to improved asthma-specific QoL after *breathing exercises* in milder asthma. No trials in more severe asthma have been conducted.

Therefore, I chose a pragmatic focus based on learning points from trials in milder asthma, and used asthma control rather than score on an available DB screening tools as an entry criterion, recognising that not all participants would have definable abnormalities in the breathing pattern. The trial therefore considers DB as a *treatable trait* that can be modified by physiotherapist delivered *breathing exercises* to improve asthma-specific QoL in patients with incompletely controlled, moderate-to-severe asthma followed in respiratory specialist settings.

Aims of thesis

The thesis aims to investigate both the constitution of asthma-specific QoL and the effect on asthma-specific QoL of add-on breathing exercises to patients with incompletely controlled, moderate-to-severe asthma, followed and treated in specialist-care settings.

Specific hypotheses and aims

Paper I

Aim: To describe breathing exercises in asthma, and the background and design of the multicentre RCT (study 3)

Study 2

Hypothesis: A theoretically developed model including demographic factors, asthma-related factors, comorbidity, and respiratory factors can explain a large proportion of variance of MiniAQLQ score.

Aim: To identify possible demographical, asthma-related, comorbidity-related, or respiratory/physical factors associated with impaired asthma-specific QoL among adult patients with incompletely controlled, moderate-to-severe asthma attending specialist care, with a focus on *treatable traits*.

Study 3

Hypothesis: Add-on physiotherapy to usual specialist care in adults with moderate-to-severe asthma referred to specialist care due to incompletely controlled asthma is superior in improving asthma-specific QoL at 6-month compared to usual care alone.

Aim: To investigate the effect of add-on breathing exercises delivered by trained physiotherapist in incompletely controlled, moderate-to-severe asthma in a randomised controlled trial design.

METHODS

The protocol paper is published and will be referred to as 'Paper I'.

The manuscripts of study 2 and 3 are not yet published, hence will be referred to as 'Study 2' and 'Study 3'.

The candidate's role in design and conduct of the trial

I (i.e., the candidate and the principal investigator) developed the protocol and overall design of the studies as well as secured the funding in close collaboration with my supervisor group. Trial centres were selected with the supervisor group, but I had the overall responsibility of employing blinded assessors to each center, teaching the trial center staff, ensuring the fidelity to the protocol and data collection as well as the day-to-day communication with the trial centres. I did all analyses using biostatistical consult as needed.

Design and Reporting

Paper I

Trial design and methods for the RCT were described in the protocol paper (Paper I).

The protocol was published December 2019[85] complying Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) recommendations,[86] and description of intervention complied Template for Intervention Description and Replication statement (TIDieR).[87]

Study 2

This was an exploratory cross-sectional study of associations of asthma-specific QoL.

Manuscript of study 2 complied Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[88]

Study 3

BEAT DB-trial was a two-armed parallel superiority multicentre randomised controlled trial.

Manuscript of study 3 complied the Consolidated Standards of Reporting Trials statement (CONSORT).[89]

The protocol paper predetermining the content of Study 3, therefor Paper I and Study 3 will be described together.

Approvals

Study 3 was approved by Region Zealand Research Ethics Committee (SJ-552) and Danish Data Protection Agency (REF-55-2016). Study 2 was approved as a part of study 3. Registration at ClinicalTrial.gov was done April 25th, 2017 (NCT03127059). Both studies were conducted in agreement with the Helsinki Declaration.

Trial management

Paper I, and Study 3

The research group, which included Uffe Bødtger, Søren Thorgaard Skou, Mike Thomas, and me (principal investigator), had the overall trial management responsibility during the trial. We had meetings (using Skype) every 1-2 months throughout the trial and additionally communication via email and Skype as needed monitoring recruitment, treatment, attrition as well as adverse events. Each centre had a *study chair* (medical doctor) with whom I and Uffe Bødtger corresponded.

Feasibility and pilot study

Paper I, and Study 3

The intervention breathing exercises (BrEX) investigated in this thesis were initially applied in a feasibility study in a convenience sample of 19 patients in Naestved Hospital from November 2015-August 2016 (scientific poster, August 2016, Appendix B-1)

Prior to the trial (Study 3), we did a pilot study at Naestved Hospital from November 2016-Marts 2017. Eligibility criteria were more restrictive compared to the final criteria listed in the paragraph *Eligible Participants*, page 34)

Inclusion criteria in the pilot study, changes between pilot and RCT criteria mentioned in parentheses:

- Referred from general practitioner to a secondary, out-patient respiratory clinic for lack of asthma control
- Asthma diagnosed by a pulmonologist
- ≥2 doctor visits at a specialised, pulmonologist-lead asthma clinic
- ACQ6 score ≥1.5 (by beginning of 2018 *score cut was lowered* to ≥0.8)

- NQ score >23 (criterion *deleted* before RCT initiation)
- Willingness and ability to give written informed consent
- Understands written and spoken Danish
- Age ≥18 years

Exclusion criteria in the pilot study, changes between pilot and RCT criteria mentioned in parentheses:

- Any severe disease, as judged by the responsible physician
- Received training in breathing exercises by physiotherapist (*added period* by beginning of 2018: last 6 months)
- Having dyspnoea from another lung disease (beside asthma) or cardiovascular disease (criterion *deleted* by beginning of 2018)
- Having a neurological disease, that precludes following instructions or closing the lips (criterion *deleted* by beginning of 2018)
- Participation in another ongoing research trials (before RCT *added*: pulmonary interventional research project).

Nurses screened 30 consecutive patients for eligibility, and we included seven.
No randomisation was used, and all pilot participants were offered 4 sessions of the BrEX-intervention, with a total duration of 2.5 hours. The BrEX were identical to the final version (see *Trial groups and Procedures (only Study 3),* page 37), although only 10 minutes of home exercise once daily.

Feasibility of data collection was tested in the pilot participants (n=7), resulting in no changes in data collection besides clarifications of the assessor test manual and improvements of patient-reported data procedures.

Evaluation of pilot study

Paper I, Study 2 and 3

Besides analyses of outcomes, we used a logbook and completed evaluating interviews with all pilot study participants after the fourth session, and interviews with physiotherapists (assessor and treating physiotherapist) in January and March 2017.

Evaluation of eligibility criteria

The use of NQ-score (>23) as an inclusion criterion prohibited otherwise eligible participants (n=12). NQ is not a predictor of response to BrEX,[61] therefor we decided to omit NQ from eligibility criteria for the RCT. On the contrary, none otherwise eligible participants were excluded with ACQ6-score between ≥0.8 and ≥1.5.

Evaluation of MiniAQLQ

MiniAQLQ at baseline (n=6): median 4.7 (range 4.2 to 5.9). One did not return baseline questionnaires although reminded multiple times (n=1).

MiniAQLQ at follow up (3 month) (n=6): median 5.0 (range 3.7 to 6.7). Missing follow up (n=1).

Change in MiniAQLQ at follow up (n=5): median 1.07; improvements n=4 (range 0.40 to 1.20 units), deterioration n=1 (-0.67 units).

Pilot study participants replied that it was easy/ somewhat easy to complete all questionnaires, which took 5-25 minutes.

Findings of interviews

- Intervention: The intervention was acceptable, easy to follow, included both instructions and corrections at visits with the physiotherapist. Importance of inclusion of breathing modification in active situations. Difficulties in the nasal breathing for one participant.
- Home exercise: Experience of practicing the exercises spontaneously during the day.
- Feedback on patient information: Had read it, however suggested to improve verbal instructions and to replace drawings with photos.
- Adherence: Difficulties to adhere to four sessions due to a busy week; the physiotherapist did not observe much change between third and fourth session.
- Effects: Subjective experience of improvements in QoL and in level of physical activity. Experience of breathing more easily and to achieve a relaxed breathing.

Findings of logbook and interviews

- Development of the guide how to implement the recruitment, assessment, and intervention in the participating centres, e.g., development of manuals, education and supervision of study staff concerning study activities as well as entry of data in study database; number of equipment sets needed; practical solution for return of activity sensors.

Patient engagement

Paper I, Study 2 and 3

Apart from involvement in the pilot study, as described in section *Feasibility and pilot study*, which included feedback by individual interviews, and as participants in the trial, patients were not engaged in the trial completion or management.

Setting

Paper I, Study 2 and 3

Paper I is the Study 3 protocol paper and includes a narrative review of BrEX in asthma. Study 2 is a sub-study of the multicentre RCT (Study 3), called the BEAT DB-trial.

Trial centres in the BEAT-DB trial were seven outpatient respiratory department and one specialized private allergy/lung clinic treating patients with incompletely controlled, moderate-to-severe asthma. Besides representing all five health care regions of Denmark, the centres represented both larger and smaller secondary care outpatient departments:

Respiratory outpatient clinics at

Naestved Hospital,
Zealand University Hospital Roskilde,
Hvidovre University Hospital,
Bispebjerg University Hospital,
Aalborg University Hospital,
Silkeborg Regional Hospital,
Odense University Hospital, and

Allergy and Lung Clinic, Elsinore (private clinic).

Eligible participants

Study 2 & Study 3

A pulmonologist at the respiratory departments and the private allergy/lung clinic screened patients in the clinic to find eligible participants using the following criteria:

Inclusion criteria

- Referred from general practitioner to a secondary, out-patient respiratory clinic for lack of asthma control
- Asthma diagnosed by a pulmonologist

- ≥2 doctor visits at a specialised, pulmonologist-lead asthma clinic
- Asthma Control Questionnaire (ACQ6) score ≥0.8
- Willingness and ability to give written informed consent
- Understands written and spoken Danish
- Age ≥18 years

Exclusion criteria

- Pregnancy
- Any severe disease, as judged by the responsible physician
- Received training in breathing exercises by physiotherapist last 6 months
- Participation in another ongoing pulmonary interventional research project.

Following modifications, registered in ClinicalTrials.gov 26 April 2018, were made to improve the recruitment rate, except for the addition to exclusion criteria:

Changed:

- The inclusion criterion ACQ6 was originally ≥1.5, but *changed to ≥0.8*, e.g., still having incomplete asthma control[15]
- The exclusion criterion "Received training in breathing exercises by physiotherapist", *added period* "last 6 months"

Added to exclusion criteria:

- Pregnancy.

Deleted from exclusion criteria:

- Having dyspnoea from another lung disease (beside asthma) or cardiovascular disease
- Having a neurological disease, that precludes following instructions or closing the lips.

Study 2

Baseline data from all participants were included in the observational study (Study 2).

Study 3

Data from all participants at all-time points, except 12-month follow up (see below) were included in the randomised controlled trial (Study 3).

Recruitment and informed consent

Study 2 & Study 3

A respiratory nurse or pulmonologist provided the patient with oral and written information on the trial aim and schedule of activities of both study arms, including an illustration of the trial flow (Figure 4).

Informed consent was obtained at screening and repeated at recruitment.

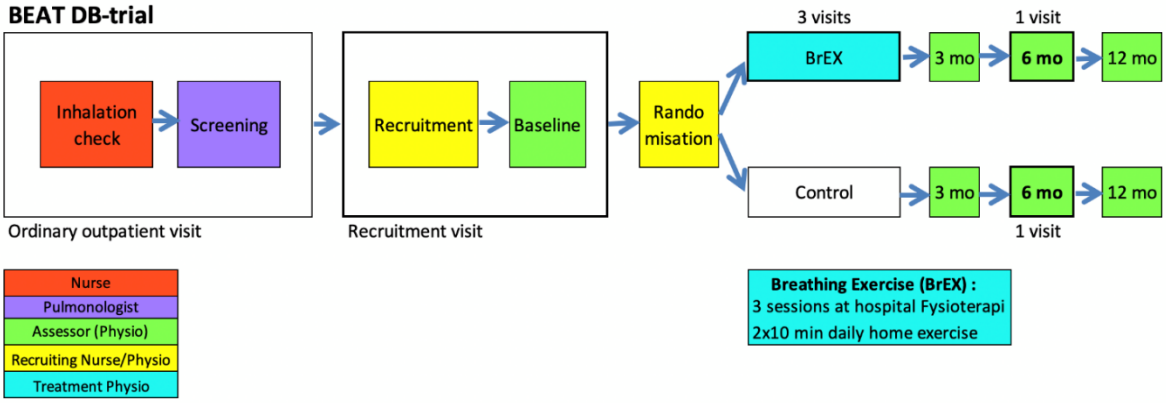

Figure 4. Participants' flow during the participation in the trial. Additional visits due to trial participation in boxes with thick frames. Follow up was 3-month, 6-month, and 12-month, but only physical assessments at the 6-month timepoint.

Randomisation and blinding

Study 2

In Study 2, only baseline data from were analysed, thus information on randomisation or blinding are only relevant for Study 3.

Study 3

After informed consent and baseline assessment, participants were consecutively randomised using a computerized random number generator (EasyTrial Inc., Aalborg, Denmark) in a 1:1 allocation ratio to either usual care (UC) alone or add-on physiotherapy (UC+BrEX). The generator used fixed blocks of four to ensure an equal group size at each centre.

Trial staff and I were blinded to the sequence-generated list. Due to the design of intervention, blinding of the participants was impossible, and he/she was informed about the allocation by e-mail. Outcome assessors stayed blinded to the allocation, with participants carefully instructed not to disclose the allocation. Analyses were performed by me in masked data.
The blinded interpretation[90] was made publicly available before preparing the manuscript for submission.[91] (See Appendix B-2)

Trial groups and Procedures (only Study 3)

Groups were named usual care (UC) and add-on breathing exercises (UC+BrEX).

Usual care (UC)

Participants in both groups received usual specialist care.
The responsible pulmonologist provided the treatment based on the individual needs of the participant's severity of disease, current level of asthma control and potential comorbidity, but without any study-related standardisation. The choice of pharmacotherapy was supported by step-up and step-down guidelines, and inhalation technique was corrected if needed.[2] The usual care was not a uniform intervention in terms of contents, in time spent (typically, 30 minutes first visit, then 15 minutes later visits), number of visits, or visit intervals, hence a real-world setting.

Considerations for breathing exercises intervention

The primary source of inspiration for using BrEX as the add-on intervention was the previous work done by Bruton *et al* (the BREATHE study),[92] by Thomas *et al*,[73] and by Holloway and West.[72] Their intervention included the *Papworth method*: rhythmic respiration using nasal, diaphragmatic breathing, 12-16 per minute, relaxation, and use of methods in rest and activity, and elements of *Buteyko technique*: nasal breathing, resisting the urge to overbreathe, and controlled breath holds.[76] However, previous trials only included patients from primary care with milder disease. We wanted to investigate a nearly identical intervention in patients treated under specialist's care, a group for whom there is a recognised evidence-gap.
Additional key elements of Buteyko (mouth taping at night; reduction of SABA use)[76] were excluded already before our pilot study as they are intrusive to the patients, have no evidence to support them and may be inappropriate for many patients.[76]

Breathing Exercises (BrEX)

BrEX included breathing pattern modifications, relaxation techniques, and combinations in rest and in activity, i.e. included *Papworth method, Buteyko technique,* and further suppression technique.[72,75,78] As mentioned, this intervention was previously investigated (most recent in the BREATHE study),[47] however translated and adapted into a Danish setting, where it was piloted (unpublished, however described in *Feasibility and pilot study*, page 31).
It was individualised to the participants' needs and abilities.

The treatment aimed at a breathing pattern with:

- Activation of diaphragm muscle during inspiration
- Nasal inhalation
- Lower chest expansion
- Relaxed tongue, jaw, shoulders and neck, i.e., no use of accessory muscles
- Expiration to functional residual capacity (FRC)
- Quiet, rhythmical at respiratory rate 12-16 per minute with a moderate tidal volume
- Slightly longer exhalation than inhalation, i.e., achieve normal tidal volume.

At beginning of each session, the physiotherapist observed the spontaneous resting breathing pattern during one minute (Observational list: Appendix C, Paper I, table 3). The pattern was evaluated. The physiotherapist instructed and guided by hand at sternum (to minimize movement) and/or at epigastric region and/or lower and lateral/dorsal thorax (to facilitate expanding movement). The participant was guided to facilitate the pattern using own hands or forearms.

Treatment was performed in a relaxed body position in side lying, supine, 'beach position', or sitting (**Figures 5-9**) and was progressed to physical activities requiring balance and coordination like standing, walking, and stair-climbing, as long the participants was able to continue the breathing pattern methods.

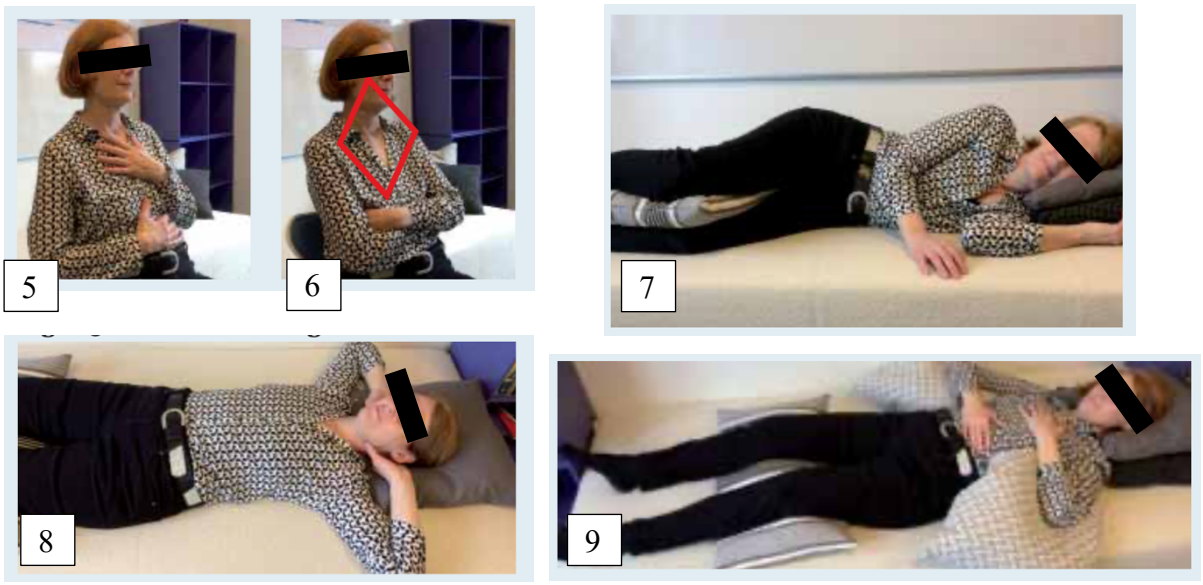

Figure 5-9. Illustrations from Booklet. *5*: Feel/facilitate diaphragmatic breathing by the right hand. *6*: or by forearms (red rhombus to remind use of nasal breathing, no movement/rest at upper chest, diaphragmatic breathing). *7-9*: positions where diaphragmatic breathing may be performed more easily.
Consent obtained to use of photos.

Breath holding exercise

Every second day three circles of:

- Breath holding at FRC (nose pinched) for 1/3 of maximally breath holding time (measured at the session), then slow inhalation, slow exhalation; repeat.

Suppression technique

As needed additionally suppression of frequent yawns or sighs, uncontrolled dry coughs, or clearings of the throat was used, e.g., when the coughing appeared:

- Close mouth, pinch nose, pause the breathing for 5-10 seconds while suppressing the cough
- Swallow forcefully
- Do 20 nose breaths (mouth closed).

Description / Session		1 60 minutes	2 30 minutes	3 30 minutes
A	Goal/schedule	X	X	X
B	Introduction to BrEX	X		
C	Observation of breathing pattern	X	X	X
D	Respiration modification a. Nasal, diaphragmatic b. Inspir-exspir-ratio c. Respir. depth d. Breath Holding Time Techniques to improve changes	X Lying/ sitting	X Standing	X +Walking stairs
E	Implementation of respiration modification into daily life		Part of D	X Keep going!
F	Relaxation techniques	X Sitting/ Lying	X	X Standing/ Walking
G	Home exercises	X	X Part of DEF	X Part of ADEF
H	Exercise diary	X		

Table 1. Overview of contain during three BrEX session, from Booklet.

Trained physiotherapists delivered the BrEX at the physiotherapy department. The intervention included three individual sessions (60 min + 30 min + 30 min) at intervals of 3-4 weeks and lasted 12 weeks counted from the initial session. See **table 1**, the planned BrEX during the tree sessions. The physiotherapist encouraged the participant to practice the BrEX methods 10 minutes twice daily at home during the 12 weeks of intervention. The participant received a booklet to support the physiotherapists' treatments (Appendix E-S1; Danish language).

All treating physiotherapists had a mandatory 10-hour introduction to the intervention at the general meeting at trial initiation and were trained by two experienced physiotherapists and me. New staff who were recruited during the course of trial were introduced and trained at a mandatory 6-hour introduction to the intervention by me in their hospital. The reduction from 10 to six hours was possible without loss of quality due to increased experience and content optimization. Further, all physiotherapists were supported by the written information and supervision online, by phone, and at meetings.

Intervention fidelity was not objectively monitored; however, I contacted all staff after two weeks and every second month to discuss challenges and experiences, and if needed supervised treatment sessions.

Outcomes

Table 2 shows an overview of outcomes used in the different studies.

Overview of outcomes and data included

Table 2; Overview of outcome measures and data used in the studies

			Study 2		Study 3	
Self-reported outcomes	Minutes[a]	Collect[b]	Descriptive	Association	Descriptive	Effectiveness
Mini-Asthma Quality of Life Questionnaire (MiniAQLQ)	6	BL, 3, 6	✓	✓	✓	✓
Asthma Control Questionnaire (ACQ6)	3	BL, 3, 6	✓	✓	✓	✓
Nijmegen Questionnaire (NQ)	4	BL, 3, 6	✓	✓	✓	✓
Hospital Anxiety and Depression Scale, anxiety (HADS-A)	6	BL, 3, 6	✓	✓	✓	✓
Hospital Anxiety and Depression Scale, depression (HADS-D)	incl	BL, 3, 6	✓	✓	✓	✓
Global Perceived Effect rate (GPE)	2	6				✓
EuroQol-5D (EQ-5D-5L)	4	BL, 3, 6	✓		✓	
Borg CR10 (resting)		BL, 6	✓	✓	✓	
Adverse events	4	3, 6				✓
Sex	4	BL	✓	✓	✓	
Age	incl	BL	✓	✓	✓	
Body Mass Index (BMI)	incl	BL	✓	✓	✓	
Smoking status	incl	BL	✓		✓	
Educational level	incl	BL	✓	✓		
Employment status	incl	BL	✓	✓		
Annual income	incl	BL	✓	✓		
Register data						
Medication (GINA step 1-5)		BL, 6	✓	✓	✓	✓
Co-morbidity		BL	✓	✓	✓	✓
Rhinosinusitis		BL	✓	✓		
Scheduled and acute medical visits		3, 6				✓
Adverse events (supplemented above)		3, 6				✓
Adherence, attendance		0-12wk				✓
Physical outcomes						
6-minute Walk Test (6MWT)		BL, 6	✓	✓	✓	✓
Number of Steps (daily avg)		BL, 3, 6			✓	✓
Physical Activity Level (PAL) (daily avg)		BL, 3, 6			✓	✓
Respiratory outcomes						
FEV1/FVC-ratio		BL, 6			✓	
FEV1 % of predicted		BL, 6	✓	✓	✓	✓
Peak expiratory flow rate (PEFR)		BL, 6			✓	
Respiratory rate		BL, 6	✓	✓		

[a]Estimated time to complete. incl: included in the estimate above. [b]Data collection timepoints were BL: baseline; 3: 3-month follow up; 6:6-month follow up; 0-12wk: BrEX sessions

Outcome measures, data collection, and data management

Self-reported outcome measures

All self-reported outcomes were delivered and collected online using EasyTrial, except Borg CR10 data. A few participants did not have access to computer/internet and completed paper-questionnaires, whereafter answers were entered the online database by central study staff.

The participants received an instruction in the email with a personal link to the questionnaires; this instruction was repeated in the frontpage when the link was activated. The instruction described how to enter the responses and how to continue from one questionnaire to the next, informed about the number of questionnaires and the estimated duration of time to complete the questionnaires. After the final questionnaire, a message appeared that thanked for participation and recommended the participant to look at short online instructions on correct medication inhalation techniques including video guides for use of inhalator and spacer (see link in Paper 1, reference no. 45).

The participants completed the questionnaires (self-reported outcomes as listed in table 2) at home in a linked identical order at all timepoints.

The estimated duration to complete each of the questionnaires was 2-6 minutes (see Table 2), with a total of 25-30 minutes. Demographical questions (sex, age, height, weight, smoking status, educational level, employment status, and annual income) were presented as one questionnaire to be completed only at baseline.

1. Mini-Asthma Quality of Life Questionnaire (MiniAQLQ) is a disease-specific outcome measure. It has 15 items concerning domains of *symptoms, emotions, environment, and activity limitation* experienced in previous two weeks. A 7-point Likert scale (1=extremely impaired to 7=not impaired) is used, and MiniAQLQ score is the mean score of the items.[29,33] (Appendix A-2)

In study 3, the between-group difference in adjusted mean change of MiniAQLQ at 6-month was the primary outcome. The Minimal Important Difference (MID) is reported as 0.5 units.[33]

Study 2	✓	Dependent variable
Study 3	✓	Primary outcome

2. Asthma Control Questionnaire (ACQ6) measures asthma symptoms (five items) using a 7-point Likert scale (0= fully controlled to 6= severely uncontrolled) plus reliever medication use (one item, 0= No use; 6= >16 puffs most days) during the previous week. The ACQ6 score is the mean score of items.[12,13]

The cut-off levels of the original ACQ (7-item) was used: ACQ<0.75 denoting well-controlled asthma, ACQ score ≥1.5 denoting uncontrolled asthma, whereas ACQ from 0.75 - 1.5 denoting incomplete controlled asthma.[15] (Appendix A-1)

Study 2	✓	Covariate
Study 3	✓	Secondary outcome

3. Nijmegen Questionnaire (NQ) was used to measure dysfunctional breathing related symptoms during previous 7 days. It has 16-item.[62] (Appendix A-3)

Study 2	✓	Covariate
Study 3	✓	Secondary outcome

4. Hospital Anxiety and Depression Scale was used as sub-scores to measure self-reported mental health: anxiety-related items (HADS-A), and depression-related items (HADS-D).[93]

Study 2	✓	Covariate
Study 3	✓	Secondary outcome

5. Global perceived effect rate (GPE) was used to evaluate the asthma-specific QoL at 6-month follow up compared to baseline (i.e., retrospectively), using on a 7-point Likert scale (e.g., -3= markedly worse; 0= no change; +3=Markedly improved).[94]

Study 3	✓	Secondary outcome

6. EuroQol-5Dimension (EQ-5D-5L) was used to describe generic self-perceived global health status in descriptive tables. EQ-5D-5L includes a 5-dimension descriptive index (range -0.59 to 1.00, i.e., worst to best) plus a Visual Analogue Scale (range 0 to 100, i.e., worst to best).[95]

7. Borg CR10 was rated at rest to measure self-perceived level of breathlessness.[96] The assessor showed the participant Borg CR10 scale, and asked: "*How do you consider the level of breathlessness right now in rest, with zero being no breathlessness at all and 10 being extreme breathlessness? Five is equal to significant breathlessness*."

Study 2	✓	Covariate

8. Adverse events (AE) were self-reported at 3 and 6-month follow up, however this information was supplemented with information collected from electronical medical reports by nurses, carefully cleaned for double entry. Events that resulted in contact to general practice or hospital were defined AE, whereas life-threatening events, hospitalisation or permanent damage were defined serious AE.[97] In blinded data, the main supervisor and I classified asthma-related AE and asthma-related serious AE (asthma exacerbations).

Study 3	✓	Explorative outcome

9. Sex, age, height, and weight. Age at baseline assessment was used. Body mass index was calculated as BMI = weight/(height^2).

Study 2	✓	Covariates

10. Smoking status, categorized as never, former, or current smokers in descriptive tables.

11. Educational level was categorised as 'No or short-term education' (no education, primary/high/secondary school), 'Middle-term education' (vocational/short higher/medium education), or Long-term education (bachelor, master/higher education, PhD).

Study 2	✓	Covariate

12. Employment status was categorised as 'Education (student)', 'Employed', 'Un-employed', or 'Outside labour market'.

Study 2	✓	Covariate

13. Annual income was reported in Euros (€) and categorised as tertiles (low, middle, high), after exclusion of participants reporting 'income <100€' or did not give information ('unknown').

Study 2	✓	Covariate

Registry data
Study staff at each trial centre extracted data from electronic medical reports on medication, comorbidity, and adverse events, and completed a data extraction sheet for each participant.

1. Medication (GINA step 1-5). Data on prescribed medication were used to define GINA steps (1-5). Level (low, medium, high daily dose) of inhaled corticosteroids (ICS) and number/combinations of second controllers were calculated into a GINA step using an un-published algorithm that adjusts to Global Initiative for Asthma 2019-report.[2]
I constructed an algorithm in Excel.[98] It converts the prescribed ICS into beclomethasone equipotent ICS doses. The interrater reliability of the algorithm and three asthma experts was investigated and showed moderate-substantial agreement with ratings of the experts (Kappa, κ $0.49 - 0.67$), however better agreement than between the experts (κ $0.32 - 0.45$). (Appendix E-S7)
Further, courses of oral corticosteroid (OCS) between baseline and 6-month follow up were used to express asthma exacerbation.

Study 2	✓	Covariate
Study 3	✓	Explorative outcome

2. Comorbidities. Frequency of comorbidities sorted into organ systems and of specific rhinosinusitis (i.e., self-reported allergic, chronic, non-allergic or vaso-motoric rhinosinusitis). Additionally, the diagnoses were used in supplementary descriptive tables. (Appendix D-2, Appendix E-S3)

Study 2	✓	Covariate

3. Adherence to BrEX home exercise program was rated by the BrEX-delivering physiotherapist, using Numeric Rating Scale (NRS) (1=not adherent to 5=perfectly adherent) at session 2 and 3. The estimation was based on talking to the participants and observing whether the participants were able to repeat BrEX given at last session.
Further, number of attended sessions as well as reasons for not attending sessions were collected. NRS-score and attention were documented using a treatment sheet.

Study 3	✓	Explorative outcome

Physical outcomes

Trained assessors assessed physical performance, spirometry and respiratory rate following a manual. They were supervised by me by phone (or at presence only at baseline assessments) only in case of technical problems or medical concerns during the assessments. The assessments were performed at the same location at baseline and follow up, either in the Respiratory Outpatient Clinic or in the Department of Physiotherapy.

1. 6-Minutes' Walk Test (6MWT) was measured in a 30-meter lane. The participant was asked to walk as far as possible for 6 minutes, while being encouraged each minute.[99]

Study 2	✓	Covariate
Study 3	✓	Secondary outcome

2. Steps per day and *Physical Activity Level* (PAL) were collected in a subgroup of participants who had a two-axial accelerometer (BodyMedia *SenseWear*®, Pittsburgh, PA, USA) on their left upper arm for 7 days, and the average of 6 days was used.[100] The assessors gave introduction how to use the accelerometer. It was attached to the arm with an elastic arm band. The participants were supposed to wear the it 23 hours per day, however to remove it before bathing/swimming.
The SenseWear measures total energy expenditure, steps, duration of physical activity and of lying down. The BodyMedia software analysed and calculated e.g., the average metabolic equivalents (METs), average step, and average PAL per day. In our trial, the central study staff used the BodyMedia software to extract data from the accelerometers on the average daily steps and average PAL.

Study 3	✓	Secondary outcome

Respiratory outcomes

1. Spirometry. Percentage of expected Forced Expired Volume in first second (FEV_1% predict.), Forced Vital Capacity (FVC), ratio FEV_1/FVC-ratio, and Peak Flow Rate (PEFR, liter/minutes) were assessed using a transportable spirometer (MedikroPro, M915, OY Finland), which was calibrated according to guidelines.[8] Reference values were based on the Global Lung Functions Initiative (GLI) 2012.[101] The assessor made sure that no contraindication was present, and explained the procedure to the patient (including to avoid obstruction or leak of the flow-transducer). The participant was sitting upright and used a nose clip. The manoeuvre was repeated until three

technical acceptable tests were performed, or maximally eight manoeuvres. The highest values were used, however reproducibility (5% or 150ml) of FVC and FEV_1 between the highest and next highest values was aimed.[8]

FEV_1/FVC-ratio and PEFR used only in descriptive table in Study 3.

Study 2	✓	Covariate
Study 3	✓	Secondary outcome

2. Respiratory rate at rest was assessed during a breathing pattern observation for 1 minute by the assessor.

Study 2	✓	Covariate

Data entry and data verification

All data were entered EasyTrial. Participants entered patient-reported outcomes online (except for BorgCR10), without verification, although for those participants who completed paper-questionnaires the central study staff entered and assured correct entry of responses.

Registry data were entered by central study staff, however for attention and adherence by the treating physiotherapists at each trial centre. Verification was performed in 100% of cases by central study staff. No data on percentages corrected by verification exist.

Physical and respiratory outcome data (6MWT, Borg CR10, spirometry, and respiratory rate) were entered by the assessors. Verification by double entry was performed by central study staff in 100% of test-sheets. Percentages corrected by verification, including data not yet analysed/reported, ranged for baseline 0-17.6% (median 2.0, interquartile range (IQR) 1.8 to 4.1), and for 6-month follow up, it ranged 0-17.9% (median 2.0, IQR 0 to 4.9). For Steps per day and PAL, central study staff was responsible for data entry; no formal verification was performed.

Statistics

All analyses were carried out using Stata/IC 16.0 (StataCorp LLC 2019, College Station, TX, USA).

Study 2

Sample size

The sample in this exploratory analysis consisted of participants consenting to study 3.

Modelling

We constructed models complying to following rules: (see **Figure 10**)

1) A Data-driven Model consisting of all covariates having significance level of $p \leq 0.1$ in the univariable regression analysis. We chose the limit at 0.1 to avoid leaving out potentially essential covariates.[102]

2) A Theoretical Model 1 forcing expected factors, i.e., previously described as having an association with asthma-specific QoL or from clinical intuition, into the model: Demographic factors (sex, age, educational level);[103] asthma-related factors (ACQ6, GINA step);[7,25] comorbidity (BMI, rhinosinusitis, anxiety);[7,44,104–106] respiratory factor (FEV_1%pred).[1,2]

3) *A Theoretical Model 2* repeating Theoretical Model 1, although FEV_1%pred. was omitted to achieve full sample (i.e., participants without FEV_1%pred. data were excluded from Theoretical Model 1)

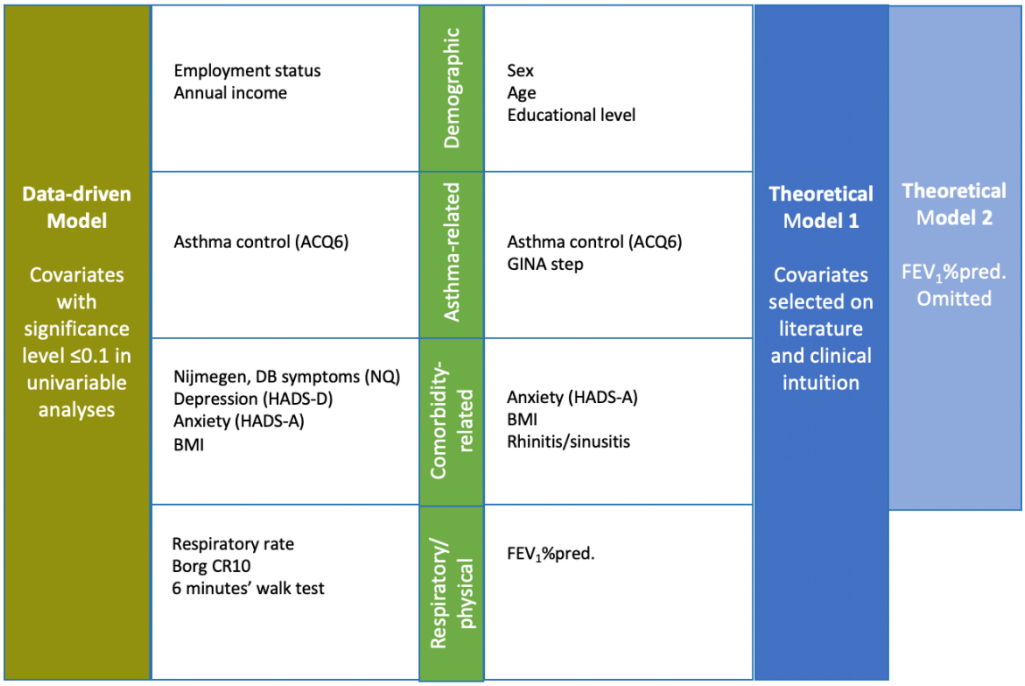

Figure 10; Multivariable linear regression models.
DB: Dysfunctional breathing

Statistical analyses

MiniAQLQ (continuous) was the dependent variable.

Testing for normal distribution were completed by Q-Q plots and Shapiro-Wilk's test.

Firstly, we performed simple linear regressions to investigate the univariable associations at significance level $p \leq 0.05$ between dependent variable and each independent covariate.

Secondly, we performed multivariable linear regression models to explore factors independently associated with MiniAQLQ, using the three above-mentioned models.

The proportions of MiniAQLQ score variance explained by the included covariates in each regression were investigated and reported as R^2, statistical significance defined as p-value ≤ 0.05.

Only participants with full data in covariates of the relevant model were included in the regression analyses (i.e., imputations were not performed).

Regression coefficients (β) were reported with 95% confidence interval (CI). A positive coefficient for a covariate should be interpret as follows: improvement of QoL score with greater covariate score and *vice versa*.

Study 3

Sample size

To calculate sample size, we used previously reported effect size of 0.38 units in MiniAQLQ[73] and a standard deviation (SD) double of the effect size[107] saying that 172 participants (86 per group) were needed to find a difference in mean change of 0.38 (SD 0.76) units in MiniAQLQ score (two-sided, type 1 error of 5%, 90% power). To allow for 10 % dropout, the aim was 190 enrolled participants.

Statistical analysis

A statistical analysis plan (SAP) was made publicly available before analyses of data began (Appendix B-2).[108]

We analysed all randomized participants according to Intention-to-treat (ITT) principle and did per-protocol analyses in UC-group (100%) versus UC+BrEX-group (with 100% session attendance). The accelerometry subgroup included participants having ≥6 day-duration of measurement (regardless < or > 23 hours of data obtained per day) at least at one timepoint (baseline, 3-month, or 6-month follow up).

We analysed between-group mean difference in change from baseline to 6-month in MiniAQLQ (primary outcome) and secondary outcomes using repeated measures mixed effects models (random factor: subject; fixed factors: treatment arm, visit, interaction between treatment arm and visit). Centres were included as a fixed effect but no models accounted for clustering at therapist level.

Number-needed-to-treat (NNT) for a clinically relevant MiniAQLQ improvement (0.5 units) was estimated as 1/('proportion improved'-'proportion deteriorated') from baseline to 6-month.[109]

We used Chi-square to test difference in GPE between groups and Mann-Whitney test to analyse change in GINA step between groups.

Finally, we used Poisson regression models to estimate the AE incidence rate ratio (IRR) with AEs, serious AEs or OCS courses as dependent outcome, and group, treatment centre, BMI, and GINA step as covariates.

RESULTS

Paper I
Paper I provides no results and is not discussed further in this section.

Study 2
Out of 314 screened patients, 193 were included. Characteristics are presented in **table 3**.
Appendix D-2 shows the distribution of self-reported comorbidities.

In the univariable regression analysis (**Table 4**), the factors significantly associated with worse asthma-specific QoL - with % of explained variance presented - were: Asthma control, 53.9%; dysfunctional breathing related symptoms, 42.0%; depression, 22.2%; anxiety, 18.3%; resting breathlessness, 13.7%; resting respiratory rate, 4.4%; and body mass index, 2.8%.
Further, factors that were protective of asthma-specific QoL were walked distance in 6 minutes, 11.5%, and having high income, 4.3%.
The 'employment status' outcome was not associated with MiniAQLQ, however it appeared that the category 'outside labour market' compared to category 'being employed' was important and associated with lower MiniAQLQ.
Outcomes that were not significantly associated were: sex, age, educational level, smoking status, asthma severity, number of comorbidities, rhinosinusitis, or lung function.

The *Data-driven Model* explained 69.9% of MiniAQLQ variance. (**Table 5**)
Factors associated with impaired asthma-specific QoL were: Asthma control and dysfunctional breathing related symptoms, whereas 'high income' was associated with protection of asthma-specific QoL. For functional performance, results was close to significance (p= 0.052).

The *Theoretical Model 1* explained 65.4% of MiniAQLQ variance. Two factors were significantly associated with worse asthma-specific QoL: Asthma control and anxiety. (**Table 6**)

The *Theoretical Model 2* (that omitted FEV_1%pred) explained 62.2% of MiniAQLQ variance, however showing identical regression coefficients for asthma control and anxiety as found in the Theoretical Model 1. (**Table 7**)

In the theoretical models (1 and 2), sex, age, educational level, asthma severity, BMI, rhinosinusitis, and for Model 1 lung function, were not associated factors of MiniAQLQ variance.

TABLE 3. Baseline characteristics of the participants (n=193)

Characteristics			Range
Demographical			
Sex			
Female	122	(63.2%)	
Male	71	(36.8%)	
Age at examination (SD)	51.6	(14.5)	18-82
Educational level			
No or short-term education	40	(20.7%)	
Middle-term education	116	(60.1%)	
Long-term education	37	(19.2%)	
Employment status			
Employed	107	(55.4%)	
Un-employed	7	(3.6%)	
Education (student)	69	(35.8%)	
Outside labour market	69	(35.8%)	
Annual income, €			134 - 301,807
Low, < 53609	56	(58.8%)	
Middle, 53609 - 107219	59	(32.2%)	
High, > 107219	49	(9.0%)	
Other	16	-	
Smoking status			
Never	117	(60.6%)	
Current	9	(4.7%)	
Former	67	(34.7%)	
Asthma-realted			
MiniAQLQ (mean, SD)[a]	4.3	(1.02)	1.2-6.3
ACQ6	2.2	(1.5-2.7)	0.5-5.0
GINA steps			
1	0	(0%)	
2	3	(1.5%)	
3	29	(15.0%)	
4	65	(33.9%)	
5	96	(49.7%)	
Comorbidity-related			
NQ	22	(15-31)	3-53
HADS, anxiety	6	(3-9)	0-20
HADS, depression	3	(1-6)	0-21
EuroQoL, EQ-5D-5L	0.745	(0.688-0.824)	0.006-1
Body Mass Index	28.3	(25.0-32.3)	15.1-56.2
Underweight, <18.5	2	(1.0%)	
Normal weight, 18.5-24.9	46	(23.8%)	
Overweight, 25-29.9	73	(37.8%)	
Obese, 30-34.9	46	(23.8%)	
Severely obese, 35-39.9	15	(7.8%)	
Extremely obese, >40	11	(5.7%)	
Rhinosinusitis	28	(14.5%)	
Allergic rhinitis	15	(7.8%)	
Chronic rhinitis	8	(4.1%)	
Sinusitis	4	(2.1%)	
Vaso motoric rhinitis	3	(1.6%)	
Number of comorbidities			0-10
0	77	(39.9%)	
1	53	(27.5%)	
2+	63	(32.6%)	
Respiratory/physical			
FEV_1 % predicted (n=176)	80	(70-89)	19-136
Respiratory rate	15	(12-17)	8-37
Borg CR10, resting	1.5	(0.5-2.5)	0-6
6 minutes walk test (n=187)	467	(419-522)	126-789

Data are median (interquartile range, IQR) and frequency (percentages), unless mentioned.

[a] AQLQ is parametric: mean and standard deviation (SD) are reported.
Income: Low, Middle, High is tertiles of income range in the sample. Other = unknown, <100 €
Education: No or short-term education (no education, primary/high/secondary school), Middle-term education (vocational/short higher/medium education), Long-term education (Bachelor, master/higher education, PhD.)
Rhinosinusitis: one participant had chronic and allergic rhinitis, 1 participant had chronic rhinitis and sinusitis.

TABLE 4. Univariable analyses of covariates

Covariates	Regression coefficient, β (95%CI)		Proportion of MiniAQLQ variance explained, R^2, p-value	
Demographical				
Sex			0.000	0.858
Male	reference			
Female	0.03	(-0.27 to 0.33)		
Age	0.00	(-0.01 to 0.01)	0.002	0.496
By educational level			0.001	0.882
No or short-term education	reference			
Middle-term education	-0.09	(-0.46 to 0.28)		0.630
Long-term education	-0.05	(-0.43 to 0.33)		0.799
By employment status			0.063	0.119
Employed	reference			
Un-employed	-0.74	(-1.51 to 0.02)		0.057
Education (student)	-0.22	(-0.87 to 0.43)		0.508
Outside labour market	-0.50	(-0.80 to -0.20)		0.001
By income group			0.043	0.023
Low, < 53609	reference			
Middle, 53609 - 107219	0.19	(-0.14 to 0.52)		0.264
High, > 107219	0.39	(0.21 to 1.29)		0.007
Smoking status			0.005	0.608
Never	reference			
Current	-0.19	(-0.88 to 0.51)		0.599
Former	0.12	(-0.19 to 0.43)		0.452
Asthma-related				
ACQ6	-0.83	(-0.94 to -0.72)	0.539	0.000
GINA steps			0.020	0.281
2	reference			
3	0.12	(-1.10 to 1.33)		0.852
4	0.02	(-1.17 to 1.20)		0.975
5	-0.23	(-1.41 to 0.94)		0.696
Comorbidity-related				
NQ	-0.06	(-0.07 to -0.05)	0.420	0.000
HADS-A	-0.10	(-0.13 to -0.07)	0.183	0.000
HADS-D	-0.13	(-0.17 to -0.10)	0.222	0.000
BMI	-0.03	(-0.05 to 0)	0.028	0.020
Rhinosinusitis	0.11	(-0.31 to 0.52)	0.001	0.614
Number of comorbidities			0.004	0.693
0	reference			
1	-0.05	(-0.41 to 0.31)		0.792
2+	-0.15	(-0.49 to 0.20)		0.396
Respiratory/Physical				
FEV_1 % predicted (n=176)	0.01	(0 to 0.01)	0.010	0.188
Respiratory rate	-0.05	(-0.08 to -0.02)	0.044	0.004
Borg CR10 (resting)	-0.27	(-0.36 to -0.17)	0.137	0.000
6 minutes' Walk Test (n=187)	0.00	(0 to 0.01)	0.115	0.000

ACQ6: 6-item Asthma Control Questionnaire

BMI: body mass index

Borg CR10: amount of breathlessness in rest using

FEV1%pred: predicted forced expiratory volume in first second

GINA steps: treatment steps recommended by Global Initiative for Asthma, defining asthma severity

HADS-A: Hospital Anxiety and Depression Scale (anxiety)

HADS-D: Hospital Anxiety and Depression Scale (depression)

MiniAQLQ: Mini-Asthma Quality of Life Questionnaire

NQ: Nijmegen Questionnaire

TABLE 5. Data-driven model, multivariable analyses of covariates

Covariates	Regression coefficient, β (95%CI)		Proportion of MiniAQLQ variance explained, R^2, p-value	
n=172			0.696	0.0000
Demographical				
By employment status				
Employed	reference			
Un-employed	0.13	(-0.43 to 0.69)		0.651
Education (student)	0.08	(-0.37 to 0.53)		0.730
Outside labour market	-0.05	(-0.28 to 0.17)		0.648
By income group				
Low, < 53609	reference			
Middle, 53609 - 107219	0.01	(-0.20 to 0.21)		0.943
High, > 107219	0.35	(0.02 to 0.69)		0.041
Asthma-related				
ACQ6	-0.60	(-0.73 to -0.47)		0.000
Comorbidity				
NQ	-0.03	(-0.04 to -0.02)		0.000
HADS-A	-0.03	(-0.06 to 0)		0.088
HADS-D	0.00	(-0.03 to 0.04)		0.877
BMI	-0.01	(-0.02 to 0.01)		0.421
Respiratory/Physical				
Respiratory rate	0.01	(-0.01 to 0.03)		0.407
Borg CR10 (resting)	-0.03	(-0.10 to 0.05)		0.482
6 Minutes' Walk Test (n=187)	0.00	(0 to 0)		0.052

This Data-driven Model included all covariates with a significance level of $p \leq 0.1$ in univariable analyses.
ACQ6: 6-item Asthma Control Questionnaire
BMI: body mass index
Borg CR10: amount of breathlessness in rest using
HADS-A: Hospital Anxiety and Depression Scale (anxiety)
HADS-D: Hospital Anxiety and Depression Scale (depression)
MiniAQLQ: Mini-Asthma Quality of Life Questionnaire
NQ: Nijmegen Questionnaire

TABLE 6. Theoretical model 1, multivariable analyses of covariates

Covariates	Regression coefficient, β (95%CI)		Proportion of MiniAQLQ variance explained, R^2, p-value	
n=176			0.654	0.0000
Demographical				
Sex				
Male	reference			
Female	-0.10	(0.31 to 0.09)		0.308
Age	0.00	(-0.01 to 0.01)		0.642
By educational level				
No or short-term education	reference			
Middle-term education	-0.20	(-0.43 to 0.04)		0.103
Long-term education	-0.09	(-0.33 to 0.16)		0.489
Asthma-related				
ACQ6	-0.75	(-0.86 to -0.64)		0.000
Gina steps				
2	reference			
3	0.19	(-0.55 to 0.94)		0.608
4	0.24	(-0.48 to 0.95)		0.519
5	0.27	(-0.45 to 0.99)		0.460
Comorbidity-related				
HADS-A	-0.07	(-0.09 to -0.05)		0.000
BMI	-0.01	(-0.03 to 0)		0.150
Rhinosinusitis	0.07	(-0.19 to 0.34)		0.600
Respiratory				
FEV_1 % predicted	0.00	(-0.01 to 0)		0.814

ACQ6: 6-item Asthma Control Questionnaire ; BMI: body mass index
FEV1%pred: predicted forced expiratory volume in first second
GINA steps: treatment steps recommended by Global Initiative for Asthma, defining asthma severity
HADS-A: Hospital Anxiety and Depression Scale (anxiety); MiniAQLQ: Mini-Asthma Quality of Life Question.

TABLE 7. Theoretical model 2, multivariable analyses of covariates

Covariates	Regression coefficient, β (95%CI)		Proportion of MiniAQLQ variance explained, R^2, p-value	
n=193			0.622	0.0000
Demographics				
Sex				
Male	reference			
Female	-0.10	(-0.30 to 0.09)		0.284
Age	0.00	(-0.01 to 0.01)		0.656
By educational level				0.882
No or short-term education	reference			
Middle-term education	-0.15	(-0.40 to 0.09)		0.227
Long-term education	-0.04	(-0.29 to 0.21)		0.735
Asthma-related				
ACQ6	-0.75	(-0.86 to -0.64)		0.000
Gina steps				0.281
2	reference			
3	0.20	(-0.59 to 0.99)		0.610
4	0.24	(-0.53 to 1.00)		0.541
5	0.23	(-0.53 to 0.99)		0.553
Comorbidity				
HADS-A	-0.07	(-0.09 to -0.05)		0.000
BMI	-0.01	(-0.02 to 0.01)		0.229
Rhinosinusitis	0.10	(-0.17 to 0.37)		0.471

This model omitted FEV1 % predicted.
ACQ6: 6-item Asthma Control Questionnaire ; BMI: body mass index
GINA steps: treatment steps recommended by Global Initiative for Asthma, defining asthma severity
HADS-D: Hospital Anxiety and Depression Scale (depression)
MiniAQLQ: Mini-Asthma Quality of Life Questionnaire

Study 3

Enrollment, allocation, and follow-up

Participants were recruited from April 27th 2017 with the first participants enrolled June 2017. Inclusion was completed September 24th 2019.

Out of 314 patients screened for eligibility, 193 were enrolled in the trial with 94 allocated to UC+BrEX-group and 99 to UC-group. All 193 were analyzed in the Intention-to-treat analyses (ITT) analyses. Non-inclusion was most often declining participation (n=38) or having ACQ6 score below the required 0.8 (n=27). The per protocol population included 76 (80.9%) of UC+BrEX participants, and total number of UC participants (n=99). (**Figure 11**, Trial profile)
The characteristics at baseline were similar in the two groups. (**Table 8**)
Comorbidities reported by group, Appendix E-S3.

The primary outcome (MiniAQLQ) was reported by 183 participants (94.8%) at 6-month (UC+BrEX n=87, 92.6%; UC, n=96, 97.0%). Other self-reported outcomes were reported by slightly less (UC+BrEX n=85, 90.4%; UC, n=95, 97.0%).

Primary outcome

We found a significant improvement in asthma-specific QoL in favour of the intervention to which UC+BrEX was allocated (between group difference in adjusted mean change of MiniAQLQ, 0.35 units, 95% confidence interval (CI) 0.07 to 0.62). Significant improvements were observed in both groups: in UC+BrEX: 0.65 units (0.46 to 0.85), and UC: 0.31 units (0.12 to 0.49). Per-protocol analysis showed a slightly larger difference in mean change: adjusted 0.38 units (0.10 to 0.66) (**Table 9, Figure 12**).

Secondary outcomes

Numbers-needed-to-treat (NNT) was 7.6 to improve from UC+BrEX:
As 47 (54%) participants in UC+BrEX and 40 (42%) in UC improved ≥0.5 units in MiniAQLQ score, whereas 11 (13%) in UC+BrEX and 17 (18%) in UC decreased ≥0.5 units.
(Appendix E-S5 Table)

Baseline to 6-month:
We found a significant, but minor difference in mean change of depression (-0.9 units, 95%CI -1.67 to -0.14) in favour of UC+BrEX, but all other secondary outcomes were non-significant between groups. Improvements were found in asthma symptom control, dysfunctional breathing related symptoms, and anxiety in both groups, however for physical and respiratory outcomes no differences were found. The difference in mean change of depression increased in per-protocol analysis. (**Table 9**)

More participants in the UC+BrEX-group rated the asthma-specific QoL moderately or markedly improved than participants in the UC-group, but without significantly difference between the groups. (Appendix E-S6a Table, E-S6b Figure)

Baseline to 3-month:
We found a significant improvement of asthma-specific QoL (between-group difference in mean change of 0.56 units, 96%CI 0.28 to 0.85) in favour of UC+BrEX (**Figure 12** and Appendix E-S4). Except for anxiety, between-group and within-UC+BrEX group improvements were observed in all self-reported outcomes. (Appendix E-S4)

Adverse events
AE and serious AE were similarly frequent in the groups, inclusive for the asthma-related events. (**Table 10** and Appendix E-S9 a, b, d)

Medication
We found no difference in change of prescribed anti-asthma medication in the two groups. (Appendix E-S7a)

Adherence
We observed a high degree of adherence to the BrEX-program:
The adherence to home exercise was rated ‘good’ or ‘excellent in 3/4 of UC+BrEX-group participants, and 4/5 attended all three sessions. (Appendix E-S8b Table, E-S8c Figure).

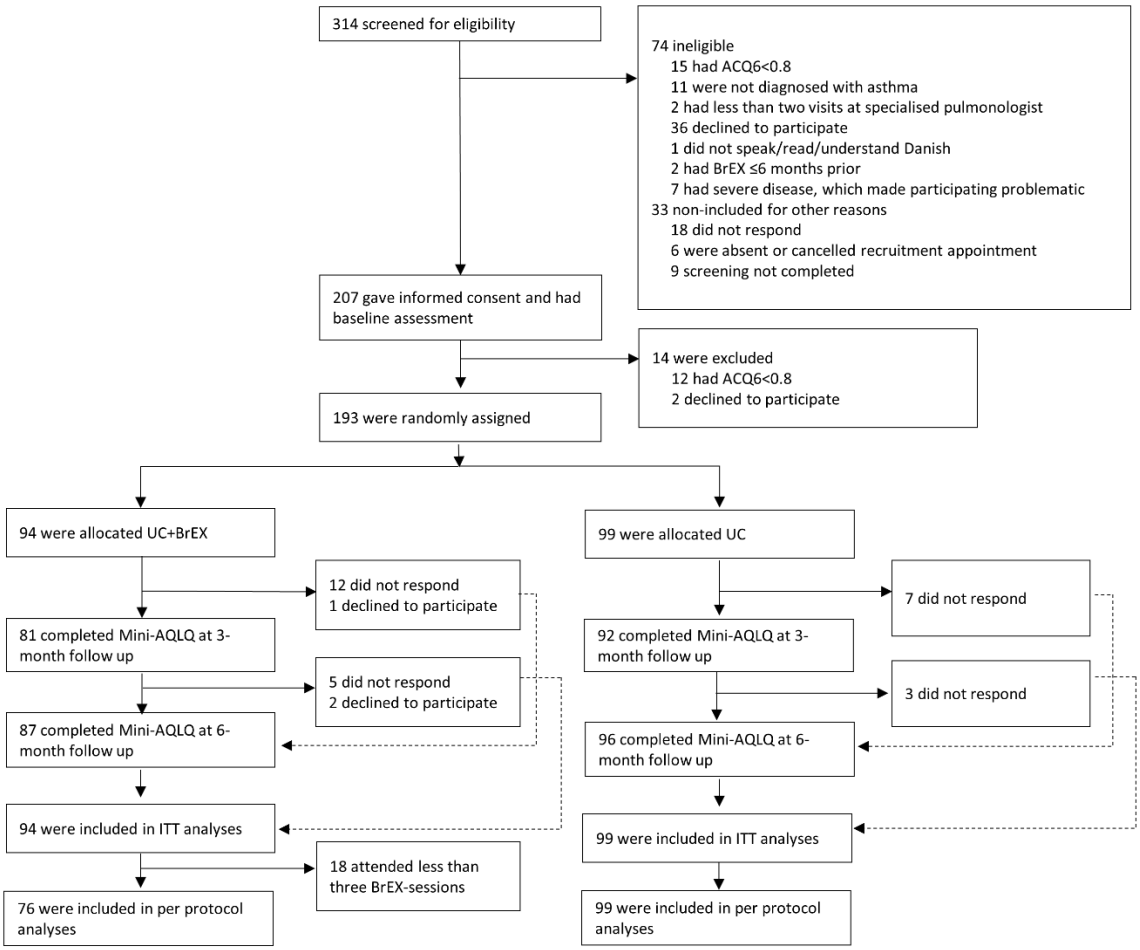

Figure 11. Trial profile, study 3

Table 8; Baseline characteristics

	UC+BrEX (n=94)		UC (n=99)	
Sex				
Female	58	(61.7%)	64	(64.7%)
Male	36	(38.3%)	35	(35.4%)
Age at inclusion	55	(44-65)	51	(42-61)
Smoking status				
Never-smokers	89	(55.3%)	95	(65.7%)
Smokers	5	(5.3%)	4	(4.0%)
Former smokers	37	(39.4%)	30	(30.3%)
Body Mass Index				
Underweight	1	(1.1%)	1	(1.0%)
Normal weight	24	(25.5%)	22	(22.2%)
Overweight	29	(30.9%)	44	(44.4%)
Obese	26	(27.7%)	20	(20.2%)
Severely obese	8	(8.5%)	7	(7.1%)
Extremely obese	6	(6.4%)	5	(5.1%)
PROMs				
MiniAQLQ	4.3	(3.7-5.1)	4.4	(3.6-5.1)
ACQ6	2.2	(1.5-2.7)	2.0	(1.2-2.7)
NQ[a]	22.9	(10.9)	23.1	(11.3)
HADS-A	5	(3-10)	6	(3-9)
HADS-D	3	(1-7)	3	(1-6)
EuroQual, EQ-5D-5L index	0.742	(0.648-0.859)	0.754	(0.7-0.824)
EuroQual, EQ-5D-5L VAS[a]	62.0	(20.7)	62.1	(19.0)
GINA steps				
1	0	(0%)	0	(0%)
2	1	(1.1%)	2	(2.0%)
3	16	(17.0%)	13	(13.1%)
4	31	(33.0%)	34	(34.3%)
5	46	(48.9%)	50	(50.5%)
Inhaled corticosteroids, ICS				
none	1	(1.1%)	1	(1.0%)
low	18	(19.2%)	20	(20.2%)
moderate	33	(35.1%)	30	(30.3%)
high	42	(44.7%)	48	(48.5%)
Number of second controller				
none	5	(5.3%)	4	(4.0%)
1	41	(43.6%)	45	(45.5%)
2	30	(31.9%)	35	(35.4%)
3	14	(14.9%)	13	(13.1%)
4+	4	(4.3%)	2	(2.0%)
Oral corticosteroids, OCS[b]	6	(6.4%)	2	(2.0%)
Biological treatment	13	(13.8%)	9	(9.1%)
Objective measures				
6-min walk test (n=90)	467	(422-528)	(n=97) 469	(417-515)
Borg CR10 (resting) (n=94)	1	(0.3-2.5)	(n=99) 2	(0.5-2.5)
FEV_1 % predicted (n=85)	80	(73-87)	(n=91) 80	(66-90)
FEV_1/FVC-ratio (n=85)	0.73	(0.66-0.80)	(n=91) 0.73	(0.67-0.79)
PEFR (liter/min) (n=85)	359	(308-421)	(n=91) 355	(282-434)
Steps per day (avg 6 days) (n=41)	7046	(4637-9517)	(n=44) 7278	(4899-10175)
PAL (avg 6 days) (n=41)	1.5	(1.4-1.6)	(n=44) 1.5	(1.4-1.6)

Data are reported as medians with interquartile range (IQR) and frequency with percentage (%), apart from [a] which are means and standard deviations (SD). [b] Maintenance oral steroids. Explicitly about co-morbidity in appendix. UC+BrEX=Breathing exercises and usual care. UC=Usual care alone. PROMs=Patient-reported outcome measures. MiniAQLQ=Mini-Asthma Quality of Life Questionnaire. ACQ6=6-item Asthma Control Questionnaire. NQ=Nijmegen Questionnaire. HADS-A=anxiety items of Hospital Anxiety and Depression Scale. HADS-D=depression items of Hospital Anxiety and Depression Scale. 6MWT=6-min walk test. FEV1%predicted=Predicted percentage of forced expiratory volume in first second. FEV1/FVC-ratio=ratio of FEV_1/forced vital capacity. PEFR=peak expiratory flow rate. PAL=average Physical Activity Level per day.

Table 9; Adjusted intention-to-treat analyses and per-protocol analyses of MiniAQLQ and secondary outcomes at 6-month

	Total no. of assessments[a]		ITT-population					
	UC+BrEX	UC	UC+BrEX (n=94)		UC (n=99)		Between-group difference	
			mean change		mean change		difference in means change	
MiniAQLQ	262	287	0.65	(0.46 to 0.85)	0.31	(0.12 to 0.49)	0.35	(0.07 to 0.62)
ACQ6	256	285	-0.32	(-0.50 to -0.15)	-0.21	(-0.38 to -0.05)	-0.11	(-0.35 to 0.13)
NQ	255	285	-3.83	(-5.52 to -2.13)	-2.78	(-4.39 to -1.17)	-1.05	(-3.38 to 1.29)
HADS-A	255	284	-1.06	(-1.73 to -0.38)	-1.11	(-1.75 to -0.47)	0.06	(-0.87 to 0.98)
HADS-D	255	284	-1.16	(-1.71 to -0.61)	-0.26	(-0.78 to 0.27)	-0.90	(-1.67 to -0.14)
6MWT	160	176	2.03	(-10.20 to 14.27)	9.03	(-2.44 to 20.50)	-7.00	(-23.77 to 9.77)
FEV_1% pred.	150	163	0.48	(-2.19 to 3.14)	-0.53	(-3.01 to 1.96)	1.00	(-2.64 to 4.65)
Steps per day	82	89	84.74	(-973.24 to 1142.72)	-245.85	(-1282.10 to 790.40)	330.59	(-1149.86 to 1811.04)
PAL	82	89	0.03	(-0.02 to 0.08)	-0.02	(-0.06 to 0.03)	0.05	(-0.02 to 0.11)
			Per-protocol population					
			UC+BrEX (n=76)		UC (n=99)		Between-group difference	
			mean change		mean change		difference in means change	
MiniAQLQ	222	287	0.68	(0.47 to 0.89)	0.31	(0.12 to 0.49)	0.38	(0.10 to 0.66)
ACQ6	216	285	-0.39	(-0.58 to -0.20)	-0.21	(-0.38 to -0.05)	-0.18	(-0.43 to 0.07)
NQ	215	285	-4.03	(-5.88 to -2.19)	-2.78	(-4.41 to -1.16)	-1.25	(-3.71 to 1.21)
HADS-A	215	284	-1.13	(-1.84 to -0.42)	-1.11	(-1.74 to -0.48)	-0.02	(-0.97 to 0.93)
HADS-D	215	284	-1.46	(-2.03 to -0.89)	-0.26	(-0.76 to 0.25)	-1.20	(-1.97 to -0.44)
6MWT	140	176	2.50	(-10.20 to 15.19)	9.03	(-2.53 to 20.58)	-6.53	(-23.69 to 10.63)
FEV_1% pred.	131	163	0.87	(-1.89 to 3.63)	-0.52	(-3.02 to 1.99)	1.39	(-2.34 to 5.11)
Steps per day	79	89	139.09	(-921.97 to 1200.14)	-248.85	(-1282.53 to 784.83)	387.93	(-1093.40 to 1869.27)
PAL	79	89	0.03	(-0.02 to 0.08)	-0.01	(-0.06 to 0.03)	0.05	(-0.02 to 0.11)

Data are adjusted mean change from baseline to 6-month including 95% CI.

[a] Possible assessments for questionnaires (at baseline + at 3-month + at 6-month): 282 for UC+BrEX (in per-protocol: 228) and 297 for UC; for FEV1%pred. and 6MWT (at baseline + at 6-month): 188 for UC+BrEX (in per-protocol: 152) and 198 for UC; steps per day and PAL (at baseline + at 3-month + at 6-month): 135 for UC+BrEX (in per-protocol population: 126) and 144 for UC.

UC+BrEX= Breathing exercises and usual care. UC= Usual care alone. MiniAQLQ=Mini-Asthma Quality of Life Questionnaire. ACQ6=6-item Asthma Control Questionnaire. NQ=Nijmegen Questionnaire. HADS-A=anxiety items of Hospital Anxiety and Depression Scale. HADS-D=depression items of Hospital Anxiety and Depression Scale. 6MWT=6-min Walk Test. FEV1%pred.=Predicted percentage of forced expiratory volume in first second. PAL=average Physical Activity Level per day.

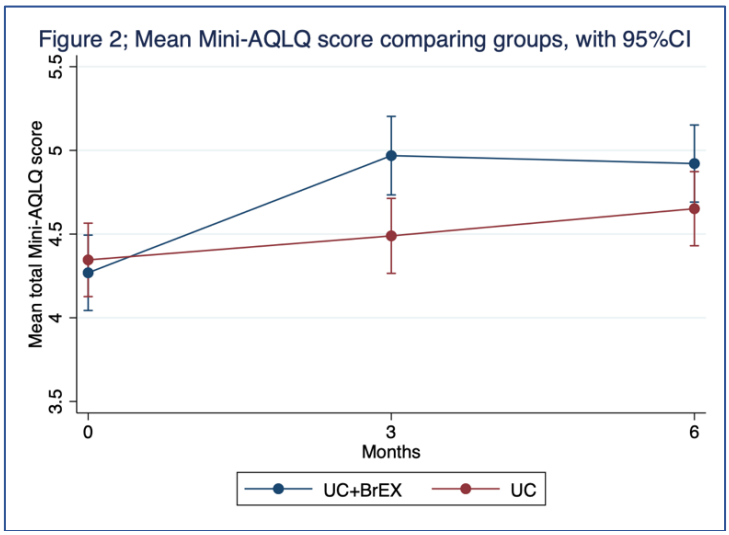

Figure 12. Mean MiniAQLQ score comparing groups

Table 10; Asthma-related adverse events, asthma-related serious adverse events, and courses of oral corticosteroids

	UC+ BrEX			UC				
	Number of participants		Number of events	Number of participants		Number of events	IRR[a]	p-value
Adverse events							1.47	0.381
0	80	(85.1%)	0	81	(81.8%)	0		
1	11	(11.7%)	11	12	(12.1%)	12		
2	1	(1.1%)	2	3	(3.0%)	6		
3+	2	(2.1%)	21	3	(3.0%)	21		
Total	94	(100%)	34	99	(100%)	39		
Serious adverse events							2.03	0.159
0	88	(93.6%)	0	90	(90.9%)	0		
1	6	(6.4%)	6	6	(6.1%)	6		
2	0	(0%)	0	3	(3.0%)	6		
Deaths	0	(0%)	0	0	(0%)	0		
Total	94	(100%)	6	99	(100%)	12		
OCS courses[b]							0.82	0.704
0	87	(92.6%)	0	93	(94.9%)	0		
1	6	(6.4%)	6	3	(3.1%)	3		
2	1	(1.1%)	2	2	(2.0%)	4		
Total	94	(100%)	8	98	(100%)	7		

[a] Incidence rate ratio (IRR): UC group compared to UC+BrEX group. [b]One missing in UC group

UC+BrEX=Breathing exercises and usual care. UC=Usual care alone. OCS=oral corticosteroids.

DISCUSSION OF RESULTS

This thesis aimed to explore the relationship between asthma-specific QoL and patient-specific, disease-related and performance factors to point out potential *treatable traits* in individuals with incompletely controlled moderate-to-severe asthma, and further to investigate the effect from physiotherapist-delivered breathing exercises given as add-on to usual care in specialized asthma clinics.

Study 2

Main findings – Associations with asthma-specific QoL

Symptom control, anxiety and dysfunctional breathing (DB) related symptoms were independently associated with poor asthma-specific QoL, and high income was protective of asthma-specific QoL in the population of incompletely controlled, moderate-to-severe asthma patients. In two different models, these factors explained most of the variance in MiniAQLQ score. Besides from income level, the identified factors are potentially amendable with pharmacological treatment of asthma and anxiety, and cognitive behavioural therapy, relaxation techniques and breathing exercises of anxiety and DB.[110]

Asthma control

As expected, asthma control is a major determinant of asthma-specific QoL.[27,111–114] Yet, the magnitude of explained QoL variance differs between studies, which may possibly be due to differences in study design (e.g., populations, definition of severity, or tools):

When asthma control was measured by Chen *et al* with the *Asthma Therapy Assessment Questionnaire*, the variance of MiniAQLQ was explained by 39% in 987 patients with predominantly severe, persistent asthma, with asthma severity defined by 2005 GINA classification system.[114] Stucky *et al* used other measurement tools finding that variance of *12-item RAND Negative Impact of Asthma on Quality of Life scale* (RAND-IAQL-12) was explained by 50% from *RAND Asthma Control Measure* (RAND-ACM) scores in 2032 individuals with predominantly mild-to-moderate asthma.[111] In our Study 2, the Theoretical Models explored covariates comparable

to these previous studies, but were able to explain 62-65% of variation in MiniAQLQ score (Table 6 & 7).

Nijmegen Questionnaire My hypothesis that a Theoretical Model would explain a larger proportion of MiniAQLQ variance was not supported by the study findings, as the Data-Driven model explained the most variance. In the Data-Driven model, DB-related symptoms were independently associated with impaired asthma-specific QoL – and in the univariable regression model, NQ explained 42% of MiniAQLQ variance. In chronic obstructive pulmonary disease (COPD), NQ has been found to be associated with disease-specific QoL (COPD Assessment Test, CAT) in a large cohort study in patients with mild-to-moderate COPD.[115] Furthermore, Sedeh *et al* found that NQ ≥23 was inversely associated with MiniAQLQ in difficult asthma.[52] Opposite to this, in patients with difficult-to-treat asthma Denton *et al* found that NQ >23 was not associated with the MiniAQLQ (OR 0.96, 95% CI 0.55 to 1.67)[116], which contradicts the result of Sedeh *et al* study and Study 2. Instead, they found an association between NQ and anxiety (OR 3.26, 1.18 to 9.01) and depression (OR 2.8, 1.14 to 6.9).[116] Minor differences in study populations and variables included may account for the observed differences.

Overlap in questionnaires

In this Study 2, we found associations between MiniAQLQ and ACQ6, and similarly between MiniAQLQ and NQ. These questionnaires measuring symptoms and impact on the patient with asthma may overlap.

ACQ6 and MiniAQLQ are both questionnaires that measure aspects of asthma control, the ACQ6 the *symptom control* and the MiniAQLQ the *impact of asthma on the patient*. There is some overlap between them, in that poor symptom control is usually associated with worse QoL, and worse QoL may increase symptom perception.[1] It is possible to have low QoL despite mild symptoms, and good QoL despite bad symptoms, depending on patient coping mechanisms, comorbidities and the psychological state impact on this relationship.[2]

A close verbal overlap occurs in some items, i.e., in symptoms (having “shortness of breath”, being disturbed by asthma during the night, and “wheezing”), and activity limitation, hence the association could be expected (Appendix A-1, A-2). However, they are separate constructs and measure separate domains of asthma.[12,29]

NQ is likely to be measuring the emotional impact of breathlessness[61] as a consequence of experienced *specific and/or general symptoms* in chest and rest of body,[62] whereas MiniAQLQ elaborately measures how the patient experiences *living with asthma in plural aspect of daily living*, e.g., in activity.[29] Yet, it appears likely that MiniAQLQ and NQ values are associated, and a strong correlation have been reported.[47] MiniAQLQ and NQ do have overlap verbally in some items such as symptoms ("chest tightness", "shortness of breath") and emotions ("afraid of no available medication" or "concerned about having asthma" versus "feelings of anxiety"), but mostly items differ between the two questionnaires (Appendix A-2, A-3). And as with MiniAQLQ and ACQ6, the NQ and MiniAQLQ are different constructs.

Therefore, DB appears to be a *treatable trait* in patients with poorly controlled moderate-to-severe asthma. Yet, the accuracy of NQ in defining DB in patients with asthma appears weak, but NQ may be more informative as a continuous variable like we included in the analyses, rather than as a dichotomous variable defined with a somewhat arbitrary value cut-off.[49,61] However, NQ is not a good predictor for improvement by BrEX and no MID exists for the use of NQ as a continuous score.[61]

Objective tool

For now, no reliable questionnaire exists that can diagnose DB. Looking for an adequate measure of DB, Todd *et al* developed the BPAT, an objective outcome measure of DB, a 'snapshot' of the breathing pattern.[64] They found only weak but significant relationship between NQ and BPAT, and similarly between AQLQ and NQ.[64] This can be consequences of being outcome measures with different constructs, and/or Todd *et al* investigated AQLQ, differently from our investigation of MiniAQLQ associations. BPAT was not available at time of the initiation of our trial, but could have provided additional insight into the association between DB and MiniAQLQ.

Lung function

Contrary to my pre-specified hypothesis, lung function was not associated with MiniAQLQ in the multivariable analysis. Likewise, Chen *et al* did not find a significant association in univariable analyses, however when they fitted FEV_1%pred. into a model of demographical covariates, FEV_1%pred and asthma severity explained additionally 5% of variance.[114] Factors contributing to this inter-study discrepancy may include differences in spirometry reference systems,[117] differences in covariates included (Chen: anxiety not present), but presumably not differences in population

concerning asthma severity as both Chen and Study 2 included similar proportions of patients with moderate-severe asthma).[114]

Anxiety

Anxiety was independently associated with asthma-specific QoL in Study 2. Anxiety disorders are more prevalent in asthma than in healthy subjects, and anxiety was independently associated with asthma-specific QoL in a large observational study by the World Health Organization, yet the study did not report the direction of this association, and did not include measures of asthma severity.[43] Lavoie *et al* reported the direction of a strong association between impaired AQLQ and generalized anxiety disorder in 794 patients treated for asthma in an outpatient clinic (ß=-0.91, $p<0.001$).[118] Recently, Robinson *et al* reported that MiniAQLQ score <3 (i.e., considerably impaired QoL) indicated moderate anxiety, equal to a Generalized Anxiety Disorder-7 Questionnaire (GAD-7) score >10 in patients treated in tertiary asthma clinic. They aimed to investigate the MiniAQLQ' usefulness as a screening tool for anxiety and reported MiniAQLQ moderate-strong correlation to GAD-7 (r=-0.59), further sensitivity 0.75 and specificity 0.76.[106] Luskin *et al* identified 'Emotional stress' as an asthma trigger, and found that 'Emotional stress' showed a strong association with poor asthma-specific QoL in patients suffering from many asthma triggers or recurrent exacerbations.[25] These findings support a clinically important, inverse association between anxiety and asthma-specific QoL: the more anxiety the poorer asthma-specific QoL.

Obesity

In Study 2, the prevalence of obese individuals was 36%, and BMI as a continuous variable was associated with asthma-specific QoL in univariable but not in the multivariable analyses. Lavoie *et al* reported that obesity (dichotomous variable: BMI ≥30, 25% of study population) was associated with impaired asthma-specific QoL using multiple analyses, however they did not include anxiety in their model,[119] as we did.

In summary, Study 2 suggests that asthma control, anxiety and DB explain most but not all of the variance in MiniAQLQ. Thus, our data support that asthma-specific QoL contains important information on living with asthma, information not fully explained by asthma severity or asthma control. Furthermore, our data suggest anxiety and DB as *treatable traits* in patients with incomplete control of moderate-to-severe asthma.

Methodological considerations – Study 2

Study 2 has several limitations.

Firstly, the cross-sectional observational design prohibits evidence of causal relationships, thus this must be investigated in a future longitudinal, randomised study design. And the validity of the found associations needs testing in a different asthma population.[120]

Secondly, analyses of predetermined models are relevant to test hypotheses. Yet, this decision can be questioned as this may exclude important covariates. Stepwise regression would allow covariates to interplay more freely.

Thirdly, no dominance analyses[121] were included, thus we cannot provide knowledge about the extent of variance each covariate in the models accounted for. Therefore, this study can only be acknowledged as explorative.

Fourthly, due to only few current smokers (4.7%) we did not include smoking status in the analyses, although a typical confounder[105,114]. This was an attempt to avoid overfitted models, as relatively few observations (n=193) were included.

However, Study 2 also has some strengths.

Firstly, we included participants with pulmonologist-diagnosed asthma, which improves external validity as opposed to previous studies including patients with self-reported asthma diagnoses.[44,105,111]

Secondly, the population investigated in Study 2 was quite similar concerning both demographical characteristics (more females, age 40-60 years, overweight) and comorbidity to previous studies on 'difficult-to-treat'[25,114] or uncontrolled asthma.[27,44,111,119]

Study 3

Main findings - Effectiveness of add-on breathing exercises

Add-on BrEX was superior to improve asthma-specific QoL compared to usual care alone. This partly supports our hypothesis; however, we did not reach the effect size that was expected in the protocol. Guidelines have recommended use of BrEX to improve asthma-specific QoL in mild-moderate asthma given as a supplement to pharmacological treatment, but no evidence existed in patients treated in specialized clinics.[70,122]

To our knowledge, our large trial is the first RCT to investigated the effect of BrEX on asthma-specific QoL in more severe asthma patients treated in secondary health sector.
This adds to the warranted opportunities for *treatable traits* in patients with asthma.[36,38]

The effect size in MiniAQLQ

The Minimal Important Difference (MID) of MiniAQLQ in the individual patient is 0.5 units, but MID investigated between-groups in RCT's is unknown[33,109] besides that it varies with context and population.[123] The authors of MiniAQLQ specified that valuable improvements on individual level exist, even when the between-group mean difference is below 0.5.[109]
Moreover, in well-conducted pharmacological RCTs, the level of 0.5 is not achieved, still the treatments benefit the asthma control and asthma-specific QoL for the individual patients. A meta-analysis in patients with uncontrolled asthma showed that adding biological treatment to their ICS improved AQLQ by 0.31 (95% CI 0.20 to 0.41), and if adding long-acting β antagonist (LABA) 0.35 (0.27 to 0.43), whereas the effects were less for other add-on controllers.[124] Compared to this, the between-group MiniAQLQ effect of 0.35 found in Study 3 was equal to (or better than) the effect of added second controllers in comparable asthma populations.

Although the within-group mean change in MiniAQLQ in UC+BrEX (0.65 units) did exceed both the individual patient MID and our anticipated 0.38 units,[85] the mean change difference in change between groups (0.35 units) did not, although it was very close to the threshold in our sample size calculation. An important reason is the relatively large improvement observed in the UC-group (0.31 units) (Table 9). Significant improvements in control groups are a common observation in clinical trials, e.g., in similar respiratory trials[47,72,73,82] and in trials investigating physical interventions.[125] Being a participant in a clinical trial receiving additional attention by concerned health care professional may improve experienced QoL, which may be some of the explanation for improvements in the UC group.[125] Furthermore, we did not collect any data to show whether participants in UC group by themselves used other kinds of breathing techniques or treatments to compensate for not being allocated to the BrEX intervention. If participants in the UC group did in fact engage in other treatment, this could potentially also result in effects in MiniAQLQ.

Recently, a Cochrane review[70] reported mean difference of 0.42 (95% CI 0.17 to 0.68) in AQLQ from BrEX in mild-to-moderate asthma. The BrEX interventions included Buteyko, Pranayama,

yoga, and BrEX similar to procedure in study 3.[70] Focusing on trials with low risk of bias, effect sizes ranged from 0.13 to 0.50 at 3-month. Taking a closer look to the trial using identical procedures as Study 3, however in mild-to-moderate asthma, the mean difference was 0.24 (95% CI 0.04 to 0.44) in MiniAQLQ at 12-month follow up.[47] I look forward to do the analyses of 12-month follow up in Study 3 and to compare our results to these previous 'long-term' results.

Effects in secondary outcomes

Study 3 failed to show between-group improvements in any of secondary outcomes at 6-month, besides from a minor improvement in depression. Within-group improvements were found in all self-reported outcome measures, except for depression in the UC-group. The BEAT DB-trial was powered to detect differences in MiniAQLQ - guided by previous MiniAQLQ effects[73] – and not in secondary outcomes, which would require a larger sample.

Indication exists that MiniAQLQ is more responsive to the effect from BrEX than other outcome measures.[47,70,73,74] Previous research found that none of: baseline lung function, end-tidal-CO_2 ($ETCO_2$), minute volume, HADS score, ACQ score, age, sex and FeNO were predictive of a response from the breathing exercises in AQLQ. (M Thomas, personal communication, 2020).

Effects of other non-pharmacological treatments to improve asthma-specific QoL have been investigated, e.g. nutrition and physical fitness,[126–128] weight reduction in obese individuals, [104,129,130] Cognitive Behavioural Therapy,[131] and establishment of multidisciplinary, multi-dimensional treatment options are warranted.[36]

Anxiety

Anxiety is overrepresented in breathing disorders, e.g., in DB-patients without asthma who report more anxiety and more hyperventilation (measured by NQ) than well-controlled asthma patients,[46] and anxiety has been reported associated with larger irregularity in breathing.[22] As in previous research investigating BrEX in asthma populations since 2007,[70,74] we investigated anxiety and depression using the well-validated HADS tool, which measures both anxiety and depression separately. The authors of HADS aimed to develop a screening tool for psychiatric disorder and the items of HADS-A (i.e., anxiety) do not directly address respiratory discomfort.[93] Yet, a well-known coincidence between anxiety, breathing complaints and asthma has been reported,[2,22,49,62,93,110] and distress by anxiety increases with increasing asthma severity.[132,133] Furthermore, a considerable

overlap may exist between anxiety, asthma control, and asthma QoL questionnaires, thus anxiety traits might be difficult to diagnose in asthmatic patients especially in severe and uncontrolled asthma.[2]

In the BrEX program, physiotherapists do provide some basic anxiety management advice (i.e., improvement of breathing pattern, and relaxation). It is plausible that reduction in anxiety may be at least part of the mechanism of the effect of BrEX, although the correlation between improvements in anxiety and improvements in QoL are only modest.[47,73]
Our trial did not directly address if treating anxiety traits is a mode of action of BrEX. Futures studies could address this to optimize and individualize the BrEX intervention.

Safety and costs
We investigated the effects of an add-on treatment in patients with incompletely controlled asthma despite specialist care. In 1985, the World Health Organization defined that rational use of medicines requires that "*patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community*" (*Rational use of medicines: progress in implementing the WHO medicines strategy*, p.1, WHO, 2006).[134]
This statement can be applied to non-pharmacological interventions, too.
In our trial, BrEX improved asthma-specific QoL with a NNT of 7.6 and was without any suggestion of harm. Adding to the BREATHE study,[47] which reported NNT of 7 for face-to-face treatment versus UC, our trial highlights that the effects of BrEX appears consistent regardless of asthma severity. BrEX is a relatively low-cost and safe intervention, again consistent with previous work in milder asthma in the BREATHE study, in which although there were costs in providing the BrEX-intervention, due to lower costs relating to improved asthma control, the overall, direct healthcare costs were lower in the BrEX-group than in the UC-group measured over 12 months, and without any observed disadvantages (adverse events, negative side effects) from BrEX.[79]

In conclusion, the primary impact of add-on BrEX appears to be improvement in living with asthma.[1,2,38] What underlies this experience of improvement is unclear and cannot be explained by improved asthma control, lung function, or physical exercise capacity, as we found no significant changes in these outcomes in the BEAT DB-trial.

These results are in line with previous studies, also showing no evidence of effect in lung function or physical performance.[47,70,72,135] However, qualitative research in patients who have had breathing exercises reports reduction of needed medication, besides, having better breathing control and being more relaxed; they experienced their health and QoL improved.[80]

Methodological considerations – Study 3

Strengths

This trial had a rigorous study design. It included the intended population, as participants had significant symptoms at baseline (mean ACQ6 2.2) with >80% treated on GINA steps 4 or 5, treated in a 'real-world' clinical care context, and in a pragmatic design giving a high recruitment rate. Further, we were able to reach the calculated power, and finally analyzed the effect using ITT principles known to decrease risk of bias.

Adverse events are rare in breathing control interventions; however, they might not have been systemically reported in all studies.[70,72,82] However, in recent studies such as the BREATHE-study[47] adverse events data were systematically collected, and we have adopted a similar rigorous system for collection of potential harms in Study 3. (Appendix E-S9) A theoretical basis for concerns for BrEX causing asthma worsening or non-asthma AEs is not apparent, as the intervention focuses on breathing control and normalisation of the breathing pattern, and does not result in stress to the cardio-respiratory system as in physical exercise interventions. The attendance rate was high (>80%) as were the ratings of adherence to home exercise (>75% rated 'good' or 'excellent', Appendix E-S8b Table), which suggests that the BrEX intervention used was well-accepted and practiced by most of the allocated participants, even though this question was not formally assessed with patient interviews.

Limitations

However also limitations existed. The nature of the intervention prohibited blinding of participants. When patients are given attention from a health care professional, the effect on experienced QoL may improve therefore a possible bias existed by the unequal duration of the procedures in the two study arms. However, the between-group difference were similar in studies on BrEX in mild-moderate asthma with and without the use of 'sham' procedures (patient education) in the control arm.[47,60,73] This suggests that the BrEX effect on MiniAQLQ is primarily delivered by content

rather than simple attention from a health care professional. Furthermore, the design mitigated bias due to all-kind contact effects as all participants continued their medical treatment contact i.e., the usual care.

This thesis is basically a thesis investigating the hypothesis that BrEX are beneficial for patients with impaired asthma control, and did not attempt to validate a priori a diagnosis of dysfunctional breathing, for the reasons made above.
We chose an asthma-related inclusion criterion (ACQ6 ≤0.8), as it has been shown that NQ is a poor discriminator of who will benefit of BrEX in an asthma population with impaired control.[61] As discussed earlier, no current test or questionnaire can accurately diagnose DB in patients with asthma. Indeed, in the pilot study, 12 out of 30 excluded patients were otherwise eligible but excluded due to NQ-score. Ideally, a test, questionnaire, or biomarker can reliably identify the patients with optimal response to a given asthma treatment, such as eosinophilia and corticosteroid treatment response. However, no such biomarker is currently available to predict response to BrEX other than the non-specific marker of ongoing impaired control despite apparently adequate pharmacotherapy, although future studies may identify more specific biomarkers (e.g., non-invasive assessments of respiratory patterns) to allow care-givers to provide personalized medicine.

Several efforts to lower risk of bias were made: blinded data-collection, double data entry of objective outcomes, and blinded data analyses. Unwillingly, I was exposed to group sizes thereby able to distinguish them, therefor my supervisors (UBT, MT, and STS) prepared the blinded interpretation[91] of results as they were all blinded to group assignment.
The trial involved many physiotherapists, nurses and doctors employed at eight different centres, thus there was a risk of heterogeneous data reporting. I have performed analyses un-adjusted for 'centres' (not shown) without any change in trial outcomes.
I consider that the results of my pragmatic multicentre trial carry a high external validity.

Efforts to improve recruitment speed
Recruitment was initiated at five hospitals between April and July 2017 with an anticipated recruitment of 220 participants within 14 months. However, by September 2017 the recruitment rate was lower than expected. Besides continuous support to study staff members, I did the following to improve recruitment throughout the course of trial:

- I gave repeated introductions to medical doctors and nurses at all clinics at staff meetings with written information on project aim and inclusion criteria
- I gave supervision-visits at all hospitals each month for the first 6 months, and then less frequently
- I forwarded a BEAT DB-trial Newsletter for staff and head of departments every or every second month
- I presented the BEAT DB-trial at the Nordic Congress for Cardiac and Respiratory Physiotherapists March 2017, at Danish Association of Physiotherapy Congress April 2018, and at several research meetings
- I visited additional hospitals to encourage inclusion as BEAT DB-trial centre and succeeded recruiting:
    - Allegy and Lung Clinic, Elsinore (*Allergi og lungeklinikken, Helsingør*, private clinic), Capital Region, March 2018
    - Regional Hospital Silkeborg (RSI), Region Mid, November 2018
    - Odense University Hospital (OUH), Region South, February 2019

  (but not Vejle Hospital (Spring 2017) or Aarhus University Hospital (Spring 2018)).

Furthermore, in January 2018 the supervisor group and I agreed to adjust the inclusion criterion of the ACQ6 ≥1.5 to ≥0.8 to allow inclusion of patients with lower symptom level, however still excludes patients with mild or absent symptoms.
We recalculated sample size in Maj 2019. Both actions were reported in study protocol.[85]
(See Paper I)

Challenge in measuring physical activity
Limited access to SenseWear® sensors was a barrier for achieving complete activity data. However, we included the tool to explore any signal suggesting that those improving in MiniAQLQ also became increasingly physical active during the trial. The MID in steps per day have not been estimated in an asthma-population, but in a COPD-population MID is estimated to 599.[136] Our investigation was not powered to find significant results in physical activity, and steps per day data were only available in 93 participants. However, it is unlikely that the result would exceed 599 steps per day, using the MID from COPD. No (MiniAQLQ) responder investigation have been made yet.

We excluded participants with <6 valid days of SenseWear data, being more restrictive than other researchers in physical activity in asthma, who included participants with 4-5 valid days.[137,138] Similarly, in COPD, researchers were less restrictive, investigating participants with 3-5 valid days.[136,139,140] It is easier to keep up an enthusiastic but 'un-natural' elevated level of physical activity for a few days than for a longer period. Therefor the decision was made to investigate the participants with ≥ 6 days of data, expecting a more normal level of physical activity.

COVID-19 challenges

Mid-March 2020, Denmark locked down like many other countries throughout Europa due to the COVID-19 pandemic. This affected 12 participants who had their 6-month follow-up cancelled. They were able and willing to complete the trial questionnaires including the primary outcome of MiniAQLQ online.

The local establishment of a COVID-19 ward implied transfer of central study staff, delaying data registration and entry of comorbidity, health-care and medication use.

All in all, the BEAT DB-trial was delayed a few months but not severely affected by the COVID-19 pandemic.

CONCLUSION

Conclusions & Implications for clinical practice

This thesis provides the first RCT-based evidence that physiotherapy - provided as *breathing exercises* - improves asthma-specific QoL in patients with incompletely controlled moderate-to-severe asthma in secondary care setting. This finding is in perfect conjunction with previous findings in patients with mild-to-moderate asthma in a primary care setting. Furthermore, the thesis provides a contemporary description of the intervention, following the TIDieR recommendation and presented in a published protocol paper prior to finishing the RCT. Breathing exercises was safe and well-tolerated and was delivered using only three visits to a physiotherapist.

The role of impairment of asthma control and symptoms from dysfunctional breathing in this population was supported by regression analyses of factors associated with asthma-specific QoL. Asthma control was consistently and independently associated with impaired asthma-specific QoL, however asthma-specific QoL was not fully explained by asthma control. Additionally, using different models, dysfunctional breathing and anxiety were independently associated with impaired asthma-specific QoL, whereas having high income was independently protective against poor asthma-specific QoL.

This suggests that asthma-specific QoL contributes with unique and relevant information in the assessment of asthma, which usually is based on phenotype, asthma control, and asthma severity. Furthermore, it supports the role of *treatable traits* in obstructive lung disease, and that the *treatable traits* tools list now can include *breathing exercises* in patients with incompletely controlled asthma regardless of asthma severity.

Perspectives

Implementation of results

The UK BREATHE study found equal impact of *breathing exercises* provided by a physiotherapist live or by DVD. Different patients might have different preferences, but easy access to digital material (DVD or online) would clearly facilitate the dissemination of the presented intervention. Many countries (including Denmark) do not have a tradition of involving physiotherapists in asthma at any stage, so there is an obvious need for education of physiotherapists, and for integration of physiotherapy in asthma care. *Breathing exercises* is already mentioned in the GINA strategy paper (2020 update) but without definition of the patient population, however it has importance that next update explicitly will define that *breathing exercises* are recommended despite severity as this paper has immense impact on national asthma guidelines.

Implications for future research

Recently, systematic evaluation of difficult-to-treat asthma has been shown to impact key individual and societal outcomes. The current thesis supports the *treatable traits approach*, which is not yet an evidence-based intervention. However, it appears promising to identify potentially amenable factors affecting our patients' disease control, mental health and/or the quality of the life.

Long-term (>12-month) effects of *breathing exercises* have not yet been described, and thus it is unknown whether 'brush-up' courses by DVD or physiotherapists can prolong the 6-month effect observed in this trial. The biomechanical mechanisms of *breathing exercises* are not clarified, and it is unknown whether a few elements drive the effect, or whether new elements would be valuable to improve the current intervention.

Possibly, future research will identify which patients who are most likely to benefit from *breathing exercises*, and if the patients would benefit from a larger living-with-asthma improving programme where *breathing exercises* is merely one of many interventions.

I do hope that this is just the beginning of a new era, where asthma patients are treated by a multidisciplinary group.

References

1. Papaioannou AI, Kostikas K, Zervas E, Kolilekas L, Papiris S, Gaga M. Control of asthma in real life: still a valuable goal? *Eur Respir Rev*. 2015;24(136):361-369. doi:10.1183/16000617.00001615

2. Global_Initiative_For_Asthma. GINA, Global Initiative for Asthma. Global strategy for asthma management and prevention, 2019. www.ginasthma.org. Published 2019. Accessed May 6, 2020. https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf

3. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *The Lancet*. 2018;391(10122):783-800. doi:10.1016/S0140-6736(17)33311-1

4. Wu AC, Greenberger PA. Asthma: Overdiagnosed, Underdiagnosed, and Ineffectively Treated. *Journal of Allergy and Clinical Immunology In Practice; Amsterdam*. 2018;6(3):801-802. doi:http://dx.doi.org/10.1016/j.jaip.2018.02.023

5. Foster JM, McDonald VM, Guo M, Reddel HK. "I have lost in every facet of my life": the hidden burden of severe asthma. *European Respiratory Journal*. 2017;50(3). doi:10.1183/13993003.00765-2017

6. Reddel HK, Taylor DR, Bateman ED, et al. An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations: Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. *Am J Respir Crit Care Med*. 2009;180(1):59-99. doi:10.1164/rccm.200801-060ST

7. Sims EJ, Price D, Haughney J, Ryan D, Thomas M. Current control and future risk in asthma management. *Allergy Asthma Immunol Res*. 2011;3(4):217-225. doi:10.4168/aair.2011.3.4.217

8. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338. doi:10.1183/09031936.05.00034805

9. Backer V, Sverrild A, Ulrik CS, Bødtger U, Seersholm N, Porsbjerg C. Diagnostic work-up in patients with possible asthma referred to a university hospital. *European Clinical Respiratory Journal*. 2015;2(1):27768. doi:10.3402/ecrj.v2.27768

10. Janson C, Accordini S, Cazzoletti L, et al. Pharmacological treatment of asthma in a cohort of adults during a 20-year period: results from the European Community Respiratory Health Survey I, II and III. *ERJ Open Res*. 2019;5(1):00073-02018. doi:10.1183/23120541.00073-2018

11. Cazzoletti L, Marcon A, Janson C, et al. Asthma control in Europe: A real-world evaluation based on an international population-based study. *Journal of Allergy and Clinical Immunology*. 2007;120(6):1360-1367. doi:10.1016/j.jaci.2007.09.019

12. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902-907. doi:10.1034/j.1399-3003.1999.14d29.x

13. Juniper EF, Svensson K, Mörk A-C, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005;99(5):553-558. doi:10.1016/j.rmed.2004.10.008

14. Schatz M, Sorkness CA, Li JT, et al. Asthma Control Test: Reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *Journal of Allergy and Clinical Immunology*. 2006;117(3):549-556. doi:10.1016/j.jaci.2006.01.011

15. Juniper EF, Bousquet J, Abetz L, Bateman ED, GOAL Committee. Identifying "well-controlled" and "not well-controlled" asthma using the Asthma Control Questionnaire. *Respir Med*. 2006;100(4):616-621. doi:10.1016/j.rmed.2005.08.012

16. Taylor DR, Bateman ED, Boulet L-P, et al. A new perspective on concepts of asthma severity and control. *Eur Respir J*. 2008;32(3):545-554. doi:10.1183/09031936.00155307

17. Currie GP, Douglas JG, Heaney LG. Difficult to treat asthma in adults. *BMJ*. 2009;338(feb24 1):b494-b494. doi:10.1136/bmj.b494

18. Denton E, Hore-Lacy F, Radhakrishna N, et al. Severe Asthma Global Evaluation (SAGE): An Electronic Platform for Severe Asthma. *J Allergy Clin Immunol Pract*. 2019;7(5):1440-1449. doi:10.1016/j.jaip.2019.02.042

19. Porsbjerg C, Ulrik C, Skjold T, et al. Nordic consensus statement on the systematic assessment and management of possible severe asthma in adults. *Eur Clin Respir J*. 2018;5(1):1440868. doi:10.1080/20018525.2018.1440868

20. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax*. 2014;69 Suppl 1:1-192.

21. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343-373. doi:10.1183/09031936.00202013

22. Barker N, Everard ML. Getting to grips with "dysfunctional breathing." *Paediatr Respir Rev*. 2015;16(1):53-61. doi:10.1016/j.prrv.2014.10.001

23. Depiazzi J, Everard ML. Dysfunctional breathing and reaching one's physiological limit as causes of exercise-induced dyspnoea. *Breathe (Sheff)*. 2016;12(2):120-129. doi:10.1183/20734735.007216

24. Chung KF, Godard P, Adelroth E, et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society. *Eur Respir J*. 1999;13(5):1198-1208. doi:10.1034/j.1399-3003.1999.13e43.x

25. Luskin AT, Chipps BE, Rasouliyan L, Miller DP, Haselkorn T, Dorenbaum A. Impact of asthma exacerbations and asthma triggers on asthma-related quality of life in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol Pract*. 2014;2(5):544-552.e1-2. doi:10.1016/j.jaip.2014.02.011

26. Bateman ED, Bousquet J, Keech ML, Busse WW, Clark TJH, Pedersen SE. The correlation between asthma control and health status: the GOAL study. *Eur Respir J*. 2007;29(1):56-62. doi:10.1183/09031936.00128505

27. Sousa JC de, Pina A, Cruz AM, et al. Asthma control, quality of life, and the role of patient enablement: a cross-sectional observational study. *Prim Care Respir J*. 2013;22(2):181-187. doi:10.4104/pcrj.2013.00037

28. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. *Chest*. 1999;115(5):1265-1270. doi:10.1378/chest.115.5.1265

29. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J*. 1999;14(1):32-38. doi:10.1034/j.1399-3003.1999.14a08.x

30. Lee E-H, Kim S-H, Choi J-H, Jee Y-K, Nahm D-H, Park H-S. Development and evaluation of an Asthma-Specific Quality of Life (A-QOL) questionnaire. *J Asthma*. 2009;46(7):716-721. doi:10.1080/02770900903067887

31. Stucky BD, Edelen MO, Sherbourne CD, Eberhart NK, Lara M. Developing an item bank and short forms that assess the impact of asthma on quality of life. *Respir Med*. 2014;108(2):252-263. doi:10.1016/j.rmed.2013.12.008

32. Eberhart NK, Sherbourne CD, Edelen MO, Stucky BD, Sin NL, Lara M. Development of a measure of asthma-specific quality of life among adults. *Qual Life Res*. 2014;23(3):837-848. doi:10.1007/s11136-013-0510-x

33. Ehrs P-O, Nokela M, Ställberg B, Hjemdahl P, Wikström Jonsson E. Brief questionnaires for patient-reported outcomes in asthma: validation and usefulness in a primary care setting. *Chest*. 2006;129(4):925-932. doi:10.1378/chest.129.4.925

34. Andreasson KH, Skou ST, Porsbjerg C, Veidal S, Bødtger U. [Dysfunctional breathing in patients with asthma]. *Ugeskr Laeg*. 2017;179(2).

35. McDonald VM, Osadnik CR, Gibson PG. Treatable traits in acute exacerbations of chronic airway diseases. *Chron Respir Dis*. 2019;16:147997311986795. doi:10.1177/1479973119867954

36. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *European Respiratory Journal*. 2016;47(2):410-419. doi:10.1183/13993003.01359-2015

37. Papaioannou AI, Diamant Z, Bakakos P, Loukides S. Towards precision medicine in severe asthma: Treatment algorithms based on treatable traits. *Respiratory Medicine*. 2018;142:15-22. doi:10.1016/j.rmed.2018.07.006

38. Tay TR, Hew M. Comorbid "treatable traits" in difficult asthma: Current evidence and clinical evaluation. *Allergy*. 2018;73(7):1369-1382. doi:10.1111/all.13370

39. Ulrik CS, Vijverberg S, Hanania NA, Diamant Z. Precision medicine and treatable traits in chronic airway diseases - where do we stand? *Current Opinion in Pulmonary Medicine*. 2020;26(1):33-39. doi:10.1097/MCP.0000000000000639

40. McDonald VM, Clark VL, Cordova-Rivera L, Wark PAB, Baines KJ, Gibson PG. Targeting treatable traits in severe asthma: a randomised controlled trial. *Eur Respir J*. 2020;55(3):1901509. doi:10.1183/13993003.01509-2019

41. Veidal S, Jeppegaard M, Sverrild A, Backer V, Porsbjerg C. The impact of dysfunctional breathing on the assessment of asthma control. *Respiratory Medicine*. 2017;123:42-47. doi:10.1016/j.rmed.2016.12.008

42. Courtney R. Breathing training for dysfunctional breathing in asthma: taking a multidimensional approach. ERJ open research. doi:10.1183/23120541.00065-2017

43. Scott KM, Von Korff M, Ormel J, et al. Mental disorders among adults with asthma: results from the World Mental Health Survey. *General Hospital Psychiatry*. 2007;29(2):123-133. doi:10.1016/j.genhosppsych.2006.12.006

44. Ali Z, Ulrik CS. Obesity and asthma: a coincidence or a causal relationship? A systematic review. *Respir Med*. 2013;107(9):1287-1300. doi:10.1016/j.rmed.2013.03.019

45. Connett GJ, Thomas M. Dysfunctional Breathing in Children and Adults With Asthma. *Front Pediatr*. 2018;6:406. doi:10.3389/fped.2018.00406

46. Hagman C, Janson C, Emtner M. A comparison between patients with dysfunctional breathing and patients with asthma: Dysfunctional breathing versus asthma. *The Clinical Respiratory Journal*. 2008;2(2):86-91. doi:10.1111/j.1752-699X.2007.00036.x

47. Bruton A, Lee A, Yardley L, et al. Physiotherapy breathing retraining for asthma: a randomised controlled trial. *Lancet Respir Med*. 2018;6(1):19-28. doi:10.1016/S2213-2600(17)30474-5

48. Thomas M, Bruton A. Breathing exercises for asthma. *Breathe*. 2014;10(4):312-322. doi:10.1183/20734735.008414

49. van Dixhoorn J, Folgering H. The Nijmegen Questionnaire and dysfunctional breathing. *ERJ Open Res*. 2015;1(1). doi:10.1183/23120541.00001-2015

50. Brannan JD, Kippelen P. Bronchial Provocation Testing for the Identification of Exercise-Induced Bronchoconstriction. *The Journal of Allergy and Clinical Immunology: In Practice*. 2020;8(7):2156-2164. doi:10.1016/j.jaip.2020.03.034

51. Thomas M, McKinley RK, Freeman E, Foy C, Price D. The prevalence of dysfunctional breathing in adults in the community with and without asthma. *Primary Care Respiratory Journal*. 2005;14(2):78-82. doi:10.1016/j.pcrj.2004.10.007

52. Sedeh FB, Von Bülow A, Backer V, et al. The impact of dysfunctional breathing on the level of asthma control in difficult asthma. *Respir Med*. 2020;163:105894. doi:10.1016/j.rmed.2020.105894

53. Vidotto LS, Carvalho CRF de, Harvey A, Jones M. Dysfunctional breathing: what do we know? *J Bras Pneumol*. 2019;45(1):e20170347. doi:10.1590/1806-3713/e20170347

54. World Health Organization. International Classification of Diseases and Related Health Problems (ICD-10). https://icd.who.int/browse10/2019/en#/R06

55. West JB, Luks A. *West's Respiratory Physiology: The Essentials*. Tenth edition. Wolters Kluwer; 2016.

56. Howell JB. The hyperventilation syndrome: a syndrome under threat? *Thorax*. 1997;52 Suppl 3:S30-34. doi:10.1136/thx.52.2008.s30

57. Boulding R, Stacey R, Niven R, Fowler SJ. Dysfunctional breathing: a review of the literature and proposal for classification. *Eur Respir Rev*. 2016;25(141):287-294. doi:10.1183/16000617.0088-2015

58. Prys-Picard CO, Kellett F, Niven RM. Disproportionate breathlessness associated with deep sighing breathing in a patient presenting with difficult-to-treat asthma. *Chest*. 2006;130(6):1723-1725. doi:10.1378/chest.130.6.1723

59. Veidal S, Jeppegaard M, Sverrild A, Backer V, Porsbjerg C. The impact of dysfunctional breathing on the assessment of asthma control. *Respir Med*. 2017;123:42-47. doi:10.1016/j.rmed.2016.12.008

60. Thomas M, McKinley RK, Freeman E, Foy C, Prodger P, Price D. Breathing retraining for dysfunctional breathing in asthma: a randomised controlled trial. *Thorax*. 2003;58(2):110-115. doi:10.1136/thorax.58.2.110

61. Thomas M, Bruton A, Ainsworth B. Use of the Nijmegen Questionnaire in asthma. *ERJ Open Res*. 2015;1(1). doi:10.1183/23120541.00033-2015

62. van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. *J Psychosom Res*. 1985;29(2):199-206. doi:10.1016/0022-3999(85)90042-x

63. Courtney R, Greenwood KM, Cohen M. Relationships between measures of dysfunctional breathing in a population with concerns about their breathing. *Journal of Bodywork and Movement Therapies*. 2011;15(1):24-34. doi:10.1016/j.jbmt.2010.06.004

64. Todd S, Walsted Es, Grillo L, Livingston R, Menzies-Gow A, Hull Jh. Novel Assessment Tool to Detect Breathing Pattern Disorder in Patients With Refractory Asthma. Respirology (Carlton, Vic.). doi:10.1111/resp.13173

65. Murray JF. The Ketchup-Bottle Method. *N Engl J Med*. 1979;300(20):1155-1157. doi:10.1056/NEJM197905173002008

66. Bott J, Blumenthal S, Buxton M, et al. Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. *Thorax*. 2009;64(Suppl 1):i1-i52. doi:10.1136/thx.2008.110726

67. Bruurs MLJ, van der Giessen LJ, Moed H. The effectiveness of physiotherapy in patients with asthma: A systematic review of the literature. *Respiratory Medicine*. 2013;107(4):483-494. doi:10.1016/j.rmed.2012.12.017

68. Shei R-J, Paris HLR, Wilhite DP, Chapman RF, Mickleborough TD. The role of inspiratory muscle training in the management of asthma and exercise-induced bronchoconstriction. *Phys Sportsmed*. 2016;44(4):327-334. doi:10.1080/00913847.2016.1176546

69. Freitas DA, Holloway EA, Bruno SS, Chaves GS, Fregonezi GA, Mendonça KM. Breathing exercises for adults with asthma. Cochrane Airways Group, ed. *Cochrane Database of Systematic Reviews*. Published online October 1, 2013. doi:10.1002/14651858.CD001277.pub3

70. Santino TA, Chaves GS, Freitas DA, Fregonezi GA, Mendonça KM. Breathing exercises for adults with asthma. *Cochrane Database Syst Rev*. 2020;3:CD001277. doi:10.1002/14651858.CD001277.pub4

71. Tehrany R, DeVos R, Bruton A. Breathing pattern recordings using respiratory inductive plethysmography, before and after a physiotherapy breathing retraining program for asthma: A case report. *Physiotherapy Theory and Practice*. 2018;34(4):329-335. doi:10.1080/09593985.2017.1400139

72. Holloway Ea, West Rj. Integrated Breathing and Relaxation Training (The Papworth Method) for Adults With Asthma in Primary Care: A Randomised Controlled Trial. Thorax. doi:10.1136/thx.2006.076430

73. Thomas M, McKinley RK, Mellor S, et al. Breathing exercises for asthma: a randomised controlled trial. *Thorax*. 2009;64(1):55-61. doi:10.1136/thx.2008.100867

74. Burgess J, Ekanayake B, Lowe A, Dunt D, Thien F, Dharmage SC. Systematic review of the effectiveness of breathing retraining in asthma management. *Expert Rev Respir Med*. 2011;5(6):789-807. doi:10.1586/ers.11.69

75. Cowie RL, Conley DP, Underwood MF, Reader PG. A randomised controlled trial of the Buteyko technique as an adjunct to conventional management of asthma. *Respiratory Medicine*. 2008;102(5):726-732. doi:10.1016/j.rmed.2007.12.012

76. Bruton A, Lewith GT. The Buteyko breathing technique for asthma: a review. *Complement Ther Med*. 2005;13(1):41-46. doi:10.1016/j.ctim.2005.01.003

77. Patel AS, Watkin G, Willig B, et al. Improvement in health status following cough-suppression physiotherapy for patients with chronic cough. *Chron Respir Dis*. 2011;8(4):253-258. doi:10.1177/1479972311422547

78. Chamberlain Mitchell SAF, Ellis J, Ludlow S, Pandyan A, Birring SS. Non-pharmacological interventions for chronic cough: The past, present and future. *Pulmonary Pharmacology & Therapeutics*. 2019;56:29-38. doi:10.1016/j.pupt.2019.02.006

79. Thomas M, Bruton A, Little P, et al. A randomised controlled study of the effectiveness of breathing retraining exercises taught by a physiotherapist either by instructional DVD or in

face-to-face sessions in the management of asthma in adults. *Health Technol Assess*. 2017;21(53):1-162. doi:10.3310/hta21530

80. Arden-Close E, Yardley L, Kirby S, Thomas M, Bruton A. Patients' experiences of breathing retraining for asthma: a qualitative process analysis of participants in the intervention arms of the BREATHE trial. *NPJ Prim Care Respir Med*. 2017;27(1):56. doi:10.1038/s41533-017-0055-5

81. Arden-Close EJ, Kirby SE, Yardley L, Bruton A, Ainsworth B, Thomas DM. Evaluation of a breathing retraining intervention to improve quality of life in asthma: quantitative process analysis of the BREATHE randomized controlled trial. *Clin Rehabil*. 2019;33(7):1139-1149. doi:10.1177/0269215519832942

82. Grammatopoulou EP, Skordilis EK, Stavrou N, et al. The Effect of Physiotherapy-Based Breathing Retraining on Asthma Control. *Journal of Asthma*. 2011;48(6):593-601. doi:10.3109/02770903.2011.587583

83. Hagman C, Janson C, Emtner M. Breathing retraining - A five-year follow-up of patients with dysfunctional breathing. *Respiratory Medicine*. 2011;105(8):1153-1159. doi:10.1016/j.rmed.2011.03.006

84. Jones M, Troup F, Nugus J, et al. Does manual therapy provide additional benefit to breathing retraining in the management of dysfunctional breathing? A randomised controlled trial. *Disability and Rehabilitation*. 2015;37(9):763-770. doi:10.3109/09638288.2014.941020

85. Andreasson KH, Skou ST, Ulrik CS, et al. Protocol for a multicentre randomised controlled trial to investigate the effect on asthma-related quality of life from breathing retraining in patients with incomplete asthma control attending specialist care in Denmark. *BMJ Open*. 2019;9(12):e032984. doi:10.1136/bmjopen-2019-032984

86. Chan A-W, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;346(jan08 15):e7586-e7586. doi:10.1136/bmj.e7586

87. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ*. 2014;348:g1687. doi:10.1136/bmj.g1687

88. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med*. 2007;4(10):e297. doi:10.1371/journal.pmed.0040297

89. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010;63(8):e1-37. doi:10.1016/j.jclinepi.2010.03.004

90. Järvinen TLN, Sihvonen R, Bhandari M, et al. Blinded interpretation of study results can feasibly and effectively diminish interpretation bias. *J Clin Epidemiol*. 2014;67(7):769-772. doi:10.1016/j.jclinepi.2013.11.011

91. Bodtger U, Skou ST, Thomas M, Andreasson (ed) KH. Blinded review of the primary endpoint results from the BEAT DB-trial: Blinded review and interpretation. Published online June 2020. https://portal.findresearcher.sdu.dk/da/publications/blinded-review-of-the-primary-endpoint-results-from-the-beat-db-t

92. Bruton A, Kirby S, Arden-Close E, et al. The BREATHE study: Breathing REtraining for Asthma — Trial of Home Exercises. A protocol summary of a randomised controlled trial. *Primary Care Respiratory Journal*. 2013;22(2):PS1-PS7. doi:10.4104/pcrj.2013.00047

93. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370. doi:10.1111/j.1600-0447.1983.tb09716.x

94. Kamper SJ, Ostelo RWJG, Knol DL, Maher CG, de Vet HCW, Hancock MJ. Global Perceived Effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. *J Clin Epidemiol*. 2010;63(7):760-766.e1. doi:10.1016/j.jclinepi.2009.09.009

95. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res*. 2013;22(7):1717-1727. doi:10.1007/s11136-012-0322-4

96. Borg E, Borg G, Larsson K, Letzter M, Sundblad B-M. An index for breathlessness and leg fatigue. *Scand J Med Sci Sports*. 2010;20(4):644-650. doi:10.1111/j.1600-0838.2009.00985.x

97. Office of the FDA, U.S. Food & Drug Administration. What is a Serious Adverse Event? *FDA*. Published online January 8, 2019. Accessed May 10, 2020. https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event

98. Andreasson, KH, Andreasson, TH, Ulrik, CS, et al. Inter-rater reliability of a novel algorithm to calculate Global Initiative for Asthma (GINA) treatment steps. In: *(Accepted Scientific Abstract for ERS Congress 2020)*. ; 2020:1 (abstr).

99. Holland AE, Spruit MA, Singh SJ. How to carry out a field walking test in chronic respiratory disease. *Breathe (Sheff)*. 2015;11(2):128-139. doi:10.1183/20734735.021314

100. Brazeau A-S, Beaudoin N, Bélisle V, Messier V, Karelis AD, Rabasa-Lhoret R. Validation and reliability of two activity monitors for energy expenditure assessment. *J Sci Med Sport*. 2016;19(1):46-50. doi:10.1016/j.jsams.2014.11.001

101. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-1343. doi:10.1183/09031936.00080312

102. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med*. 2008;3(1):17. doi:10.1186/1751-0473-3-17

103. Trupin L, Katz PP, Balmes JR, et al. Mediators of the socioeconomic gradient in outcomes of adult asthma and rhinitis. *Am J Public Health*. 2013;103(2):e31-38. doi:10.2105/AJPH.2012.300938

104. Peters U, Dixon A, Forno E. Obesity and Asthma. *J Allergy Clin Immunol*. 2018;141(4):1169-1179. doi:10.1016/j.jaci.2018.02.004

105. Souza ECC de, Pizzichini MMM, Dias M, et al. Body mass index, asthma, and respiratory symptoms: a population-based study. *J Bras Pneumol*. 2020;46(1):e20190006. doi:10.1590/1806-3713/e20190006

106. Robinson R, Barber K, Jones G, Blakey J, Burhan H. Exploring the relationship between generalised anxiety/depression scales and asthma-specific quality of life/control questionnaires in a specialist asthma clinic. *Journal of Asthma*. Published online April 9, 2020:1-9. doi:10.1080/02770903.2020.1744640

107. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. 2003;41(5):582-592. doi:10.1097/01.MLR.0000062554.74615.4C

108. Andreasson KH, Skou ST, Petersen I, Bodtger U. Statistical Analysis Plan Breathing Exercises in Asthma Targeting Dysfunctional Breathing – the BEAT DB trial, revision — Syddansk Universitet. Accessed September 11, 2020. https://portal.findresearcher.sdu.dk/da/publications/statistical-analysis-plan-breathing-exercises-in-asthma-targeting-2

109. Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. *BMJ*. 1998;316(7132):690-693. doi:10.1136/bmj.316.7132.690

110. Thomas M, Bruton A, Moffatt M, Cleland J. Asthma and psychological dysfunction. *Prim Care Respir J*. 2011;20(3):250-256. doi:10.4104/pcrj.2011.00058

111. Stucky BD, Sherbourne CD, Edelen MO, Eberhart NK. Understanding asthma-specific quality of life: moving beyond asthma symptoms and severity. *European Respiratory Journal*. 2015;46(3):680-687. doi:10.1183/09031936.00225014

112. AL-Balushi AD, Thomas S, Marzooq DA. A Study on Quality of Life versus Asthma Control in Mild to Moderate Persistent Asthma Patients Treated at a Secondary Care Hospital in Oman. ResearchGate. Accessed August 28, 2020. https://www.researchgate.net/publication/336130502_A_Study_on_Quality_of_Life_versus_Asthma_Control_in_Mild_to_Moderate_Persistent_Asthma_Patients_Treated_at_a_Secondary_Care_Hospital_in_Oman

113. Gosavi S, Nadig P, Haran A. Factors Contributing Towards Poor Asthma Control in Patients on Regular Medication - PubMed. *J Clin Diagn Res*. 2016(Jun;10(6):):OC31-5. doi:10.7860/JCDR/2016/18670.8052

114. Chen H, Gould MK, Blanc PD, et al. Asthma control, severity, and quality of life: Quantifying the effect of uncontrolled disease. *Journal of Allergy and Clinical Immunology*. 2007;120(2):396-402. doi:10.1016/j.jaci.2007.04.040

115. Brien SB, Stuart B, Dickens AP, et al. Independent determinants of disease-related quality of life in COPD – scope for nonpharmacologic interventions? *Int J Chron Obstruct Pulmon Dis*. 2018;13:247-256. doi:10.2147/COPD.S152955

116. Denton E, Bondarenko J, Tay T, et al. Factors Associated with Dysfunctional Breathing in Patients with Difficult to Treat Asthma. *J Allergy Clin Immunol Pract*. 2019;7(5):1471-1476. doi:10.1016/j.jaip.2018.11.037

117. Quanjer PH, Pretto JJ, Brazzale DJ, Boros PW. Grading the severity of airways obstruction: new wine in new bottles. *European Respiratory Journal*. 2014;43(2):505-512. doi:10.1183/09031936.00086313

118. Lavoie KL, Boudreau M, Plourde A, Campbell TS, Bacon SL. Association Between Generalized Anxiety Disorder and Asthma Morbidity: *Psychosomatic Medicine*. 2011;73(6):504-513. doi:10.1097/PSY.0b013e318222e9fc

119. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med*. 2006;100(4):648-657. doi:10.1016/j.rmed.2005.08.001

120. Altman DG, Vergouwe Y, Royston P, Moons KGM. Prognosis and prognostic research: validating a prognostic model. *BMJ*. 2009;338(may28 1):b605-b605. doi:10.1136/bmj.b605

121. Azen R, Budescu DV. The dominance analysis approach for comparing predictors in multiple regression. *Psychological Methods*. 2003;8(2):129-148. doi:10.1037/1082-989X.8.2.129

122. Levy Ml, Thomas M, Small I, Pearce L, Pinnock H, Stephenson P. Summary of the 2008 BTS/SIGN British Guideline on the management of asthma. Primary care respiratory journal : journal of the General Practice Airways Group. doi:10.3132/pcrj.2008.00067

123. King MT. A point of minimal important difference (MID): a critique of terminology and methods. *Expert Rev Pharmacoecon Outcomes Res*. 2011;11(2):171-184. doi:10.1586/erp.11.9

124. Bateman ED, Esser D, Chirila C, et al. Magnitude of effect of asthma treatments on Asthma Quality of Life Questionnaire and Asthma Control Questionnaire scores: Systematic review and network meta-analysis. *J Allergy Clin Immunol*. 2015;136(4):914-922. doi:10.1016/j.jaci.2015.03.023

125. Waters L, Reeves M, Fjeldsoe B, Eakin E. Control Group Improvements in Physical Activity Intervention Trials and Possible Explanatory Factors: A Systematic Review. *Journal of Physical Activity and Health*. 2012;9(6):884-895. doi:10.1123/jpah.9.6.884

126. Toennesen LL, Meteran H, Hostrup M, et al. Effects of Exercise and Diet in Nonobese Asthma Patients-A Randomized Controlled Trial. *J Allergy Clin Immunol Pract*. 2018;6(3):803-811. doi:10.1016/j.jaip.2017.09.028

127. Hansen ESH, Pitzner-Fabricius A, Toennesen LL, et al. Effect of aerobic exercise training on asthma in adults: a systematic review and meta-analysis. *Eur Respir J*. 2020;56(1). doi:10.1183/13993003.00146-2020

128. Pitzner-Fabricius A, Toennesen LL, Backer V. Can training induce inflammatory control in asthma, or is it symptom control only? *Curr Opin Pulm Med*. 2020;26(1):56-61. doi:10.1097/MCP.0000000000000648

129. Ulrik CS. Asthma and obesity: is weight reduction the key to achieve asthma control? *Curr Opin Pulm Med*. 2016;22(1):69-73. doi:10.1097/MCP.0000000000000226

130. Okoniewski W, Lu KD, Forno E. Weight Loss for Children and Adults with Obesity and Asthma. A Systematic Review of Randomized Controlled Trials. *Annals ATS*. 2019;16(5):613-625. doi:10.1513/AnnalsATS.201810-651SR

131. Williams MT, Johnston KN, Paquet C. Cognitive Behavioral Therapy for People with Chronic Obstructive Pulmonary Disease: Rapid Review. *COPD*. 2020;Volume 15:903-919. doi:10.2147/COPD.S178049

132. Lavoie KL, Bouthillier D, Bacon SL, et al. Psychologic Distress and Maladaptive Coping Styles in Patients With Severe vs Moderate Asthma. *Chest*. 2010;137(6):1324-1331. doi:10.1378/chest.09-1979

133. Dafauce L, Romero D, Carpio C, et al. Psycho-demographic profile in severe asthma and effect of emotional mood disorders and hyperventilation syndrome on quality of life. *BMC Psychol*. 2021;9(1):3. doi:10.1186/s40359-020-00498-y

134. World Health Organization. Rational use of medicines: progress in implementing the WHO medicines strategy. Published online May 11, 2006. https://apps.who.int/gb/ebwha/pdf_files/EB118/B118_6-en.pdf

135. Löwhagen O, Bergqvist P. Physiotherapy in Asthma Using the New Lotorp Method. Complementary therapies in clinical practice. doi:10.1016/j.ctcp.2014.07.004

136. Demeyer H, Burtin C, Hornikx M, et al. The Minimal Important Difference in Physical Activity in Patients with COPD. Subramanian SK, ed. *PLoS ONE*. 2016;11(4):e0154587. doi:10.1371/journal.pone.0154587

137. Bahmer T, Waschki B, Schatz F, et al. Physical activity, airway resistance and small airway dysfunction in severe asthma. *Eur Respir J*. 2017;49(1):1601827. doi:10.1183/13993003.01827-2016

138. Bruno A, Uasuf CG, Insalaco G, et al. Nutritional status and physical inactivity in moderated asthmatics: A pilot study. *Medicine*. 2016;95(31):e4485. doi:10.1097/MD.0000000000004485

139. Fastenau A, van Schayck OC, Gosselink R, Aretz KC, Muris JW. Discrepancy between functional exercise capacity and daily physical activity: a cross-sectional study in patients with mild to moderate COPD. *Primary Care Respiratory Journal*. 2013;22(4):425-430. doi:10.4104/pcrj.2013.00090

140. Hansen H, Bieler T, Beyer N, et al. Supervised pulmonary tele-rehabilitation versus pulmonary rehabilitation in severe COPD: a randomised multicentre trial. *Thorax*. 2020;75(5):413-421. doi:10.1136/thoraxjnl-2019-214246

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Appendices

Appendix A

A-1	Asthma Control Questionnaire, ACQ
A-2	MiniAsthma Quality of Life Questionnaire, MiniAQLQ
A-3	Nijmegen Questionnaire, NQ

Appendix B

B-1	Preliminary results from implementation of a rare Danish physiotherapy service; Dysfunctional breathing assessment and treatment; Scientific Poster, August 2016
B-2	Statistical Analyses Plan, Breathing Exercises in Asthma Targeting Dysfunctional Breathing – the BEAT DB trial
B-3	Blinded review of the primary endpoint results from the BEAT DB-trial

Appendix C

C-1	Paper I **Protocol for a multicentre randomised controlled trial to investigate the effect on asthma-related quality of life from breathing retraining in patients with incomplete asthma control attending specialist care in Denmark**
C-S1	Supplementary online material: Trial information Protocol BrEX Description 12 item interview list

Appendix D

D-1	Study 2 manuscript, pre-submission **Factors associated with asthma-specific quality of life: a cross sectional analysis of 193 patients with moderate-to-severe asthma**
D-2	Supplementary online material: Types and frequency of comorbidities in included participants

Appendix E

E-1	Study 3, manuscript, submitted **Breathing exercises for asthma patients in specialist care - a multicentre randomised trial**
E-S1-11	Extended supplementary material: BrEX Booklet (in Danish) Tables and figures related to the manuscript

Appendices A

Appendix A-1 Asthma Control Questionnaire

Developed by E.F. Juniper, P.M. O'Byrne, G.H. Guyatt, P.J. Ferrie, D.R. King.
Eur Respir J 1999; 14: 902-907

Appendix

ASTHMA CONTROL QUESTIONNAIRE©

Please answer questions 1–6.

Circle the number of the response that best describes how you have been during the past week

1. On average, during the past week, how often were you **woken by your asthma** during the night?	0	Never
	1	Hardly ever
	2	A few minutes
	3	Several times
	4	Many times
	5	A great many times
	6	Unable to sleep because of asthma
2. On average, during the past week, how **bad were your asthma symptoms when you woke** up in the morning?	0	No symptoms
	1	Very mild symptoms
	2	Mild symptoms
	3	Moderate symptoms
	4	Quite severe symptoms
	5	Severe symptoms
	6	Very severe symptoms
3. In general, during the past week, how **limited were you in your activities** because of your asthma?	0	Not limited at all
	1	Very slightly limited
	2	Slightly limited
	3	Moderately limited
	4	Very limited
	5	Extremely limited
	6	Totally limited
4. In general, during the past week, how much **shortness of breath** did you experience because of you asthma?	0	None
	1	A very little
	2	A little
	3	A moderate amount
	4	Quite a lot
	5	A great deal
	6	A very great deal
5. In general, during the past week, how much of the time did you **wheeze**?	0	Not at all
	1	Hardly any of the time
	2	A little of the time
	3	A moderate amount of the time
	4	A lot of the time
	5	Most of the time
	6	All the time
6. On average, during the past week, how many **puffs of short-acting bronchodilator** (eg. Ventolin) have you used each day?	0	None
	1	1–2 puffs most days
	2	3–4 puffs most days
	3	5–8 puffs most days
	4	9–12 puffs most days
	5	13–16 puffs most days
	6	More than 16 puffs most days
To be completed by a member of the clinic staff		
7. FEV_1 pre-bronchodilator:	0	>95% predicted
	1	95–90%
FEV_1 predicted	2	89–80%
	3	79–70%
FEV_1 % predicted	4	69–60%
	5	59–50%
(Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)	6	<50% predicted

This table was copied from: *Development and validation of a questionnaire to measure asthma control.* E.F. Juniper, P.M. O'Byrne, G.H. Guyatt, P.J. Ferrie, D.R. King. Eur Respir J 1999; 14: 902-907

Please note that the version used in BEAT DB-trial omitted item 7 i.e., ACQ6.

Appendix A-2 Mini Asthma Quality of Life Questionnaire

Developed by E.F. Juniper, G.H. Guyatt, F.M. Cox, P.J. Ferrie, D.R. King Eur Respir J 1999; 14: 32-38

Appendix 2: Mini Asthma Quality of Life Questionnaire (MiniAQLQ)©

Please complete *all* questions by circling the number that best describes how you have been during the *last 2 weeks as a result of your asthma*.
In general, how much of the time *during the last 2 weeks* did you:

		All of the time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
1. S	Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
2. En	Feel bothered by or have to avoid DUST in the environment?	1	2	3	4	5	6	7
3. Em	Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
4. S	Feel bothered by COUGHING?	1	2	3	4	5	6	7
5. Em	Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
6. S.	Experience a feeling of CHEST TIGHTNESS or CHEST HEAVINESS?	1	2	3	4	5	6	7
7. En	Feel bothered by or have to avoid CIGARETTE SMOKE in the environment?	1	2	3	4	5	6	7
8. S	Have DIFFICULTY GETTING A GOOD NIGHT'S SLEEP as a result of your asthma?	1	2	3	4	5	6	7
9. Em	Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7
10. S	Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. En	Feel bothered by or have to avoid going outside because of WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

How limited have you been during the last 2 weeks doing these activities as a result of your asthma?

		Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
12. A	STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
13. A	MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
14. A	SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
15. A	WORK-RELATED ACTIVITIES* (tasks you have to do at work)	1	2	3	4	5	6	7

*If you are not employed or self-employed, these should be tasks you have to do most days.
S: symptoms; En: environment; Em: emotions; A: activities.

This table was copied from *Development and validation of the Mini Asthma Quality of Life Questionnaire* by E.F. Juniper, G.H. Guyatt, F.M. Cox, P.J. Ferrie, D.R. King
Eur Respir J 1999; 14: 32-38

Appendix A-3 Nijmegen Questionnaire

Developed by Jan van Dixhoorn and Hans Folgering.
Journal of Psychosomatic Research, Vol 29, no. 2, p199-206, 1985

TABLE 2 | The Nijmegen Questionnaire, Please circle the number in the column that best represents what you have felt recently*.

	Never	Rarely	Sometimes	Often	Very often
Chest pain	0	1	2	3	4
Feeling tense	0	1	2	3	4
Blurred vision	0	1	2	3	4
Dizzy spells	0	1	2	3	4
Feeling confused	0	1	2	3	4
Faster or deeper breathing	0	1	2	3	4
Short of breath	0	1	2	3	4
Tight feelings in the chest	0	1	2	3	4
Bloated feeling in the stomach	0	1	2	3	4
Tingling fingers	0	1	2	3	4
Unable to breathe deeply	0	1	2	3	4
Stiff fingers or arms	0	1	2	3	4
Tight feelings round mouth	0	1	2	3	4
Cold hands or feet	0	1	2	3	4
Palpitations	0	1	2	3	4
Feelings of anxiety	0	1	2	3	4
Subtotals					
Total					

A total score of 23 or more has been used to screen for dysfunctional breathing in a UK community setting (17). Cut-off scores to detect "abnormality" will depend on a comparison with normal values in the same setting and culture in which the questionnaire is used.

This table is copied from: Dysfunctional Breathing in Children and Adults With Asthma By Gary J. Connett and Mike Thomas, Front. Pediatr. 6:406. doi: 10.3389/fped.2018.00406

Appendices B

B-1 Preliminary results from implementation of a rare Danish physiotherapy service; Dysfunctional breathing assessment and treatment (Scientific Poster, August 2016)

B-2 Statistical Analyses Plan, Breathing Exercises in Asthma Targeting Dysfunctional Breathing – the BEAT DB trial

B-3 Blinded review of the primary endpoint results from the BEAT DB-trial

Preliminary results from implementation of a rare Danish physiotherapy service; Dysfunctional breathing assessment and treatment

Karen Hjerrild Andreasson[1,2,3], Søren Thorgaard Skou[1,4], Uffe Bødtger[2,3,5].
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Background

Dysfunctional breathing (DB) is a well-established cause of dyspnoe and can exist alone or coexist with asthma.
Yet, DB is rarely diagnosed in Danish asthma clinics, and very few clinics provide treatment. The only evidence-based therapy is targeted physiotherapy.
This is the first Danish report on the implementation of a physiotherapy service for DB assessment and treatment.

Materials & Methods

Naestved Hospital has offered physiotherapy for DB since November 2015, implemented and delivered in co-operation between physiotherapists and pulmonologists.
Visit 1: The patient completes the *Nijmegen Questionnaire* (NQ; 0=best; 64=worst; >23 suggestive DB) and the respiratory pattern is evaluated.
Visit 1- up to 5 (during typically 4 months): Individual sessions on breathing exercises (nasal-diaphragmatic), including physical activity (abdominal muscle strength, aerobic exercise), and relaxation.
At home: 10 minutes exercise.
(Figure 1 and 2)

Results

(Nov. 2015 - Aug. 2016)
Evaluated for DB, N=19
Confirmed DB (NQ-Score>23), n=14
Change in NQ-score at the end of the treatment program, median = -9, n=8
(Figure 3)

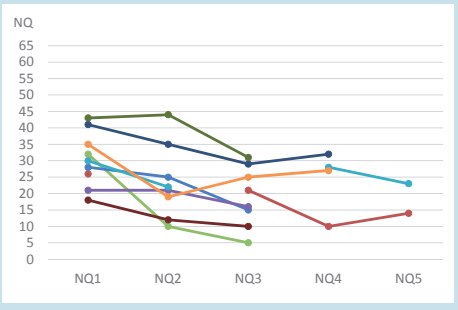

Figure 3; Effects from breathing exercises
The individual decrease in NQ-scores for patients, who has had three or more sessions.
NQ1-NQ5: The NQ-score at the beginning of each Physio-session.

Conclusions

A physiotherapy service of Dysfunctional breathing assessment and therapy can be implemented by dedicated pulmonologists and physiotherapists.
The cases indicate that the intervention reduces symptoms and improves level of activity.

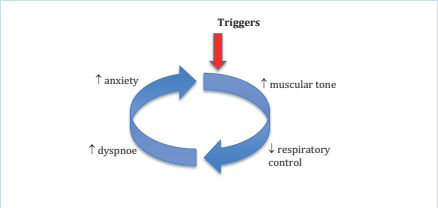

Figure 1; Triggers can alter the respiratory pattern and cause symptoms
Triggers can be stress factors like anxiety, pulmonary disease, other somatic disease, and mental or emotional stress. Symptoms may in turn accelerate negatively. Triggers can have their origin in the past.

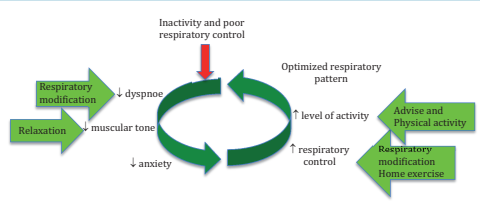

Figure 2; How breathing exercises can lead to an optimized respiratory pattern
The different elements of the intervention are shown in the light-green arrows.

The following cases illustrate the diversity in symptoms and in the effects of the intervention.

Case 1 Female, 57 years, BMI 23.
Unexplained, invalidating dyspnoe, despite extensive cardiopulmonary assessment.
Has not enough air for bicycling.
Respiratory frequency (RF) 20.

Received 3 Physio-sessions:
NQ-decrease from 21 to 16.
Completes 50 km bicycling race.
Less dyspnoe. RF 12.

Case 2 Female, 52 years, BMI 20.
Takes inhaled steroids for asthma.
Sudden events of dyspnoe.
Continuous coughs.
A high physical activity level initially (swimming, walking, bicycling).
RF 5. Large ventilation volume.
Tends to forget to breathe.

Received 4 Physio-sessions:
NQ-decrease from 35 to 27.
Reduced ventilation volume. RF 8.
Less dyspnoe. No coughs.

Case 3 Female, 49 years, BMI 24.
Invalidating attacks of dyspnoe in rest.
Speech-related dyspnoe.
Speaks fast (long sentences). RF 20.

Received 3 Physio-sessions:
NQ-decrease from 32 to 5.
Speed of speech reduced.
Less dyspnoe. No anxiety. RF 14.
She perceives the respiratory modification as an integrated habit.

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Statistical Analysis Plan

Breathing Exercises in Asthma Targeting Dysfunctional Breathing – the BEAT DB trial

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Version 1.0

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Revised version 1.1: September 11th 2020

Statistical Analysis Plan (SAP) for the BEAT DB trial

Section 1: Administrative information

Trial and Trial registration

- 1a: Descriptive title and acronym

Breathing Exercises in Asthma Targeting Dysfunctional Breathing, the BEAT DB-trial.
The BEAT DB-trial is a randomised, controlled, assessor-blinded multicentre superiority trial (RCT) with two parallel groups of adult patients suffering from incomplete asthma control. The primary endpoint is change in asthma-related quality of life (miniAQLQ) at 6 months from initiating the intervention, that is, 12 weeks after intervention period.

- 1b: Trial registration:

ClinicalTrials.gov ID: NCT03127059. Original registration date: April 26th 2017.

SAP version

- 2: Version 1.0, May 12th 2020
- Version 1.1, September 9th 2020

Protocol version

- 3: Protocol version been used

This Statistical Analyses Plan (SAP) was developed based on the protocol approved by the Ethics Committee, Region Zealand (SJ-552) (Protocol version 2.6, January 11th 2019) and the published trial protocol for the RCT (December 31st 2019)[1]. This SAP follows the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials[2], and it was made publicly available before any analyses began.

SAP Revisions

- 4a: Revision history
- 4b: Justification for revision
- 4c: Timing of revision

Protocol version	Updated SAP version no.	Section number changed	Reason	Date changed
2.6, January 11th 2019	1.1	27: Analysis methods to be used.	27: A fixed factor was left out of the original SAP.	1st August 2020

		28: Handling of missing data. 29: Details on required additional analyses.	28: No need for test of robustness, therefor multiple imputation was not prioritised. 29: Replaced planned method with a more precise method to estimate number needed to treat (NNT).	

Roles and responsibility

- 5: Names, affiliations, and roles of SAP contributors

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Signatures

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Date: September 11th 2020

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Date: September 11th 2020

Statistical consultant' signature

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Date:

Revised version 1.1: Signed pages from Version 1.0, attached at the end of this document

- 6c: Main supervisor' signature

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Date:

Revised version 1.1: Signed pages from Version 1.0, attached at the end of this document

Supervisor' signature

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Date: September 11th 2020

Section 2: Introduction

Background and rationale

- 7: Synopsis of trial background

Patients with asthma may experience dyspnoea despite optimized pharmacological treatment [3,4]. This can be caused by comorbidities, among them dysfunctional breathing, which beside of dyspnoea can be observed as altered breathing pattern, frequent sighing or coughing, and hyperventilation, which has a large impact on quality of life (QOL) [4–7].

Breathing exercises (BrEX) include retraining of the breathing pattern, implementation of this in rest and activity, and relaxation [1,8]. It is a low-cost and relatively easy intervention delivered by trained physiotherapists, which improves asthma-related QOL in patients with mild to moderate asthma [8]. However, a recent systematic review reported a lack of trials investigating BrEX in adult patients with severe asthma [9]. In Denmark, patients with moderate to severe asthma are referred from general practitioners to be treated in outpatient departments in secondary care[10].

Objectives

- 8: Objectives and hypotheses

The objectives of this trial is to investigate if a 12week breathing exercise (UC+BrEX) intervention, delivered individually by physiotherapists in three sessions as an add-on to usual care, is superior to usual care alone (US) in adult patients (≥18 years) with moderate to severe asthma and incomplete asthma control referred to specialist care in improving asthma-related QOL at 6-month. Secondarily, to investigate if the patients assigned to UC+BrEX will improve more in lung function, gait distance, and physical activity level compared to US.

The hypothesis is that the participants randomized to UC+BrEX will improve more in asthma-related QOL, and in lung function, gait distance, and physical activity level than the participants randomized to UC alone.

Section 3: Study Methods

Trial design

- 9: Brief description of design

This is a multicentre two-armed parallel randomized (1:1 ratio) controlled trial conducted at seven public hospitals and one private *allergy and lung clinic* (recruitment and UC) and at physiotherapy departments (assessments and UC+BrEX) at the same seven hospitals[a] in all five health care regions in Denmark.

Primary endpoint is the between-group difference in change of the Asthma Quality of Life Questionnaire in the shortened 15-items version (miniAQLQ)[11] between participants allocated to UC+BrEX and participants allocated to UC at the 6-month follow up.
Secondary 3-month and 12-month follow up of between-group difference of miniAQLQ as well as lung function, gait distance, and physical activity level and other secondary outcomes in the RCT is described in the published open access protocol[1].

Patients with uncontrolled asthma from the outpatient pulmonary departments or the private specialized clinic (see items 23, 24) who fulfilled the inclusion criteria, not fulfilling any of the exclusion criteria (see in- and exclusion criteria in item 22), and consenting to participated in the trial, were randomized to either UC+BrEC-group or UC-group.

[a]The private specialized clinic only participated in recruiting participants and in delivery of UC intervention, thus all other trial activities (e.g. baseline and follow up assessment, randomization, and BrEX intervention) were delivered at the hospital nearest to the participant' residence.

Randomization

- 10: Randomization details

After baseline assessment participants were randomly allocated to UC or UC+BrEX in a 1:1 allocation ratio by computer-generated randomization using EasyTrial (EasyTrial APS, Aalborg, Denmark). Fixed blocks of four stratified by center was used to assure equal size of groups at the seven centers (see item 9, note [a]). The chief investigator and all project workers were blinded to the generation sequence. The nurses at the centers activated the EasyTrial randomization function defining the group allocation and informed the patient of group allocation.

Blinding

The assessors were blinded to the allocation. The chief investigator, the physiotherapists who delivered the BrEX, and the participants were impossible to blind.

Sample size

- 11: Full sample size calculation

Sample size was calculated based on the between-group effect size of miniAQLQ-score (0.38) in a study in mild to moderate asthmatic patients[12] with a calculated standard deviation of 0.76[13].
The sample size needed was 172 to detect a 0.38-unit difference between groups in MiniAQLQ-score (SD of 0.76, power of 90%, and p value of 0.05 (two-sided)). To allow for drop-outs (10%), we aimed to

randomize 190 participants. Fully description of sample size calculation is accessible in the published trial protocol[1].

Framework

- 12: Framework (Description of hypothesis framework)

As the UC+BrEX group received an add-on intervention, both primary and secondary outcomes assessed for between-group effects in this trial are tested for superiority in favour of UC+BrEX. The lower bound of the 95% confidence interval (95%CI) excluding the superiority margin (i.e. 0.38) in miniAQLQ-score will be interpreted as a lack of clinical important difference.

Statistical interim analysis and stopping rules

- 13: Specification of planned interim analysis and/or stopping rules

There were no pre-planned interim analyses or stopping rules.

Timing of final analysis

- 14: Details of timing of all analyses

The primary follow up (6-month) was conducted 6 months after baseline (for UC-group) respectively 6 months after the first session of BrEX (for UC+BrEX group). This follow up included the objective assessments and patient-reported measures (including the primary outcome) and was completed in the week after the 6-month-timepoint or up to 4 weeks after (see table 1).

All primary and secondary outcomes will be analysed collectively by the chief investigator (for blinded statistical analyses, see item 32), supervised by Inge Petersen, statistician. These analyses will comprise data from all follow ups (baseline, 3-month, 6-month). The main RCT article will report outcome presented as *Primary or Secondary Outcome Measures* at ClinicalTrials.gov (ID: NCT03127059), whereas *Other Outcomes Measures* will be reported in the main article or afterwards in secondary reports. The 12-month follow up will be analysed and reported in a subsequent report when this data collection is completed.

Short-term and long-term follow up, i.e. at 3 months and 12 months after baseline or first BrEX session (se start of item 14), respectively, were completed using a questionnaire. The participants were urged to complete questionnaire within five days, and were/will be reminded by e-mail, SMS, and ultimately by phone-call.

Timing of outcome assessments

- 15: Timing of outcome assessments

An overview of baseline characteristics, outcomes measures and their time points are presented in table 1; a detailed description can be read in the published open access protocol[1].

Table 1; Overview of data collection in BEAT DB trial	Baseline	3 months	6 months	12 months
Primary endpoint				
MiniAsthma Quality of Life Questionnaire (MiniAQLQ) *a*	@	@	@	@
Secondary endpoints				
Patient-reported information				
Asthma Control Questionnaire (ACQ6)	@	@	@	@
Nijmegen Questionnaire (NQ)	@	@	@	@
Hospital Anxiety and Depression Scale (HADS)	@	@	@	@
EuroQol-5D (EQ-5D-5L)	@	@	@	@
Global Perceived Effect rate (GPE)	N/A	@	@	@
Patient Acceptable Symptom State (PASS)	N/A	@	@	@
Treatment Failure (TF)	N/A	@	@	@
Smoking status	@		@	@
Socio Economic Status (SES) *b*	@			
Foster Score	@		@	
Anthropometric				
Gender	@			
Age	@			
Height, cm	@			
Weight, kg	@			
Body Mass Index (BMI)	@			
Register data				
Medication (treatment step 1-5) *c*	@		@	@
Co-morbidity	@			
Scheduled and acute medical visits (prev.6mo)			@	@
Adverse events	N/A	@	@	@
Adherence	N/A	@		
Functional capacity				
6-minute Walk Test (6MWT) *d*	@		@	
Count Scale (CS)	@		@	
Breath Holding Time (BHT)	@		@	
Respiratory Pattern Observation	@		@	
Physical activity (SenseWear) average of 6 days *e*				
Total Energy Expenditure, kJ (daily avg)	@	@	@	
Average METs (daily avg)	@	@	@	
Physical Activity Level (PAL) (daily avg)	@	@	@	
Number of Steps (daily avg)	@	@	@	
Lung parameters *f*				
Expiratory volume in first second (FEV1)	@		@	
Forced vital capacity (FVC)	@		@	
Ratio (FEV1/FVC) % of predicted	@		@	
FEV1 % of predicted	@		@	
Peak expiratory flow rate (PEF)	@		@	
Maximal Inspiratory Pressure (MIP)	@		@	

a Primary outcome is MiniAQLQ at 6 months follow-up

b SES includes educational level, annual family income, work status

c Reliever and controller medication

d Including Borg CR10

e Subgroup will be measured. 3 months follow up only until April 2018

f Reference values for spirometry: GLI2012

Section 4: Statistical Principles

Confidence intervals and *p*-values

- 16: Level of significance

All statistical tests carried out to measure the between-group effects, will consist of two-sided tests with a 5% significance level (p=.05).

- 17: Adjustment for multiplicity

Since this study has one clearly defined primary outcome and all other outcomes serve as supportive outcomes, no adjustments for multiplicity are needed.

- 18: Confidence intervals

All confidence intervals presented will be 95% and two-sided.

Adherence and protocol deviations

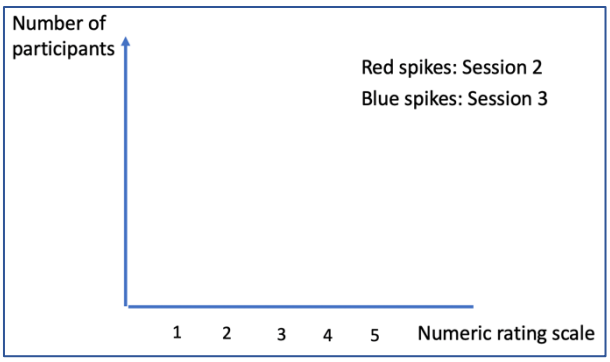
- 19a: Definition and assessments of adherence to the intervention

Good adherence with BrEX is defined as completion of three treatment sessions, i.e. 100%. This was documented in the database (EasyTrial). Additionally, the physiotherapists evaluated the adherence to the home exercise program at sessions 2 and 3 using a numeric rating scale 1–5 (1=no adherence, 5=excellent adherence).

- 19b: Description of how adherence will be presented

Adherence will be presented as the number and percentage of participants completing three session. A supplementary graph will show the home exercise program adherence (see Mock-graph).

Legend: *Mock-graph*; NRS of adherence to home exercise of participants in UC+BrEX-group (N=94).



- 19c, 19d: Protocol deviations

The following is defined as major protocol deviations which may compromise the scientific value of the trial:

More than 10% lost to follow up at the primary endpoint

Less than 50% in the UC+BrEX group participated in all three treatment sessions

All major protocol deviations will be reported in the main article.

Analysis population

- 20: Definition of analysis populations

In the primary analysis of the trial outcomes and the safety analysis (adverse events (AE)), all participants will be included according to their randomized allocation, following the Intention-To-Treat (ITT) principle. This is the full analysis set, defined as an analysis set being as complete and as close to the ITT principle of including all randomized participants as possible[14].
In addition, a secondary per protocol analysis will be performed.
The per protocol population excludes participants in UC+BrEX group with poor adherence, i.e. <100% of three BrEX-sessions.

No information exists on UC group having had treatment similar to BrEX outside the trial, but they were asked not to receive any.

Section 5: Trial Population

Screening data

- 21: Reporting of screening data

Recruitment period: April 26th April 2017 – September 24th 2020.
Total number of eligible subjects during recruitment period will be presented in a flow diagram in the main article. For further information, see items 9c, 19d, 23, 24.

Eligibility

- 22: Summary of eligibility criteria

Inclusion criteria:

- Referred from GP to a secondary, outpatient respiratory clinic for lack of asthma control
- Asthma diagnosed by a pulmonologist
- ≥2 doctor visits at a specialised, pulmonologist-lead asthma clinic
- Age≥18 years
- ACQ6 score ≥0.8
- Willing and able to give written informed consent
- Speaks, reads and understands Danish.

Exclusion criteria:

- Trained in breathing exercises by physiotherapist during the last 6 months
- Pregnancy

- Any severe disease as judged by the responsible physician
- Participating in another respiratory interventional research project.

Recruitment and withdrawal

- 23, 24: Information to be included in the CONSORT flow diagram

Recruitment:

Participants were recruited at

- Department of Respiratory Medicine at the following:

Naestved Hospital, Hvidovre Hospital, Bispebjerg Hospital, Zealand University Hospital Roskilde, Aalborg University Hospital, Silkeborg Regional Hospital, and Odense University Hospital,

- Allergy & Lung Clinic, Elsinore, (private specialized clinic).

Information to be included in the CONSORT flow diagram

- All patients screened for eligibility
- All patients who met one or more exclusion criteria, with reasons
- All patients who consented to be included in the trial
- All patients included in the baseline assessment
- All participants allocated to each intervention-arms[b]
- All participants who withdraw from intervention and/or follow up, including time (level) and reasons
- All participants with complete follow up data at 3 and 6-months[c]
- All participants lost to follow up, with reasons for both intervention-arms
- All participants included in the ITT and per protocol for both intervention-arms.

[b] All participants receiving BrEX (see also adherence, item 19a, 19b).

[c] Participants in both intervention arms who have completed miniAQLQ (primary outcome) will be summarized at each follow up.

Baseline patient characteristics

- 25a: List of baseline characteristics to be summarized

Baseline characteristics will be presented for each intervention-groups in the main article:

- Gender
- Age at inclusion
- Smoking status

- Body Mass Index, categories:
  - underweight, normal weight, overweight, obese, severely obese, extremely obese
- Comorbidity, number:
  - 0, 1, 2, 3, 4+
- GINA step (Asthma severity):
  - 1, 2, 3, 4, 5
- Inhaled corticosteroids (ICS) treatment level:
  - None, low, moderate, high
- Oral corticosteroid (OCS) treatment
- Biological treatment
- Number of second controllers:
  - 1, 2, 3, 4, 5, 6, 7 (etc)

Patient-reported outcome:

- miniAQLQ
- ACQ6
- NQ
- HADS, anxiety
- HADS, depression
- EuroQual, EQ-5D-5L, index
- EuroQual, VAS

Objective outcome:

- 6 minutes' walk test (6MWT)
- Borg CR10:
  - Resting, after 6MWT

Spirometry:

- FEV1% predicted
- FEV1/FVC % predicted
- Peak flow rate, (PEF)

Accelerometry:

- Average daily steps
- Physical activity level (PAL)

In supplementary the following will be presented

- Annual income, €, categories:
  - Low, middle, high

- Work status, categories:
  - employed, unemployed, education, outside labor market
- Educational level, categories:
  - low (no education, Primary school, High school/Secondary school),
  - medium (Vocational education, Shorter higher education, Medium higher education),
  - high (Bachelor, Master/Higher education, Ph.D.)
- Count scale, number
  - Resting
- Breath holding time, sec.
- Respiration rate

For further details, please refer to the published open access trial protocol[1].

- 25b: Details on descriptive summary of baseline characteristics

Continuous data will be summarized by mean with standard deviations (SD) if data are normally distributed and median with interquartile range (IQR) if data are skewed. Categorical data will be summarized by numbers and percent (%). As recommended by CONSORT[15], no formal tests for significant differences between groups at baseline will be performed.

Section 6: Analysis

Outcome definitions

- 26a, 26b: Specification of outcomes and timing

Overview of outcomes and timing is given in table 1 (item 15).

- 26c: Any calculations used to derive the outcome

For patient-reported outcomes the following calculations will be made to find the scores of each questionnaire:

- miniAsthma Quality of Life Questionnaire (MiniAQLQ): the mean of the 15 item[11]
- Asthma Control Questionnaire (ACQ6): the mean of the 6 items[16,17]
- Nijmegen Questionnaire (NQ): the sum of the 16 items[18]
- Hospital Anxiety and Depression Scale (HADS): the sum of the 7 anxiety-related items, and the sum of the 7 depression-related items[19]
- EuroQol-5D (EQ-5D-5L): index profile calculated using the crosswalk of EQ-5D-5L Index Value Calculator for MAC, developed for the EuroQol Group, version 1.0.

To derive medication treatment step (so called GINA step 1-5 that expresses the asthma severity):

- Defined daily dose (DDD) of inhaled Corticosteroids and numbers/combinations of second controllers were calculated in an algorithm[20], using GINA report 2019[4] treatment steps.

Analysis methods

- 27: Analysis methods to be used

The primary endpoint, i.e. between-group difference in change in the miniAQLQ at the 6-month follow up will be analyzed in repeated measures mixed effects model with subject being a random factor and treatment arm [treatment arm included in revised version, 1.1.], visit (i.e. baseline, 3-month and 6-month follow up) and interaction between visit and treatment arm[21] (UC+BrEX or UC; see item 32: Intervention A or Intervention B) being fixed factors. The model will be adjusted for treatment centre.
Interpretation of lack of clinical important difference, see item 12.
Secondary continuous outcomes will be analyzed using the same model.
Model assumptions will be analyzed for normal distribution of residuals, and if assumptions of normality are violated, confidence intervals will be estimated using Bootstrapping estimation methods.
We will report estimated marginal means with p-values and 95% CI for superiority assessment.
The occurrence of adverse events (AE) will be compared between groups at the 6-month follow up using an appropriate method, if sufficient number of AEs occurs then Poisson regression model with a robust error variance or similar.
The categorial outcome measures (e.g. GINA step, Global Perceived Effect) will be analyzed using Chi2-test or Fisher's Exact Test, as appropriate.
Data at 12-month will be included in subsequent secondary analyses of long-term treatment results.

Revised SAP version 1.1:
If no violation of assumptions of normality for primary outcome exists, all the bootstrapped estimated results will be reported in the supplementary appendix.

- 27e: Planned sensitivity analyses

Explore the effect of treatment centre on between-group difference in change of miniAQLQ:
Analyze the response of treatment (BrEX) and asthma severity (GINA step) due to treatment centre.

- 27f: Planned subgroup analyses

Per protocol analysis: (see also item 20): mixed effects model as above stated in UC+BrEX-participants with 100% of three BrEX-sessions.

A subgroup of participants i.e. all from Hvidovre and Naestved Hospitals but only participants until April 2018 at Bispebjerg Hospital, Zealand University Hospital (Roskilde), and Aalborg University Hospital used accelerometry (SenseWear) for 6 days at baseline and at 6-month follow up. Mixed effects model as stated above will be used to analyze between-group difference in change in physical activity level (SenseWear data).

Missing data

- 28: Handling of missing data

Repeated measures mixed model is robust for managing variables with missing data[22] therefor no imputation methods will be needed.

Deleted from version 1.1 [version 1.0: , but as planned in the protocol, we will test robustness with and with-out multiple imputation.]

Additional analyses

- 29: Details on required additional analyses

Numbers Needed to Treat analysis

[version 1.0, deleted:
We will estimate numbers-needed-to-treat (NNT) for one participant to improve at least corresponding to the clinically relevant difference in miniAQLQ, 0.5 units[23], using the formula 1/(TER−MER), using:

- TER, the event rate in the UC+BrEX group, and
- MER, the event rate in the UC group.

Further, we will calculate the trial-specific MID (0.38 units)/responder threshold by subtracting the mean miniAQLQ score for participants reporting to have experienced a 'small but not important change' in Global Perceived Effect (GPE) from those reporting 'important change' in GPE at 6 months.

These additional analyses will be use to estimate the trial-specific cut-offs for clinically relevant differences in miniAQLQ (primary outcome)]

Revised SAP version 1.1:
To estimate Number needed to treat (NNT), we will use a matrix developed by Guyatt et al[24], as follows: A clinically relevant improvement in Mini-AQLQ (0·5 units) will be calculated using the formula 1/('proportion that improved'-'proportion that deteriorated') from receiving UC+BrEX as compared to UC alone.

	UC+BrEX (proportion)		
UC (proportion)	Improved (x)	Unchanged (y)	Deteriorated (z)
Improved (a)	ax	ay	az
Unchanged (b)	bx	by	bz
Deteriorated (c)	cx	cy	cz

NNT= (1/(bx + cx + cy) − (ay + az + bz))

Improved = Increased by more than 0·5; Unchanged = Changed between − 0·5 and 0·5; Deteriorated = Fell by more than 0·5. NNT=Number-needed-to-treat. Matrix according to Guyatt, Juniper, Walter, Griffith, Goldstein, BMJ 1998;316:690–3

Table S3b; Number needed to treat, individual positive response by >0·5 units of Mini-AQLQ

Additional analyses will be used to estimate the responder profiles of those who had moderate-large improvement of miniAQLQ (primary outcome) from BrEX to guide the clinical interpretation of the results, and will be reported in the main article or afterwards in secondary reports.

Further exploratory analyses will be conducted if found relevant.

Harms

- 30: Handling of adverse events

Participants have been asked about experienced adverse events (AE) at each follow up, recorded on standardized forms. Additionally, data on usage (acute and planned) of the respiratory department and/or the outpatient department during the trial period, i.e. all pulmonary related AEs will be collected from medical reports for each participant. Additional information may have to be requested from the recruiting hospitals.

Definition of AE: Respiratory events or other events during the trial, which may be related to aspects of trial participation leading to contact with the GP or hospital.

Definition of serious AEs: Life threatening or resulting in hospitalization[25].

AEs will be evaluated for severity and categorized into non-serious and serious AEs regardless of being trial-related or non-trial related and will be descriptively reported for both randomization groups.

Statistical software

- 31: Details of statistical software to be used

STATA 16.1 (or an updated version if applicable) (StataCorp, College Station, TX, USA).

References

- 32: Reference to Data management

Data safety and confidentiality

Danish Data Protection Agency (REG-55–2016) approved the data collection and storage. Personal information concerning the participants are kept securely and separate from data files and participants are pseudonymized in the data.

Verification of data

Objective outcome measures collected at baseline and 6-month follow up have been verified by double data entry. The verification was performed by three research workers not involved in trial design, data collection, or intervention.

Blinded statistical analyses

To ensure allocation-blinded statistical analyses, two external researchers are involved before the data files will be handed over to be analysed:

a) one researcher will export raw data files in EasyTrial (research database),

b) another researcher will rename the intervention groups (into 'Intervention A' and 'Intervention B') concealed to the research group (mentioned in item 5), and drop variables that may identify the participants (e.g. baseline number), but keep a unique identifier for each participant.

Execution of blinded interpretations on results

The blinded results of Intervention A compared with Intervention B will be presented to the research group who will interpret the results to agree on two alternative written conclusions, one if Intervention A was UC+BrEX, and one if Intervention B was UC+BrEX. Then, unblinding of the code will take place[26].

References

1. Andreasson KH, Skou ST, Ulrik CS, et al. Protocol for a multicentre randomised controlled trial to investigate the effect on asthma-related quality of life from breathing retraining in patients with incomplete asthma control attending specialist care in Denmark. *BMJ Open*. 2019;9(12):e032984. doi:10.1136/bmjopen-2019-032984

2. Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. *JAMA*. 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556

3. British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax*. 2014;69 Suppl 1:1-192.

4. Global_Initiative_For_Asthma. GINA, Global Initiative for Asthma. Global strategy for asthma management and prevention, 2019. www.ginasthma.org. Published 2019. Accessed May 6, 2020. https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf

5. Connett GJ, Thomas M. Dysfunctional Breathing in Children and Adults With Asthma. *Front Pediatr*. 2018;6:406. doi:10.3389/fped.2018.00406

6. Boulding R, Stacey R, Niven R, Fowler SJ. Dysfunctional breathing: a review of the literature and proposal for classification. *Eur Respir Rev*. 2016;25(141):287-294. doi:10.1183/16000617.0088-2015

7. Depiazzi J, Everard ML. Dysfunctional breathing and reaching one's physiological limit as causes of exercise-induced dyspnoea. *Breathe (Sheff)*. 2016;12(2):120-129. doi:10.1183/20734735.007216

8. Bruton A, Lee A, Yardley L, et al. Physiotherapy breathing retraining for asthma: a randomised controlled trial. *Lancet Respir Med*. 2018;6(1):19-28. doi:10.1016/S2213-2600(17)30474-5

9. Santino TA, Chaves GS, Freitas DA, Fregonezi GA, Mendonça KM. Breathing exercises for adults with asthma. *Cochrane Database Syst Rev*. 2020;3:CD001277. doi:10.1002/14651858.CD001277.pub4

10. Porsbjerg C, Ulrik C, Skjold T, et al. Nordic consensus statement on the systematic assessment and management of possible severe asthma in adults. *Eur Clin Respir J*. 2018;5(1):1440868. doi:10.1080/20018525.2018.1440868

11. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J*. 1999;14(1):32-38. doi:10.1034/j.1399-3003.1999.14a08.x

12. Thomas M, McKinley RK, Mellor S, et al. Breathing exercises for asthma: a randomised controlled trial. *Thorax*. 2009;64(1):55-61. doi:10.1136/thx.2008.100867

13. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. 2003;41(5):582-592. doi:10.1097/01.MLR.0000062554.74615.4C

14. Tripepi G, Chesnaye NC, Dekker FW, Zoccali C, Jager KJ. Intention to treat and per protocol analysis in clinical trials. *Nephrology (Carlton)*. Published online March 8, 2020. doi:10.1111/nep.13709

15. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010;63(8):e1-37. doi:10.1016/j.jclinepi.2010.03.004

16. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902-907. doi:10.1034/j.1399-3003.1999.14d29.x

17. Juniper EF, Svensson K, Mörk A-C, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005;99(5):553-558. doi:10.1016/j.rmed.2004.10.008

18. van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. *J Psychosom Res*. 1985;29(2):199-206. doi:10.1016/0022-3999(85)90042-x

19. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370. doi:10.1111/j.1600-0447.1983.tb09716.x

20. Andreasson, KH, Andreasson, TH, Ulrik, CS, et al. Inter-rater reliability of a novel algorithm to calculate Global Initiative for Asthma (GINA) treatment steps. In: *(Accepted Scientific Abstract for ERS Congress 2020)*. ; 2020:1 (abstr).

21. Twisk J, Bosman L, Hoekstra T, Rijnhart J, Welten M, Heymans M. Different ways to estimate treatment effects in randomised controlled trials. *Contemp Clin Trials Commun*. 2018;10:80-85. doi:10.1016/j.conctc.2018.03.008

22. Ranstam J, Turkiewicz A, Boonen S, Van Meirhaeghe J, Bastian L, Wardlaw D. Alternative analyses for handling incomplete follow-up in the intention-to-treat analysis: the randomized controlled trial of balloon kyphoplasty versus non-surgical care for vertebral compression fracture (FREE). *BMC Med Res Methodol*. 2012;12:35. doi:10.1186/1471-2288-12-35

23. Ehrs P-O, Nokela M, Ställberg B, Hjemdahl P, Wikström Jonsson E. Brief questionnaires for patient-reported outcomes in asthma: validation and usefulness in a primary care setting. *Chest*. 2006;129(4):925-932. doi:10.1378/chest.129.4.925

24. Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. *BMJ*. 1998;316(7132):690-693. doi:10.1136/bmj.316.7132.690

25. Office of the FDA, U.S. Food & Drug Administration. What is a Serious Adverse Event? *FDA*. Published online January 8, 2019. Accessed May 10, 2020. https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event

26. Järvinen TLN, Sihvonen R, Bhandari M, et al. Blinded interpretation of study results can feasibly and effectively diminish interpretation bias. *J Clin Epidemiol*. 2014;67(7):769-772. doi:10.1016/j.jclinepi.2013.11.011

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Blinded review of the primary endpoint results from the BEAT DB-trial

Blinded review and interpretation

Bødtger, Uffe; Skou, Søren Thorgaard; Thomas, Mike; Andreasson, Karen Hjerrild

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Blinded review of the primary endpoint results from the trial:

Breathing Exercises in Asthma Targeting Dysfunctional Breathing – the BEAT DB-trial

Introduction

This document presents the results of the primary outcome, mini Asthma Quality of Life Questionnaire (mini-AQLQ), of the BEAT DB-trial. Additionally, it presents results from the secondary outcomes, defined in the trial registration (registration number NCT03127059) and the published trial protocol[1].

Results from the intention-to-treat analysis of the primary endpoint

Between-group differences

There was a statistically significant difference of 0.34 (crude) and 0.35 (adjusted) units between groups in the mean change of the mini-AQLQ from baseline to the 6 months follow-up.

Within-group differences

Both groups improved significantly in mini-AQLQ from baseline to the 6 months follow-up. Group A improved 0.65 units (15%) while Group B improved 0.31 units (7%) with a number needed to treat (NNT) of 8.3 for one patient to improve at least 0.5 units in Group A compared to Group B.

Results from the secondary intention-to-treat analysis

Between-group differences

Between-groups differences in change from baseline to the 6 months follow-up in the 6-item Asthma Control Questionnaire (ACQ6), Anxiety and Depression (HADS-A, HADS-D), Nijmegen Questionnaire (NQ), 6-Minute Walk Test (6MWT), predicted Forced Expiration Volume in first second (FEV_1%pred) and Steps per day did not differ significantly between Group A and Group B. However, there were consistent numerical trends in favour of the intervention to which Group A was allocated expect for 6MWT, which was in favour of the intervention to which Group B was allocated.

Within-group changes

Both groups improved significantly in ACQ6, HADS-A, and NQ from baseline to the 6 months follow-up. HADS-D improved significantly in Group A.

Interpretation 1: "Group A received breathing exercises in addition to usual care"
Our results show that breathing exercises in addition to usual care is more efficacious than usual care alone in patients with uncontrolled moderate-to-severe asthma followed by respiratory physicians in terms of improving asthma-related quality of life (mini-AQLQ).
The between group differences were substantial and considered clinically relevant, but was not accompanied by statistically significant between-group differences in asthma control (ACQ6), perceived level of breathing discomfort (NQ), physical capacity (6MWT), physical activity (steps per day) or lung function (FEV_1%pred), although all the PROMs showed a numerical trend to larger improvements in the breathing exercise group.

This is the first trial to investigate the effect of breathing exercises in addition to usual care compared with usual care alone in patients with moderate-to-severe asthma treated in a difficult asthma secondary care setting. For the first time, it provides high-quality evidence that breathing exercises in addition to usual care in patients with moderate-to-severe asthma is superior to usual care alone in improving asthma-related quality of life after 6 months. Both groups improved substantially in mini-AQLQ, ACQ6 and NQ suggesting that a usual care program is also efficacious in moderate-to-severe asthma. However, adding breathing exercises to this treatment program will improve asthma-related quality of life further.
The results support previous findings in patients with mild-to-moderate asthma followed by primary care physicians[2]. The magnitude of improvement is slightly larger but similar to that seen in milder primary care patients[2], and is similar to the quality of life improvement associated with additional pharmacological interventions for patients with asthma uncontrolled on standard first-line medication (ICS)[3].

Since the results are in favour of breathing exercises in addition to usual care, this confirms our primary hypothesis described in the Statistical Analyses Plan[4] that the participants randomized to breathing exercises in addition to usual care will improve more in asthma-related QOL than participants randomized to usual care alone.

The trial supports the adjuvant use of breathing exercises in the management of patients with moderate-to-severe asthma attending a secondary care clinic.

Interpretation 2: "Group A received usual care alone"

Our results show that usual care alone is more efficacious in improving asthma-related quality of life (mini-AQLQ) than breathing exercises in addition to usual care in patients with uncontrolled moderate-to-severe asthma followed by respiratory physicians. The results indicate that patients with uncontrolled moderate-to-severe asthma on average have an inferior outcome if breathing exercises is added to usual care, suggesting that adding a physiotherapeutic treatment has a negative effect on their 6-month outcome. This is in contrast to findings in patients wither milder forms of asthma[2].

Since usual care alone is more efficacious, and cheaper, breathing exercises seem only applicable in a sub-group of patients with moderate-to-severe asthma not able to participate in usual care.

Since the results are in favour of usual care alone, this means that our primary hypothesis described in the Statistical Analyses Plan[4] cannot be confirmed.

The trial indicates that breathing exercises should not be offered to patients with moderate-to-severe asthma attending a hospital based difficult asthma clinic.

Signatures

Date 26/06-2020

Uffe Bødtger

Date 26.6.2020

Mike Thomas

Date: 23/6-20

Søren Thorgaard Skou

References

1. Andreasson KH, Skou ST, Ulrik CS, et al. Protocol for a multicentre randomised controlled trial to investigate the effect on asthma-related quality of life from breathing retraining in patients with incomplete asthma control attending specialist care in Denmark. *BMJ Open*. 2019;9(12):e032984. doi:10.1136/bmjopen-2019-032984

2. Bruton A, Lee A, Yardley L, et al. Physiotherapy breathing retraining for asthma: a randomised controlled trial. *Lancet Respir Med*. 2018;6(1):19-28. doi:10.1016/S2213-2600(17)30474-5

3. Bateman ED, Esser D, Chirila C, et al. Magnitude of effect of asthma treatments on Asthma Quality of Life Questionnaire and Asthma Control Questionnaire scores: Systematic review and network meta-analysis. *J Allergy Clin Immunol*. 2015;136(4):914-922. doi:10.1016/j.jaci.2015.03.023

4. Andreasson, KH, Skou, ST, Petersen, I, Bodtger, U. Statistical Analysis Plan; Breathing Exercises in Asthma Targeting Dysfunctional Breathing – the BEAT DB trial. Published online May 13, 2020. https://findresearcher.sdu.dk:8443/ws/portalfiles/portal/169652319/Statistical_analysis_plan_BEAT_DB_trial_13May2020.pdf

Appendices C

C-1 Paper I

Protocol for a multicentre randomised controlled trial to investigate the effect on asthma-related quality of life from breathing retraining in patients with incomplete asthma control attending specialist care in Denmark

C-S1 Supplementary online material:

Trial information Protocol

BrEX Description

12 item interview list

BMJ Open

Protocol for a multicentre randomised controlled trial to investigate the effect on asthma-related quality of life from breathing retraining in patients with incomplete asthma control attending specialist care in Denmark

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ABSTRACT

Introduction and aim Uncontrolled asthma is a global health challenge with substantial impact on quality of life (QoL) and overall healthcare costs. Unrecognised and/or unmanaged comorbidities often contribute to presence of uncontrolled asthma. Abnormalities in breathing pattern are termed dysfunctional breathing and are not only common in asthma but also lead to asthma-like symptoms and reduced QoL, and, in keeping with this, improvement with breathing normalisation. Evidence-based guidelines recommend breathing retraining interventions as an adjuvant treatment in uncontrolled asthma. Physiotherapy-based breathing pattern modification interventions incorporating relaxation have been shown to improve asthma-related QoL in primary care patients with impaired asthma control. Despite anecdotal reports, effectiveness of breathing retraining in patients referred to secondary care with incomplete asthma control has not been formally assessed in a randomised controlled trial (RCT). We aim to investigate the effect of breathing exercises on asthma-related QoL in patients with incomplete asthma control despite specialist care.

Methods and analysis This two-armed assessor-blinded multicentre RCT will investigate the effect of physiotherapist-delivered breathing retraining on asthma QoL questionnaire (MiniAQLQ) in addition to usual specialist care, recruiting from seven outpatient departments and one specialised clinic representing all regions of Denmark during 2017–2019. We will include 190 consenting adults with incomplete asthma control, defined as Asthma Control Questionnaire 6-item score ≥0.8. Participants will randomly be allocated to either breathing exercise programme in addition to usual care (BrEX +UC) or UC alone. BrEX compiles three physiotherapy sessions and encouragement to perform home exercise daily. Both groups continue usual secondary care management. Primary outcome is between-group difference in MiniAQLQ at 6 months. Secondary outcomes include patient-reported outcome measures, spirometry and accelerometer.

Ethics and dissemination Ethics Committee, Region Zealand (SJ-552) and Danish Data Protection Agency (REG-55–2016) approved the trial. Results will be reported in peer-reviewed scientific journals.

Trial registration number NCT03127059; Pre-results.

Strengths and limitation of this study

- ► This trial investigates the effects of physiotherapist-delivered breathing pattern modification and relaxation on asthma-related quality of life in patients with incomplete asthma control despite attending specialist care, a resource demanding group where evidence for management strategies are lacking.
- ► The multicentre design including participants at secondary care centres in all regions of Denmark comparing a clinically relevant and low-cost intervention with usual care supports external validity.
- ► Participants and treatment providers cannot be blinded due to the nature of the intervention.

BACKGROUND

Asthma is a chronic, common, heterogeneous disease characterised by variable airflow obstruction due to airway inflammation and bronchial hyperreactivity.[1] Globally, asthma affects around 300 million people. Dyspnoea is a very important symptom, which significantly restricts physical activity and quality of life (QoL).[1 2]

Asthma-related QoL describes the subjective impairment conferred by asthma on a person's life, and is a key patient-reported

outcome.[3] It is impaired in most patients with asthma, and may be assessed by the validated MiniAsthma Quality of Life Questionnaire (MiniAQLQ).[4] Several factors affect asthma-related QoL: (a) asthma-specific such as severity and type of asthma symptoms, (b) asthma-related such as triggers and comorbidities and (c) 'patient-related' factors, such as emotional stability, overall stamina, education and income.[5–7]

Asthma-related QoL is only moderately associated with asthma control, and asthma control remains the key metric for assessing the impact of living with asthma.[6] Asthma control is currently defined as absence of key symptoms and signs of asthma (dyspnoea or coughing during nighttime or exercise, exacerbations, and emergency healthcare usage), and no asthma-related impairment of activity or QoL.[2] A tool widely used to measure asthma control is the Asthma Control Questionnaire (ACQ), which is available in 5-item, 6-item or 7-item versions, where item 7 is lung function expressed as percentage of expected forced expiratory volume in first second (FEV1 % expected).[8 9]

More than 10% of the asthma population has difficult-to-treat asthma with poor asthma control despite substantial pharmacological treatment (ie, Global Initiative for Asthma, GINA, steps 4–5).[2 10 11] This subgroup uses high levels of asthma-related healthcare resources due to increased symptom burden, medication usage, prevalence of comorbidities, smoking, sick leave, higher exacerbation rates and emergency department visits compared with patients with asthma control.[2 12] Likewise, individual costs to medication, unemployment, poorer education, sick leave, and early retirement are substantial too. True severe asthma is seldom the cause of difficult-to-treat asthma. Common causes are inadequate treatment (eg, adherence, inhaler technique), triggers (eg, smoking, allergens), erroneous asthma diagnoses or comorbidities (both: eg, non-asthma respiratory disease, obesity, rhinitis, cardiovascular diseases, dysfunctional breathing (DB), neuromuscular disease or poor cardiorespiratory fitness).[2 13–17]

Abnormalities in breathing pattern are usually referred to as DB. The extreme disordered breathing patterns range from fast and shallow to slow and deep. The first, for example, rate 20–40, thoracic breathing also known as hyperventilation, and the latter, for example, rate 5–8, diaphragmatic and whole thorax breathing, large tidal volume close to total lung capacity resulting in high ventilation volume.[18 19] However, both patterns result in increased minute volume. A patient with disordered breathing pattern may sigh often to compensate for over-inflated lung and elevated tidal volume (eg, end of tidal volume over functional residual capacity, FRC) to achieve FRC (relaxation pressure of lung plus chest wall equals the atmospheric pressure).[19 20] DB is well-recognised but ill-defined disorder that often coexists with asthma but may be an isolated problem and cause persistent or intermittent dyspnoea, coughing, loss of voice, chest tightness, anxiety and fatigue.[2 13 15 21 22] There is no consensus on diagnostic criteria.[21] The Nijmegen Questionnaire (NQ) is the commonly used screening tool,[22–24] and estimates a prevalence of DB of 25% in Danish patients with severe asthma.[25] However, the use of the NQ as a screening tool for DB in asthma has been questioned,[26] and the NQ does not predict a response to intervention in controlled trials of breathing retraining.[27 28]

In asthma, pharmacological treatment targets airway inflammation, bronchoconstriction and possible comorbidities. Non-pharmacological treatment focuses on reduction of airway inflammation by avoidance of triggers, diet and physical fitness, and (in obese) weight reduction, to improve asthma control.[2 29] Physiotherapy has gained increasing attention as part of asthma care as many patients with asthma explicit signs of DB pattern.[15 30]

Trained physiotherapists provide breathing exercises (BrEX) including re-education or modification of the breathing pattern. This involves instructions that encourage nasal route of breathing, mainly diaphragmatic respiratory movement, and normalising respiratory rate and tidal volume.[31–33]

In controlled trials in people with mild and moderate asthma (GINA steps 1–3), BrEX are safe, reduce symptoms, improve QoL and asthma control, but does not change lung function parameters or airways inflammation.[28 34–37] Interestingly, the clinical effect of BrEX is unrelated to baseline NQ scores.[26]

Recent systematic reviews of BrEX in moderate to severe asthma conclude that the methodological quality and poor methods descriptions leave insufficient evidence for a firm recommendation.[1 32 38 39]

A previous, well-performed pragmatic-designed trial investigated a similar intervention (delivered by a DVD or face-to-face by a single physiotherapist) in patients in primary care in UK.[28] The Danish healthcare system shares many similarities with the British NHS: Free health service for all citizens, all patients have a general practitioner (GP) who is the gate-keeper to secondary care. Asthma GINA steps 1–4 is the responsibility of the GPs, who can refer to the local hospital's Respiratory Service in case of diagnostic uncertainty or lack of control. There are few multidisciplinary clinics for 'difficult-to-control asthma' in Denmark (total population 5.6 million inhabitants).

However, patients with more difficult to control asthma attending secondary, outpatient respiratory clinic have not to date been studied. Therefore, we decided to perform an adequately powered, randomised controlled clinical trial of well-defined BrEX in a well-characterised cohort of patients referred from GP due to lack of control and still having suboptimal control (ACQ6 score ≥0.8) of pulmonologist-diagnosed asthma after ≥2 consultations with a pulmonologist.

Thus, the present pragmatic multicentre trial will contribute to the existing (sparse) evidence on physiotherapy in asthma concerning target group (secondary care) and intervention (multicentre), the latter improving external validity of our findings.

The aim of our randomised controlled trial (RCT) is to compare changes in the key patient-reported outcome

asthma-related QoL (MiniAQLQ scores) in patients undergoing a BrEX programme (three sessions and encouragement to do daily home exercise during 12 weeks) in addition to usual specialist care (US) with patients receiving specialist care management. Secondarily, we will investigate the effects of the intervention on important patient-reported outcomes, including lung function, gait distance and physical activity level.

METHODS AND ANALYSES

Trial design

The trial is designed as a randomised, controlled, assessor-blinded multicentre superiority trial with two parallel groups with a primary endpoint of change in asthma-related quality of life (MiniAQLQ) at 6 months from initiating the intervention, that is, 12 weeks after intervention period.

The benefits achieved at 6 months are hypothesised to be maintained at 12 months.

Main trial information is presented in online supplementary file table S1.

The trial protocol conforms to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT),[40] and the Template for Intervention Description and Replication (TIDieR) will be used.[41] The schedule of enrolment, interventions and assessments is shown in figure 1.

The trial is registered on 26 April 2017. Enrolment started at the first centre on 26 April 2017 and at the last centre in January 2019. A much lower recruitment rate than expected were observed in the first months of the trial and the following actions were taken: inclusion criteria were modified (Protocol Version 2.4, see Participants), additional recruiting centres were initiated in March 2018, October 2018, and January 2019 (Protocol Versions 2.4–2.6, March 2018–January 2019), and based also on high retention rate, the sample size was revised based on updated power calculation in May 2019. We expect to end recruitment in October 2019.

Patient and public involvement

Participants in a pilot study on breathing retraining in asthma gave formal feedback on the intervention including information, patient instruction and follow-up (KH Andreasson, ST Skou, M Thomas, U Bodtger, 2017, 'Breathing Exercise pilot study', unpublished).

Participants

The target population is patients with physician diagnosed and specialist confirmed asthma, including patients with fixed airway obstruction, cough-variant asthma or other forms without current evidence of variable airflow obstruction,[42] and incomplete asthma control despite specialist-provided asthma care and regular use of moderate-dose to high-dose inhaled steroids with or without a second controller (GINA steps 3–5). The diagnosis of asthma is not simple, and variable airflow limitation can be difficult to demonstrate in patients currently on treatment.[14 43] Restricting the trial to those able to display physiological reversibility on treatment at recruitment into the trial would have resulted in a biassed and unrepresentative sample.

Danish respiratory outpatient clinics at Naestved, Roskilde, Bispebjerg, Aalborg, Hvidovre, Silkeborg and Odense hospitals, and the private Allergy & Lung Clinic, Elsinore (*Allergi og Lungeklinikken Helsingør*) will recruit consecutively during a 30-month inclusion period. Recruitment is expected to be finalised 31 October 2019.

The recruitment target is 190 participants with incomplete asthma control, randomly allocated 1:1 to intervention or control groups. At recruitment, ACQ6 ≥1.5 is used to identify participants with uncontrolled asthma. Modification was done 1 January 2018 to improve inclusion rates: participants will need to have an ACQ6 score ≥0.8 and to be in a stable phase of their asthma defined as no treatment changes in the month preceding randomisation to be randomised, while still having incomplete asthma control.

Inclusion criteria

- Referred from GP to a secondary, outpatient respiratory clinic for lack of asthma control.
- Asthma diagnosed by a pulmonologist.
- ≥2 doctor visits at a specialised, pulmonologist-lead asthma clinic.
- Age≥18 years.
- ACQ6 score ≥0.8.
- Willing and able to give written informed consent.
- Speaks, reads and understands Danish.

Exclusion criteria

- Trained in breathing exercises by physiotherapist last 6 months.
- Pregnancy.
- Any severe disease as judged by the responsible physician.
- Participating in another respiratory interventional research project.

Recruitment procedure and consent

The trial flow is outlined in figure 2. Written advertisements in the clinics pre-inform patients on the possibility of trial participation to motivate participation. The respiratory nurse or the pulmonologist will enrol eligible participants during the scheduled visit (which routinely includes ACQ6 scoring). The nurse will provide the initial oral and written trial information, and the pulmonologist will screen for eligibility. The participant will receive thorough verbal and written trial information and will have to return for a separate visit where a nurse or a physiotherapist will provide detailed information on the trial and respond to participant queries before written informed consent is obtained. Consent paper form, online supplementary file S2. If the enrolment rate is inadequate to

	TRIAL PERIOD					
	Enrolment	Allocation	Post-allocation			
TIMEPOINT	$-t_1$	0	t_1 0 months	t_2 3 months	t_3 6 months	t_4 12 months
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Inhalation check	X					
Randomisation		X				
INTERVENTIONS:						
Breathing Exercises			3 visits			
Usual specialist care			X			
ASSESSMENTS:						
Baseline, PROM	X					
Baseline, Objective measurements	X					
Demographic data	X					
Follow up, PROM				X	X[a]	X
Follow up, Objective measurements					X	
Adverse events				X	X	X
Medication usage						X[b]

Figure 1 The figure details the schedule of enrolment, interventions and assessments of BEAT DB trial in accordance with the Standard Protocol Items: Recommendations for Interventional Trials template.[40] BEAT DB trial: this acronym is used in ClinicalTrial.gov registration. [a]Primary endpoint is at 6 months follow-up. [b]Data collection of medication usage from baseline before allocation throughout until 12 months after allocation will be done at 12-months follow-up. BEAT DB, Breathing Exercises in Asthma Targeting Dysfunctional Breathing; PROM, patient-reported outcome measures.

meet the recruitment target, more centres will be invited to participate.

Randomisation procedure and concealment of allocation

After completion of baseline assessment, participants will randomly be allocated to UC with or without BrEX in a 1:1 allocation ratio by computer-generated randomisation using EasyTrial (EasyTrial APS, Aalborg, Denmark) in fixed blocks of four stratified by centre to assure equal size of groups at the seven centres. The chief investigator and all project workers will be blinded to the generation sequence. The nurse will activate the EasyTrial randomisation function to reveal the allocated group for each individual participant. This information will be forwarded to the participants by e-mail sent from EasyTrial. After allocation, the chief investigator will be informed and will ask the local physiotherapists to invite participants in the BrEX +UC group to initiate the intervention.

Blinding

The nature of the trial precludes blinding of participants or the physiotherapists delivering BrEX. Outcome assessors are blinded to the randomisation result, and participants will be reminded not to disclose their treatment allocation to the outcome assessor. Nurses who will perform extraction of clinical data from medical reports,

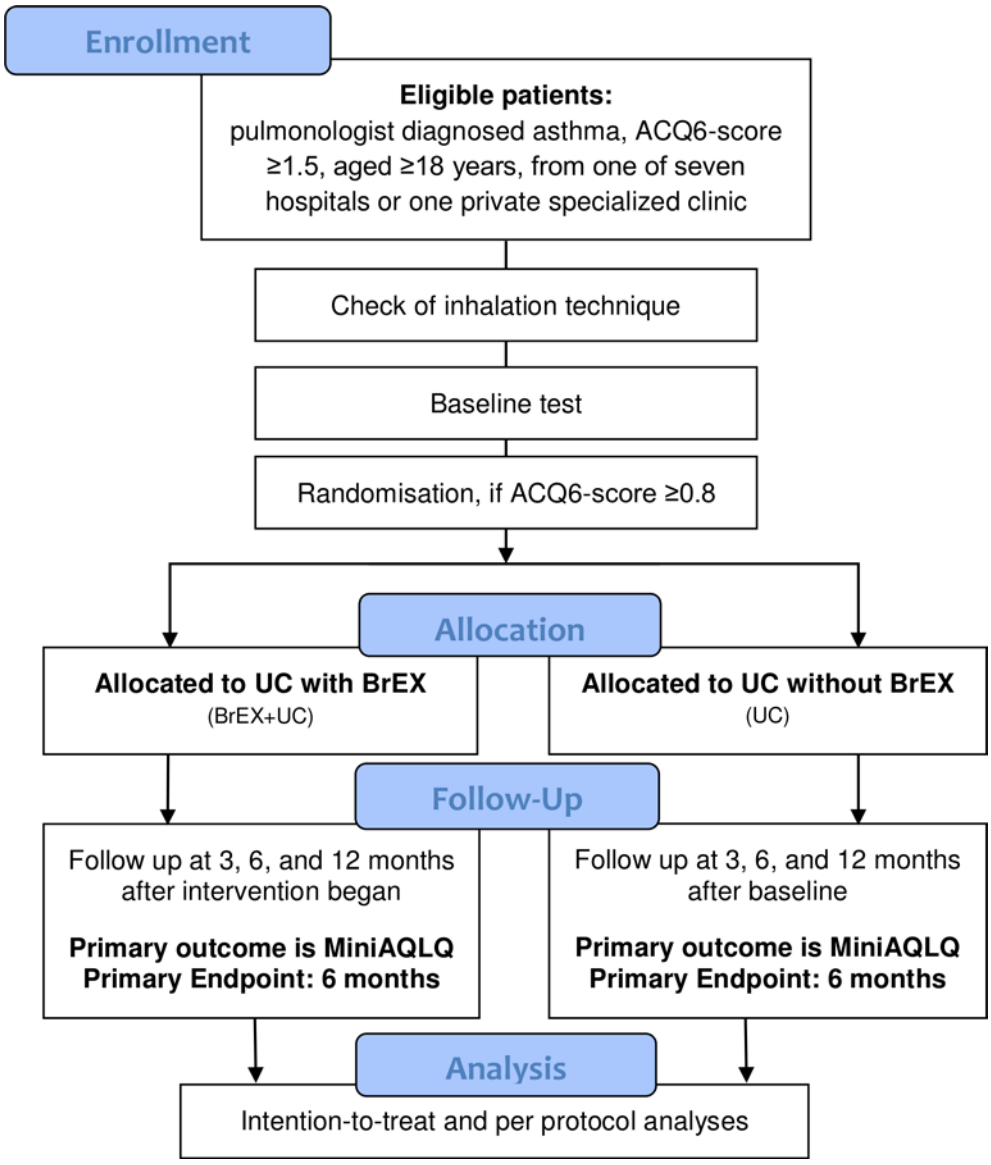

Figure 2 Patient flow through the RCT BEAT DB trial. Consolidated Standards of Reporting Trials (CONSORT) flow diagram 2010. BEAT DB, Breathing Exercises in Asthma Targeting Dysfunctional Breathing; ACQ6, asthma control questionnaire; BrEX, breathing exercises; MiniAQLQ, miniasthma quality of life questionnaire; RCT, randomised controlled trial; UC, usual specialist care.

and the statistician who will perform the analyses will also blinded to the allocation.

Blinded results (presented as group A compared with group B) will be presented to the research group, who will interpret the blinded results and prepare two alternative conclusions, prior to unblinding of the trial results.[44]

Interventions

At baseline, all participants will receive individual instruction in optimal inhalation technique by a respiratory nurse, who will also encourage the participant to use online video instructions.[45]

As the design is a pragmatic 'real-world setting' trial without standardisation of asthma therapy, the pharmacological treatment will be the choice of the responsible respiratory specialist, including changes, discontinuation or add-on of any treatment/combination. Treatment with positive expiratory pressure devices is not prohibited. The patient will be randomised to either usual care with Breathing Exercises (BrEX +UC) or usual care alone (UC).

Breathing Exercises (BrEX)

BrEX consists of three physiotherapist-sessions with duration of 60 min (initial session=week 1) and 30 min (at weeks 4 and 9, ± 7 days).

BrEX session one is t_1 in the group of usual specialist care with BrEX (BrEX +UC) figure 1.

The participant will be encouraged to do 10 min of home exercise twice daily.[32] The entire intervention combines elements of the Papworth method[46] and the Buteyko technique.[47]

Key points in the intervention are

Table 1 Overview of the BrEX intervention

Items	Description
1. Brief name	BrEX (Breathing EXercises).
2. Why	Previous studies showed the feature included in BrEX to be essential for persons with dysfunctional breathing and asthma The BrEX is simple and requires no devices to perform but fits in daily living. The goal of the intervention is that the patient incorporates an ideal breathing pattern and that this pattern becomes automated
3. What materials	The patient will be provided written materials with illustrations of elements of BrEX, including the home exercises. The physiotherapists will be provided a manual, including a schedule of anticipated progression
4. What procedure	Each BrEX session will include an initial interview (online supplementary file S4, 12-item interview list) and an observation of the breathing pattern (table 3). Features of BrEX are breathing pattern modification in rest and combined with physical activity and relaxation, breath holding exercise, handling of uncontrolled coughing, frequent sighing or yawning and patient education
5. Who provides	BrEX will be provided by physiotherapists, who are trained in the BrEX intervention at a mandatory 10-hour introduction, followed by thorough written information and telephone support (training and support given by the chief investigator), and have at least 1 year of experience in pulmonary physiotherapy
6. How	BrEX will be delivered individually and face-to-face
7. Where	In outpatient departments of physiotherapy at seven public hospitals in Denmark
8. When and how much	A 12-week intervention period featuring three physiotherapy sessions delivered in week 1, 4 and 9 (±7 days); the initial session will last for 60 min, and others for 30 min. Participants will be asked to do 10 min of home exercise twice daily throughout the 12 weeks
9. Tailoring	BrEX will be individualised in pace of progression and combinations, or of regression and simplicity according to interview at each session start and observations during the session
10. Modifications	N/A. Modifications will be reported (if any)
11. How well (planned)	Besides the introduction, the physiotherapists will adhere to a BrEX manual. Participants will be filling out a training diary
12. How well (actual)	N/A. This will be reported in the primary paper

This description is in accordance with the Template for Intervention Description and Replication, Hoffmann *et al.,* 2014.[41]
BrEX, Breathing EXercises; N/A, Not applicable.

- Modification/normalisation of respiratory rate and/or depth of breath by rhythmic, nasal inspiration, and diaphragmatic breathing, by long expiration, and by breath holding at FRC.[32 46 47] Uncontrolled, non-phlegm coughing and frequent sighing are often seen in patients with disordered breathing pattern. The participant will be trained to reduce sighing and/or coughing by a suppression-technique.[48]
- Relaxation,[32 46] especially of the neck, jaw, tongue and shoulders. We will emphasise the lowering of muscle tone in these areas and boost the feeling of gravity. The participant will be asked to 'let go' to get full support from the surroundings (pillow, plint, chair and ground) to increase feeling of being carried.
- Use of the breathing modification during walk and other physical activities.[32 46]
- Daily home exercise of BrEX.

The participant will receive a booklet covering all exercises in text and illustrations, theoretical information about breathing patterns and modification, and a page designated for an individualised home programme specified by the treating physiotherapist.

See TIDieR table (table 1) and Supplementary note for details on the BrEX intervention (online supplementary S3), and 12-item interview list (online supplementary S4). Danish version of the participant booklet and an English translation will be available on request, when the trial data collection has finished.

Usual specialist care

Participants in both groups will receive UC, which will be provided at the discretion of the responsible pulmonologist based on the individual needs of the participant's severity of disease and current level of asthma control. The UC is not a uniform intervention neither in contents nor in time spent (range 15–30 min), number of visits, nor visit intervals. The choice of pharmacotherapy is supported by step-up and step-down guidelines.[2]

The UC without BrEX group will be the control group in the trial and baseline date equals t_1 in this group figure 1.

Data collection procedure and retention

Data will be collected at baseline (t_1) and at 3, 6 and 12 months (t_2–t_4). Overview of outcome collection is showed in table 2. Before RCT initiation, all assessors will be introduced to, trained in, and supervised in the assessment procedure by the chief investigator. All assessors will be provided trial-specific assessment manuals, which have been tested in a pilot study (KH Andreasson, ST Skou, M Thomas, U Bodtger, 2017, 'Breathing Exercise pilot study', unpublished).

Patients-reported outcome measures (PROM) will be collected using online questionnaires in EasyTrial. Participants will receive invitation and links by e-mail, and—if necessary—an SMS reminder 2 weeks later (t_1-t_4 plus 2 weeks).

SenseWear (SW) data (accelerometry) will be extracted and entered by a research assistant not involved in any clinical parts of the trial.

Objective assessments will be done at the hospitals at baseline and at 6-month follow-up (±4 weeks) following a standardised procedure. The assessor will manually complete a datasheet, which will be entered as an electronic CaseReportForm in EasyTrial later.

The 6-month follow-up visit (t_3) will be planned by phone with the participant by a coordinating research assistant. Two days before the scheduled follow visit, the participant will receive standard reminders by e-mail and SMS. If the visit is not completed, no matter the cause, the coordinating research assistant will contact the participant by phone to reschedule the visit within the prespecified time frame of maximally +4 weeks.

Participants will be prompted to complete 3-month and 12-month follow-ups every second week until completion, reminders sent as SMS and e-mails after 2 weeks, and a phone call after 4 weeks.

If a participant discontinues the assigned allocation without withdrawing the consent, we will prompt him/her to remain in the trial that is, to complete the remaining follow-up visits/online questionnaires.

Reasons for non-adherence (eg, lack of interest, comorbidity reasons, exacerbation, emigration) and for non-retention (consent withdrawal, lost to follow-up) will be recorded.

Outcomes

Demographic data will be collected at baseline: gender, age, body mass index, smoking status and socioeconomic status (educational level, work status, and income).

Primary outcome

Primary outcome is the between-group mean change in Mini*Asthma Quality of Life Questionnaire* (MiniAQLQ) from baseline to 6-month follow-up.[4] MiniAQLQ is a validated, 15-item disease-specific PROM on experiences in symptoms, activity limitation, emotions and environment during the previous 2 weeks. A 7-point Likert scale (1=maximum impairment; 7=no impairment) is used, and MiniAQLQ-score is the mean of all items. In

Table 2 Overview of data collection in BEAT DB

	Baseline	3 months	6 months	12 months
Primary endpoint				
MiniAsthma Quality of Life Questionnaire (MiniAQLQ)*	@	@	@	@
Secondary endpoints				
Patient-reported information				
Asthma Control Questionnaire (ACQ6)	@	@	@	@
Nijmegen Questionnaire (NQ)	@	@	@	@
Hospital Anxiety and Depression Scale (HADS)	@	@	@	@
EuroQol-5D (EQ-5D-5L)	@	@	@	@
Global Perceived Effect rate (GPE)	N/A	@	@	@
Patient Acceptable Symptom State (PASS)	N/A	@	@	@
Treatment Failure (TF)	N/A	@	@	@
Smoking status	@		@	@
Socio-economic Status (SES)†	@			
Foster Score	@		@	
Anthropometric				
Gender	@			
Age	@			
Height, cm	@			
Weight, kg	@			
Body Mass Index (BMI)	@			
Register data				
Medication (treatment step 1–5)‡	@		@	@
Comorbidity	@		@	@
Scheduled and acute medical visits (prev.6mo)			@	@
Adverse events (AEs)	N/A	@	@	@
Adherence	N/A	@		
Functional capacity				
6 min Walk Test (6MWT)§	@		@	
Count Scale (CS)	@		@	
Breath Holding Time (BHT)	@		@	
Respiratory pattern observation	@		@	
Physical activity (SenseWear) average of 6 days¶				
Total energy expenditure (TEE), kJ (daily avg)	@	@	@	
Average METs (daily avg)	@	@	@	
Physical Activity Level (PAL) (daily avg)	@	@	@	

Continued

Table 2 Continued

	Baseline	3 months	6 months	12 months
Number of Steps (daily avg)	@	@	@	
Lung parameters**				
Expiratory volume in first second (FEV1)	@		@	
Forced vital capacity (FVC)	@		@	
Ratio (FEV1/FVC) % of predicted	@		@	
FEV1 % of predicted	@		@	
Peak expiratory flow rate (PEF)	@		@	
Maximal Inspiratory Pressure (MIP)	@		@	

*Primary outcome is MiniAQLQ at 6 month follow-up.
†SES includes educational level, annual family income, work status.
‡Reliever and controller medication.
§Including Borg CR10.
¶Subgroup will be measured. 3 month follow-up only until April 2018.
**Reference values for spirometry: GLI2012.
BEAT DB, Breathing Exercises in Asthma Targeting Dysfunctional Breathing; METs, metabolic equivalents; N/A, Not applicable.

moderate to severe asthma cohorts, MiniAQLQ has good reliability (ICC 0.83–0.86) and strong validity (criteria validity to AQLQ, $r \geq 0.80$; construct validity against ACQ, $r=0.69$).[4 49] The Danish version of MiniAQLQ is validated linguistically, although cultural adaptation is missing.[50 51]

Secondary outcome measures

Secondary (continuous) outcome measures are the between-group mean change for each. All secondary outcomes will be considered supportive of the primary outcome, that is, conclusions will only be guided by the primary outcome.[52 53]

Patient-reported outcomes

ACQ6 is the 6-item questionnaire version on asthma control addressing five symptoms using a 7-point Likert scale (0=fully controlled; 6=severely uncontrolled), and reliever medication use (0=No use; 6=More than 16 puffs most days) during the previous 7 days. Test–retest reliability of ACQ is excellent (ICC 0.83–0.90).[8 9] ACQ6 is valid in moderate to severe asthma; Cronbach's α is 0.86 (KH Andreasson, U Bodtger, ST Skou, M Thomas, J Comins, 2019, 'Rasch validation of the Asthma Control Questionnaire', unpublished results). ACQ score <0.75 corresponds to well-controlled asthma, ACQ score ≥1.5 denotes uncontrolled asthma, whereas ACQ from 0.75 to 1.5 correspond to incomplete asthma control or partly controlled asthma.[2 8 54]

NQ is a reliable 16-item screening questionnaire designed to assess subjective sensations compatible with hyperventilation during previous 7 days.[23]

Hospital Anxiety and Depression Scale (HADS) contains seven items concerning anxiety, and seven concerning depression and uses 4-point Likert scales; a low score indicates least mental health problems.[55] Asthma and disordered breathing pattern are known as associated with anxiety and depression.[56 57]

Global perceived effect (GPE) rate will be used as a retrospective evaluation of effect of asthma-related QoL as well as asthma control on a 7-point Likert scale.[58 59] This global transition rating enables investigation of the validity and the interpretability of the primary outcome.[59 60] This will be followed by the dichotomous *Patient Acceptable Symptom State* (PASS) that evaluates treatment success from the participant's perspective related to level of asthma-related QoL and to asthma control.[61] If the participant considers the symptom state to be 'non-acceptable', the participant will be asked whether he/she considers the state so unsatisfactory that *Treatment Failure* (TF) has occurred, answered by 'yes' or 'no'. GPE, PASS and TF will be used at all follow-ups.

EuroQol-5Dimension is a generic QoL tool consisting of a 5-dimension descriptive index (ranging from −0.59 to 1.00) and a Visual Analogue Scale (ranging from 0 to 100) describing self-perceived health status.[62 63]

Foster Score will be used to define the numbers of days (0–7) per week that the participant reports having taken his/her medication as prescribed.[64]

Objective performance outcomes

Physical activity level (PAL), metabolic equivalents, numbers of steps, and total energy expenditure (TEE) will be measured by a two axial *accelerometer* (SenceWear, SW) (BodyMedia *SenseWear*, Pittsburgh, PA, USA) monitoring activity during 6 days.[65] This is measured in all participants included May 2017–May 2018, hereafter only in participants from Naestved and Hvidovre Hospitals.

Functional capacity will be measured by *6 min Walk Test* (6MWT). The 6MWT is a validated measure of response to physical activity intervention in respiratory research.[66]

Dyspnoea level will be measured before and after 6MWT. To rate perceived dyspnoea the validated *Borg CR10* will be used,[67] as well as the *Count Scale* (CS).[68] CS implies that the participant loudly counts starting from one to as high as possible at a constant speed of 2 counts per second, guided by a metronome, during one exhalation from maximum inspiratory level.

*Breathing pattern observation during 60*s, following a non-validated 10-item observational list assesses the respiratory pattern at rest. See table 3.

Breath Holding Time (BHT)[69] will be measured in seconds from respiratory resting position (eg, FRC) until first involuntary respiratory muscle motion.

Spirometry (MedikroPro, M915, OY Finland) will be used to measure FEV1, forced vital capacity (FVC), FEV1/FVC ratio and peak expiratory flow rate.[70] Predicted values will be calculated using GLI2012.[71]

Table 3 Breathing pattern, 10-item observational list

Items observed for 60 s			
Respiration frequency	RF:		
Rhythmic respiration	Yes	No	
Inspiration initiated upper thorax	Yes, only	Yes, partly	No
Inspiration initiated by diaphragm	Yes, only	Yes, partly	No
Nasal inspiration	Yes, only	Yes, partly	No
Clearing of throat (cough slightly)	Number:		
Sighing (solitary large inhalation and exhalation)	Number:		
Yawning	Number:		
Coughing (non-productive)	Number:		
Bodily movement	Yes	No	
Method			
The participant is at rest in sitting position. The observer sits a little beside the viewpoint of the participant. The observer sits facing the participant, uses a time watch, and follows instruction: Introduce to the participant: *I will observe your breathing pattern for 1 min* *I will inform you, when the minute starts* *You are supposed to sit calm* *We are not allowed to talk meanwhile* Start the time watch after a participant's expiration Observe and judge subjectively the rhythm, the inspiratory movement initiation, bodily movement and the route of breathing Count clearings of throat, sighs, yawns, and coughs Stop observing after 60 s. Note results in the table.			

This list of observation items includes features that can define the breathing pattern. Karen H. Andreasson developed the list for the BEAT DB trial. Version 30 April 2019.
BEAT DB, Breathing Exercises in Asthma Targeting Dysfunctional Breathing; RF, respiration frequency.

Inspiratory muscle strength (Maximal Inspiratory Pressure, MIP) will be measured by KH2 (POWER Breathe, Southam, Warwickshire, UK).[72]

Register data from medical records

We will extract medication prescriptions and comorbidity at baseline, and medication prescriptions, comorbidity, adverse events (AEs; eg, emergency room visits), and number of consultations at specialist care respiratory nurses and/or pulmonologists from baseline until 12-month follow-up from electronic medical records.

Adherence

Participants in BrEX +UC group will be asked to complete a BrEX home training diary during the 12 weeks of intervention. Number of exercising days and minutes used will be described. At sessions 2 and 3, the physiotherapist will evaluate the adherence to the home exercise programme in a numeric rang scale 1–5 (1=no adherence, 5=excellent adherence). The physiotherapist will re-schedule any missed appointments. Good adherence with BrEX is defined as completion of three treatment sessions.

Data management and data monitoring

Data storage follows requirements in GDPR and will be kept confident and safe in EasyTrial during and after the trial. The Danish Data Protection Agency (REG-55–2016) has approved the trial. Only the chief investigator will have access to the full dataset. Security is enforced by personal password and SMS passcode accompanied with limited assignation at different levels of EasyTrial to the individual worker. All paper forms are designated pseudonyms and transported in code-locked bag to locked file cabinet at Naestved Hospital.

All paper-based data will be verified by an independent duplicate data entry.

No stopping guidelines are scheduled and no Data Monitoring Committee is involved, as the interventions and assessments are deemed safe in former trials.

Sample size

As argued by Norman *et al*,[73] no universal minimal important difference (MID) exists, as MID depends on the clinical setting, population and the intervention. However, it can often be estimated as half a standard deviation (SD).[73] Thomas *et al*. (breathing exercises vs education by a nurse in mild to moderate asthma) found a 0.38 change in MiniAQLQ score.[27]

We will use the effect size found in Thomas *et al*[27] as MID in our sample calculation (with a calculated SD of 0.76) and expect to find a similar or higher effect size, as (a) BrEX will be an add-on intervention to standard specialist care instead of a head-to-head comparison as in Thomas *et al*, and (b) as this secondary care asthma population is expected to have a higher disease burden due to asthma, that is, greater room for improvement.

There is an inherent risk of the trial being underpowered because the SD of MiniAQLQ after BrEX in secondary care is unknown. However, based on previous studies,[27 28] we expect that our SD will be sufficient to reflect the population.

For the present trial, the sample size needed is 172 to detect a 0.38 unit difference between groups in MiniAQLQ score (SD of 0.76, power of 90%, and p value of 0.05 (two-sided)). To allow for drop-outs, we will aim to randomise 190 participants.

Statistical methods

Analysis of primary and secondary outcomes

Data will be analysed on an intention-to-treat basis, thus regardless of protocol adherence, using appropriate parametric or non-parametric tests depending on data distribution. Primary endpoint (between-group difference in change in the MiniAQLQ at 6-month follow-up) and other continuous variables will be analysed using a mixed effects model with subject being a random factor and visit (ie, baseline, 3 months and 6 months) and treatment arm (BrEX +UC or UC) being fixed factors and adjusted for baseline imbalance and treatment centre. These analyses will start in April 2020. Per protocol analyses in participant with good adherence

will be done. Data at 12 months will be included in subsequent secondary analyses of long-term treatment results.

Imputations will only be done to explore results of SW, and sensitivity analyses (with and with-out imputation) will test robustness of these results. We will conduct an analysis of SW data to explore the effect of the intervention on PAL, TEE and steps per day.

Secondary analyses include a numbers-needed-to-treat (NNT) estimation and trial-specific cut-offs for clinically relevant differences in MiniAQLQ (primary outcome) to guide the clinical interpretation of the results. We will estimate NNT as formula 1/(TER–MER), TER being the event rate (proportion of responders, ie, participants improving at least corresponding to the clinically relevant difference, 0.5 units)[49] in the BrEX group, and MER the event rate in the usual care group. We will calculate the trial-specific MID/responder threshold by subtracting the mean MiniAQLQ score for those reporting to have experienced a 'small but not important change' in GPE from those reporting 'important change' in GPE at 6 months.

Both adjusted and unadjusted results will be reported including 95% CIs. No interim analyses will be made. STATA 15.0 (StataCorp LP) will be used. P values<0.05 will be regarded statistically significant. Statistical analyses plan will be made publicly available before any analyses and unblinding of data.

ETHICS, DISSEMINATION AND PERSPECTIVES OF THE TRIAL

Ethics and auditing

Region Zealand Research Ethics Committee approved this trial (SJ-552), and it will be conducted in agreement with the Helsinki declaration. Written informed consents will be obtained from all participants. At the recruitment interview, the participants will be informed that if they are allocated to usual care group they will be provided physiotherapy (BrEX) later, given the RCT will find a clinically relevant benefit.

Before informed written consent is obtained, potential participants will receive written information about the trial, after which research team members (nurse or physiotherapist, trained and supervised by chief investigator) will inform about the trial and answer any questions from the potential trial participant. The Regional Committees on Health Research Ethics are annually selecting a number of trials for auditing. The audit process is independent of research groups and sponsors.

Adverse events

We will ask participants about experienced AEs at every follow-up using open-probe questions, and record on standardises forms for reporting and analysis. Additionally, the medical records will be checked at 12 months follow-up for all AEs occurring during period of trial. We define an AE as respiratory events or other events during the trial, which may be related to aspects of trial participation leading to contact with the GP or hospital. All serious AEs, defined as life threatening or resulting in hospitalisation,[74] will be recorded. If a participant sustains a trial related harm, the hospital assurance covers him/her.

Dissemination of results and protocol amendments

All results will be published, regardless positive, negative or inconclusive, in peer-reviewed journals in due time after trial completion and to follow the Consolidated Standards of Reporting Trials (CONSORT) statement.[52]

Exclusion criteria were modified on first of March 2018 when (a) other known cause of dyspnoea (eg, cardiovascular disease, other respiratory disease) and (b) neurological disease (cannot follow an instruction or close lips) were deleted.

Any important protocol modification will be reported to the Ethics Committee for approval, and they will be registered at ClinicalTrials.gov.

Perspective and additional knowledge for clinical practice

The present trial will provide evidence of the effectiveness of the BrEX programme in patients with incomplete asthma control despite attending specialist care and adhering to moderate to high doses inhaled corticosteroids (ICS) with/without a second controller (GINA steps 3–5).[2] Asthma control is not obtained in the majority of patients,[14 75 76] and new measures to improve patients' daily life with asthma are needed. The trial results will add pivotal information to future evidence-based guidelines and clinical practice. Although primarily an effectiveness trial, we will also gain potential insights into the characteristics of responders and into the mechanisms of effectiveness. In particular, we will explore the predictive value of reduced BHT, comorbid anxiety and depression (HADS), socioeconomic status, smoking status, and PAL at baseline.

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Contributors KHA, UB, STS and MT (Research group, ie, 'steering committee') contributed substantially to the concept and design of this trial. The chief investigator (KHA) developed manuals for recruitment, assessment, and treatment, written information, applications for grants, and approval assignments, made registry at ClinicalTrial.gov, introduced and supervised the recruitment, assessment, and treatment procedures to all involved physiotherapists and nurses, and led the data collection. UB, STS, and MT gave feedback. STS specifically contributed in description of the statistical analyses.KHA drafted the manuscript. All authors (KHA, STS, CSU, HM, KS, JSJ, KDA, KBR, CP, MT, and UB) provided intellectual feedback to the manuscript and approved the final version.

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Disclaimer The funders have no part in the design of the trial and will not have any role in its execution, analyses, interpretation of results, or decision related to reports of the results. The funders did not have any role in this trial other than to provide funding.

Competing interests STS is an associate editor of the Journal of Orthopaedic & Sports Physical Therapy, has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all of which are outside the submitted work. He is co-founder of GLA:D®, a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

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REFERENCES

1 O'Connor E, Patnode CD, Burda BU. Breathing Exercises and/or Retraining Techniques in the Treatment of Asthma: Comparative Effectiveness [Internet]. In: *AHRQ comparative effectiveness reviews*. 71. Rockville, MD: Agency for Healthcare Research and Quality (US), 2012.
2 GINA, Global Initiative for Asthma. Global strategy for asthma management and prevention, 2018. Available: http://www.ginastma.org
3 Reddel HK, Taylor DR, Bateman ED, *et al*. An official American thoracic Society/European respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59–99.
4 Juniper EF, Guyatt GH, Cox FM, *et al*. Development and validation of the mini asthma quality of life questionnaire. *Eur Respir J* 1999;14:32–8.
5 Luskin AT, Chipps BE, Rasouliyan L, *et al*. Impact of asthma exacerbations and asthma triggers on asthma-related quality of life in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol Pract* 2014;2:544–52.
6 Correia de Sousa J, Pina A, Cruz AM, *et al*. Asthma control, quality of life, and the role of patient enablement: a cross-sectional observational study. *Prim Care Respir J* 2013;22:181–7.
7 Bateman ED, Bousquet J, Keech ML, *et al*. The correlation between asthma control and health status: the goal study. *Eur Respir J* 2007;29:56–62.
8 Juniper EF, O'Byrne PM, Guyatt GH, *et al*. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902–7.
9 Juniper EF, Svensson K, Mörk A-C, *et al*. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005;99:553–8.
10 Porsbjerg C, Ulrik C, Skjold T, *et al*. Nordic consensus statement on the systematic assessment and management of possible severe asthma in adults. *Eur Clin Respir J* 2018;5.
11 Currie GP, Douglas JG, Heaney LG. Difficult to treat asthma in adults. *BMJ* 2009;338:b494.
12 Solomon BK, Wilson KG, Henderson PR, *et al*. A breathlessness Catastrophizing scale for chronic obstructive pulmonary disease. *J Psychosom Res* 2015;79:62–8.
13 British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax* 2014;69(Suppl 1):1–192.
14 Chung KF, Wenzel SE, Brozek JL, *et al*. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343–73.
15 Barker N, Everard ML. Getting to grips with 'dysfunctional breathing'. *Paediatr Respir Rev* 2015;16:53–61.
16 Chung KF, Godard P, Adelroth E, *et al*. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task force on Difficult/Therapy-Resistant asthma. European respiratory Society. *Eur Respir J* 1999;13:1198–208.
17 Depiazzi J, Everard ML. Dysfunctional breathing and reaching one's physiological limit as causes of exercise-induced dyspnoea. *Breathe* 2016;12:120–9.
18 Boulding R, Stacey R, Niven R, *et al*. Dysfunctional breathing: a review of the literature and proposal for classification. *Eur Respir Rev* 2016;25:287–94.
19 Barker NJ, Jones M, O'Connell NE, *et al*. Breathing exercises for dysfunctional breathing/hyperventilation syndrome in children. *Cochrane Database Syst Rev* 2013:CD010376.
20 West JB, Luks AM. *Respiratory physiology: the essentials*. 10 edn. Philadelphia: Wolters Kluwer, 2016.
21 Connett GJ, Thomas M. Dysfunctional breathing in children and adults with asthma. *Front Pediatr* 2018;6.
22 Courtney R, Greenwood KM, Cohen M. Relationships between measures of dysfunctional breathing in a population with concerns about their breathing. *J Bodyw Mov Ther* 2011;15:24–34.
23 van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen questionnaire in recognition of the hyperventilation syndrome. *J Psychosom Res* 1985;29:199–206.
24 van Dixhoorn J, Folgering H. The Nijmegen questionnaire and dysfunctional breathing. *ERJ Open Res* 2015;1:00001-2015.
25 Veidal S, Jeppegaard M, Sverrild A, *et al*. The impact of dysfunctional breathing on the assessment of asthma control. *Respir Med* 2017;123:42–7.
26 Thomas M, Bruton A, Ainsworth B. Use of the Nijmegen questionnaire in asthma. *ERJ Open Res* 2015;1:00033-2015.

27 Thomas M, McKinley RK, Mellor S, *et al*. Breathing exercises for asthma: a randomised controlled trial. *Thorax* 2009;64:55–61.
28 Bruton A, Lee A, Yardley L, *et al*. Physiotherapy breathing retraining for asthma: a randomised controlled trial. *Lancet Respir Med* 2018;6:19–28.
29 Toennesen LL, Meteran H, Hostrup M, *et al*. Effects of exercise and diet in nonobese asthma Patients—a randomized controlled trial. *J Allergy Clin Immunol* 2018;6:803–11.
30 Stanton AE, Vaughn P, Carter R, *et al*. An observational investigation of dysfunctional breathing and breathing control therapy in a problem asthma clinic. *J Asthma* 2008;45:758–65.
31 Bott J, Blumenthal S, Buxton M, *et al*. Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. *Thorax* 2009;64(Suppl 1):i1–52.
32 Thomas M, Bruton A. Breathing exercises for asthma. *Breathe* 2014;10:312–22.
33 Bruurs MLJ, van der Giessen LJ, Moed H. The effectiveness of physiotherapy in patients with asthma: a systematic review of the literature. *Respir Med* 2013;107:483–94.
34 Hagman C, Janson C, Emtner M. Breathing retraining - a five-year follow-up of patients with dysfunctional breathing. *Respir Med* 2011;105:1153–9.
35 Grammatopoulou EP, Skordilis EK, Stavrou N, *et al*. The effect of physiotherapy-based breathing retraining on asthma control. *J Asthma* 2011;48:593–601.
36 Thomas M, McKinley RK, Freeman E, *et al*. Breathing retraining for dysfunctional breathing in asthma: a randomised controlled trial. *Thorax* 2003;58:110–5.
37 Prem V, Sahoo RC, Adhikari P. Comparison of the effects of Buteyko and pranayama breathing techniques on quality of life in patients with asthma - a randomized controlled trial. *Clin Rehabil* 2013;27:133–41.
38 Freitas DA, Holloway EA, Bruno SS, *et al*. Breathing retraining for adults with asthma. *The Cochrane Library* 2013.
39 Burgess J, Ekanayake B, Lowe A, *et al*. Systematic review of the effectiveness of breathing retraining in asthma management. *Expert Rev Respir Med* 2011;5:789–807.
40 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
41 Hoffmann TC, Glasziou PP, Boutron I, *et al*. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348:g1687.
42 Backer V, Sverrild A, Ulrik CS, *et al*. Diagnostic work-up in patients with possible asthma referred to a university hospital. *Eur Clin Respir J* 2015;2.
43 Taylor DR, Bateman ED, Boulet L-P, *et al*. A new perspective on concepts of asthma severity and control. *Eur Respir J* 2008;32:545–54.
44 Järvinen TLN, Sihvonen R, Bhandari M, *et al*. Blinded interpretation of study results can feasibly and effectively diminish interpretation bias. *J Clin Epidemiol* 2014;67:769–72.
45 Astma-Allergi_Danmark. Brug din astmamedicin rigtigt (Danish) (use your asthma medication correctly)., 2016. Available: http://astma.astma-allergi.dk/styrpaateknikken
46 Holloway EA, West RJ. Integrated breathing and relaxation training (the Papworth method) for adults with asthma in primary care: a randomised controlled trial. *Thorax* 2007;62:1039–42.
47 Cowie RL, Conley DP, Underwood MF, *et al*. A randomised controlled trial of the Buteyko technique as an adjunct to conventional management of asthma. *Respir Med* 2008;102:726–32.
48 Chamberlain Mitchell SAF, Garrod R, Clark L, *et al*. Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. *Thorax* 2017;72:129–36.
49 Ehrs P-O, Nokela M, Ställberg B, *et al*. Brief questionnaires for patient-reported outcomes in asthma: validation and usefulness in a primary care setting. *Chest* 2006;129:925–32.
50 Juniper E. Cultural adaptation and linguistic validation. secondary cultural adaptation and linguistic validation, 2016. Available: http://www.qoltech.co.uk; http://www.qoltech.co.uk/language_lists.html - acq
51 Acquadro C, Conway K, Giroudet C, *et al*. *Linguistic validation manual for patient-reported outcomes (PRO) instruments*. Lyon, France: MAPI Research Institute, 2004.
52 Moher D, Hopewell S, Schulz KF, *et al*. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c869.
53 EMEA. *Points to consider on multiplicity issues in clinical trials*. London: European Medicines Agency, 2002: 10.
54 Juniper EF, Bousquet J, Abetz L, *et al*. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006;100:616–21.
55 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
56 Hagman C, Janson C, Emtner M. A comparison between patients with dysfunctional breathing and patients with asthma. *Clin Respir J* 2008;2:86–91.
57 Agache I, Ciobanu C, Paul G, *et al*. Dysfunctional breathing phenotype in adults with asthma - incidence and risk factors. *Clin Transl Allergy* 2012;2:18.
58 Kamper SJ, Ostelo RWJG, Knol DL, *et al*. Global perceived effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. *J Clin Epidemiol* 2010;63:760–6.
59 Guyatt GH, Norman GR, Juniper EF, *et al*. A critical look at transition ratings. *J Clin Epidemiol* 2002;55:900–8.
60 Fischer D, Stewart AL, Bloch DA, *et al*. Capturing the patient's view of change as a clinical outcome measure. *JAMA* 1999;282:1157–62.
61 Kvien TK, Heiberg T, Hagen KB. Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (pass): what do these concepts mean? *Ann Rheum Dis* 2007;66(Suppl 3):iii40–1.
62 Janssen MF, Pickard AS, Golicki D, *et al*. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013;22:1717–27.
63 Sørensen J, Davidsen M, Gudex C, *et al*. Danish EQ-5D population norms. *Scand J Public Health* 2009;37:467–74.
64 Foster JM, Smith L, Bosnic-Anticevich SZ, *et al*. Identifying patient-specific beliefs and behaviours for conversations about adherence in asthma. *Intern Med J* 2012;42:e136–44.
65 Brazeau A-S, Karelis AD, Mignault D, *et al*. Test–retest reliability of a portable monitor to assess energy expenditure. *Appl Physiol Nutr Metab* 2011;36:339–43.
66 Holland AE, Spruit MA, Singh SJ. How to carry out a field walking test in chronic respiratory disease. *Breathe (Sheff)* 2015;11:128–39.
67 Borg E, Borg G, Larsson K, *et al*. An index for breathlessness and leg fatigue. *Scand J Med Sci Sports* 2010;20:644–50.
68 Wang H-yan, Xu Q-fen, Yuan W, *et al*. A new method for rating dyspnea during exercise in patients with chronic obstructive pulmonary disease. *Chin Med J (Engl)* 2013;126:3616–20.
69 Courtney R, Cohen M. Investigating the claims of Konstantin Buteyko, M.D., Ph.D.: the relationship of breath holding time to end tidal CO2 and other proposed measures of dysfunctional breathing. *J Altern Complement Med* 2008;14:115–23.
70 Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
71 Quanjer PH, Stanojevic S, Cole TJ, *et al*. Multi-Ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
72 Langer D, Jacome C, Charususin N, *et al*. Measurement validity of an electronic inspiratory loading device during a loaded breathing task in patients with COPD. *Respir Med* 2013;107:633–5.
73 Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003;41:582–92.
74 Food and Drug Administration. What is a serious adverse event? Secondary what is a serious adverse event?Available: http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm
75 Janson C, Accordini S, Cazzoletti L, *et al*. Pharmacological treatment of asthma in a cohort of adults during a 20-year period: results from the European community respiratory health survey I, II and III. *ERJ Open Res* 2019;5.
76 Cazzoletti L, Marcon A, Janson C, *et al*. Asthma control in Europe: a real-world evaluation based on an international population-based study. *J Allergy Clin Immunol* 2007;120:1360–7.

S1, Supplementary Table

This table shows the main trial information, according to World Health Organization trial Registration Data Set.

It follows Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.

Table 1 Trial Registration data

Data category	Information
Primary registry and trial identifying number	Clinicaltrials.gov NCT03127059
Data of registration in primary registry	April 26, 2017
Secondary identifying numbers	The local Ethics Committee, Zealand (SJ-552) Danish Data Protection Agency (REG-55-2016)
Source(s) of monetary or material support	Naestved, Slagelse and Ringsted Hospitals' Research Fund, Region Zealand Health Scientific Research Foundation, The Danish Foundation TrygFonden (ID: 117031), and the Association of Danish Physiotherapist's Research Fund.
Primary sponsor	Department of Physiotherapy and Occupational Therapy and Department of Respiratory Medicine, Naestved-Slagelse-Ringsted Hospitals, Denmark.
Secondary sponsors	University of Southern Denmark
Contact for public queries	KHA, PT, MSc, khad@regionsjaelland.dk
Contact for scientific queries	KHA, PT, MSc, khad@regionsjaelland.dk
Public Title	Asthma and physiotherapy
Scientific title	Protocol for a multicentre randomised controlled trial to investigate the effect on asthma related quality of life from breathing retraining in patients with incomplete asthma control attending specialist care.
Country of recruitment	Denmark
Health condition(s) or problem(s) studied	The effectiveness of a breathing retraining programme as an adjuvant treatment for patients with incomplete asthma control attending specialist clinics.
Intervention(s)	a) Breathing exercises with usual care b) Usual care
Key inclusion and exclusion criteria	Inclusion: • Referred from GP to a secondary, out-patient respiratory clinic for lack of asthma control

	• Age ≥ 18 years, both genders • Pulmonologist-diagnosed asthma • Previously ≥2 doctor visits at a specialised, pulmonologist-lead asthma clinic • Incomplete asthma control (Asthma Control Questionnaire (6 items, ACQ6) -score ≥ 0.8) Exclusion: • Trained in breathing exercises by physiotherapist last 6 months • Pregnancy • Any other severe disease as judged by the responsible physician • Participating in another pulmonary interventional research-project.
Study type	Interventional, superiority trial, 1:1.
	Allocation: randomised, controlled, two parallel groups, assessor blinded.
	Primary purpose: assessment of treatment efficacy.
	Phase 3
Date of first enrolment	27th April 2017
Target sample size	190
Recruitment status	Recruiting
Primary outcome(s)	Mini Asthma Quality of Life Questionnaire (target time point 6 months).
Key Secondary outcomes	ACQ6, Nijmegen Questionnaire, Hospital Anxiety and Depression Scale, EuroQual-5 Dimensions, Global Perceived Effect Rate, Physical Activity Level, number of steps daily, 6 Minute Walk Test, FVC % predicted, FEV1 % predicted, maximal inspiratory pressure, medication (treatment step 1-5).

SUPPLEMENTARY NOTE S3, DESCRIPTION OF INTERVENTION

This supplementary file is connected to

Protocol for a multicentre randomised controlled trial to investigate the effect on asthma related quality of life from breathing retraining in patients with incomplete asthma control attending specialist care in Denmark *(BMJ Open* 2019;. doi: bmjopen-2019-032984)

Karen Hjerrild Andreasson *et al*.

Item 1. Brief Name

The BEAT DB (Breathing Exercises in Asthma Targeting Dysfunctional Breathing) –trial will use a version of breathing exercises with a composition a little different from breathing retraining former used in clinical trials. We will define our version in the following paragraphs and will use the shortened name *BrEX* (Breathing EXercises).

Description of BrEX adheres to the Template for Intervention Description and Replication (TIDieR),[1].

Item 2. Why: Describe any rationale, theory, or goal of the elements essential to the intervention

BrEX combines breathing pattern modification, relaxation, education, and physical activities,[2,3]. Previous studies showed these elements to be essential for persons with dysfunctional breathing and asthma,[3-5].

The intervention is simple and requires no devices to perform but fits in daily living. The goal of the intervention is that the patient incorporates an ideal breathing pattern and this pattern becomes automated.

The intervals between sessions (three respectively four weeks) are chosen to secure time for usage and challenges from daily life to arise, and thus opportunity to supervise the participant in how to handle these challenges.

The aim for the education is to provide the theoretical knowledge about causes of dysfunctional breathing and thereby reassure the participant that the breathlessness and air hunger is not dangerous. The initial inhalation check is of great importance to make sure the participant can take his/her medication and in worst case prevent an asthma attack.

The extreme disordered breathing patterns range from fast and shallow to slow and deep. The first e.g. rate 20-40, thoracic breathing also known as hyperventilation, and the latter e.g. rate 5-8, diaphragmatic and whole thorax breathing, large tidal volume close to total lung capacity resulting in high ventilation volume,[6,7]. However, both patterns result in increased minute volume. A patient with disordered breathing pattern may sigh often to compensate for over-inflated lung and

elevated tidal volume (e.g. end of tidal volume over FRC) to achieve FRC (relaxation pressure of lung plus chest wall equals the atmospheric pressure),[7,8]. Uncontrolled, non-phlegm coughing is often seen in patients with disordered breathing pattern. The participant will be trained to reduce sighing and/or coughing by a suppression technique[9].

Breathlessness can elevate feelings of anxiety thus increase peripheral muscle tone,[2,5,10]. Therefore, the respiratory auxiliary muscles (neck, upper chest, and shoulder) will often be activated. Relaxation will be used aiming for a lower muscle tone of neck, jaw, tongue and shoulders. These regions of the body are also chosen as relaxation here may influence muscle tone in the entire body (empirical experience). We will emphasize the feeling of gravity. The feeling of being supported from the surroundings as well as the ability to 'let go' are used as this can easily be translated into activities of daily living contrary to 'hold-relax'-method (slowly repeated and few seconds lasting isometric muscle contractions followed by muscle relaxation in parts of the body).

Item 3. What (materials)

The usual care (UC)-group will not receive any material besides the initial written information given at recruitment.

Only the BrEX-participants will receive a 16-paged booklet that explains the dysfunctional breathing entity and its symptoms. Further, the booklet defines the exercises in text supplied with pictures of positions and explanations of their intended effect. In the booklet the physiotherapist will specify which exercises and on what level the participant will have to do them at home.
The BrEX–participants will be given a home exercise diary and information on how to report in it.

The physiotherapists who provide the BrEX-intervention will receive a 5-page manual, a schedule of the elements that incorporate the intervention including the anticipated progression, and a two-paged journal for easy documentation during the sessions.
The 5-paged BrEX manual, the Danish version of the participant booklet (A) and an English translation (B) will be available on request, when the trial data collection has finished.

Item 4. What (procedures)

Both the usual specialist care (UC)-group and the BrEX+UC-group will continue their scheduled and/or acute appointments and treatments (e.g. pharmacological) at the outpatient ward throughout the trial period. None respiratory physiotherapy, besides BrEX for the BrEX+UC-group is provided.
The BrEX+UC-group will be given the additional BrEX:

Medical history

Anamnestic information on the frequency, severity and situations of breathing pattern symptoms (primarily dyspnoea), habitual physical activity level (training habits) will be obtained, besides the personal 'request of change in management' (individual goal setting).

The latter will be used to facilitate patient involvement and to enable the participant evaluation of implementation of intervention at the third session.

Each session will initiate with a) a 12-items interview on experience of symptoms from breathing pattern during the last 7 days (Twelve items list, Supplementary file, **S4**; A criteria list elaborated with inspiration from *Dysfunctional Breathing criterion list* by C. Hagman, C. Janson, M. Emtner), and b) an 60 sec observation of the breathing pattern while resting using a non-validated assessment tool (table **2**).

Breathing exercises

Breathing exercises will typically proceed from sitting position (introduction) then through positions of supine, side lying, beach-position (supine with hands under the head), sitting, leaning (in standing) the back to a wall, standing, and walking.

Progression of the activities includes less support from surface, elevated point of gravity, and involvement/ inclusion of transfer or activity (stationary biking, walking faster, stair climbing).

Breathing pattern modification and physical activity

The participant will be instructed to do nasal inspiration, diaphragmatic breathing, in a rhythmic frequency of 12 cycles per minute with an intake of about 500 ml per breath,[8].

The depth of breath is allowed to grow with more intense activity, but the participant will be guided to continue (or re-establish) this breathing pattern during his/her progression of activity level and/or complexity.

The physiotherapists will facilitate by hands on thorax and epigastria, and guide diaphragmatic breathing verbally during the breathing modification.

Breath-holding exercise

The participant will be advised to challenge his/her tolerance of air hunger in a breath-holding exercise. The breath holding exercise is preceded by assessment of Breath-Holding Time (BHT) measured in seconds from the respiratory resting position, e.g. functional residual capacity (FRC),

Andreasson KH, *et al*. *BMJ Open* 2019; 9:e032984. doi: 10.1136/bmjopen-2019-032984

when the participant closes the mouth and pinches his/her nose to obstruct the nasal pathway, until the breathlessness cannot be tolerated any longer,[11].
In the present trial, the breath-holding exercise contains cycles of breath-holds in a respiratory pattern of inspiration, expiration, and pause of one third of the BHT, repeated three times.

Handling coughs, sighs, and yawns
In case of uncontrolled coughing, frequent sighing or yawning the participant will be advised to do a three steps action; 1) close mount, pinch nose, and pause the breathing for 5-10 seconds, suppressing the need for breathing, 2) swallow powerfully, and 3) twenty slow nasal breaths.
This is inspired from cough suppression technique,[9].

Relaxation
Relaxation will be introduced in side lying or supine position to achieve the least required muscular activity.
The participant will be instructed to lower muscle tone in neck, jaw, tongue, and shoulders, and to boost the feeling of gravity.
The participant must avoid biting the teeth together and the tongue is supposed to lie wide and soft covering the teeth and gently touch the inside of the lip. If the jaw and tongue are tensed, the participant will be instructed to mobilize the jaw joints by opening his/her mouth maximally and to stick out his/her tongue as far as possible before returning to a relaxed position of jaw and tongue with closed lips.

He/she will be asked to ‘let go’ to get full support from the surroundings (pillow, plint, chair, ground) to increase feeling of being carried.
The physiotherapists will facilitate by compression downwards by hands on head, shoulder, and hip/knee during the relaxation. To facilitate the low tone in the tongue, the physiotherapist will do slow compression with the thump under jaw.

Education
Repetition of the theoretical background for dysfunctional breathing will be given to relate the observations done by the participant and the physiotherapist.

In addition to the physical treatment, the patient will receive general (simplified) explanation about overbreathing and hyperventilation, the physiological and muscular response, and known triggers. Throughout the sessions, the elements and their intention are explained to the patient.

Home exercise, an additional activity

Physiotherapist-sessions and home exercises will interact to support adherence. The patient is expected to continue doing home exercises 10 minutes twice daily throughout 12 weeks.

Item 9. Tailoring/titration

Adjustment of intervention

At the beginning of second and third session, the participant will be asked about obstacles (e.g. other things/incidences that intervene), difficulties (e.g. problems in doing the program) and success (e.g. positive experience in implementing the program).

The therapist will give feedback and discuss/evaluate how implementing of breathing modification can improve.

Progression/Combinations

Progression of the intervention will follow the concept, but is to be individualised by the physiotherapist for every participant related to

- Pace of progression and combination, or if needed regression and simplicity.
- Adjustment of the amount of surface (less vs. more)
- Advancement in position. The participant has to manage rhythmic nasal diaphragmatic breathing in supine (or side lying) before activities in sitting can start, and likewise in sitting before standing and transferring activities can start.
- Complexity of the activity.
    - Inclusion of breathing pattern modification during relaxation. This is considered advanced level, as many dysfunctional breathing patients have difficulties with the combination.
    - Inclusion of relaxation technique in breathing pattern modification during activity (see above).

Item 5. Who provided – intervention provider

Physiotherapists with at least 1 year of experience in respiratory physiotherapy, employed to treat pulmonary patients at the included hospitals, will provide the BrEX-intervention during their employed working hours. The departments will be reimbursed for their salary.

Training and supportive activities will be given to the physiotherapists to standardize the BrEX education.

Before initiation of the trial:

- A mandatory 10 hour-introduction to the intervention, covering description of the disease, the diagnostics, the typical patient, examples of typical and more extreme cases, and a supervised hands-on session. The chief investigator (physiotherapist) and two pulmonologists will give the theoretical introductive lectures. The practical lectures will be held by advanced physiotherapists, who have 2-4 years of clinical experience in treatment of breathing pattern modification in patients with asthma (chief investigator and two other physiotherapists).
- Before treating the trial participants, the physiotherapists will treat two patients similar to the target-population.
- The physiotherapists will be given a 5-paged manual.

During the trial period:

- Treatment support by meetings, phone, and/or e-mail throughout the trial period. Questions about treatment decisions will be discussed with the chief investigator.

Item 6. How

The BrEX-intervention will be given individually 'face-to-face' and supervised by the physiotherapist at three sessions to observe performance and ensure optimal breathing modification and progression/regression by adjusting the amount of surface (less vs. more) or the complexity of the activity. The daily additional home exercises (twice, each of 10 minutes) are supervised only at the sessions with the physiotherapist.

Item 7. Where

BrEX-intervention will be performed in the physiotherapy department at seven public hospitals, covering all regions of Demark. BrEX will be delivered in an undisturbed room, an undisturbed corridor, and an undisturbed staircase.

Equipment used for the BrEX-intervention is an armchair, a couch, 2-3 pillows, a 500-gram bag of rice (or a book of about 500-gram), and an ergometer bicycle.

Item 8. When and how much

BrEX will be delivered during 12-week interventional period in 3 sessions of 60 minutes (equals week 1), 30 minutes, and 30 minutes in week 4, and 9. The allowed displacement of second and third session is +/- 7 days.

The patient is expected to continue doing home exercises 10 minutes twice daily throughout 12 weeks.

The breathing modification, home exercise program and relaxation will be included from the start although breathing modification combined with activity will be included later according to the individual participant status.

Item 10. Modifications

N/A. Modifications will be reported (if any).

Item 11. How well - planned

BrEX will be delivered independently at seven centers. All physiotherapists will adhere to a BrEX-manual (intervention protocol).

The physiotherapist will document attendance at sessions in the research database (EasyTrial, EasyTrial APS, Aalborg, Denmark). The participants of the BrEX-intervention will be informed to fill out a training diary. At session 2 and 3, the physiotherapists evaluate adherence to the home exercise program using range from 1-5 (1 no adherence, 5 completely adherent).

Item 12. How well – actual

N/A. This will be reported in the primary paper.

References

1. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ*. 2014;348:g1687.
2. Thomas M, Bruton A. Breathing exercises for asthma. *Breathe* 2014;10(4):312-22.
3. Bruton A, Lee A, Yardley L, et al. Physiotherapy breathing retraining for asthma: a randomised controlled trial. *Lancet Respir Med* 2018;6(1):19-28.
4. Thomas M, McKinley RK, Mellor S, et al. Breathing exercises for asthma: a randomised controlled trial. *Thorax* 2009;64(1):55-61.
5. Holloway EA, West RJ. Integrated breathing and relaxation training (the Papworth method) for adults with asthma in primary care: a randomised controlled trial. *Thorax* 2007;62(12):1039-42.
6. Boulding R, Stacey R, Niven R, et al. Dysfunctional breathing: a review of the literature and proposal for classification. *Eur Respir Rev* 2016;25(141):287-94.
7. Barker NJ, Jones M, O'Connell NE, et al. Breathing exercises for dysfunctional breathing/hyperventilation syndrome in children. *Cochrane Database Syst Rev* 2013(12):CD010376.
8. West JB, Luks AM. *Respiratory Physiology The Essentials*. 10/ed nt ed. Philadelphia: Wolters Kluwer, 2016.
9. Chamberlain Mitchell SA, Garrod R, Clark L, et al. Physiotherapy, and speech and language therapy intervention for patients with refractory chronic cough: a multicentre randomised control trial. *Thorax* 2017;72(2):129-36.
10. Laurino RA, Barnabe V, Saraiva-Romanholo BM, et al. Respiratory rehabilitation: a physiotherapy approach to the control of asthma symptoms and anxiety. *Clinics* 2012;67(11):1291-97.
11. Courtney R, Cohen M. Investigating the claims of Konstantin Buteyko, M.D., Ph.D.: the relationship of breath holding time to end tidal CO2 and other proposed measures of dysfunctional breathing. *J Altern Complement Med* 2008;14(2):115-23.

S4, Supplementary file

Twelve items interview list

Manual:

The physiotherapist reads each question.

The participant answers 'yes' or 'no'.

Have had this experience during last 7 days:

1. It feels heavy to breathe (difficult inspiratory breathing)
2. Unable to take deep breaths
3. Frequent sighing or yawning (or large inhalation)
4. Frequent need to clear the throat
5. Muscle and joint tenderness in the upper part of the chest (sternocostal joints and/or intercostal muscles)
6. Uncontrolled coughing (hacking cough)
7. Chest tightness
8. Sensation of a lump in the throat
9. Breathlessness in rest
10. Breathlessness in activity
11. Difficult nose breathing
12. Previous or current effects of stress

Karen H. Andreasson elaborated this interview list with inspiration from *DB criterion list* by C. Hagman, C Janson, M Emtner: *Breathing retraining - A five-year follow-up of patients with dysfunctional breathing.* Respiratory Medicine (2011) 105, 1153e1159)

Version 30th April 2019

Appendices D

D-1 Study 2 manuscript, pre-submission

Factors associated with asthma-specific quality of life: a cross sectional analysis of 193 patients with moderate-to-severe asthma

D-2 Supplementary online material:

Types and frequency of comorbidities in included participants

TITLE PAGE

ORIGINAL RESEARCH

Factors associated with asthma-specific quality of life: a cross sectional analysis of 193 patients with moderate-to-severe asthma

Karen Hjerrild Andreasson, Søren T. Skou, Charlotte Suppli Ulrik, Hanne Madsen, Kirsten Sidenius, Karin Dahl Assing, Celeste Porsbjerg, Jannie Rhod Bloch-Nielsen, Mike Thomas, Uffe Bodtger

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Text, word count: 2711 (out of 3500)

Abstract, word count: 232 (out of 250)

Abstract:

Background: Quality of life (QoL) is impaired in patients with moderate-to-severe asthma resulting in limitations in health, productivity, family and social life. Asthma is complex and heterogeneous, and the determinants of asthma-specific QoL are incompletely understood.

Objective: We assessed cross-sectional associations between asthma-specific QoL with self-reported and objectively measured factors in 193 patients with symptomatically uncontrolled moderate-to-severe asthma from eight asthma clinics in Denmark.

Methods: Asthma-specific QoL was measured using Mini Asthma Quality of Life Questionnaire (MiniAQLQ). Univariable and multivariable regression analyses were performed to determine demographical, disease-related, comorbidity-related, and respiratory/physical factors associated with MiniAQLQ

Results: In univariable analysis, the factors significantly ($p \leq 0.02$) associated with impaired MiniAQLQ score, with percentage of explained variance were: asthma symptom control, 53.9% (6-item Asthma Control Questionnaire, ACQ6); dysfunctional breathing related symptoms, 42.0% (Nijmegen questionnaire, NQ); depression, 22.2%, anxiety 18.3% (Hospital Anxiety and Depression questionnaire); resting breathlessness, 13.7% (Borg CR10); functional performance, 11.5% (6 Minute Walk Test, 6MWT); resting respiratory rate, 4.4%; high income, 4.3%; and body mass index, 2.8%. In multivariable regression analysis, the factors independently associated with impaired MiniAQLQ score were: asthma symptom control, anxiety, dysfunctional breathing related symptoms, contrary to 'high income', which were protective of asthma-specific QoL. These models explained 62.2-69.6% of variance in MiniAQLQ.

Conclusion: Symptom control, anxiety, and dysfunctional breathing related symptoms were all associated with MiniAQLQ, suggesting that they might be targets to improve QoL in patients with moderate-to-severe asthma.

Highlights box. providing answers (no longer than 35 words) to the following questions.

Highlights

What is already known about this topic?

Asthma control is strongly associated with asthma-specific quality of life.

What does this article add to our knowledge?

Psychological dysfunction and dysfunctional breathing related symptoms are also independently associated with impaired QoL in patients with moderate-to-severe uncontrolled asthma attending specialist clinics.

How does this study impact current management guidelines?

To improve patient's experience of having more severe asthma, in addition to improving symptoms, interventions targeted to improve anxiety and dysfunctional breathing may also be beneficial.

Keywords:

MiniAsthma Quality of Life Questionnaire; 6-items Asthma Control Questionnaire; Hospital Anxiety and Depression Scale; Univariable and multivariable regressions.

Abbreviations used

6MWT: 6-minutes' Walk Test

ACQ6: 6-item Asthma Control Questionnaire

BMI: body mass index

Borg CR10: amount of breathlessness in rest using

EuroQoL-5D-5L: European Quality of Life Questionnaire, 5 dimensions, 5 levels

FEV_1%pred: predicted forced expiratory volume in first second

GINA: Global Initiative for Asthma

HADS-A: Hospital Anxiety and Depression Scale (anxiety)

HADS-D: Hospital Anxiety and Depression Scale (depression)

MiniAQLQ: MiniAsthma Quality of Life Questionnaire

NQ: Nijmegen Questionnaire

QoL: Quality of Life

RCT: randomised controlled trial

RR: Respiration Rate

STROPE: Strengthening the Reporting of Observational Studies in Epidemiology

INTRODUCTION

Asthma is a very common disease affecting more than 300 million individuals worldwide, and the prevalence is increasing.[1–3] The individual and societal burden of uncontrolled asthma is large, particularly in patients with moderate-to-severe asthma attending specialist 'difficult asthma' clinics.[1,4–6] Asthma biological severity, symptom control, risk control and disease-specific quality-of-life (QoL) describe different and complementary domains of asthma control.[1,3,7] Asthma-specific QoL can be assessed by validated questionnaires, and is a separate but overlapping domain to severity and symptom control, reflecting the patient's experience of their condition and the extent to which their illness affects their daily life. It is, however, generally not formally included in treatment decision recommendations in asthma guidelines.[2] Impaired asthma-specific QoL occurs at all levels of asthma severity, but is more common in those with severe disease and poor control, particularly in those referred for specialist care. Impaired QoL reflects the patient's experience, including the psychosocial consequences of living with asthma, decreased physical activity, impaired social activities, and limited career options, and so is highly relevant to those who suffer from this currently incurable long term condition.[1,8–10]

A variety of factors may potentially affect a patient's experience of having asthma including psychosocial factors, health literacy, comorbidities (eg, anxiety, obesity, rhinitis),[6,9,11–16] in addition to specific asthma factors such as lung function, symptom control and biological disease severity.[6,17] The possible identification of treatable traits affecting asthma-specific QoL may provide targeted interventions to improve the life of people with asthma[18].

Results from previous studies exploring factors associated with asthma-specific QoL in moderate-to-severe asthma suggest that asthma symptom control is a major determinant for asthma-specific QoL, but does not completely explain QoL impairment, with other asthma-related, personal and comorbidity-related factors also possibly having an impact. However, these studies have several limitations, eg. due

to small sample size, mild or uncertain asthma severity, or rarely used asthma-specific QoL measurement tools, so the precise determinants of impaired QoL in people with asthma are not currently clear.

The Asthma Quality of Life Questionnaire and it's shorter vision (MiniAQLQ) are well validated and widely used asthma-specific QoL tools, and include the domains of symptoms, emotions, activity limitation, and environmental influence.[19] The effect of individual and combinations of potential associated factors on asthma-specific QoL have not yet been appropriately investigated in patients with moderate-to-severe asthma attending specialist care.[15,17,20]

The aim of the present study was to identify possible demographical, asthma-related, comorbidity-related, or respiratory/physical factors associated with impaired asthma-specific QoL among adult patients with uncontrolled moderate-to-severe asthma attending specialist care, with a focus on identifying potentially treatable traits.

METHODS

Study design, subjects and setting

This cross-sectional study used baseline data from the multicentre RCT, BEAT DB-trial (NCT03127059)[21] approved by Region Zealand Research Ethics Committee (SJ-552). The reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[22]

The target population was patients with uncontrolled asthma referred to specialized care from general practice. Participants were recruited between April 2017 and September 2019 at eight secondary asthma care clinics in Denmark: seven outpatient departments at public hospitals, and one private lung/allergy clinic. Eligible participants were included if pulmonologist-diagnosed asthma, ≥2 visits in a specialized asthma care setting, 6-item Asthma Control Questionnaire (ACQ6)-score ≥0.8, and aged ≥18 years. Exclusion criteria were other severe disease (eg, cancer, severe heart failure) or pregnancy.

Outcome of interest

The dependent variable was asthma-specific QoL, assessed by the validated MiniAQLQ score, expressed as the mean of 15 items scored on a 7-point Likert scale (1=maximum impairment; 7=no impairment).[19,23]

Covariates

Covariates (ie, the independent variables) included four categories:

1) Demographical data:

Sex, age, smoking status, educational level,[24] employment status, and annual income.

Smoking status was categorised never, former, or current smokers. Educational level was grouped into 'No or short-term education' (no education, primary/high/secondary school), 'Middle-term education' (vocational/short higher/medium education), or Long-term education (bachelor, master/higher education, PhD). Annual income was reported in Euros (€) and grouped into tertiles (low, middle, high), with exclusion of patients reporting 'unknown' or 'income <100€'.

2) Asthma-related variables:

Asthma symptom control (6-item Asthma Control Questionnaire, ACQ6),[25] and asthma severity (GINA treatment steps).[2]

3) Comorbidity-related variables:

Dysfunctional breathing related symptoms (Nijmegen Questionnaire, NQ,[26] anxiety and depression (Hospital Anxiety and Depression Scale (HADS-A and HADS-D)[27], body mass index (BMI, included as a continuous variable in regression models, but presented as categorical variable in Table 1), rhinosinusitis (self-reported allergic, chronic, non-allergic or vaso-motoric rhinosinusitis), total number of comorbidities (by organ systems).

4) Respiratory/physical factors

Lung function (predicted forced expiratory volume in first second, FEV1%pred.),[28,29] resting respiratory rate (RR), breathlessness at rest (Borg CR10),[30] and 6-minutes' Walk Test distance (6MWT, in meters).[31]

Data collection

Questionnaires, demographical information, smoking status, hight and weight were patient-reported collected electronically online. Medication prescription and comorbidity data were extracted from the medical record. Objective outcomes and Borg CR10 were obtained at physical examination measured by trained assessors.

Modelling

Initially, univariable analysis of each variable was performed to assess the association with MiniAQLQ. To assess which factors were independently associated with MiniAQLQ, we then constructed three separate multivariable regression models: a 'data-driven model', and 2 'theoretical models', defined below (see Figure 1).

1) The Data-driven Model included all covariates with a significance level of $p \leq 0.1$ in univariable analyses. We chose the significance limit at 0.1 to avoid leaving out potentially important variables.[32]

2) The Theoretical Model 1 was developed based on restricting the model to factors previously described as having an association with asthma-specific QoL in the literature and from clinical intuition, and 'forcing' these expected factors into the model. These were:

Demographic factors (sex, age, educational level),[24] asthma-related factors (ACQ6, GINA step),[6,17] comorbidity (BMI, rhinosinusitis, anxiety)[6,9,11,13,15], and respiratory factor FEV_1%pred. as restricted airway flow due to asthma giving the typical asthma symptoms of wheezing and dyspnoea has impact on asthma-specific QoL.[1,2]

3) *The Theoretical Model 2* was a repetition of the Theoretical Model, but omitting FEV_1%pred. We did this due to missing data on FEV_1%pred. to achieve full sample in the regression analyses, as the modelling requires data on each included variable to be present.

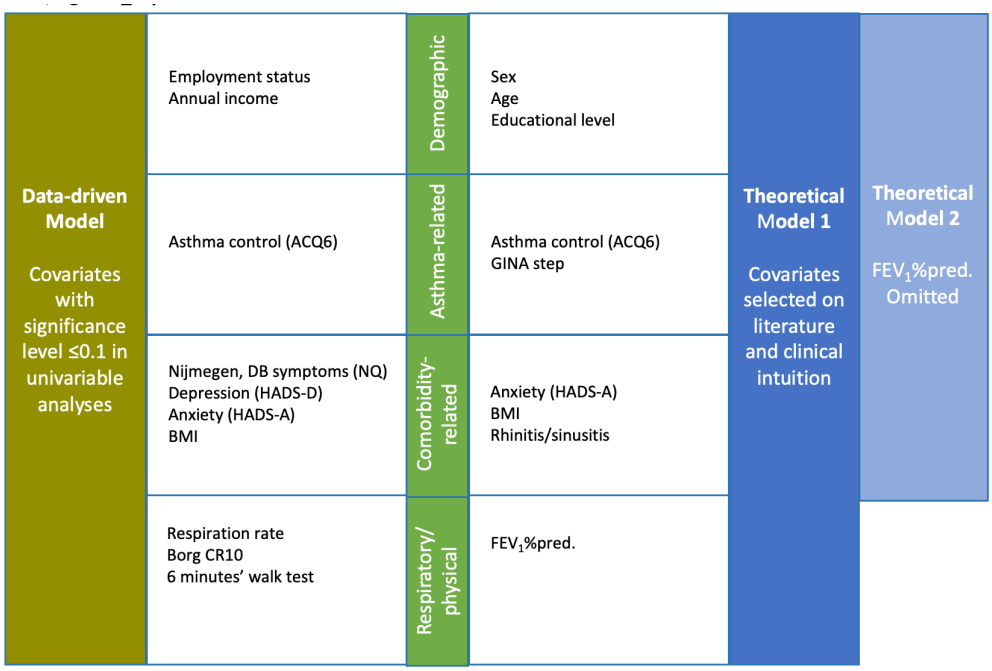

Figure 1. Multivariable linear regression models.
DB: Dysfunctional breathing

Statistical methods

We used Stata/IC 16.0 (StataCorp LLC 2019, College Station, TX, USA) to carry out analyses.

The empirical sample assessed in this exploratory analysis consisted of those consenting to a randomised controlled trial of breathing retraining, described and reported elsewhere.[21]

The dependent variable MiniAQLQ was used as continuous in all models. Testing for normal distribution were performed by QQ plots and Shapiro Wilks test.

Firstly, we performed simple linear regressions to explore the univariable associations at significance level $p \leq 0.1$ between MiniAQLQ (dependent variable) and each independent covariate.

Secondly, we constructed multivariable linear regression models to investigate independent associations with MiniAQLQ, using the three models defined above. These models included continuous, binominal and categorical covariates.

Further, both in univariable and multivariable regressions, we investigated the proportion of MiniAQLQ score variance explained (in tables presented as R^2) by covariates in the relevant model, with statistical significance defined as p-value ≤ 0.05.

In all regression analyses, no imputations were performed, thus only participants without missing data in the relevant model variables were included. Regression coefficients (β) are reported with 95%CI, and should be interpreted as greater QoL with greater score in the covariate when the coefficient is positive, and *vice versa*.

RESULTS

Participants

We included 193 participants with moderate-to-severe asthma. Missing data were occurred for spirometry (*n*=17, 8.8%: technical problem *n*=6, difficulties to complete three useful manoeuvres, eg, due to coughing in first second, *n*=11), in 6MWT due to walking impairment (*n*=6, 3.1%), and annual income (*n*=16, 8.3%) due to reported income <100 €.

Characteristics of participants are listed in table I, and full comorbidities list in Table A I in the Online Repository materials.

****TABLE I, Baseline characteristics****

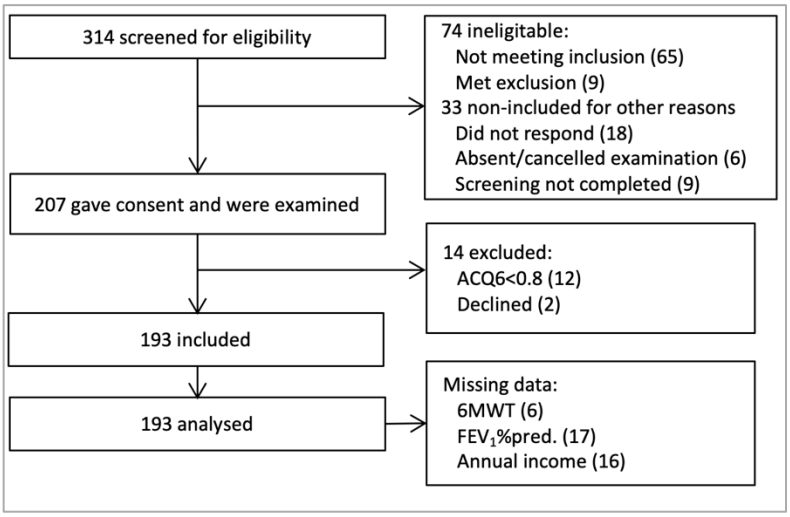

Figure 2. Flowchart of recruitment, examination, inclusion and analyses

Univariable analyses

Among asthma-related covariates, ACQ6 explained 53.9% of variance of MiniAQLQ ($p<0.001$), with greater ACQ6 score (more symptoms) being associated with lower QoL (table II). However, asthma severity (assessed as GINA step) was not significantly associated with MiniAQLQ.

Among comorbidity-related covariates, NQ explained 42.0% ($p<0.001$), HADS-A 18.3% ($p<0.001$), HADS-D 22.2% ($p<0.001$), and BMI 2.8% ($p=0.020$) of the variance of MiniAQLQ, whereas neither rhinosinusitis, nor the number of comorbidities were significantly associated with MiniAQLQ.

Of respiratory/physical covariates, resting Borg CR10 (explaining 13.7% of the variance, $p<0.001$), 6MWT (11.5%, $p<0.001$), and RR (4.4%, $p=0.004$) were significantly associated with MiniAQLQ. However, lung function was not associated with MiniAQLQ (Table II).

Significant demographical covariate was 'high annual income' ($p=0.007$) with 'annual income' outcome explaining 4.3% of the variance of MiniAQLQ. Having high income was associated with greater QoL. The 'employment status' outcome was not associated with MiniAQLQ, however it appeared that the category 'outside labour market' compared to 'being employed' was important ($p=0.001$) and associated with lower MiniAQLQ. Neither sex, age, nor educational level were significantly associated with MiniAQLQ.

****TABLE II. Univariable analyses of covariates****

Multivariable analyses

Data-driven Model (Table III)

The Data-driven Model ($n=172$) developed from the significant univariable covariates at the $p<0.1$ level revealed ACQ6 (ß=-0.6, $p<0.001$), HADS-A (ß=-0.03, $p=0.088$), NQ (ß=-0.03, $p<0.001$), and 'high

income' (ß=0.35, *p*=0.041) were associated with MiniAQLQ, whereas employment status, HADS-D, BMI, Borg CR10, RR, and 6MWT were not associated (Table III). This model explained 69.6% (*p*<0.001) of variance of MiniAQLQ.

Greater scores in ACQ6, HADS-A, or NQ were associated with impairment of asthma-specific QoL, whereas higher income was associated with preservation of asthma-specific QoL.

**** TABLE III. Data-driven Model, multivariable analyses of covariates ***

Theoretical Model 1 (Table IV)

In the Theoretical Model 1 (n=176), only the asthma-related covariate ACQ6 (p<0.001) and comorbidity-related covariate HADS-A (p<0.001) – but not sex, age, educational level, GINA step, BMI, rhinosinusitis, or lung function (FEV_1%pred.) – were independently associated with MiniAQLQ. This model however explained less of the MiniAQLQ variance (65.4%, p<0.001), than the data-driven model above.

**** TABLE IV. Theoretical model, multivariable analyses of covariates***

Theoretical Model 2 (Table V).

The Theoretical Model 2 (n=193) omitting lung function (FEV_1%pred.) decreased variance explained to 62.2% (p<0.001) but similar regression coefficients found in the Theoretical Model. Sex, age, educational level, GINA step, BMI, or rhinosinusitis were not associated with MiniAQLQ (see Table A II in the Online Repository materials).

**** TABLE V. Alternative Theoretical Model, multivariable analyses of covariates***

DISCUSSION

In this cross-sectional study on adults with moderate-to-severe asthma, we found that symptom control, anxiety and dysfunctional breathing related symptoms were all independently associated with impaired asthma-specific QoL, and that high income was protective. These factors explained the majority of the variance in MiniAQLQ scores. Most of the factors are potentially modifiable with appropriate treatment, eg, pharmacological treatment, treatment of comorbidities, relaxation techniques, cognitive behavioural therapy, breathing retraining, and/or physical exercise[33], suggesting that targeting them might be a step towards improving asthma-related QoL for patients with more severe disease attending specialist care. Previous studies have highlighted a strong association between asthma control and asthma-specific QoL across different scoring systems and different analytical methods.[3,8,10,34,35]. Chen *et al* found that asthma control (assessed by the Asthma Therapy Assessment Questionnaire) explained 39% of the MiniAQLQ variance in 987 patients with unclear asthma severity,[3] while Stucky *et al* showed that the RAND Asthma Control Measure explained 50% of the variance of Asthma-related QoL assessed by the RAND-IAQL-12.[8] Our two Theoretical Models included the same covariates as these two previous studies, however explained 62-65% of MiniAQLQ variance (Table IV).

Anxiety was also independently associated with Asthma-related QoL. A World Health Organisation survey (n=85,088) found that odds for anxiety disorders was 1.5 (95%CI 1.4 to 1.7) in individuals with asthma compared to those without asthma.[36] The association between anxiety and asthma control is well-documented.[6,11,33] Reports also address the association between anxiety and Asthma-related QoL, however using other tools. Lavoie *et al* reported a strong association between generalized anxiety disorder and AQLQ (ß=-0.91, p<0.001) in 794 patients treated for asthma in an outpatient clinic.[37] In the present study only few had anxiety disorder diagnosis, but anxiety was still a significant factor in

predicting poor asthma-specific QoL. Luskin *et al* investigated the impact of asthma triggers and exacerbations on Asthma-related QoL in a large prospective cohort of 2679 patients.[17] The asthma trigger 'Emotional stress' was strongly associated with poor Asthma-related QoL in patients with a high number of asthma triggers or frequent exacerbations.[17] Robinson *et al* recently investigated whether MiniAQLQ could be used to screen for anxiety in a tertiary asthma clinic.[11] and reported that a MiniAQLQ score <3, indicating significantly impaired QoL, was associated with moderate anxiety with a sensitivity 0.75 and specificity 0.76, supporting an association between Asthma-related QoL and anxiety. GAD-7 and MiniAQLQ also have a moderate to strong correlation (r=-0.59) in this report.[11] Our finding are also consistent with a large epidemiological cross sectional study[17], in which anxiety also emerged as an independent factor in all models..

Anxiety may be accompanied by a change in breathing pattern, and Denton *et al,* using a cut-off NQ score of >23 to define dysfunctional breathing in patients similar to our study, ie, 'difficult-to-treat asthma', reported that anxiety was independently associated with DB,[20]. In our study, using NQ score as a continuous variable, we found it to be significantly associated with Asthma-related QoL. A similar independent relationship between NQ score and QoL has recently been reported in COPD patients,[38] suggesting that the NQ may be more informative as a continuous variable than as a single value cut-off binary diagnostic screening instrument to define dysfunctional breathing in populations with known respiratory disease.[39,40]

BMI has been reported to be a predictor of asthma control,[15] and Lavoie *et al* reported that obesity (BMI ≥30, 25% of study population) was associated with lower Asthma-related QoL using multiple analyses, however without including anxiety in their model.[14] In our study (n=72, 36% were obese), we also found that BMI was associated with Asthma-related QoL in univariable yet not in the multivariable analyses

(tables II and III). In contrast to Lavoie et al, we analysed BMI as a continuous variable and included more covariates, which may explain the difference.

Finally, having high income had an independently protective effect on asthma-specific QoL in our study. This aligns with previous reports on socioeconomic status as a factor of maintained health related QoL in patients with long term conditions.[16,24] High income may be a proxy for numerous life-style and psychometric factors including more diverse strategies for living with asthma.

Our study has several limitations. Due to the cross-sectional observational study design, confirmation of causality is impossible, and requires prospective, interventional randomised clinical studies. All participants were patients consenting to participate in a RCT on breathing exercises in poorly controlled moderate-to-severe asthma[21], potentially affecting the generalizability to the broader populations of asthma patients in clinical practice. However, the pragmatic study design and broad eligibility criteria of the RCT reduces the severity of the selection bias. Our study has the same demographic distribution of sex (female majority), age (40-60 years), BMI (overweight) and comorbidity as in comparable association studies and of 'difficult-to-treat' asthma clinic populations, [3,17] and of studies on patients with uncontrolled asthma.[8,10,14,15] Furthermore, whereas earlier studies used patient-reported asthma diagnosis as inclusion criteria,[8,13,15] we used pulmonologist-diagnosed asthma to improve external validity of findings in moderate-to-severe asthma. We included 193 participants, thus limiting the number of possible covariates to include. Therefore, in an attempt to reduce risk of overfitting the models, we pooled different rhinitis types (allergic, non-allergic, chronic) and sinusitis into a single covariate, and we excluded smoking status – a very common confounder in observational studies [3,13] due to very few observations of current smoking (*n*=9, 4.7%).

In summary, our data suggest that asthma control, anxiety, and dysfunctional breathing symptoms are all independently associated with asthma-specific QoL, the key variable reflecting the patient's perspective and experience of their condition, in a population of more severe asthmatic patients attending specialist asthma care in Denmark. These factors are all potentially modifiable, thereby suggesting potentially interventions to improve asthma-related QoL through a combination of appropriately targeted pharmacological and non-pharmacological strategies.[18]

CONCLUSION

Asthma control, anxiety, and dysfunctional breathing symptoms were all independently associated with asthma-related QoL in a population of patients with moderate-to-severe asthma attending specialist care. These factors are all potentially modifiable by appropriately targeted interventions. Impaired quality of life in patients with severe asthma has a number of drivers, suggesting that each patient requires thorough assessment and a multi-dimensional, personalised approach to optimise key patient outcomes.

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Disclosure

Conflicts of interest

Professor ST Skou is associate editor of the Journal of Orthopaedic & Sports Physical Therapy, has received grants from The Lundbeck Foundation, personal fees from Munksgaard, all of which are outside the submitted. He is co-founder work of Good Life with Osteoarthritis in Denmark (GLA:D®), a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

The author reports no other potential conflicts of interest.

References

1. Papaioannou AI, Kostikas K, Zervas E, Kolilekas L, Papiris S, Gaga M. Control of asthma in real life: still a valuable goal? *Eur Respir Rev*. 2015;24(136):361-369. doi:10.1183/16000617.00001615

2. Global_Initiative_For_Asthma. GINA, Global Initiative for Asthma. Global strategy for asthma management and prevention, 2019. www.ginasthma.org. Published 2019. Accessed May 6, 2020. https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf

3. Chen H, Gould MK, Blanc PD, et al. Asthma control, severity, and quality of life: Quantifying the effect of uncontrolled disease. *Journal of Allergy and Clinical Immunology*. 2007;120(2):396-402. doi:10.1016/j.jaci.2007.04.040

4. Foster JM, McDonald VM, Guo M, Reddel HK. "I have lost in every facet of my life": the hidden burden of severe asthma. *European Respiratory Journal*. 2017;50(3). doi:10.1183/13993003.00765-2017

5. Wu AC, Greenberger PA. Asthma: Overdiagnosed, Underdiagnosed, and Ineffectively Treated. *Journal of Allergy and Clinical Immunology In Practice; Amsterdam*. 2018;6(3):801-802. doi:http://dx.doi.org/10.1016/j.jaip.2018.02.023

6. Sims EJ, Price D, Haughney J, Ryan D, Thomas M. Current control and future risk in asthma management. *Allergy Asthma Immunol Res*. 2011;3(4):217-225. doi:10.4168/aair.2011.3.4.217

7. Taylor DR, Bateman ED, Boulet L-P, et al. A new perspective on concepts of asthma severity and control. *Eur Respir J*. 2008;32(3):545-554. doi:10.1183/09031936.00155307

8. Stucky BD, Sherbourne CD, Edelen MO, Eberhart NK. Understanding asthma-specific quality of life: moving beyond asthma symptoms and severity. *European Respiratory Journal*. 2015;46(3):680-687. doi:10.1183/09031936.00225014

9. Peters U, Dixon A, Forno E. Obesity and Asthma. *J Allergy Clin Immunol*. 2018;141(4):1169-1179. doi:10.1016/j.jaci.2018.02.004

10. Sousa JC de, Pina A, Cruz AM, et al. Asthma control, quality of life, and the role of patient enablement: a cross-sectional observational study. *Prim Care Respir J*. 2013;22(2):181-187. doi:10.4104/pcrj.2013.00037

11. Robinson R, Barber K, Jones G, Blakey J, Burhan H. Exploring the relationship between generalised anxiety/depression scales and asthma-specific quality of life/control questionnaires in a specialist asthma clinic. *Journal of Asthma*. Published online April 9, 2020:1-9. doi:10.1080/02770903.2020.1744640

12. Bruton A, Lee A, Yardley L, et al. Physiotherapy breathing retraining for asthma: a randomised controlled trial. *Lancet Respir Med*. 2018;6(1):19-28. doi:10.1016/S2213-2600(17)30474-5

13. Souza ECC de, Pizzichini MMM, Dias M, et al. Body mass index, asthma, and respiratory symptoms: a population-based study. *J Bras Pneumol*. 2020;46(1):e20190006. doi:10.1590/1806-3713/e20190006

14. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med*. 2006;100(4):648-657. doi:10.1016/j.rmed.2005.08.001

15. Ali Z, Ulrik CS. Obesity and asthma: a coincidence or a causal relationship? A systematic review. *Respir Med*. 2013;107(9):1287-1300. doi:10.1016/j.rmed.2013.03.019

16. Pate CA, Zahran HS, Bailey CM. Impaired health-related quality of life and related risk factors among US adults with asthma. *J Asthma*. 2019;56(4):431-439. doi:10.1080/02770903.2018.1466314

17. Luskin AT, Chipps BE, Rasouliyan L, Miller DP, Haselkorn T, Dorenbaum A. Impact of asthma exacerbations and asthma triggers on asthma-related quality of life in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol Pract*. 2014;2(5):544-552.e1-2. doi:10.1016/j.jaip.2014.02.011

18. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *European Respiratory Journal*. 2016;47(2):410-419. doi:10.1183/13993003.01359-2015

19. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J*. 1999;14(1):32-38. doi:10.1034/j.1399-3003.1999.14a08.x

20. Denton E, Bondarenko J, Tay T, et al. Factors Associated with Dysfunctional Breathing in Patients with Difficult to Treat Asthma. *J Allergy Clin Immunol Pract*. 2019;7(5):1471-1476. doi:10.1016/j.jaip.2018.11.037

21. Andreasson KH, Skou ST, Ulrik CS, et al. Protocol for a multicentre randomised controlled trial to investigate the effect on asthma-related quality of life from breathing retraining in patients with incomplete asthma control attending specialist care in Denmark. *BMJ Open*. 2019;9(12):e032984. doi:10.1136/bmjopen-2019-032984

22. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med*. 2007;4(10):e297. doi:10.1371/journal.pmed.0040297

23. Ehrs P-O, Nokela M, Ställberg B, Hjemdahl P, Wikström Jonsson E. Brief questionnaires for patient-reported outcomes in asthma: validation and usefulness in a primary care setting. *Chest*. 2006;129(4):925-932. doi:10.1378/chest.129.4.925

24. Trupin L, Katz PP, Balmes JR, et al. Mediators of the socioeconomic gradient in outcomes of adult asthma and rhinitis. *Am J Public Health*. 2013;103(2):e31-38. doi:10.2105/AJPH.2012.300938

25. Juniper EF, Svensson K, Mörk A-C, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005;99(5):553-558. doi:10.1016/j.rmed.2004.10.008

26. van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. *J Psychosom Res*. 1985;29(2):199-206. doi:10.1016/0022-3999(85)90042-x

27. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370. doi:10.1111/j.1600-0447.1983.tb09716.x

28. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338. doi:10.1183/09031936.05.00034805

29. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-1343. doi:10.1183/09031936.00080312

30. Borg E, Borg G, Larsson K, Letzter M, Sundblad B-M. An index for breathlessness and leg fatigue. *Scand J Med Sci Sports*. 2010;20(4):644-650. doi:10.1111/j.1600-0838.2009.00985.x

31. Holland AE, Spruit MA, Singh SJ. How to carry out a field walking test in chronic respiratory disease. *Breathe (Sheff)*. 2015;11(2):128-139. doi:10.1183/20734735.021314

32. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med*. 2008;3(1):17. doi:10.1186/1751-0473-3-17

33. Thomas M, Bruton A, Moffatt M, Cleland J. Asthma and psychological dysfunction. *Prim Care Respir J*. 2011;20(3):250-256. doi:10.4104/pcrj.2011.00058

34. AL-Balushi AD, Thomas S, Marzooq DA. A Study on Quality of Life versus Asthma Control in Mild to Moderate Persistent Asthma Patients Treated at a Secondary Care Hospital in Oman. ResearchGate. Accessed August 28, 2020. https://www.researchgate.net/publication/336130502_A_Study_on_Quality_of_Life_versus_Asthma_Control_in_Mild_to_Moderate_Persistent_Asthma_Patients_Treated_at_a_Secondary_Care_Hospital_in_Oman

35. Gosavi S, Nadig P, Haran A. Factors Contributing Towards Poor Asthma Control in Patients on Regular Medication - PubMed. *J Clin Diagn Res*. 2016(Jun;10(6):):OC31-5. doi:10.7860/JCDR/2016/18670.8052

36. Scott KM, Von Korff M, Ormel J, et al. Mental disorders among adults with asthma: results from the World Mental Health Survey. *General Hospital Psychiatry*. 2007;29(2):123-133. doi:10.1016/j.genhosppsych.2006.12.006

37. Lavoie KL, Boudreau M, Plourde A, Campbell TS, Bacon SL. Association Between Generalized Anxiety Disorder and Asthma Morbidity: *Psychosomatic Medicine*. 2011;73(6):504-513. doi:10.1097/PSY.0b013e318222e9fc

38. Brien SB, Stuart B, Dickens AP, et al. Independent determinants of disease-related quality of life in COPD – scope for nonpharmacologic interventions? *Int J Chron Obstruct Pulmon Dis*. 2018;13:247-256. doi:10.2147/COPD.S152955

39. van Dixhoorn J, Folgering H. The Nijmegen Questionnaire and dysfunctional breathing. *ERJ Open Res*. 2015;1(1). doi:10.1183/23120541.00001-2015

40. Thomas M, Bruton A, Ainsworth B. Use of the Nijmegen Questionnaire in asthma. *ERJ Open Res*. 2015;1(1). doi:10.1183/23120541.00033-2015

Appendix D-1, cont. **Tables to the manuscript**

Factors associated with asthma-specific quality of life: a cross sectional analysis of 193 patients with moderate-to-severe asthma

TABLE I. Baseline characteristics of the participants (n=193)

Characteristics			Range
Demographical			
Sex			
Female	122	(63.2%)	
Male	71	(36.8%)	
Age at examination (SD)	51.6	(14.5)	18-82
Educational level			
No or short-term education	40	(20.7%)	
Middle-term education	116	(60.1%)	
Long-term education	37	(19.2%)	
Employment status			
Employed	107	(55.4%)	
Un-employed	7	(3.6%)	
Education (student)	69	(35.8%)	
Outside labour market	69	(35.8%)	
Annual income, €			134 - 301,807
Low, < 53609	56	(58.8%)	
Middle, 53609 - 107219	59	(32.2%)	
High, > 107219	49	(9.0%)	
Other	16	-	
Smoking status			
Never	117	(60.6%)	
Current	9	(4.7%)	
Former	67	(34.7%)	
Asthma-realted			
MiniAQLQ (mean, SD)[a]	4.3	(1.02)	1.2-6.3
ACQ6	2.2	(1.5-2.7)	0.5-5.0
GINA steps			
1	0	(0%)	
2	3	(1.5%)	
3	29	(15.0%)	
4	65	(33.9%)	
5	96	(49.7%)	
Comorbidity-related			
NQ	22	(15-31)	3-53
HADS, anxiety	6	(3-9)	0-20
HADS, depression	3	(1-6)	0-21
EuroQoL, EQ-5D-5L	0.745	(0.688-0.824)	0.006-1
Body Mass Index	28.3	(25.0-32.3)	15.1-56.2
Underweight, <18.5	2	(1.0%)	
Normal weight, 18.5-24.9	46	(23.8%)	
Overweight, 25-29.9	73	(37.8%)	
Obese, 30-34.9	46	(23.8%)	
Severely obese, 35-39.9	15	(7.8%)	
Extremely obese, >40	11	(5.7%)	
Rhinosinusitis	28	(14.5%)	
Allergic rhinitis	15	(7.8%)	
Chronic rhinitis	8	(4.1%)	
Sinusitis	4	(2.1%)	
Vaso motoric rhinitis	3	(1.6%)	
Number of comorbidities			0-10
0	77	(39.9%)	
1	53	(27.5%)	
2+	63	(32.6%)	
Respiratory/physical			
FEV_1 % predicted (n=176)	80	(70-89)	19-136
Respiratory rate	15	(12-17)	8-37
Borg CR10, resting	1.5	(0.5-2.5)	0-6
6 minutes walk test (n=187)	467	(419-522)	126-789

Data are median (interquartile range, IQR) and frequency (percentages), unless mentioned.

[a] AQLQ is parametric: mean and standard deviation (SD) are reported.
Income: Low, Middle, High is tertiles of income range in the sample. Other = unknown, <100 €
Education: No or short-term education (no education, primary/high/secondary school), Middle-term education (vocational/short higher/medium education), Long-term education (Bachelor, master/higher education, PhD.)
Rhinosinusitis: one participant had chronic and allergic rhinitis, 1 participant had chronic rhinitis and sinusitis.

TABLE II. Univariate analyses of covariates

Covariates	Regression coefficient, β (95%CI)		Proportion of Mini-AQLQ variance explained, R^2, p-value	
Demographical				
Sex			0.000	0.858
Male	reference			
Female	0.03	(-0.27 to 0.33)		
Age	0.00	(-0.01 to 0.01)	0.002	0.496
By educational level			0.001	0.882
No or short-term education	reference			
Middle-term education	-0.09	(-0.46 to 0.28)		0.630
Long-term education	-0.05	(-0.43 to 0.33)		0.799
By employment status			0.063	0.119
Employed	reference			
Un-employed	-0.74	(-1.51 to 0.02)		0.057
Education (student)	-0.22	(-0.87 to 0.43)		0.508
Outside labour market	-0.50	(-0.8 to -0.2)		0.001
By income group			0.043	0.023
Low, < 53609	reference			
Middle, 53609 - 107219	0.19	(-0.14 to 0.52)		0.264
High, > 107219	0.39	(0.21 to 1.29)		0.007
Smoking status			0.005	0.608
Never	reference			
Current	-0.19	(-0.88 to 0.51)		0.599
Former	0.12	(-0.19 to 0.43)		0.452
Asthma-related				
ACQ6	-0.83	(-0.94 to -0.72)	0.539	0.000
GINA steps			0.020	0.281
2	reference			
3	0.12	(-1.1 to 1.33)		0.852
4	0.02	(-1.17 to 1.2)		0.975
5	-0.23	(-1.41 to 0.94)		0.696
Comorbidity-related				
NQ	-0.06	(-0.07 to -0.05)	0.420	0.000
HADS-A	-0.10	(-0.13 to -0.07)	0.183	0.000
HADS-D	-0.13	(-0.17 to -0.1)	0.222	0.000
BMI	-0.03	(-0.05 to 0)	0.028	0.020
Rhinosinusitis	0.11	(-0.31 to 0.52)	0.001	0.614
Number of comorbidities			0.004	0.693
0	reference			
1	-0.05	(-0.41 to 0.31)		0.792
2+	-0.15	(-0.49 to 0.2)		0.396
Respiratory/Physical				
FEV_1 % predicted (n=176)	0.01	(0 to 0.01)	0.010	0.188
Respiration rate	-0.05	(-0.08 to -0.02)	0.044	0.004
Borg CR10 (resting)	-0.27	(-0.36 to -0.17)	0.137	0.000
6 minutes' Walk Test (n=187)	0.00	(0 to 0.01)	0.115	0.000

ACQ6: 6-item Asthma Control Questionnaire
BMI: body mass index
Borg CR10: amount of breathlessness in rest using
FEV1%pred: predicted forced expiratory volume in first second
GINA steps: treatment steps recommended by Global Initiative for Asthma, defining asthma severity
HADS-A: Hospital Anxiety and Depression Scale (anxiety)
HADS-D: Hospital Anxiety and Depression Scale (depression)
Mini-AQLQ: Mini-Asthma Quality of Life Questionnaire
NQ: Nijmegen Questionnaire

TABLE III. Data-driven model, multiple analyses of covariates

Covariates	Regression coefficient, β (95%CI)		Proportion of Mini-AQLQ variance explained, R^2, p-value	
n=172			0.696	0.0000
Demographical				
By employment status				
Employed	reference			
Un-employed	0.13	(-0.43 to 0.69)		0.651
Education (student)	0.08	(-0.37 to 0.53)		0.730
Outside labour market	-0.05	(-0.28 to 0.17)		0.648
By income group				
Low, < 53609	reference			
Middle, 53609 - 107219	0.01	(-0.2 to 0.21)		0.943
High, > 107219	0.35	(0.02 to 0.69)		0.041
Asthma-related				
ACQ6	-0.60	(-0.73 to -0.47)		0.000
Comorbidity				
NQ	-0.03	(-0.04 to -0.02)		0.000
HADS-A	-0.03	(-0.06 to 0)		0.088
HADS-D	0.00	(-0.03 to 0.04)		0.877
BMI	-0.01	(-0.02 to 0.01)		0.421
Respiratory/Physical				
Respiration rate	0.01	(-0.01 to 0.03)		0.407
Borg CR10 (resting)	-0.03	(-0.1 to 0.05)		0.482
6 minutes' Walk Test (n=187)	0.00	(0 to 0)		0.052

ACQ6: 6-item Asthma Control Questionnaire
BMI: body mass index
Borg CR10: amount of breathlessness in rest using
HADS-A: Hospital Anxiety and Depression Scale (anxiety)
HADS-D: Hospital Anxiety and Depression Scale (depression)
Mini-AQLQ: Mini-Asthma Quality of Life Questionnaire
NQ: Nijmegen Questionnaire

This Data-driven Model included all covariates with a significance level of $p \leq 0.1$ in univariate analyses.

TABLE IV. Theoretical model, multiple analyses of covariates

Covariates	Regression coefficient, β (95%CI)		Proportion of Mini-AQLQ variance explained, R^2, p-value	
	n=176		0.654	0.0000
Demographical				
Sex				
Male	reference			
Female	-0.10	(0.31 to 0.09)		0.308
Age	0.00	(-0.01 to 0.01)		0.642
By educational level				
No or short-term education	reference			
Middle-term education	-0.20	(-0.43 to 0.04)		0.103
Long-term education	-0.09	(-0.33 to 0.16)		0.489
Asthma-related				
ACQ6	-0.75	(-0.86 to -0.64)		0.000
Gina steps				
2	reference			
3	0.19	(-0.55 to 0.94)		0.608
4	0.24	(-0.48 to 0.95)		0.519
5	0.27	(-0.45 to 0.99)		0.460
Comorbidity-related				
BMI	-0.01	(-0.03 to 0)		0.150
Rhinosinusitis	0.07	(-0.19 to 0.34)		0.600
HADS-A	-0.07	(-0.09 to -0.05)		0.000
Respiratory				
FEV_1 % predicted (n=176)	0.00	(-0.01 to 0)		0.814

ACQ6: 6-item Asthma Control Questionnaire
BMI: body mass index
FEV1%pred: predicted forced expiratory volume in first second
GINA steps: treatment steps recommended by Global Initiative for Asthma, defining asthma severity
HADS-A: Hospital Anxiety and Depression Scale (anxiety)
Mini-AQLQ: Mini-Asthma Quality of Life Questionnaire

TABLE V. Alternative theoretical model, multiple analyses of covariates

Covariates	Regression coefficient, β (95%CI)		Proportion of Mini-AQLQ variance explained, R^2, p-value	
n=193			0.622	0.0000
Demographics				
Sex				
Male	reference			
Female	-0.10	(-0.3 to 0.09)		0.284
Age	0.00	(-0.01 to 0.01)		0.656
By educational level				0.882
No or short-term education	reference			
Middle-term education	-0.15	(-0.4 to 0.09)		0.227
Long-term education	-0.04	(-0.29 to 0.21)		0.735
Asthma-related				
ACQ6	-0.75	(-0.86 to -0.64)		0.000
Gina steps				0.281
2	reference			
3	0.20	(-0.59 to 0.99)		0.610
4	0.24	(-0.53 to 1)		0.541
5	0.23	(-0.53 to 0.99)		0.553
Comorbidity				
HADS-A	-0.07	(-0.09 to -0.05)		0.000
BMI	-0.01	(-0.02 to 0.01)		0.229
Rhinosinusitis	0.10	(-0.17 to 0.37)		0.471

ACQ6: 6-item Asthma Control Questionnaire
BMI: body mass index
GINA steps: treatment steps recommended by Global Initiative for Asthma, defining asthma severity
HADS-A: Hospital Anxiety and Depression Scale (anxiety)
Mini-AQLQ: Mini-Asthma Quality of Life Questionnaire

Appendix D-2 **Supplementary online material**

TABLE A I. Types and frequency of comorbidities in included participants

Categories and diagnoses	Number participants having one or more	N=193	
Allergy or hypersensitive reactions	20		
Allergic rhinitis, J304, J301		15	(7.8%)
Atopic Dermatitis, L209		5	(2.6%)
Multi allergy or Allergy UNS, T78.4		3	(1.6%)
Urticaria, L500		2	(1.0%)
Cancer	9		
Malignant neoplasm of connective and soft tissue of head, face and neck, C490		1	(0.5%)
Leukemia, C950		1	(0.5%)
Malign melanoma, C435		2	(1.0%)
Mamma cancer, N639		3	(1.6%)
Mantle cell lymphoma, C831		1	(0.5%)
Malignant neoplasm of sigmoid colon, C187		1	(0.5%)
Cardiovascular	16		
Ischemic heart disease, I21, I200, I259, I219		8	(4.1%)
Atrial fibrilation, I489, I480		4	(2.1%)
Chronic heart failure, Z035, Z035E, I351		3	(1.6%)
Aortic insufficiency, I351		2	(1.0%)
Endocrine or Immune mechanism	25		
Immune defect, D849		1	(0.5%)
Diabetes mellitus 1, E109A		1	(0.5%)
Diabetes mellitus 2, E119A, E119		8	(4.1%)
Severe obesity, E66		9	(4.7%)
Alfa1 antitryp deficiency, E88		1	(0.5%)
Sarcoidosis, D86		2	(1.0%)
Cushing syndrome, E249		1	(0.5%)
Hypothyroidism, E039		6	(3.1%)
Thyrotoxicosis, E05		3	(1.6%)
Gastro-intestinal/-oesophageal	23		
Irritable bowel syndrome, K58, K590, K598, K599		10	(5.2%)
Morbus Crohn, K509		2	(1.0%)
Retentio ventriculi, K318H		1	(0.5%)
Unspecified GI disease, K929, R102		5	(2.6%)
Ischemic colitis, K551		1	(0.5%)
Endometriose, N809		1	(0.5%)
Coeliac disease, K900		1	(0.5%)
Reflux, gastro-øsefageal, K21		7	(3.6%)
Functional dyspepsia, K309		2	(1.0%)
Dysphagia, R139		2	(1.0%)
Lung	18		
Bronchiectasis, J479		9	(4.7%)
Chronic obstructive pulmonary disease, J44, J448, J449		9	(4.7%)
Mental	14		
Alcohol abuse, F10		2	(1.0%)
Anxiety, F419		3	(1.6%)
Depression, F33		7	(3.6%)
Adjustments disorders, F079, F419, F4323		2	(1.0%)
Eating disorder, F50		1	(0.5%)
Bipolar disorder, F31		1	(0.5%)
Musculoskeletal or connective tissue	31		
Granulomatose with polyangiitis (Wegener), M313		1	(0.5%)
Artritis UNS, M139		1	(0.5%)
Osteoarthritis, M161A, M179		6	(3.1%)
Joint pain, M255, M109, M239, M759, M751A, M774, S434, S134		4	(2.1%)
Supraspinatus lesion, S460B2		2	(1.0%)
Discusprolaps, M501, M511		3	(1.6%)
Fibromyalgy, M797		1	(0.5%)
Psoriasis artropati, L405		1	(0.5%)
Reumatoid artritis, M069		3	(1.6%)
Back pain, M549, M542, M47		4	(2.1%)

Deformaties of spine, M42.0, M472, M480		5	(2.6%)
Non-malignant pain disorder, R522		1	(0.5%)
Muscle spasm/pain, M626		1	(0.5%)
Tension headache, G442		1	(0.5%)
Extremity pain, M796		4	(2.1%)
Arthritis temporalis with reum. polymyalgia, M315A		1	(0.5%)
Neurological	14		
Multible sclerosis, G35, G379 (UNS)		1	(0.5%)
Epilepsia, G409		2	(1.0%)
Migraine, G43		4	(2.1%)
Neuropatic disorders, G900, G542, G587, G629, G258		5	(2.6%)
Intra cranial injury, S065		1	(0.5%)
Syringomyelia, G950B		1	(0.5%)
Renal	2		
Chronic renal failure, N189, N199		2	(1.0%)
Sensory organs	5		
Deafness, H910, H911, H919, H905		5	(2.6%)
Upper airway	30		
Chronic Rhinitis, J310		8	(4.1%)
Nosal septum deviation, J342		2	(1.0%)
Nasal polyps, J330		7	(3.6%)
Obstructive Sleep Apnoea, G4732		11	(5.7%)
Chronoc sinuitis, J32		4	(2.1%)
Vaso motoric rhinitis, J300		3	(1.6%)
Vocal Cord Dysfunction, J38.3		1	(0.5%)
Total number of comorbidity cases		245	

Frequency (with percentages) of diagnoses with ICD10 codes for included participants

Appendices E

E-1	Study 3, manuscript, submitted **Breathing exercises for asthma patients in specialist care - a multicentre randomised trial**
E-S1-11	Extended supplementary materials: BrEX Booklet (in Danish) Tables and figures related to the manuscript

Title

Breathing exercises for asthma patients in specialist care: a multicentre randomised trial

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Take Home-Message

Breathing Exercises delivered individually by physiotherapists as supplement to usual secondary care are well-accepted, safe and improve asthma-related quality of life in patients with incompletely controlled moderate-to-severe asthma.

Abstract

Background: Despite effective pharmacotherapy, most asthmatic attending specialist care have impaired quality of life (QoL). Breathing exercises (BrEX) improve QoL in mild asthma, yet their effectiveness in more severe asthma is uncertain.

Methods: Symptomatic adults attending respiratory outpatient clinics were randomised to usual specialist care (UC) or UC plus BrEX (UC+BrEX), with three sessions of individual physiotherapy plus home exercises. Primary outcome was asthma-related QoL (Mini-Asthma Quality of Life Questionnaire (Mini-AQLQ)) at 6-month. Secondary outcomes included lung function, 6-minutes' Walk Test (6MWT), physical activity, Nijmegen Questionnaire, Hospital Anxiety and Depression Scale (HADS), Global Perceived Effect, and adverse events (AE).

Findings: 193 participants were allocated to UC+BrEX (n=94) or UC (n=99). At 6-month, UC+BrEX was superior in the intention-to-treat primary outcome analysis (adjusted mean difference 0.35, 95% CI 0.07 to 0.62), with number-needed-to-treat of 7.6, with improvements remaining in per-protocol analysis, (0.38, 0.10 to 0.66). There were no between-group differences in secondary outcomes, other than a minor improvement in HADS-depression favouring the UC+BrEX (-0.90, 95% CI -1.67 to -0.14). Significant within-group improvements were observed for all patient-reported questionnaires in UC+BrEX but not in UC. No within-group or between-group differences were found in lung function or 6MWT. Asthma-related AEs occurred in 14.9% of UC+BrEX and 18.1% of UC participants (p=0.38). Asthma exacerbations occurred in 9.6% of UC+BrEX and 10.2% of UC participants (p=0.79).

Interpretation: BrEX as add-on to usual care in respiratory specialist clinics seems to be a safe and effective treatment, improving asthma-related QoL in symptomatic patients with moderate-to-severe asthma.

Key words: Asthma; quality of life; breathing exercises.

Introduction

Asthma is a common chronic and heterogeneous disease characterised by reversible airway obstruction, airway inflammation and bronchial hyperresponsiveness [1]. It presents with non-specific symptoms including dyspnoea, wheezing, coughing, and results in impaired QoL for most patients [2]. Asthma severity is defined by the level of pharmacological treatment required to achieve control, and may be categorised by the daily dose of inhaled corticosteroids (ICS) and the requirement for second controllers, expressed as treatment steps 1-5 according to Global Initiative for Asthma (GINA) [1, 3]. Most patients requiring high levels of pharmacotherapy should be under specialist care [1]. Drug and device effectiveness has improved markedly, but complete asthma control, defined by the minimisation of symptoms and risk of exacerbations [1, 4], is achieved by less than 50% of patients with moderate-to-severe asthma [1, 5, 6] and aggressive pharmacologic escalation strategies fail to prevent persisting symptoms and QoL impairment for some [7], suggesting that additional non-pharmacological interventions may be helpful.

Breathing pattern abnormalities have been described in asthma [8], with breathing retraining interventions aimed to normalise breathing patterns shown to improve asthma-related QoL in patients with mild-to-moderate asthma [8, 9]. Breathing retraining delivered by trained physiotherapists is a safe and inexpensive intervention that has been investigated in a few randomised trials [8, 10, 11]. Breathing exercises (BrEX) is a broader term including breathing retraining, relaxation techniques, and practice of the methods in activity [12].

Based on this evidence, BrEX are advocated as add-on treatment in mild-to-moderate asthma in many asthma guidelines, including GINA [1] and the BTS-SIGN UK guideline [13]. However, the effects of BrEX in a more severe asthma population attending specialist clinics has not previously been rigorously investigated. A recent meta-analysis emphasises a lack of trials investigating patients with severe asthma attending specialist asthma clinics [14].

We hypothesised that usual care with add-on BrEX in adults with moderate-to-severe asthma managed in specialist care due to uncontrolled asthma would be superior in improving asthma-related QoL at 6-month compared to usual care alone.

Methods

Study design, participants, and randomisation

We report a two-armed parallel group assessor-blinded multicentre randomised controlled trial (RCT) in seven outpatient respiratory departments and one specialized private clinic in Denmark. The protocol was published [12], ethically approved by Region Zealand Research Ethics Committee (SJ-552) and registered with ClinicalTrials.gov (NCT03127059) prior to commencement. Consenting adult patients (≥18 years) attending specialist care, having impaired asthma control (Asthma Control Questionnaire, ACQ, score ≥1.5) were recruited. Exclusion criteria were pregnancy, previous BrEX training prior to inclusion, participation in another respiratory interventional trial, or having comorbidity making participation problematic. Eligibility screening was conducted by the treating pulmonologist, and consent and ACQ6 score were repeated at baseline assessment. In January 2018, the ACQ6 inclusion criterion was adjusted by reducing the ACQ6 cut off score from ≥1.5 to ≥0.8, thereby still recruiting participants with incomplete asthma control despite current clinic treatment, but reducing the level of symptoms necessary, since only a low proportion met the higher symptom criterion.

The trial was conducted in Denmark at respiratory outpatient clinics at Naestved Hospital, Zealand University Hospital Roskilde, Hvidovre University Hospital, Bispebjerg University Hospital, Aalborg University Hospital, Silkeborg Regional Hospital, Odense University Hospital, and the private Allergy and Lung Clinic, Elsinore. This represented all health care regions of Denmark and included larger and smaller outpatient departments accepting general practitioners' referrals with uncontrolled asthma.

After providing informed consent and baseline assessment, participants were randomised by random number generation (EasyTrial Inc. Denmark) in 1:1 ratio, to add-on physiotherapy (UC+BrEX) or usual care (UC), concealed to trial staff, outcome assessors and data analysts (see trial protocol [12] for further details). Blinded interpretation [15] was made publicly available before unblinding [16].

Procedures

UC was delivered at all locations. BrEX were delivered at hospital physiotherapy units, with participants from the private clinic referred to the closest unit. At each unit, 2-4 physiotherapists delivered BrEX, all trained and familiar with BrEX as usual practice.

UC was planned or acute clinic visits, including assessment of control, pharmacotherapy adjustment, and self-care instruction [1].

BrEX are described in details in the trial protocol [12]. Briefly, BrEX were delivered face-to-face, with three individual sessions (60 min + 30 min + 30 min) with 3-4 weeks intervals, plus instructions for home practice 10 minutes twice daily. BrEX included breathing retraining and relaxation techniques individualised to participants' needs and abilities. All received a supporting booklet (supplementary S1).

BrEX included [12]: nasal inhalation and exhalation if possible; breathing from diaphragm and lower chest; shoulder neck, tongue and jaw relaxation; exhalation prolongation; exhalation to functional residual capacity; aiming for respiration frequency of 12-16/min. If frequent yawns, dry coughs, or sighs were observed, suppression techniques were taught. BrEX progressed from a relaxed body position to use in active situations (*e.g.* standing, walking). The programme complied with descriptions by Bruton [17].

Outcomes

The primary outcome was a comparison of between-groups mean change in Mini-AQLQ [9] at 6-month in the ITT population.

Secondary outcomes included validated patient-reported outcome measures (PROMs), objective physiological assessments, and extracted data from medical record:

Asthma symptoms were assessed by the 6-item Asthma Control Questionnaire (ACQ6) [18], dysfunctional breathing-related symptoms by Nijmegen Questionnaire (NQ) [19], psychological domains by Hospital Anxiety and Depression Scale (HADS-Anxiety(A), HADS-Depression(D)) [20], Global Perceived Effect (7-point Likert scale) [21], and patient-reported adverse events (AE). 6-min Walk Test (6MWT) was performed to assess functional exercise capacity, and spirometry (MedikroPro, M915, OY, Finland) to assess lung function as percentage of predicted forced expiratory volume in first second (FEV_1%pred.), using Global Lung Functions Initiative 2012 reference values [22]. Accelerometry (BodyMedia SenseWear, USA) was performed in participants recruited until April 2017, thereafter only at Naestved and Hvidovre Hospitals over a 6-day period (23h per day) with average steps per day and physical activity level (PAL) measured [23]. Data were extracted from routine medical records on comorbidities, prescribed anti-asthmatic medication, and acute/planned hospital or emergency unit visits. Asthma severity was classified by GINA 2019 step [1].

AEs were defined as events leading to medical contact, serious AEs (SAEs) as life-threatening events or hospitalization [24]. Asthma-related AEs were defined as respiratory symptoms triggering unscheduled healthcare contacts, and assessed as study related or unrelated.
Attendance of BrEX sessions was monitored, and adherence to home exercise was estimated by the treating physiotherapists, using a numeric rating scale (NRS, 1=no adherence, 5=excellent adherence).
Outcomes are presented in detail in the protocol [12]; for details of GINA step calculation, AEs questionnaire, AEs classification, and adherence/attendance of BrEX sessions, see supplementary materials.

Statistical analysis

Sample size calculation was based on an effect size of 0.38 in Mini-AQLQ reported in less severe patients [11] and standard deviation (SD) as twice the effect size [25]. At a two-sided type 1 p-value of 0.05, 172 participants (86 in each group) provided 90% power to detect a mean difference 0.38 (SD 0.76). We aimed to enroll 190 participants to allow for 10% attrition. A priori, the statistical analysis plan was made publicly available [26].
Repeated measures mixed effects model with subject being a random factor and treatment arm, visit (*i.e.* baseline, 3-month and 6-month follow up), and interaction between treatment arm and visit as fixed factors, with adjustment for treatment centre, were used in the primary outcome analysis, with similar methods used for most secondary outcomes at 3-month and 6-month follow up, (ACQ6, NQ, HADS-A, HADS-D, 6MWT, FEV_1%pred., steps per day, and PAL, and Mini-AQLQ at 3-month). Participants were included in accelerometry subgroup analyses (n= 93) if the duration of measurement was ≥6 days at ≥1 of baseline assessment, 3-month, and 6-month follow up. Per-protocol analysis were also performed using mixed effects model, including UC+BrEX participants attending all three BrEX sessions and all participants in UC group.
Number-needed-to-treat (NNT) was calculated using the recommended formula based on the published individual patient minimum important difference (MID) in mini-AQLQ score, 0.5 units [27] [27]. Chi-square and Mann-Whitney test was used where appropriate. Incidence rate ratio (IRR) comparisons between groups are reported using Poisson regression models with treatment center, GINA step, and BMI as covariates. Pre-specified sensitivity analyses are reported in the supplementary materials. We used STATA 16.1 (StataCorp, College Station, TX, USA) for analyses.

Results

Between April 2017 and September 2019, 314 patients were screened for eligibility, and 193 were randomised, 94 to UC+BrEX and 99 to UC (further details in figure 1 and supplementary S2). Baseline characteristics were similar between groups (table 1; supplementary S3).

Table 1; Baseline characteristics

	UC+BrEX (n=94)		UC (n=99)	
Sex				
Female	58	(61.7%)	64	(64.7%)
Male	36	(38.3%)	35	(35.4%)
Age at inclusion	55	(44-65)	51	(42-61)
Smoking status				
Never-smokers	89	(55.3%)	95	(65.7%)
Smokers	5	(5.3%)	4	(4.0%)
Former smokers	37	(39.4%)	30	(30.3%)
Body Mass Index				
Underweight	1	(1.1%)	1	(1.0%)
Normal weight	24	(25.5%)	22	(22.2%)
Overweight	29	(30.9%)	44	(44.4%)
Obese	26	(27.7%)	20	(20.2%)
Severely obese	8	(8.5%)	7	(7.1%)
Extremely obese	6	(6.4%)	5	(5.1%)
PROMs				
Mini-AQLQ	4.3	(3.7-5.1)	4.4	(3.6-5.1)
ACQ6	2.2	(1.5-2.7)	2.0	(1.2-2.7)
NQ[a]	22.9	(10.9)	23.1	(11.3)
HADS-A	5	(3-10)	6	(3-9)
HADS-D	3	(1-7)	3	(1-6)
EuroQual, EQ-5D-5L index	0.742	(0.648-0.859)	0.754	(0.700-0.824)
EuroQual, EQ-5D-5L VAS[a]	62.0	(20.7)	62.1	(19.0)
GINA steps				
1	0	(0%)	0	(0%)
2	1	(1.1%)	2	(2.0%)
3	16	(17.0%)	13	(13.1%)
4	31	(33.0%)	34	(34.3%)
5	46	(48.9%)	50	(50.5%)
Inhaled corticosteroids, ICS				
none	1	(1.1%)	1	(1.0%)
low	18	(19.2%)	20	(20.2%)
moderate	33	(35.1%)	30	(30.3%)
high	42	(44.7%)	48	(48.5%)
Number of 2nd controller(s)				
None	5	(5.3%)	4	(4.0%)
1	41	(43.6%)	45	(45.5%)
2	30	(31.9%)	35	(35.4%)
3	14	(14.9%)	13	(13.1%)
4+	4	(4.3%)	2	(2.0%)
Oral corticosteroids, OCS[b]	6	(6.4%)	2	(2.0%)
Biological treatment	13	(13.8%)	9	(9.1%)
Objective measures				
6-min walk test	(n=90) 467	(422-528)	(n=97) 469	(417-515)
Borg CR10 (resting)	(n=94) 1	(0.3-2.5)	(n=99) 2	(0.5-2.5)
FEV_1 % predicted	(n=85) 80	(73-87)	(n=91) 80	(66-90)
FEV_1/FVC-ratio	(n=85) 0.73	(0.66-0.80)	(n=91) 0.73	(0.67-0.79)
PEFR (liter/min)	(n=85) 359	(308-421)	(n=91) 355	(282-434)

Steps per day (avg 6 days)	(n=41)	7046	(4637-9517)	(n=44)	7278	(4899-10175)
PAL (avg 6 days)	(n=41)	1.5	(1.4-1.6)	(n=44)	1.5	(1.4-1.6)

Data are reported as medians with interquartile range (IQR) and frequency with percentage (%), apart from [a] which are means and standard deviations (SD). [b] Maintenance oral corticosteroids. Explicitly about co-morbidity in supplementary materials. UC+BrEX=Breathing exercises and usual care. UC=Usual care alone. PROMs=Patient-reported outcome measures. Mini-AQLQ=Mini-Asthma Quality of Life Questionnaire. ACQ6=6-item Asthma Control Questionnaire. NQ=Nijmegen Questionnaire. HADS-A=anxiety items of Hospital Anxiety and Depression Scale. HADS-D=depression items of Hospital Anxiety and Depression Scale. 6MWT=6-min walk test. FEV1%predicted=predicted percentage of forced expiratory volume in first second. FEV1/FVC-ratio=ratio of FEV_1/forced vital capacity. PEFR=peak expiratory flow rate. PAL=average Physical Activity Level per day.

At 6-month, 183 (94.8%) answered Mini-AQLQ, 87 (92.6%) in UC+BrEX, 96 (97.0%) in UC. The other PROMs were completed by 85 (90.4%) and 95 (96.0%), respectively. Medication use data was available for 192 (99.5%) (one missing in UC group). Follow-up assessment of physiological outcomes was limited by COVID-10-related attendance issues, and were completed by 72 (76.6%) of UC+BrEX versus 82 (82.8%) of UC participants. 6MWT were completed by 70 (74.5%) of UC+BrEX versus 79 (79.8%) of UC participants. FEV_1%pred. was measured in 65 (69.1%) of UC+BrEX versus 72 (72.7%) of UC participants. 3-month, Mini-AQLQ was answered by 81 (86.2%) in UC+BrEX and 92 (92.9%) in UC, other PROMs by 76 (80.9%) in UC+BrEX and 90 (90.9%) in UC. Accelerometry was collected in 93 participants.
76 (80.9%) of UC+BrEX and 99 (100%) of UC completed full protocol requirements and were included in the per-protocol analyses (figure 1).

Figure 1:* Trial profile*
****Legend to Figure 1**; ITT= intention-to-treat. Mini-AQLQ= Mini-Asthma Quality of Life Questionnaire. UC= Usual care alone. UC+BrEX= Breathing exercises and usual care.**

For the primary outcome, Mini-AQLQ at 6-months, a significant adjusted difference was seen favouring UC+BrEX of 0.35 (95% CI 0.07 to 0.62). Both groups improved significantly from baseline, adjusted mean change in UC+BrEX: 0.65 (0.46 to 0.85), and UC: 0.31 (0.12 to 0.49). In the per-protocol analysis, the difference in mean change was slightly larger: adjusted 0.38 (0.10 to 0.66) (table 2; figure 2). A significant difference favouring UC+BrEX was also seen at 3-months, 0.56 (0.28 to 0.85) (supplementary S4).

Table 2; Adjusted intention-to-treat analyses and per-protocol analyses of Mini-AQLQ and secondary outcomes at 6-month

	Total no. of assessments[a]		ITT-population					
	UC+BrEX	UC	UC+BrEX (n=94)		UC (n=99)		Between-group difference	
			mean change		mean change		difference in means change	
MiniAQLQ	262	287	0.65	(0.46 to 0.85)	0.31	(0.12 to 0.49)	0.35	(0.07 to 0.62)
ACQ6	256	285	-0.32	(-0.50 to -0.15)	-0.21	(-0.38 to -0.05)	-0.11	(-0.35 to 0.13)
NQ	255	285	-3.83	(-5.52 to -2.13)	-2.78	(-4.39 to -1.17)	-1.05	(-3.38 to 1.29)
HADS-A	255	284	-1.06	(-1.73 to -0.38)	-1.11	(-1.75 to -0.47)	0.06	(-0.87 to 0.98)
HADS-D	255	284	-1.16	(-1.71 to -0.61)	-0.26	(-0.78 to 0.27)	-0.90	(-1.67 to -0.14)
6MWT	160	176	2.03	(-10.20 to 14.27)	9.03	(-2.44 to 20.50)	-7.00	(-23.77 to 9.77)
FEV_1% pred.	150	163	0.48	(-2.19 to 3.14)	-0.53	(-3.01 to 1.96)	1.00	(-2.64 to 4.65)
Steps per day	82	89	84.74	(-973.24 to 1142.72)	-245.85	(-1282.10 to 790.40)	330.59	(-1149.86 to 1811.04)
PAL	82	89	0.03	(-0.02 to 0.08)	-0.02	(-0.06 to 0.03)	0.05	(-0.02 to 0.11)
			Per-protocol population					
			UC+BrEX (n=76)		UC (n=99)		Between-group difference	
			mean change		mean change		difference in means change	
Mini-AQLQ	222	287	0.68	(0.47 to 0.89)	0.31	(0.12 to 0.49)	0.38	(0.10 to 0.66)
ACQ6	216	285	-0.39	(-0.58 to -0.20)	-0.21	(-0.38 to -0.05)	-0.18	(-0.43 to 0.07)
NQ	215	285	-4.03	(-5.88 to -2.19)	-2.78	(-4.41 to -1.16)	-1.25	(-3.71 to 1.21)
HADS-A	215	284	-1.13	(-1.84 to -0.42)	-1.11	(-1.74 to -0.48)	-0.02	(-0.97 to 0.93)
HADS-D	215	284	-1.46	(-2.03 to -0.89)	-0.26	(-0.76 to 0.25)	-1.20	(-1.97 to -0.44)
6MWT	140	176	2.50	(-10.20 to 15.19)	9.03	(-2.53 to 20.58)	-6.53	(-23.69 to 10.63)
FEV_1% pred.	131	163	0.87	(-1.89 to 3.63)	-0.52	(-3.02 to 1.99)	1.39	(-2.34 to 5.11)
Steps per day	79	89	139.09	(-921.97 to 1200.14)	-248.85	(-1282.53 to 784.83)	387.93	(-1093.40 to 1869.27)
PAL	79	89	0.03	(-0.02 to 0.08)	-0.01	(-0.06 to 0.03)	0.05	(-0.02 to 0.11)

Data are adjusted mean change from baseline to 6-month including 95% CI.
[a]Possible assessments for questionnaires (at baseline + at 3-month + at 6-month): 282 for UC+BrEX (in per-protocol: 228) and 297 for UC; for FEV1%pred. and 6MWT (at baseline + at 6-month): 188 for UC+BrEX (in per-protocol: 152) and 198 for UC; steps per day and PAL (at baseline + at 3-month + at 6-month): 135 for UC+BrEX (in per-protocol population: 126) and 144 for UC.
UC+BrEX= Breathing exercises and usual care. UC= Usual care alone. Mini-AQLQ=Mini-Asthma Quality of Life Questionnaire. ACQ6=6-item Asthma Control Questionnaire. NQ=Nijmegen Questionnaire. HADS-A=anxiety items of Hospital Anxiety and Depression Scale. HADS-D=depression items of Hospital Anxiety and Depression Scale. 6MWT=6-min Walk Test. FEV1%pred.=Predicted percentage of forced expiratory volume in first second. PAL=average Physical Activity Level per day.

*******Figure 2*: Mean total Mini-Asthma Quality of Life Questionnaire comparing groups (95%CI)**

****Legend to figure 2:** Mean total Mini-Asthma Quality of Life Questionnaire (95%CI) comparing groups at baseline, 3-month and 6-month follow up. Higher score denotes improved quality of life. UC+BrEX= Breathing exercises and usual care. UC= Usual care alone.**

An improvement by ≥0.5 of Mini-AQLQ was observed in 47 (54%) in UC+BrEX and 40 (42%) in UC, deterioration in 11 (13%) in UC+BrEX and 17 (18%) in UC, providing NNT 7.6 for UC+BrEX (supplementary S5).
A between-groups difference in HADS-D of -0.9 (-1.67 to -0.14) favouring UC+BrEX was the only statistically significant difference among secondary outcomes. However, persistent non-significant trends towards greater improvement from baseline to 6-month were seen in most PROMs in the UC+BrEX group (table 2). Significant within-group improvements were observed in both groups for ACQ6, NQ, and HADS-A, but not in physiological measures including 6MWT, FEV_1%pred., in steps per day, or daily PAL.
Global Perceived Effect improvement at 6-month were reported by 43.0% of UC+BrEX compared to 30.9% of UC (p=0.091) (supplementary S6).
Most participants did not change GINA step during the trial (UC+BrEX 84.0%, and UC 82.7%). Similar proportions were stepped-up (6.4% versus 5.1%) and -down (9.6% versus 12.2%) (between groups p=0.507) (supplementary S7).

All three physiotherapy sessions were attended by 76 (80.9%), with 1(1.1%) attending none, 11 (11.7%) one and 6 (6.4%) attending two, respectively. Adherence to home exercises was assessed by physiotherapists as “good” or “excellent” (NRS 4-5) in 75.7% (supplementary S8).

In total, 505 AEs were reported by 150 participants, 259 events (51.1%) in 73 participants in UC+BrEX and 246 events (48.9%) in 77 participants in UC. 14 SAEs were observed in 14 UC+BrEX, vs. 21 in 17 UC participants, most commonly asthma exacerbations (supplementary S9a-b). No SAEs were considered to be trial-related. SenseWear use gave local allergic reas in 12 participants but this AE was unrelated to trial interventions. There was no difference in incidence rates of SAEs (p≥0.283) or in asthma-related SAEs (p≥0.159) between groups (table 3; supplementary S9a).
34 asthma-related AEs causing unscheduled healthcare contact occurred in 14 participants in UC+BrEX group, and 39 in 18 participants in UC group (table 3). Exacerbation occurred in 9.6% of UC+BrEX and 10.2% of UC participants (p=0.787) (supplementary S9d).

Table 3; Asthma-related adverse events, asthma-related serious adverse events, and courses of oral corticosteroids

	UC+ BrEX			UC				
	Number of participants		Number of events	Number of participants		Number of events	IRR[a]	p-value
Adverse events							1.47	0.381
0	80	(85.1%)	0	81	(81.8%)	0		
1	11	(11.7%)	11	12	(12.1%)	12		
2	1	(1.1%)	2	3	(3.0%)	6		
3+	2	(2.1%)	21	3	(3.0%)	21		
Total	94	(100%)	34	99	(100%)	39		
Serious adverse events							2.03	0.159
0	88	(93.6%)	0	90	(90.9%)	0		
1	6	(6.4%)	6	6	(6.1%)	6		
2	0	(0%)	0	3	(3.0%)	6		
Deaths	0	(0%)	0	0	(0%)	0		
Total	94	(100%)	6	99	(100%)	12		
OCS courses[b]							0.82	0.704
0	87	(92.6%)	0	93	(94.9%)	0		
1	6	(6.4%)	6	3	(3.1%)	3		
2	1	(1.1%)	2	2	(2.0%)	4		
Total	94	(100%)	8	98	(100%)	7		

[a]Incidence rate ratio (IRR): UC group compared to UC+BrEX group. [b]One missing in UC group

UC+BrEX=Breathing exercises and usual care. UC=Usual care alone. OCS=oral corticosteroids.

Discussion

BrEX are advocated in evidence-based guidelines as add-on treatment to improve QoL for patients with mild-to-moderate asthma with persisting impaired control, but despite anecdotal reports of effectiveness in the difficult asthma setting, rigorous RCT evidence has till now been lacking [13, 14]. Our large multicentre RCT shows that breathing exercises delivered as three sessions by trained physiotherapists supplemented by daily home exercises are safe and effective as an add-on treatment to usual care in adults with uncontrolled asthma under the care of specialists in hospital-based asthma clinic settings, with an effect size similar to that of studies in milder disease, and consistent with previous studies without physiological effects. This is novel evidence in this patient population. In the era of personalised, precision medicine, it provides an additional evidence-based treatment option for patients with impaired asthma control despite standard pharmacological management.

The individual patient MID of Mini-AQLQ is 0.5 units, although the MID for between-group mean differences in controlled studies is unclear [27, 28], and varies according to population and context [29]. However, meta-analyses report that in pharmacological placebo-controlled trials, a between-group difference of 0.5 is unachievable, and smaller differences indicate clinically important benefits. Indeed, the interpretation advice of the AQLQ developers explicitly states that important benefits are associated with differences of below 0.5 [27]. Bateman [6] investigated the effect of ICS and controllers on AQLQ in meta-analysis, reporting AQLQ benefits above placebo associated with second controllers (*e.g.* biological treatment or long-acting β antagonist (LABA)) in patients uncontrolled on ICS alone were 0.305 (95% CI 0.202 to 0.408) for biological treatments and 0.349 (0.271 to 0.427) for LABA, with lesser effect for other options. The patient improvement of 0.35 that we report for BrEX is similar to or greater than that of additional controllers in a comparable population.

The recent Cochrane review [14] of BrEX in adults with mild-to-moderate asthma including four different kinds of breathing interventions (Buteyko, Pranayama, yoga, and BrEX similar to our) reported a mean effect size of 0.42 (95% CI 0.17 to 0.68). The recent trial in milder asthma [17], reported an effect size of 0.24 (95% CI 0.04 to 0.44) for face-to-face BrEX compared to usual care.

Our trial was powered on Mini-AQLQ, as previous research indicated that the effects of BrEX are largest for QoL [8, 11, 14, 17], which was confirmed in our more severe population. We observed

significant within-group improvements in all PROMs for UC+BrEX, but not for UC, including symptom scores and psychological metrics, but although numerical improvements were larger for UC+BrEX, there were no significant between group differences other than for HADS-D. It is possible that larger studies could show differences in other outcomes, such as asthma symptoms and psychological well-being. In keeping with previous research, we saw non-significant numerical trends to less asthma-related AEs and to less asthma exacerbations in the UC+BrEX, again suggesting that a larger study or a meta-analysis may show benefits. However, the main effect of BrEX appears to be on improving the patient's experience of their asthma.
Similar to previous trials [14, 17, 30, 31], we did not find significant changes in lung function, nor in PAL or in 6MWT to account for the QoL benefits, implying that the intervention did not work by changing the underlying pathophysiology, but rather enabled patients to cope better with their long term and incurable disease [1, 4].

A limitation was the impossibility of blinding participants to allocation, since they clearly knew whether they had received BrEX. This may have led to non-specific, contextual effects in the active group from a professional giving time and attention to a patient. In previous work of BrEX for milder asthma, attempts were made to control for attention by allocating the 'control' group to a similar professional contact with a nurse providing non-personalised asthma education [10, 11], but subsequent trials without an 'active' control showed similar between group differences [17], suggesting that these do indeed relate to program contents. In our trial, ongoing professional contact within UC ensures the 'control' group continued to receive professional support, mitigating against contact effects. All data collection and analyses were blinded, so within the pragmatic, 'real-world' setting, we made efforts to minimize sources of bias.

We succeeded in recruiting a previously unstudied population, randomising 193 participants, with >80% treated at GINA steps 4 or 5, with 94.8% retention rate for the primary outcome. A high attendance rate for physiotherapy sessions and high scores in adherence to home exercise indicated that the intervention was well-tolerated, acceptable and practiced by most. We recruited from different departments representing all Danish health regions, with a number of different physiotherapists delivering BrEX, all experienced at providing BrEX, and attempted to standardisation delivery as much as possible, observing consistent effects across centres. The multicentre and multi-therapist aspects as well as the inclusion of larger and smaller outpatient

departments from all regions of Denmark give confidence in generalisability. Similarly, the constancy with previous studies in milder populations is reassuring. The biomechanical mechanisms underlying the QoL improvement, and relative effectiveness of components of the intervention are currently unclear, and require future studies to elucidate. Additionally, the persistence of benefits and the need for reinforcement instruction require further investigation.
In summary, we found that add-on physiotherapist-delivered BrEX improve QoL in patients with uncontrolled, moderate-to-severe asthma receiving standard asthma care by respiratory specialists, but continuing to have poor control, are without evidence of harm, and so may be offered to such patients as a therapeutic option.

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Data sharing
De-identified participant data collected for the trial will be made available according to Danish legislation on reasonable request (until five years after trial closure), contact principal investigator, khad@regionsjaelland.dk

Related documents are available:
Trial protocol published BMJ Open 2019;**9**:e032984. doi:10.1136/bmjopen-2019-032984
Booklet (Danish) in supplementary materials.
Statistical analysis Plan. See URL in reference list.
Blinded interpretation. See URL in reference list.

Contributors
KHA, UB, STS, and MT (Research group, i.e. 'steering committee') contributed substantively to the concept and design of this trial. The chief investigator (KHA) developed manuals (recruitment, assessment, and treatment) and written information, applied for grants, assigned for approvals, registered at ClinicalTrials.gov, introduced and supervised the recruitment, assessment, and treatment procedures to all involved nurses and physiotherapists and, and led the data collection,

and data verification. UB, STS, and MT gave feedback. STS specifically contributed in description of the statistical analyses. KHA analysed data and drafted the manuscript. All authors (KHA, STS, CSU, CP, KS, JBN, KDA, HM, MT, and UB) provided intellectual feedback to the manuscript and approved the final version.

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Conflicts of interest

KHA has nothing to disclose. STS is associate editor of the Journal of Orthopaedic & Sports Physical Therapy, has received grants from The Lundbeck Foundation, personal fees from Munksgaard and TrustMe-ED, all of which are outside the submitted. He is co-founder work of Good Life with Osteoarthritis in Denmark (GLA:D®), a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice. CSU has received personal fees for lectures, advisory boards etc. from AZ, GSK, Chiesi, Novartis, Boehringer-Ingelheim, Actelion, ALK-Abello, Mundipharma, TEVA and Orion Pharma. HM has nothing to disclose. KS has nothing to disclose. KDA has nothing to disclose. CP has nothing to disclose. JBN has nothing to disclose. Neither MT nor any member of his close family has any shares in pharmaceutical companies. In the last 3 years he has received speaker's honoraria for speaking at sponsored meetings or satellite symposia at conferences from the following companies marketing respiratory and allergy products: GSK, Novartis. He has received honoraria for attending advisory panels with: Boehringer Inglehiem, GSK, Novartis. UB has nothing to disclose.

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References

1. Global_Initiative_For_Asthma. GINA, Global Initiative for Asthma. Global strategy for asthma management and prevention, 2019 [Internet]. www.ginasthma.org 2019 [cited 2020 May 6].Available from: https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf.

2. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *The Lancet* 2018; 391: 783–800.

3. Taylor DR, Bateman ED, Boulet L-P, Boushey HA, Busse WW, Casale TB, Chanez P, Enright PL, Gibson PG, de Jongste JC, Kerstjens H a. M, Lazarus SC, Levy ML, O'Byrne PM, Partridge MR, Pavord ID, Sears MR, Sterk PJ, Stoloff SW, Szefler SJ, Sullivan SD, Thomas MD, Wenzel SE, Reddel HK. A new perspective on concepts of asthma severity and control. *Eur. Respir. J.* 2008; 32: 545–554.

4. Papaioannou AI, Kostikas K, Zervas E, Kolilekas L, Papiris S, Gaga M. Control of asthma in real life: still a valuable goal? *Eur Respir Rev* 2015; 24: 361–369.

5. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet L-P, Brightling C, Chanez P, Dahlen S-E, Djukanovic R, Frey U, Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness RL, Teague WG. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur. Respir. J.* 2014; 43: 343–373.

6. Bateman ED, Esser D, Chirila C, Fernandez M, Fowler A, Moroni-Zentgraf P, FitzGerald JM. Magnitude of effect of asthma treatments on Asthma Quality of Life Questionnaire and Asthma Control Questionnaire scores: Systematic review and network meta-analysis. *J. Allergy Clin. Immunol.* 2015; 136: 914–922.

7. Bateman ED, Bousquet J, Keech ML, Busse WW, Clark TJH, Pedersen SE. The correlation between asthma control and health status: the GOAL study. *Eur. Respir. J.* 2007; 29: 56–62.

8. Burgess J, Ekanayake B, Lowe A, Dunt D, Thien F, Dharmage SC. Systematic review of the effectiveness of breathing retraining in asthma management. *Expert Rev Respir Med* 2011; 5: 789–807.

9. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur. Respir. J.* 1999; 14: 32–38.

10. Thomas M, McKinley RK, Freeman E, Foy C, Prodger P, Price D. Breathing retraining for dysfunctional breathing in asthma: a randomised controlled trial. *Thorax* 2003; 58: 110–115.

11. Thomas M, McKinley RK, Mellor S, Watkin G, Holloway E, Scullion J, Shaw DE, Wardlaw A, Price D, Pavord I. Breathing exercises for asthma: a randomised controlled trial. *Thorax* 2009; 64: 55–61.

12. Andreasson KH, Skou ST, Ulrik CS, Madsen H, Sidenius K, Jacobsen JS, Assing KD, Rasmussen KB, Porsbjerg C, Thomas M, Bodtger U. Protocol for a multicentre randomised controlled trial to investigate the effect on asthma-related quality of life from breathing retraining in patients with incomplete asthma control attending specialist care in Denmark. *BMJ Open* 2019; 9: e032984.

13. Levy Ml, Thomas M, Small I, Pearce L, Pinnock H, Stephenson P. Summary of the 2008 BTS/SIGN British Guideline on the management of asthma [Internet]. Primary care respiratory journal : journal of the General Practice Airways Group Prim Care Respir J; 2009 [cited 2020 Aug 12].Available from: https://pubmed.ncbi.nlm.nih.gov/19209371/.

14. Santino TA, Chaves GS, Freitas DA, Fregonezi GA, Mendonça KM. Breathing exercises for adults with asthma. *Cochrane Database Syst Rev* 2020; 3: CD001277.

15. Järvinen TLN, Sihvonen R, Bhandari M, Sprague S, Malmivaara A, Paavola M, Schünemann HJ, Guyatt GH. Blinded interpretation of study results can feasibly and effectively diminish interpretation bias. *J Clin Epidemiol* 2014; 67: 769–772.

16. Bodtger U, Skou ST, Thomas M, Andreasson (ed) KH. Blinded review of the primary endpoint results from the BEAT DB-trial: Blinded review and interpretation. [Internet]. the University of Southern Denmark through the SDU Research Portal.; 2020.Available from: https://portal.findresearcher.sdu.dk/da/publications/blinded-review-of-the-primary-endpoint-results-from-the-beat-db-t.

17. Bruton A, Lee A, Yardley L, Raftery J, Arden-Close E, Kirby S, Zhu S, Thiruvothiyur M, Webley F, Taylor L, Gibson D, Yao G, Stafford-Watson M, Versnel J, Moore M, George S, Little P, Djukanovic R, Price D, Pavord ID, Holgate ST, Thomas M. Physiotherapy breathing retraining for asthma: a randomised controlled trial. *Lancet Respir Med* 2018; 6: 19–28.

18. Juniper EF, Svensson K, Mörk A-C, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005; 99: 553–558.

19. van Dixhoorn J, Duivenvoorden HJ. Efficacy of Nijmegen Questionnaire in recognition of the hyperventilation syndrome. *J Psychosom Res* 1985; 29: 199–206.

20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361–370.

21. Kamper SJ, Ostelo RWJG, Knol DL, Maher CG, de Vet HCW, Hancock MJ. Global Perceived Effect scales provided reliable assessments of health transition in people with musculoskeletal

disorders, but ratings are strongly influenced by current status. *J Clin Epidemiol* 2010; 63: 760-766.e1.

22. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright PL, Hankinson JL, Ip MSM, Zheng J, Stocks J, ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur. Respir. J.* 2012; 40: 1324–1343.

23. Brazeau A-S, Karelis AD, Mignault D, Lacroix M-J, Prud'homme D, Rabasa-Lhoret R. Test-retest reliability of a portable monitor to assess energy expenditure. *Appl Physiol Nutr Metab* 2011; 36: 339–343.

24. Office of the FDA, U.S. Food & Drug Administration. What is a Serious Adverse Event? *FDA* [Internet] FDA; 2019 [cited 2020 May 10]; Available from: https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event.

25. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003; 41: 582–592.

26. Andreasson KH, Skou ST, Petersen I, Bodtger U. Statistical Analysis Plan Breathing Exercises in Asthma Targeting Dysfunctional Breathing – the BEAT DB trial, revision — Syddansk Universitet [Internet]. [cited 2020 Sep 11].Available from: https://portal.findresearcher.sdu.dk/da/publications/statistical-analysis-plan-breathing-exercises-in-asthma-targeting-2.

27. Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. *BMJ* 1998; 316: 690–693.

28. Ehrs P-O, Nokela M, Ställberg B, Hjemdahl P, Wikström Jonsson E. Brief questionnaires for patient-reported outcomes in asthma: validation and usefulness in a primary care setting. *Chest* 2006; 129: 925–932.

29. King MT. A point of minimal important difference (MID): a critique of terminology and methods. *Expert Rev Pharmacoecon Outcomes Res* 2011; 11: 171–184.

30. Löwhagen O, Bergqvist P. Physiotherapy in Asthma Using the New Lotorp Method [Internet]. Complementary therapies in clinical practice Complement Ther Clin Pract; 2014 [cited 2020 May 19].Available from: https://pubmed.ncbi.nlm.nih.gov/25130138/?from_single_result=lotorp&expanded_search_query=lotorp.

31. Holloway Ea, West Rj. Integrated Breathing and Relaxation Training (The Papworth Method) for Adults With Asthma in Primary Care: A Randomised Controlled Trial [Internet]. Thorax Thorax; 2007 [cited 2020 May 19].Available from: https://pubmed.ncbi.nlm.nih.gov/17573445/?from_term=papworth&from_pos=10.

Figures for

Breathing exercises for asthma patients in specialist care: a multicentre randomised trial

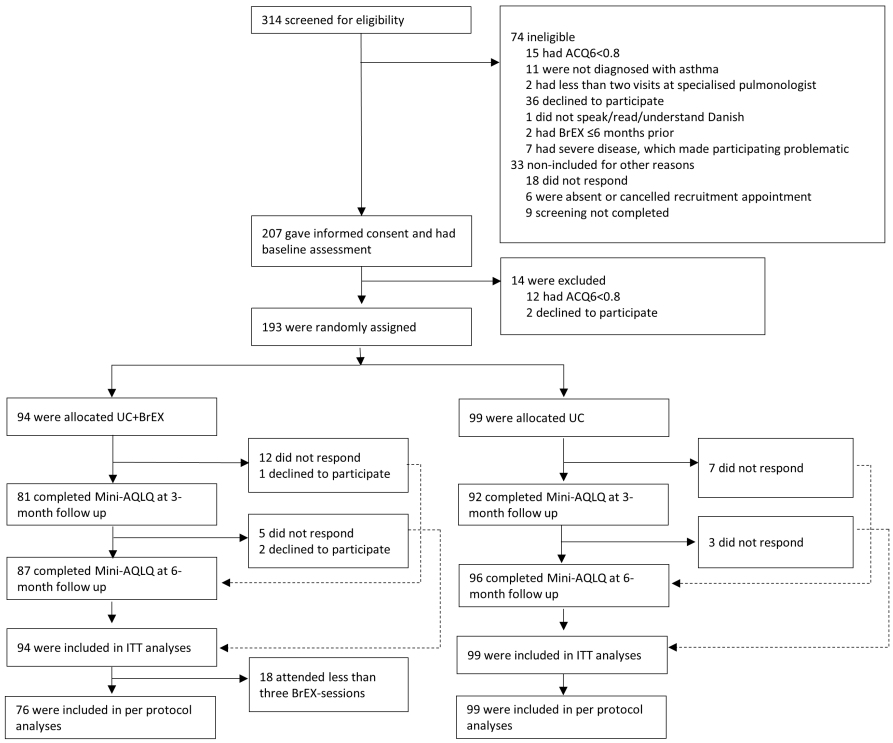
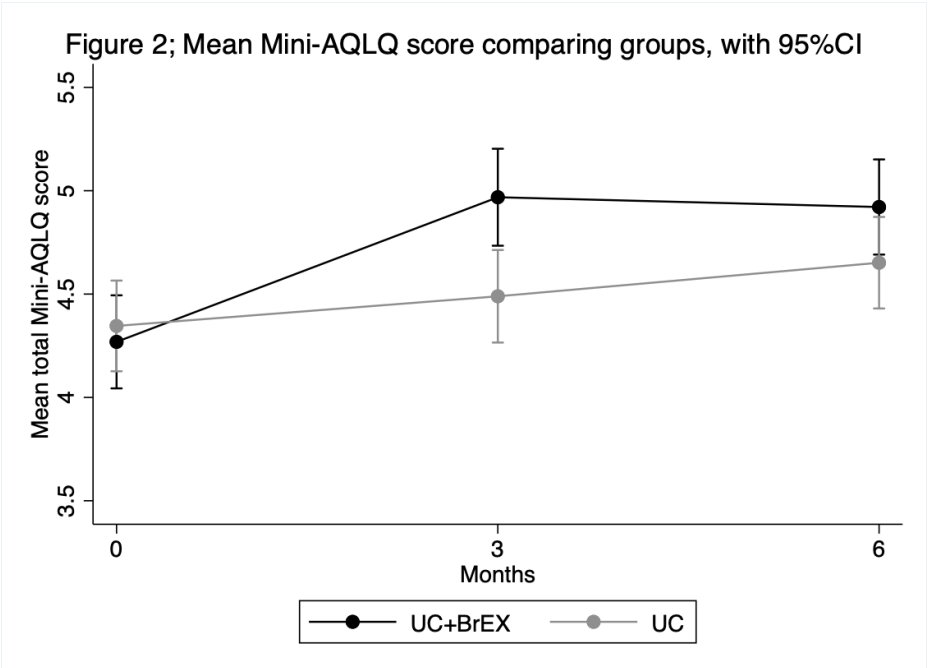


Figure 1; Trial profile



Extended supplementary materials to

Breathing exercises for asthma patients in specialist care: a multicentre randomised trial

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Content

Booklet for Breathing Exercises participants, Danish (S1)

The booklet has not yet been translated into English. However, we present the version used in the trial:

Breathing Exercises

Fysioterapi til patienter med astma
og dysfunktionel vejrtrækning

Deltagerinformation, vejrtrækningsgenoptræning og hjemmetræning

REGION SJÆLLAND
– vi er til for dig

BEAT DB-study

Breathing Exercises in Asthma Targeting Dysfunctional Breathing

Et forskningsprojekt – tak for din hjælp!
I England er der forsket i denne behandling til patienter med dysfunktionel vejrtrækning samt mild til moderat astma, som havde deres astmaforløb hos en praktiserende læge.
Man fandt effekt af behandlingen i form af bedre livskvalitet, dæmpede astmasymptomer og et mindre behov for den hurtigtvirkende astmamedicin (SABA).

Det er vigtigt at undersøge om behandlingen også har effekt for de, som har moderat til svær astma, og som derfor har astmaforløb i et lungeambulatorium. Derfor gennemfører vi et forskningsprojekt. Ved at deltage hjælper du os med at undersøge effekten. Det skal du have en stor tak for!
Er du i tvivl om noget, kan du spørge din fysioterapeut eller ringe til projektlederen.

God fornøjelse med BrEX.
Venlig hilsen,

Fysioterapeut: _____

Lokal koordinator: _____

Karen Hjerrild Andreasson, projektleder, fysioterapeut.
Næstved Sygehus, Tlf. 24 25 49 26

Breathing Exercises (BrEX) indeholder
- Vejrtrækningsgenoptræning
- Afspænding
- Behandling, instruktion og opfølgning hos fysioterapeut 3 gange
- Daglig hjemmetræning, 2 x 10 minutter

Det samlede forløb varer 12 uger.

BrEX er en dansk udgave af et behandlingskoncept, som anvendes i England.

I denne deltagerinformation kan du læse om dysfunktionel vejrtrækning og vejrtrækningsgenoptræningens formål og indhold.

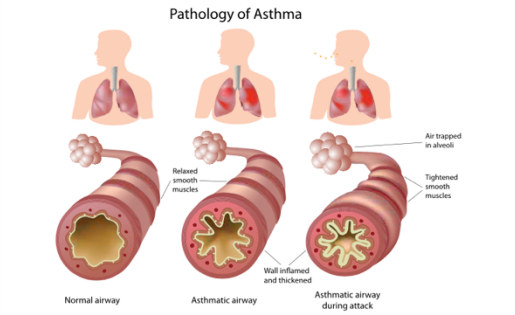
Formål med BrEX er at
- Sikre optimal vejrtrækningsteknik i hvile og under aktivitet
- Fjerne åndenød og ubehaget ved besværet vejrtrækning
- Fjerne hyperventilation, der udvasker CO_2 fra blodet og derfor bl.a. kan give svimmelhed, prikken i fingre og udtalt lufthunger
- Skabe god kapacitet til at være fysisk aktiv

Metoden til at opnå det er at
- Acceptere lufthunger i hvile og under fysisk aktivitet i begyndelsen
- Trække vejret gennem næsen
- Bruge mellemgulvs-musklen ved vejrtrækningen
- Nedsætte/ normalisere vejrtrækningshyppigheden
- Tage mindre luft ind ved vejrtrækningen og puste ud længere, end man plejer
- Modvirke tendens til suk, gab og host
- Bruge afspændingsteknik
- Fastholde god vejrtrækning, mens man er fysisk aktiv

Vi trækker vejret fra start til slut
Vejrtrækning er noget af det mest basale, mennesker gør. At trække vejret var det allerførste vi kunne efter fødslen. Vi er afhængige af det gennem hele livet. Sådan ca. 12-14 gange i minuttet.
Måden vi trækker vejret på, hænger tæt sammen med, hvor anstrengte vi er, hvordan vores humør og mentale tilstand har det, om vi har feber og forbigående lungesygdom (lungebetændelse, eksempelvis).

Vejrtrækningen finder sit optimale leje, hvor den
- har balance mellem ventilationsvolumen, dvs. luftmængden under ind- og udånding.
- har balance mellem optagelse af ilt (O_2) til blodbanen og udskillelse af kuldioxid (CO_2) derfra.
- bruger mindst mulig kraftanstrengelse til vejrtrækning.

Astma og vejrtrækning
Astma er en kronisk lungesygdom. Som patient med astma oplever man i perioder, at det er svært at få luft ind i og ud af lungerne. Vejrtrækningen føles tung og kræver meget energi. Man kan opleve åndenød.
Vores luftrør (bronkier) er opbygget af brusk-ringe og muskulatur og har inderst en slimhinde (figur 1).



Figur 1 Luftrøret hos raske (til venstre) har god passage.
Passagen er begrænset (der er obstruktion) i luftrøret ved astma (midtfor).
Især ved et astmaanfald (til højre) hæver slimhinden (vist med gul farve), den glatte muskulatur bliver spændt (bronkospasme) og der dannes slim. Illustration: Shutterstock.com

Ved astma har man tendens til betændelse (inflammation) i bronkierne. Inflammationen gør, at bronkierne over-reagerer ved kold og tør luft, ved irritanter (*triggers* f.eks. røg), og ved det, man evt. er allergisk overfor (f.eks. kat). Reaktionen er sammentrækning af den glatte muskulatur (bronkospasme), hævelse af slimhinden og øget slimproduktion (figur 1).

Symptomerne på over-reaktion i bronkierne opstår først 5-8 minutter efter at patienten med astma er startet med f.eks. at løbe. Hvis åndenøden opstår med det samme, er det mere sandsynligt, at årsagen til åndenød er dysfunktionel vejrtrækning.

Dysfunktionel vejrtrækning
Det sker, at automatikken i vejrtrækningen påvirkes. Den ændrede vejrtrækning kaldes dysfunktionel, fordi den er uhensigtsmæssig (på engelsk *dysfunctional breathing*).

Dysfunktionel vejrtrækning ses sommetider ved kronisk lungesygdom (f.eks. astma), ved tilbagevendende psykisk belastning (f.eks. angst eller stress), efter operation i maven og ved stærke smerter.

Dysfunktionel vejrtrækning kan 'komme og gå' eller være tilstede nærmest hele tiden - også i hvile. Den kan vise sig som en meget hurtig, overfladisk eller konstant meget dyb vejrtrækning (begge typer er hyperventilation), som uregelmæssig vejrtrækning, som ukontrolleret hoste, hyppige suk eller gab og som manglende evne til at tage en dyb vejrtrækning. Meget ofte har man åndenød.
Men bliv ikke bekymret: Åndenød skader ikke lungerne!

Det er en ubevidst, men uheldig vane, når man har dysfunktionel vejrtrækning.

Dysfunktionel vejrtrækning kan udtørre luftrørsslimhinden og skabe (*trigge*) bronkospasme, dermed forværre astma.
Måske tager man så mere astmamedicin – ofte uden at opleve mindre åndenød ved det. For ændringen af vejrtrækningsmønstret skyldes en ubalance i hjernens impulser, som aktiverer vejrtrækningsmuskler omkring brystkassen. Det er ikke i selve lungerne og bronkierne, at problemet sidder. Astmamedicin hjælper derfor ikke på dysfunktionel vejrtrækning.

Men det er *vigtigt at fortsætte med at bruge den astmamedicin*, du har fået ordineret. Hvis du skal reducere i medicinen, skal du aftale det med din ambulatorielæge.

Hyperventilation
Hyperventilation er den hyppigste form for dysfunktionel vejrtrækning. Hyperventilation er for stor gennemluftning af lungerne. Populært sagt er *vejrtrækningen i for højt gear*.
Man hyperventilerer, hvis man trækker vejret med små, overfladiske og meget hurtige vejrtrækninger, men også hvis man har meget dybe/tunge åndedrag.

Når ventilationsvolumen er for stor, udvaskes CO_2 (kuldioxid) for hurtigt fra lungerne. Det forskyder blodets surhedsgrad (pH-værdien stiger). Det frigør calcium-ioner i plasma. Calcium-ionerne binder sig til protein, hvilket gør nervesystemet mere irritabelt (sensitivt). Det er grunden til, at man kan mærke snurren/prikken og opleve krampe.

Hyperventilation og dysfunktionel vejrtrækning mærkes også som:
- udtalt åndenød, selv ved let anstrengelse
- åndenød, når man taler eller spiser
- besvær med at tage en dyb vejrtrækning/ at være "opblæst"
- følelse af klump/ ubehag i halsen
- krilrende hoste
- hyppige gab
- overvældende træthed/ udmattelse
- manglende overblik
- svimmelhed, sortnen for øjnene
- hukommelses-/ koncentrationsbesvær
- indre uro/ angst
- hovedpine
- hjertebanken/ trykken for brystet
- snurren/ stikken i fingre og tær
- sovende fornemmelse ved munden
- oppustet mave

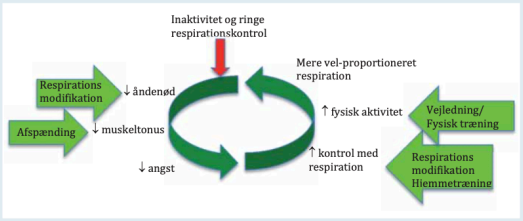
Hyperventilation er ikke i sig selv farligt – i værste fald besvimer man, hvorefter CO_2-niveauet retter sig.

Under vejrtrækningsgenoptræningen kan du opleve at skulle vænne dig til et andet CO_2 niveau. Det kan føles ubehageligt. Men efter nogle dage, måske uger, vil ubehaget forsvinde. Vær tålmodig!

Den overfladiske, hurtige vejrtrækning har også betydning for luftrørsslimhinden og for skeletmuskler:
- Det hurtige luftskifte vil udtørre slimhinden, hvilke kan fremkalde sammentrækning af bronkie-muskulaturen (bronkospasme).
- Muskler omkring skuldre og hals kan blive overbelastede, forkortede og ømme.

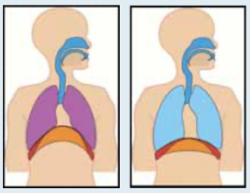
Metoderne i vejrtrækningsgenoptræningen hedder *Breathing Exercises*
Øvelserne genoptræner åndedrætscentret i hjernen til at trække vejret med et hensigtsmæssigt mønster og til at undgå ukontrolleret hoste, suk og gab (figur 2).

Man kan, som nævnt, godt opleve det ubehageligt i starten, fordi blodets sammensætning af gasarter normaliseres, men i løbet af nogle dage vænner man sig til den. Mange patienter oplever hurtigt positiv effekt.



Figur 2 Vejrtrækningsgenoptræningens enkelte dele er vist med lysegrønne pile. Genoptræningen skal hjælpe til at opleve mindre åndenød, at kunne være mere fysisk aktiv og at opnå en mere velproportioneret vejrtrækning. Egen illustration.

Diafragmatisk vejrtrækning
Vejrtrækning skal ske med mellemgulvet. Mellemgulvet hedder også diafragma og er en tynd muskel, som adskiller brysthule og bughule. Den står som et kuplet sejl/ en faldskærm op på undersiden af lungerne. Det er vist som rød linje på illustrationen (figur 3).



Figur 3 Ved indånding ændrer diafragma form fra kuplet (venstre billede) til flad (højre billede), vist med den røde farve. Illustration fra www.diafragma_ademhaling.gif

Diafragma hæfter på indersiden af de nederste ribben, på brystbenet og rygsøjlen (se figur 12, side 14).

Når musklen er aktiv (kontraherer sig), ændrer den form fra kuplet til flad. Dermed skaber den det undertryk i brysthulen, som suger luft ind i lungerne, ligesom når man fylder en cykelpumpe med luft (se figur 13, side 14).

Diafragmas funktion sammenlignes tit med et stempel. Når man er forpustet under f.eks. løb er diafragmas stempelbevægelse større og hurtigere, mens den er rolig og har moderat bevægelse, når man er i hvile.

Diafragmas bevægelse nedad presser samtidig bugindholdet sammen, og fordi mavens forside (bugvæggen) er blød, vil diafragmas aktivitet ses og mærkes på maven. Derfor man siger 'træk vejret helt ned i maven'.

Mærk diafragmatisk vejrtrækning
Lig på ryggen med én hånd på øverste del af maven og én hånd på brystet.
Brug puder under hoved og albuer, så du ligger behageligt.
Brug en pude under knæene (figur 4).
- Pust helt ud og tag så en maksimal indånding.
- Skuldrene og brystbenet må ikke bevæge sig.
- Mærk at bugvæggen løfter sig.
- Slap af og lad luften slippe ud.
- Mærk at bugvæggen sænker sig igen.

Figur 4

Man starter fra basis
I arbejdet med vejrtrækningen starter man fra basen: liggende, rolig, fokuseret.

Der er flere metoder til at mærke og forbedre diafragmatisk vejrtrækning:

Liggende eller siddende
- Hænder på brystben og på den øverste del af maven; kun hånden på maven må bevæges, den anden skal være i ro (Figur 4 og 5).
- Diamant-vejrtrækning: Næsevejrtrækning, afslappede skuldre, diafragmatisk bevægelse ("diamanten" er markeret med rød rombe, figur 6). Arme foldede om maven: mærk at arme skubbes frem, men at skuldre bliver nede/i ro (figur 6).

Liggende
- Læg en ½-kilo-rispose eller en tung bog på den øverste del af maven.
- Beach-position: rygliggende med hænderne under hovedet (figur 7).

Figur 5

Figur 6

Figur 7

Figur 8

Siddende eller stående
- Mærk brystryggens bevægelse mod stolens ryglæn.
- 'Sid' op ad væg, mærk diafragmatisk vejrtrækning og brystryggens bevægelse mod væggen (figur 8).
- Se i spejl.

Næsevejrtrækning
Træk vejret gennem næsen fremover; det
- mindsker tendens til hyperventilation ved at begrænse indåndingen,
- renser, opvarmer og fugter indåndingsluften, så luftrørsslimhinden generes mindre,
- hjælper måske til at trække vejret med diafragma.

I starten vil man mangle luft, men det bliver hurtigt bedre.
Efter lidt tilvænning kan du også trække vejret gennem næsen, når du er aktiv.

Hvis du er tæt i næsen, kan du afprøve næseskylning med lunken vand med en let saltopløsning. Hvis det ikke hjælper, kan du tale med din lægen om det måske kan være helårssnue (høfeber).

Mindre luft i lungerne
Man dæmper hyperventilation og at være 'opblæst' (dynamisk hyperinflation) ved
- mindre dyb vejrtrækning,
- længere udånding,
- lille pause inden næste indånding.

Rytme: 2-3-2, 2-3-3, eller 2-3-4, hvor tallene angiver antal taktslag på indånding-udånding-pause.

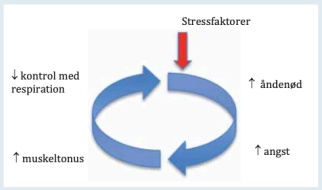
At holde vejret
Hver anden dag skal du træne tolerancen overfor lufthunger ved at holde vejret efter en almindelig *udånding*. Du udsætter den næste vejrtrækning. (Se figur 14 side 15, bunden af 'tidal volumen').
Sammen med fysioterapeuten finder du det antal sekunder, du skal træne ved.

Hoste, gab, suk
Hoste, gab og suk kan være tegn på hyperventilation.
Når det opstår, skal du 'synke det væk' med 4 trin

1. Luk munden, hold for næsen, og har vejrtrækningspause i 5-10 sekunder.
2. Hold igen – undertryk behovet for at hoste/ gabe/ sukke.
3. Synk kraftigt.
4. Træk vejret roligt gennem næsen, 20 gange.

Afspænding
Åndenød er ubehageligt. Svær åndenød kan give uro og ængstelse. Det sætter kroppen i alarmberedskab: Det *sympatiske nervesystem* bliver aktiveret. Arbejdet med at forsøge at få luft, og ængstelsen i sig selv, sætter kroppens muskler på overarbejde (øger muskeltonus).

Andre stressfaktorer kan f.eks. være arbejds- eller familierelaterede bekymringer.
En negativ cirkel kan starte: åndenød, mere ængstelse, øget muskeltonus, mindre kontrol over vejrtrækningen, mere åndenød (figur 9).



Figur 9
Stressfaktorers mulige effekt på vejrtrækningen.
Stressfaktorerne kan være angst, lungesygdom, anden fysisk sygdom eller mental/ emotionel stress.
Det kan være tidligere begivenheder.
Egen illustration

Afspænding er vigtig, både ved astma og ved dysfunktionel vejrtrækning. Det hjælper at 'slippe speederen'/ have mindre travlt, og i stedet skabe ro for sig selv i løbet af dagen. Man behøver ikke at ligge ned for at spænde af.

Afspændingsmetode – tyngdefølelse
Afspænding er en aktiv situation med fokus på tyngde, ro og åndedræt. Man aktiverer det *parasympatiske nervesystem*.

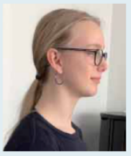
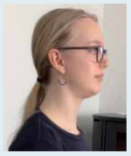
Kæbe, tunge, nakke og skuldre
- Sid/ lig behageligt, så du er godt støttet af underlaget/stolen.
- Saml forsigtigt læber, men lad kæben blive ved at 'hænge' inde i munden.
- Hvis du sidder: Rank nakken, så hovedet balancerer (figur 10).
- Gør tungen bred og blød, og lad den fylde frem mod inderside af underlæbe og ud over tænder i undermunden.
- Hvis du ligger på siden: Lad den øverste hånd ligge fladt i madrassen (figur 11). Mærk at tungen falder ned mod nederste kind.
- Træk vejret roligt gennem næsen.
- Brug diafragmatisk vejrtrækning.
- Giv slip i nakke- og skuldermuskler – fald ned.

Hvis det er vanskeligt at slippe muskelspændingen ved kæbe og i tungen, kan du indlede med:
- Kæbe: Bevæg kæben frem-tilbage, side-side, gabe grundigt.
- Tunge: Ræk tungen langt ud over underlæben.

Brug denne metoden i løbet af dagen, hver dag. Den kan bruges hvor som helst. Giv dig selv fornemmelse af at have god tid – også selvom du kun bruger kort tid.

Øv den i mange forskellige situationer, hvor du trænger til en pause, f.eks.:
-
-
-

Udvid afspændingen:
- Lad tankerne samle sig om en del af kroppen (kæbe-tunge, hals-skuldre, arme, mave-ryg, ben).
- Tag 2-3 næsevejrtrækninger, som ikke er for dybe, hvert sted.
- Mærk efter fornemmelse af tyngde - *du falder længere ned på underlaget/ stolen* - for hver udånding.

Figur 10 Kvinden er 'sammenbidt' på billedet til venstre. Hun er mere rank med afspændt kæbe og tunge til højre, hvor hun fylder mere i vinklen mellem kæbe og hals.

Figur 11 Kvinden lægger sin øverste hånd fladt mod underlaget.

Overordnet program - Stigende sværhedsgrad
Som regel starter vejrtrækningsøvelserne i liggende stilling, med kroppen i ro. I liggende stilling er det som regel lettest at bemærke vejrtrækningen – og at ændre på den.

Sværhedsgraden stiger således: Liggende → siddende → stående → gående. Hvis fysioterapeuten skønner, at du har gavn af en anden rækkefølge, vil han/ hun vejlede dig.

I skemaet over de tre fysioterapi-sessioner kan du se, hvad vi forventer, du når.

	Beskrivelse / Session	1 60 minutter	2 30 minutter	3 30 minutter
A	Dialog, Mål/plan	X	X	X
B	Information om BrEX	X		
C	Testning af Respir kvalitet	X	X	X
D	Respir-modifikation a. Nasal, diafragmatisk b. Inspir-exspir-forholdet c. Respir dybde d. BHT Teknikker til at tydeliggøre ændringen	X Liggende /siddende	X Stående	X +Trappe
E	Implementering af respir-modifikation i hverdagen		Del af D	X At holde ved
F	Afspænding, tyngdefølelse	X Siddende /sideliggende	X	X Stå/gå
G	Selvtræningsprogram	X	X Del af DEF	X Del af ADEF
H	Træningsdagbog	X		

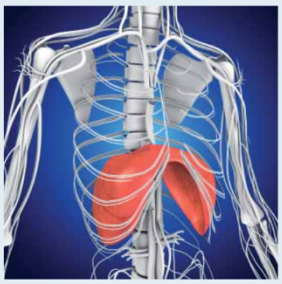
Hos enkelte deltagere er skemaets *dosering og rækkefølge ikke logisk*. Nogen har vanskelig hhv. lettere ved at mærke 'i kroppen' eller at genoptræne optimalt vejrtrækningsmønster. Nogen har muskel- og/eller led-problemer.

Fysioterapeuten tilpasser tempo og øvelsesvalg sammen med dig. Så vidt muligt inddrager I alle elementer i BrEX.
Fysioterapeuten kan notere variationer i forhold til skemaet.

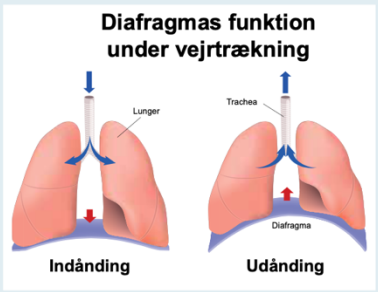
I *træningsdagbogen*, som du får udleveret, skal du notere, hvor meget du træner.

I forskningsprojektet kan det desværre ikke lade sig gøre, at fysioterapeuten vejleder/behandler dig for evt. *andre problemer*, end det vejrtrækningsmæssige.

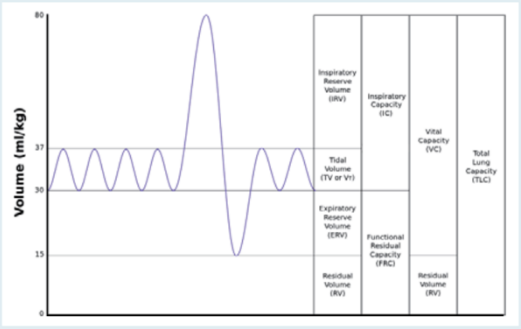
Illustrationer



Figur 12 Mellemgulvsmusklen (diafragma) hæfter på indersiden af de nederste ribben, på brystbenet og rygsøjlen. Musklen adskiller bryst- og bughule.
Illustration: Shutterstock.com



Figur 13 Mellemgulvet bevæger sig nedad ved indånding og opad ved udånding. Luftrøret hedder trachea.
Illustration: Shutterstock.com



Figur 14 Skema over lunge-fyldningsgrad (volumen)

Daglig hjemmetræning – den gode vane
Hjemmetræning er *meget vigtig for at indarbejde teknikken*.
Beslut dig for faste tidspunkter. Dagligt i 2 x 10 minutter.

I starten kan du måske kun holde til få minutters træning. Men øg tiden op til de 10 minutter.

Husk
Træn vejrtrækning
- Træk luften ind gennem næsen.
- Mærk at bugvæggen bevæger sig fremad i den øverste del af maven.
- Tag ikke meget luft ind.
- Undgå at bide sammen. Slap af i kæbe, tunge, nakke, skuldre.
- Pust lidt længere ud, end du plejer.
- Hold en rytme med: _____
- Tag 10 rolige vejrtrækninger.

Tag en kort pause og gentag øvelsen nogle gange.

Afprøv i udgangsstilling: _____

Udvid det til følgende udgangsstillinger: _____

Træn vejrtrækning under fysisk aktivitet
F.eks. rejse-sætte dig, gå, steppe på stedet, lave høje knæløft, gå på trapper.

Husk desuden: _____

Lav afspænding _____

Hver *anden* dag: Hold vejret 3 gange i _____ sekunder.

Noter i din træningsdagbog.

Til dine og fysioterapeutens noter/ Mål og plan:

Breathing Exercises in Asthma Targeting Dysfunctional Breathing; BEAT DB-study er et forskningsprojekt, som finder sted på syv sygehuse i Danmark i 2017-2020.

Forskningsprojektet udgår fra Afdelingen for Fysioterapi og Ergoterapi og Lungemedicinsk Afdeling, Næstved-Slagelse-Ringsted sygehuse.

I projektet indgår Afdelinger for *Fysioterapi og Ergoterapi* og *Lungemedicinske ambulatorier* på Næstved, Roskilde, Aalborg, Silkeborg, Odense, Hvidovre og Bispebjerg hospitaler samt Allergi og Lungeklinikken i Helsingør.

Bispebjerg Hospital

Hvidovre Hospital

AALBORG UNIVERSITETSHOSPITAL – i gode hænder

midt regionmidtjylland

REGION SJÆLLAND SJÆLLANDS UNIVERSITETSHOSPITAL – vi er til for dig

REGION SJÆLLAND NÆSTVED SYGEHUS – vi er til for dig

Allergi og Lungeklinikken Helsingør

OUH Odense Universitetshospital

Forskningsprojektet har modtaget økonomisk støtte fra:

- TrygFonden
- Næstved-Slagelse-Ringsted sygehuses Forskningsråd
- Region Sjællands Forskningsfond
- Danske Fysioterapeuters Forskningsfond

Med støtte fra TrygFonden

SDU SYDDANSK UNIVERSITET

REGION SJÆLLAND NÆSTVED, SLAGELSE OG RINGSTED SYGEHUSE – vi er til for dig

REGION SJÆLLAND – vi er til for dig

Denne informationsfolder er lavet af Karen Hjerrild Andreasson i samarbejde med fysioterapeuterne Lone Schaadt og Martin Dam Sørensen, Bispebjerg Hospital.
Forsidefoto: Shutterstock.com. Øvrige fotos: K.H. Andreasson.

Patient-Related Objectives: Generating better Rehabilitation, treatment, Exercise and Diagnostics – Region Zealand

PROgrez

Næstved Sygehus
Ringstedgade 61, 4700 Næstved
Telefon 56 51 20 00

www.regionsjaelland.dk

Version 4, juni 2019

Varenummer: 8852 Tryk: Av-afdelingen, Næstved Sygehus Redaktør: khad

Recruitment process (S2)

Table S2a; Recruitment process

	Screened	Recruited	Recruited of screened (%)	Transferred to another centre	Transferred from another centre	Included at centre
Allergy and Lung Clinic, Elsinore	12	8	66.7	8	0	0
Bispebjerg University Hospital	36	19	52.8	0	7	26
Hvidovre University Hospital	79	44	55.7	0	0	44
Naestved Hospital	56	34	60.7	0	3	37
Odense University Hospital	51	42	82.4	1	0	41
Silkeborg Regional Hospital	16	10	62.5	0	0	10
Zealand University Hospital, Roskilde	32	20	62.5	1	0	19
Aalborg University Hospital	32	16	50.0	0	0	16
Total	**314**	**193**	**61.5**	**10**	**10**	**193**

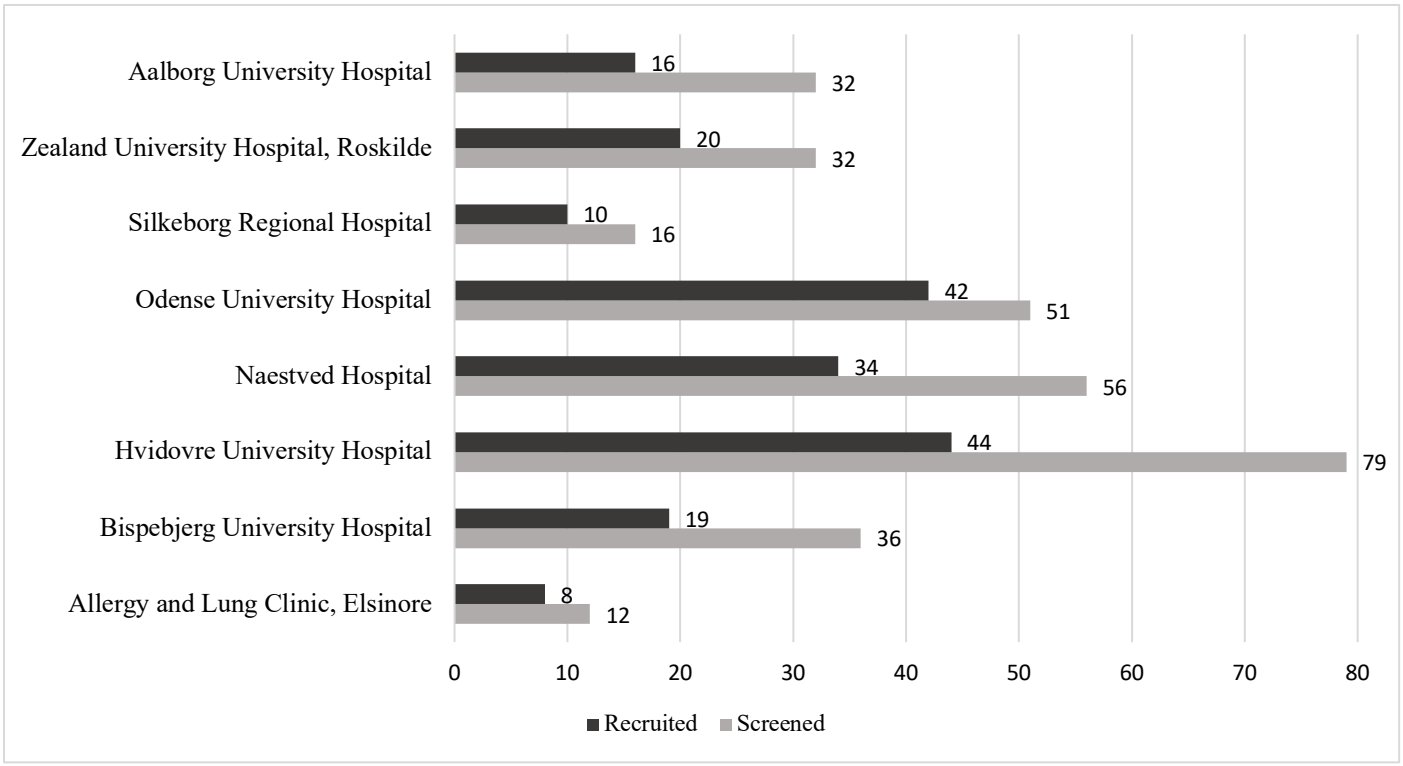


Figure S2b; Patients screened for eligibility and participants recruited

Total group, baseline characteristics:
Mean, standard deviation (SD) age at inclusion was 51.3 (14.5), range18-82) years, and 63.2% were female. Mean, SD Mini-AQLQ score was 4.3 (1.02), median (inter quartile range, IQR) ACQ6 score 2.2 (1.5-2.67).

Full report on comorbidities at baseline (S3)

Table S3; Types and frequency of comorbidities by group

	UC+BrEX		UC	
	Number participants having one or more		Number participants having one or more	
Allergy or hypersensitive reactions	10		10	
Allergic rhinitis, J304, J301	8	(8.5%)	7	(7.1%)
Atopic Dermatitis, L209	3	(3.2%)	2	(2.0%)
Multi allergy or Allergy UNS, T78.4	2	(2.1%)	1	(1.0%)
Urticaria, L500	0	(0%)	2	(2.0%)
Cancer	3		6	
Malignant neoplasm of connective and soft tissue of head, face and neck, C490	0	(0%)	1	(1.0%)
Leukemia, C950	0	(0%)	1	(1.0%)
Malign melanoma, C435	1	(1.1%)	1	(1.0%)
Mamma cancer, N639	1	(1.1%)	2	(2.0%)
Mantle cell lymphoma, C831	0	(0%)	1	(1.0%)
Malignant neoplasm of sigmoid colon, C187	1	(1.1%)	0	(0%)
Cardiovascular	11		5	
Ischemic heart disease, I21, I200, I259, I219	5	(5.3%)	3	(3.0%)
Atrial fibrilation, I489, I480	2	(2.1%)	2	(2.0%)
Chronic heart failure, Z035, Z035E, I351	2	(2.1%)	1	(1.0%)
Aortic insufficiency, I351	2	(2.1%)	0	(0%)
Endocrine or Immune mechanism	13		12	
Immune defect, D849	0	(0%)	1	(1.0%)
Diabetes mellitus 1, E109A	0	(0%)	1	(1.0%)
Diabetes mellitus 2, E119A, E119	3	(3.2%)	5	(5.1%)
Severe obesity, E66	6	(6.4%)	3	(3.0%)
Alfa1 antitryp deficiency, E88	1	(1.1%)	0	(0%)
Sarcoidosis, D86	1	(1.1%)	1	(1.0%)
Cushing syndrome, E249	1	(1.1%)	0	(0%)
Hypothyroidism, E039	3	(3.2%)	3	(3.0%)
Thyrotoxicosis, E05	2	(2.1%)	1	(1.0%)
Gastro-intestinal/-oesophageal	14		9	
Irritable bowel syndrome, K58, K590, K598, K599	5	(5.3%)	5	(5.1%)
Morbus Crohn, K509	2	(2.1%)	0	(0%)
Retentio ventriculi, K318H	1	(1.1%)	0	(0%)
Unspecified GI disease, K929, R102	4	(4.3%)	1	(1.0%)
Ischemic colitis, K551	1	(1.1%)	0	(0%)
Endometriose, N809	1	(1.1%)	0	(0%)
Coeliac disease, K900	0	(0%)	1	(1.0%)
Reflux, gastro-øsefageal, K21	5	(5.3%)	2	(2.0%)
Functional dyspepsia, K309	2	(2.1%)	0	(0%)
Dysphagia, R139	0	(0%)	2	(2.0%)
Lung	9		9	
Bronchiectasis, J479	4	(4.3%)	5	(5.1%)
Chronic obstructive pulmonary disease, J44, J448, J449	5	(5.3%)	4	(4.0%)
Mental	8		6	
Alcohol abuse, F10	2	(2.1%)	0	(0%)
Anxiety, F419	2	(2.1%)	1	(1.0%)
Depression, F33	4	(4.3%)	3	(3.0%)
Adjustments disorders, F079, F419, F4323	1	(1.1%)	1	(1.0%)
Eating disorder, F50	0	(0%)	1	(1.0%)
Bipolar disorder, F31	0	(0%)	1	(1.0%)
Musculoskeletal or connective tissue	16		15	
Granulomatose with polyangiitis (Wegener), M313	1	(1.1%)	0	(0%)
Artritis UNS, M139	1	(1.1%)	0	(0%)
Osteoarthritis, M161A, M179	3	(3.2%)	3	(3.0%)

Joint pain, M255, M109, M239, M759, M751A, M774, S434, S134		2	(2.1%)	2	(2.0%)
Supraspinatus lesion, S460B2		0	(0%)	2	(2.0%)
Discusprolaps, M501, M511		1	(1.1%)	2	(2.0%)
Fibromyalgy, M797		1	(1.1%)	0	(0%)
Psoriasis artropati, L405		1	(1.1%)	0	(0%)
Reumatoid artritis, M069		2	(2.1%)	1	(1.0%)
Back pain, M549, M542, M47		2	(2.1%)	2	(2.0%)
Deformaties of spine, M42.0, M472, M480		4	(4.3%)	1	(1.0%)
Non-malignant pain disorder, R522		0	(0%)	1	(1.0%)
Muscle spasm/pain, M626		0	(0%)	1	(1.0%)
Tension headache, G442		1	(1.1%)	0	(0%)
Extremity pain, M796		2	(2.1%)	2	(2.0%)
Arteritis temporalis with reum. polymyalgia, M315A		1	(1.1%)	0	(0%)
Neurological	4			10	
Multible sclerosis, G35, G379 (UNS)		0	(0%)	1	(1.0%)
Epilepsia, G409		1	(1.1%)	1	(1.0%)
Migraine, G43		0	(0%)	4	(4.0%)
Neuropatic disorders, G900, G542, G587, G629, G258		3	(3.2%)	2	(2.0%)
Intra cranial injury, S065		0	(0%)	1	(1.0%)
Syringomyelia, G950B		0	(0%)	1	(1.0%)
Renal	1			1	
Chronic renal failure, N189, N199		1	(1.1%)	1	(1.0%)
Sensory organs	1			4	
Deafness, H910, H911, H919, H905		1	(1.1%)	4	(4.0%)
Upper airway	18			12	
Chronic Rhinitis, J310		4	(4.3%)	4	(4.0%)
Nosal septum deviation, J342		2	(2.1%)	0	(0%)
Nasal polyps, J330		4	(4.3%)	3	(3.0%)
Obstructive Sleep Apnoea, G4732		7	(7.4%)	4	(4.0%)
Chronoc sinuitis, J32		3	(3.2%)	1	(1.0%)
Vaso motoric rhinitis, J300		2	(2.1%)	1	(1.0%)
Vocal Cord Dysfunction, J38.3		1	(1.1%)	0	(0%)
Total number of comorbidities		134		111	

Frequency (with percentages) of diagnoses with ICD10 codes for included participants.
UC+BrEX= Breathing exercises and usual care. UC= Usual care alone.

Secondary outcomes: 3-month follow up in PROMs (S4)

We observed a significant between-group adjusted mean (95% CI) difference of 0.56 (0.28 to 0.85) in Mini-AQLQ improvement from baseline in favour of UC+BrEX (Figure 2). Significant within-group improvement in Mini-AQLQ, ACQ6, NQ, HADS-A, and HADS-D were observed in the UC+BrEX group only, and the between-group changes favouring the UC+BrEX group were significant for all outcomes, excepts for HADS-A (Table S4).

Table S4; Adjusted intention-to-treat and per-protocol analyses of secondary outcomes at 3-month

	Total no. of assessments [a]		ITT-population		
	UC+BrEX	UC	UC+BrEX (n=94) mean change	UC (n=99) mean change	Between-group difference difference in mean change
Mini-AQLQ	175	191	0.72 (0.51 to 0.92)	0.16 (-0.04 to 0.35)	0.56 (0.28 to 0.85)
ACQ6	170	190	-0.38 (-0.56 to -0.19)	-0.04 (-0.21 to 0.14)	-0.34 (-0.60 to -0.09)
NQ	170	190	-3.39 (-5.18 to -1.60)	-0.23 (-1.87 to 1.42)	-3.16 (-5.59 to -0.73)
HADS-A	170	189	-0.87 (-1.61 to -0.13)	-0.36 (-1.04 to 0.33)	-0.52 (-1.52 to 0.49)
HADS-D	170	189	-1.05 (-1.61 to -0.50)	-0.26 (-0.78 to 0.25)	-0.79 (-1.54 to -0.03)
			Per-protocol population		
			UC+BrEX (n=76) mean change	UC (n=99) mean change	Between-group difference difference in mean change
Mini-AQLQ	146	191	0.73 (0.50 to 0.95)	0.15 (-0.04 to 0.35)	0.57 (0.28 to 0.87)
ACQ6	141	190	-0.41 (-0.62 to -0.21)	-0.04 (-0.21 to 0.14)	-0.38 (-0.65 to -0.11)
NQ	141	190	-3.56 (-5.52 to -1.60)	-0.23 (-1.89 to 1.44)	-3.33 (-5.90 to -0.76)
HADS-A	141	189	-0.97 (-1.76 to -0.18)	-0.36 (-1.03 to 0.32)	-0.61 (-1.65 to 0.43)
HADS-D	141	189	-1.25 (-1.83 to -0.67)	-0.27 (-0.76 to 0.23)	-0.98 (-1.75 to -0.22)

Data are adjusted mean change from baseline to 3-month including 95% CI.

[a] Possible assessments for questionnaires (at baseline + at 3-month): 188 for UC+BrEX (in per-protocol: 152) and 198 for UC.

UC+BrEX=Breathing exercises and usual care. UC=Usual care alone. Mini-AQLQ=Mini-Asthma Quality of Life Questionnaire. ACQ6=6-item Asthma Control Questionnaire. NQ=Nijmegen Questionnaire. HADS-A=anxiety items of Hospital Anxiety and Depression Scale. HADS-D=depression items of Hospital Anxiety and Depression Scale.

Number-needed-to-treat, NNT (S5)

Table S5a; Change in Mini-AQLQ score from baseline to 6-month

	UC+BrEX (n=87)	**UC** (n=96)
Improved (>0.5 units)	47 (54.0%)	40 (41.7%)
Unchanged (-0.5 to 0.5 units)	29 (33.3%)	39 (40.6%)
Deteriorated (>0.5 units)	11 (12.6%)	17 (17.7%)

Table S5b; Number needed to treat, individual positive response by >0·5 units of Mini-AQLQ

	UC+BrEX (proportion)		
UC (proportion)	Improved (0.54) (x)	Unchanged (0.33) (y)	Deteriorated (0.13) (z)
Improved (0.42) (a)	0.23	0.14	0.05
Unchanged (0.41) (b)	0.22	0.14	0.05
Deteriorated (0.18) (c)	0.10	0.06	0.02

NNT= (1/(bx + cx + cy) − (ay + az + bz)) = 7.6

Improved = Increased by more than 0.5; Unchanged = Changed between − 0.5 and 0.5; Deteriorated = Fell by more than 0.5. NNT=Number-needed-to-treat. Matrix according to Guyatt, Juniper, Walter, Griffith, Goldstein, BMJ 1998;316:690–3

Global Perceived Effect (S6)

Table S6a, Global perceived effect						
	UC+BrEX		UC		Total	
Large worsening	2	(2.3%)	3	(3.2%)	5	(2.8%)
Moderate worsening	4	(4.7%)	5	(5.3%)	9	(5.0%)
Small worsening	14	(16.3%)	18	(19.1%)	32	(17.8%)
Unchanged	29	(33.7%)	39	(41.5%)	68	(37.8%)
Small improvement	16	(18.6%)	18	(19.1%)	34	(18.9%)
Moderate improvement	13	(15.1%)	7	(7.4%)	20	(11.1%)
Large improvement	8	(9.3%)	4	(4.3%)	12	(6.7%)
Total number	86	(100%)	94	(100%)	180	(100%)
Mann-Whitney: p=0.0828						

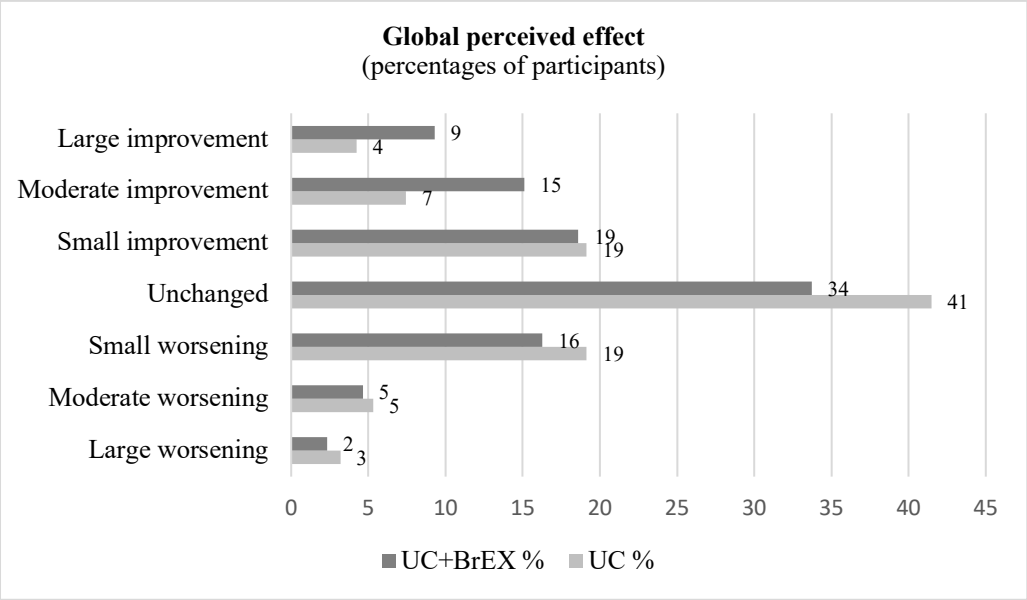


Figure S6b

Participants were asked: "Compared to 6 months ago, how is your asthma-related quality of life now?".
The 7-point Likert scale ranged from "-3= Markedly worse" over "0= No change" to "+3= Markedly improved".

Table S6c, Global perceived effect, dichotomized			
	UC+BrEX	UC	Total
Worsening or unchanged	49 (57.0%)	65 (69.1%)	114 (63.3%)
Improvement	37 (43.0%)	29 (30.9%)	66 (36.6%)
Total	86	94	180
Pearson chi2 test, p=0.091			
UC+BrEX missing n=8, UC missing n=5			

Use of anti-asthmatic medication and GINA step calculation (S7)

Methods

We reported asthma severity as GINA step calculated by a novel algorithm (using Excel) complying with the 2019 GINA report in treatment steps using beclomethasone equipotent defined daily dose (DDD) of inhaled corticosteroid (ICS) plus combinations of second controllers. Other steroids' potencies were calculated into (according to the 2019 GINA report):

Beclomethasone (hydrofluoroalkane propellant) ICS equipotency
- Low daily dose 100-200 µg
- Moderate daily dose >200-400 µg
- High daily dose >400 µg

by dividing the dose of ICS as follows:
- Ciclosenid dose /0.8
- Fluticason dose /1,25
- Budesonid dose /2
- Mometasone dose /1.1

The algorithm has moderate to substantial agreement with experts' ratings (κ 0.49-0.67), thus better than agreement between experts (κ 0.32-0.45).

Table S7a; Proportions of GINA step change from baseline to 6-month

	UC+BrEX		UC	
	n=94		n=98	
Decreased				
-3	1	(1.1%)	0	(0%)
-2	2	(2.1%)	4	(4.1%)
-1	6	(6.4%)	8	(8.2%)
Unchanged	79	(84.0%)	81	(82.7%)
Increased				
+1	5	(5.3%)	5	(5.1%)
+2	1	(1.1%)	0	(0%)

Mann-Whitney: p=0.5071

Attendance of BrEX sessions and adherence to home exercise (S8)

Attendance of BrEX sessions were collected (reasons for missing sessions, table S8a) and adherence to home exercise in the UC+BrEX group was estimated by the treating physiotherapists, using a numeric rating scale (NRS, 1=no adherence, 5=excellent adherence) at session 2 and 3 (table S8b, figure S8c); the estimation was based on talking to the patients and observing how correct the patients were able to repeat exercises given at last session.

Table S8a; Reasons for not attending BrEX session

	No of participants
Participant cancelled (illness)	2
Participant cancelled (other reason[a])	10
Absence without reason	1
Absence without reason/ cancelled (illness)[b]	1
Other reasons for not attending	4
Total	18

[a] Data on reasons for cancellations only defined if because of illness.

[b] A single participant who only attended one session had absence due to illness (2nd session) and without reason (3rd session).

Table S8b; Adherence to home exercise

Numeric Rating Scale	Session 2 (n=78)	Session 3 (n=75)
1: No adherence	2 (2.6%)	3 (4.0%)
2: Low adherence	3 (3.9%)	2 (2.7%)
3: Moderate adherence	14 (18.0%)	13 (17.3%)
4: Good adherence	29 (37.2%)	28 (37.3%)
5: Excellent adherence	30 (38.5%)	29 (38.7%)

Numeric Rating Scale judged by physiotherapists of the participants adherence. Missing data for 16 participants at session 2, and for 19 participants at session 3

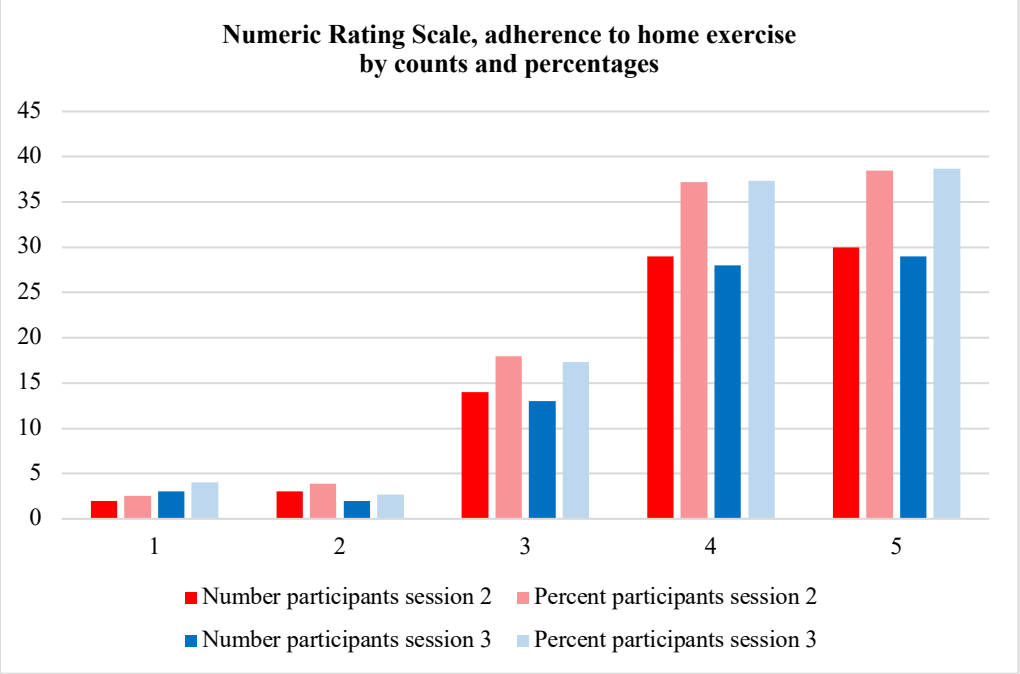


Figure S8c Numeric Rating Scale judged by physiotherapists (1=no adherence, 5=excellent adherence). Session 2, n=78; session 3, n=75. Missing data (no attendance or no data) for 16 participants at session 2, and for 19 at session 3.

Adverse events; questionnaire and results (S9)

Methods

We used patient-reported adverse events (AE) (semi-open probe questionnaire: number, type, and date of events, and place of treatment) at 3- and 6-month.

English version of the adverse events questionnaire

The questionnaire was an online electronic case report form (eCRF) sent to the participant.
Only by answering "yes" to the screening question, the four sub-questions and 'subsequent message' showed up.

Introduction:
We want to achieve knowledge about safety of the treatments in the study. Therefore, we will ask for information about adverse events that you have experienced.
We are interested in the period from your first visit at physiotherapist, when the baseline testing in this physiotherapy project was done until today (about 6 months).

Screening questions:
Did you visit your general practitioner (GP) or have you been to hospital during the last 6 months?
This also relates to issues that are NOT related to your breathing. (answer Yes / No)

Sub-questions:

- Number of events: (specify number)
- What was the reason for the visits at GP or hospital? (open answer)
- Which medical doctor/GP or which hospital? (open answer)
- Please enter the approximate date/period for your visit at the medical doctor/ at the hospital?

Subsequent message to participant:
If we judge that you have sought medical doctor / been to the hospital because of a serious adverse event, we will contact you later to hear about the duration of the consequences of the event.

Two authors (KHA, UB) classified asthma-related events without unmasking group allocation as related, unrelated, or possibly related to interventions, using information extracted from medical reports and the self-reporting from the participants to help determine the potential attribution of the event.

Statistical analyses

Frequency of attendance of BrEX sessions, home exercise adherence, AEs, serious AEs, and oral corticosteroids (OCS) courses are reported. To estimate the AE incidence rate ratio (IRR) between groups, we used Poisson regression models (with scaling standard errors in case of overdispersion) with AEs, SAEs, OCS courses, or exacerbation as dependent variables, and treatment center, GINA step, and BMI as covariates.

Table S9a; Number of all types adverse events reported by participants

	UC+ BrEX			UC			UC vs UC+BrEX	
	Number of participants		Number of events	Number of participants		Number of events	IRR[a]	p-value
Adverse events							0.92	0.657
0	21	(22.3%)	0	22	(22.2%)	0		
1	30	(31.9%)	30	25	(25.3%)	25		
2	12	(12.8%)	24	21	(21.2%)	42		
3	6	(6.4%)	18	11	(11.1%)	33		
4	5	(5.3%)	20	6	(6.1%)	24		
5	5	(5.3%)	25	3	(3.0%)	15		
6	3	(3.2%)	18	3	(3.0%)	18		
7	1	(1.1%)	7	1	(1.0%)	7		
8	4	(4.3%)	32	2	(2.0%)	16		
9	0	(0%)	0	1	(1.0%)	9		
10	3	(3.2%)	30	2	(2.0%)	20		
11	1	(1.1%)	11	0	(0%)	0		
12	2	(2.1%)	24	1	(1.0%)	12		
20	1	(1.1%)	20	0	(0%)	0		
25	0	(0%)	0	1	(1.0%)	25		
Total	94	(100%)	259	99	(100%)	246		
Serious adverse events							1.45	0.283
0	80	(85.1%)	0	82	(82.8%)	0		
1	14	(14.9%)	14	13	(13.1%)	13		
2	0	(0%)	0	4	(4.0%)	8		
Deaths	0	(0%)	0	0	(0%)	0		
Total	94	(100%)	14	99	(100%)	21		

[a] Incidence rate ratio (IRR): UC group compared to UC+BrEX group.

Table S9b; Frequency of serious adverse events by group from baseline to 6-month

Types of serious adverse events	All participants		UC+ BrEX			UC		
	Number of participants having one or more	Number of events	Number of participants		Number of events	Number of participants		Number of events
Allergy/pulmonary/upper airways	19	22						
Asthma exacerbation			6	(6.4%)	6	9	(9.0%)	12
Pneumonia			1	(1.1%)	1	1	(1.0%)	1
Pneumothorax			1	(1.1%)	1	0	(0%)	0
Nasal surgery			1	(1.1%)	1	0	(0%)	0
Cancer	2	3						
Bladder			0	(0%)	0	1	(1.0%)	1
Kidney			0	(0%)	0	1	(1.0%)	2
Cardiovascular	2	2						
AMI			0	(0%)	0	1	(1.0%)	1
Cardiac pain			1	(1.1%)	1	0	(0%)	0
Endocrine	1	1						
Hypocalcaemia			0	(0%)	0	1	(1.0%)	1
Gastro-intestinal	3	3						
Infektion			2	(2.1%)	2	1	(1.0%)	1
Gynecology	1	1						
Complications after gyn. surgery			0	(0%)	0	1	(1.0%)	1
Musculoskeletal or connective tissue	7	7						
Damage on connective tissue			0	(0%)	0	2	(2.0%)	2
Fracture			0	(0%)	0	2	(2.0%)	2
Back pain			0	(0%)	0	1	(1.0%)	1
Arteritis Temporalis			1	(1.1%)	1	0	(0%)	0
Infection of joint			1	(1.1%)	1	0	(0%)	0
Neurology	1	1						
Subdural haemorrhage			1	(1.1%)	1	0	(0%)	0
Renal	1	1						
Calculus of kidney			1	(1.1%)	1	0	(0%)	0
Virology	1	1						
Herpes zoster			1	(1.1%)	1	0	(0%)	0
Total	38	42	17		17	21		25

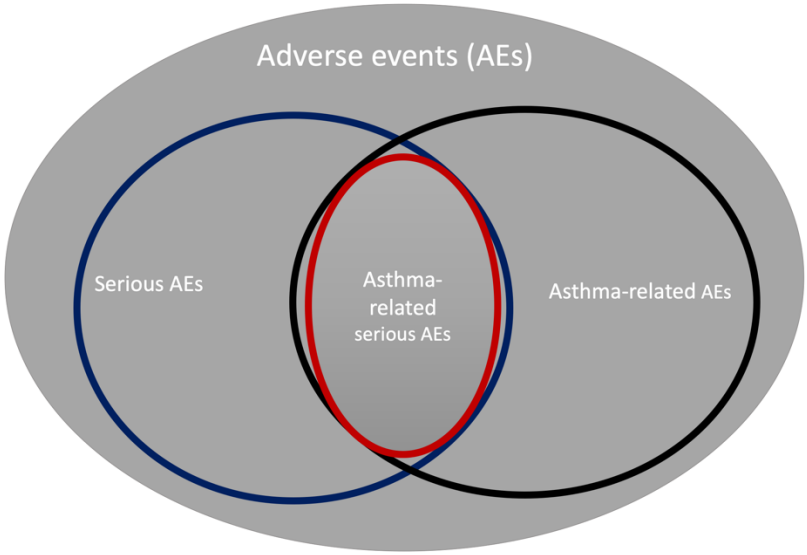


Figure S8c; Structure of adverse events (AE) categories

Figure S9c
Figure S9c visualises how the of categories of adverse events overlap and are reported.

Table S9d; Frequency of participants experiencing asthma exacerbation during course of trial

	UC+BrEX (n=94)		UC (n=98)[a]			
	Number of participants		Number of participants		IRR	p-value
SAE, but no registry of OCS course	2	(2.1%)	5	(5.1%)		
OCS course, but no registry of SAE	3	(3.2%)	1	(1.0%)		
Both SAE and OCS course at same time points[b]	4	(4.3%)	4	(4.1%)		
Total	9	(9.6%)	10	(10.2%)	1.13	0.787

[a]Medication data missing for one participant in UC group

[b]One UC+BrEX participant had additionally one OCS course at another timepoint without SAE registry.
IRR=Incidence rate ratio; OCS=Oral corticosteroids; SAE=Serious adverse event; UC+BrEX=Breathing exercises and usual care; UC=Usual care alone.

Sensitivity analyses: Bootstrapped adjusted table on primary and secondary outcomes at 6-month (S10)

Table S10; Adjusted and bootstrapped intention-to-treat analyses of primary outcome miniAQLQ and secondary outcomes at 6-month

	Total no. of assessments[a]		ITT-population					
	UC+BrEX	UC	UC+BrEX (n=94)		UC (n=99)		Between-group difference	
			mean change		mean change		difference in mean change	
Mini-AQLQ	262	287	0.65	(0.42 to 0.89)	0.31	(0.10 to 0.51)	0.35	(0.04 to 0.65)
ACQ6	256	285	-0.32	(-0.53 to -0.12)	-0.21	(-0.4 to -0.03)	-0.11	(-0.38 to 0.16)
NQ	255	285	-3.83	(-5.94 to -1.71)	-2.78	(-4.51 to -1.06)	-1.05	(-3.69 to 1.60)
HADS-A	255	284	-1.06	(-1.89 to -0.22)	-1.11	(-1.83 to -0.39)	0.05	(-1.06 to 1.17)
HADS-D	255	284	-1.16	(-1.91 to -0.41)	-0.26	(-0.85 to 0.34)	-0.90	(-1.89 to 0.08)
6MWT	160	176	2.03	(-13.97 to 18.03)	9.03	(-6.38 to 24.44)	-7.00	(-28.88 to 14.88)
FEV_1%pred.	150	163	0.48	(-2.52 to 3.47)	-0.53	(-4.03 to 2.98)	1.00	(-3.55 to 5.56)
			Per-protocol population					
			UC+BrEX (n=76)		UC (n=99)		Between-group difference	
			mean change		mean change		difference in mean change	
Mini-AQLQ	222	287	0.68	(0.44 to 0.93)	0.31	(0.11 to 0.50)	0.38	(0.06 to 0.69)
ACQ6	216	285	-0.39	(-0.63 to -0.16)	-0.21	(-0.40 to -0.03)	-0.18	(-0.48 to 0.12)
NQ	215	285	-4.03	(-6.42 to -1.64)	-2.78	(-4.59 to -0.98)	-1.25	(-4.25 to 1.75)
HADS-A	215	284	-1.13	(-1.98 to -0.28)	-1.11	(-1.83 to -0.40)	-0.02	(-1.13 to 1.09)
HADS-D	215	284	-1.46	(-2.22 to -0.70)	-0.26	(-0.81 to 0.29)	-1.20	(-2.15 to -0.25)
6MWT	140	176	2.50	(-13.75 to 18.74)	9.03	(-6.11 to 24.16)	-6.53	(-29.24 to 16.18)
FEV_1%pred.	131	163	0.87	(-2.21 to 3.95)	-0.52	(-3.92 to 2.88)	1.39	(-3.16 to 5.94)

Data are adjusted mean change from baseline to 6-month including 95% CI.
[a]Possible assessments for questionnaires (at baseline + at 3-month + at 6-month): 282 for UC+BrEX (in per-protocol: 228) and 297 for UC; for FEV1%pred. and 6MWT (at baseline + at 6-month): 188 for UC+BrEX (in per-protocol: 152) and 198 for UC.
UC+BrEX= Breathing exercises and usual care. UC= Usual care alone. Mini-AQLQ=Mini-Asthma Quality of Life Questionnaire. ACQ6=6-item Asthma Control Questionnaire. NQ=Nijmegen Questionnaire. HADS-A=anxiety items of Hospital Anxiety and Depression Scale. HADS-D=depression items of Hospital Anxiety and Depression Scale. 6MWT=6-min Walk Test. FEV1%pred.=Predicted percentage of forced expiratory volume in first second. PAL=average Physical Activity Level per day.

Sensitivity analyses: GINA step adjusted analyses on primary and secondary outcomes at 6-month (S11)

Results of sensitivity analyses with adjustment for asthma severity (GINA-step) instead of treatment centre showed no difference in mean between group in Mini-AQLQ, although a trend in favour of UC+BrEX existed (p=0.056). No significant difference between groups in ACQ6 or HADS-D, but within-group improvements in ACQ6 in both groups, and in HADS-D for UC+BrEX group (table S11).

Table S11; GINA step adjusted analyses of primary outcome Mini-AQLQ and secondary outcomes at 6-month

	Total no. of assessments[a]		ITT-population		
	UC+BrEX	UC	UC+BrEX (n=94) mean change	UC (n=99) mean change	Between-group difference difference in means change
Mini-AQLQ	262	287	0.66 (0.46 to 0.86)	0.31 (0.12 to 0.50)	0.35 (0.08 to 0.62)
ACQ6	256	285	-0.33 (-0.51 to -0.15)	-0.22 (-0.39 to -0.04)	-0.11 (-0.36 to 0.14)
NQ	255	285	-3.83 (-5.67 to -1.99)	-2.79 (-4.55 to -1.04)	-1.04 (-3.57 to 1.50)
HADS-A	255	284	-1.07 (-1.79 to -0.36)	-1.21 (-1.89 to -0.52)	0.13 (-0.85 to 1.12)
HADS-D	255	284	-1.15 (-1.77 to -0.53)	-0.35 (-0.94 to 0.25)	-0.80 (-1.66 to 0.06)

Data are adjusted mean change from baseline to 6-month including 95% CI.

[a] Possible assessments for questionnaires (at baseline + at 3-month + at 6-month): 282 for UC+BrEX and 297 for UC.
UC+BrEX=Breathing exercises and usual care. UC=Usual care alone. Mini-AQLQ=Mini-Asthma Quality of Life Questionnaire. ACQ6=6-item Asthma Control Questionnaire. NQ=Nijmegen Questionnaire. HADS-A=anxiety items of Hospital Anxiety and Depression Scale. HADS-D=depression items of Hospital Anxiety and Depression Scale.