The REPLACE study

Can exercise replace inhaled corticosteroid treatment in asthma?

A randomized, clinical trial

Study protocol for The REPLACE study

Protocol version 3, 02 October 2017.

Clinicaltrials.gov Trial registration identifier: NCT03290898

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CLINICAL STUDY PROTOCOL

The REPLACE study

Can exercise replace inhaled corticosteroid treatment in asthma?

A randomized, clinical trial

Project responsible: Vibeke Backer[1], Professor, Chief physician, MD, DMSci

Project manager & Investigator: Anders Pitzner-Fabricius[1], MD, PhD-student

Investigator: Christian Dall[2], PhD, PT, MSc

Investigator: Morten Hostrup[3], Associate Professor, PhD, Cand.Scient.

Investigator: Marius Henriksen[2], Professor, PhD, PT

Investigator: Louise Tønnesen[1], MD, PhD-student

Sponsor: Respiratory Research Unit, Department of Respiratory Medicine, Bispebjerg University Hospital, Copenhagen, Bispebjerg Bakke 23, DK-2400 NV, Denmark. CVR: 29190623

1: Department of Respiratory Medicine, Bispebjerg University Hospital, Copenhagen

2: Department of Physio- and Occupational Therapy, Bispebjerg-Frederiksberg Hospital, University of Copenhagen

3: Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen

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1 Summary

The aim of this study is to investigate whether exercise as a supplementary treatment in asthma is of such a magnitude, that it is possible and safe to reduce asthma patients in inhaled corticosteroid. The study is a randomized, controlled parallel group, clinical trial. Outcome assessor is blinded throughout the first 6 months.

2 Background

Inflammation in asthma

Asthma is an inflammatory disease characterized by local airway inflammation and airway hyperresponsiveness (AHR). However, recent research has shown, that asthma patients have increased *systemic inflammation* measured with high sensitivity C-Reactive Protein (hsCRP)[1] and elevated pro-inflammatory cytokines such as IL-6, IL-8 and TNF-a in serum[2 3] when compared to healthy subjects.

Effects of exercise on asthma control and inflammation

Physical exercise reduces low-grade inflammation in healthy individuals[4] and exercise has proven to attenuate inflammation in other inflammatory diseases such as diabetes, hypertension and cardiovascular disease.[5] Exercise in asthma patients is safe and improves aerobic fitness. Studies shows that exercise in asthmatics reduce systemic and airway inflammation, decrease risk of exacerbation and improves quality of life.[6 7 8 9 10] Additionally a meta-analysis evaluated the effects of exercise on airway inflammation in asthma and concluded that exercise might reduce the number of airway inflammatory cells[11] but the included studies were too heterogeneous to draw any conclusions.
The next step in the evaluation of the effects of exercise in asthma will be to investigate if the beneficial effects of exercise are in a magnitude that allows for down-titration of ICS without worsening asthma symptoms. Reduced ICS usage by means of regular exercise, will not only mean improved health and quality of life among the patients, but also represents an important risk reduction in the development of adverse effects of ICS and may reduce costs related to ICS.
Such a study has, to our best of knowledge, not previously been conducted.

Rationale

- Asthma patients have increased levels of systemic and local inflammation
- Physical exercise decreases the level of systemic inflammation in healthy persons and in asthmatics
- Physical exercise reduces airway inflammation and improves asthma symptom control
- Decreased systemic inflammation is associated with reduced airway inflammation and better asthma control

Hypothesis

- Physical exercise intervention leads to an improved asthma control as measured by Asthma Control Questionnaire (ACQ-5) in such a magnitude that inhaled corticosteroid can be reduced in asthmatics.

3 **Methods**

3.1

Design

Randomized, parallel group, outcome assessor blinded, intervention study of 150 asthmatics running over 12 months. Following baseline examinations, participants will be randomized (2:1; 2 to exercise – 1 to control) to either 6 months of supervised high intensity spinning exercise 3 times weekly or a control group (usual lifestyle).

3.2

Recruiting asthma patients

Patients will be recruited from general practices and private pulmonary medical practices throughout the Copenhagen area. Asthma patients attending an Outpatient Department of Respiratory Medicine at any Hospitals within the Capital or Zealand region will be handed a letter of invitation to participate in the study.

Moreover, advertising will be done (posters) at Universities and schools in Copenhagen, on the social media (e.g. Facebook), on the homepage www.forsoegsperson.dk, in newspapers and in magazines.

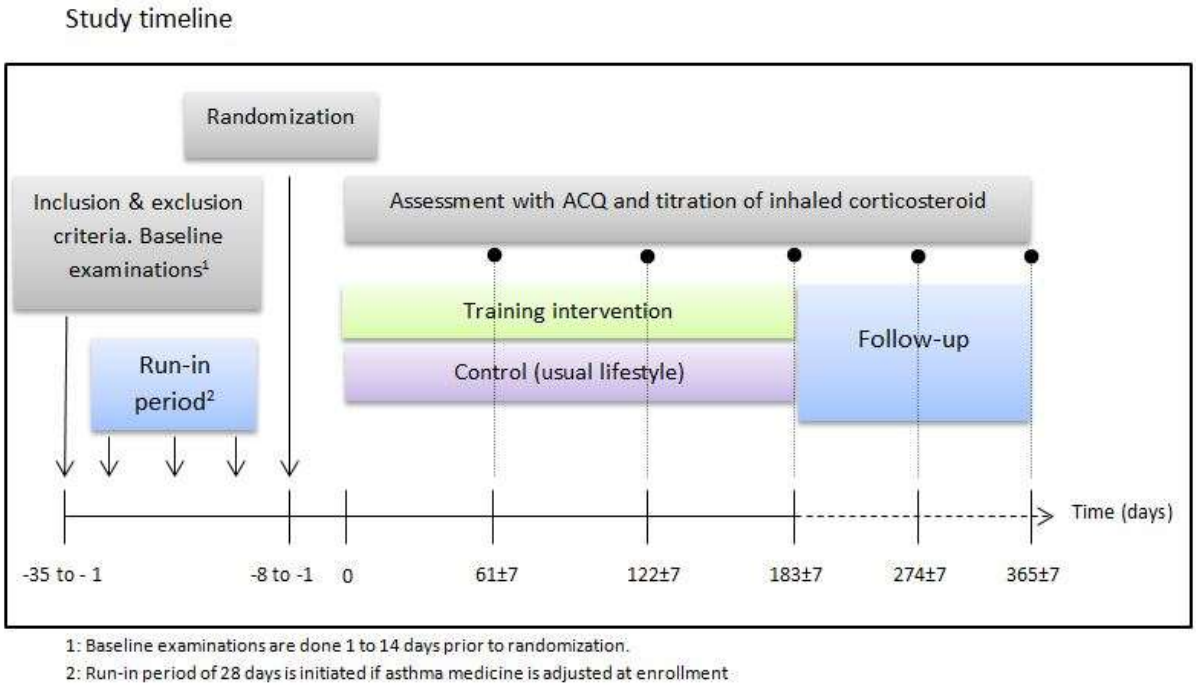
3.3

Patients flow and timeline of study

The recruiting and inclusion of study participants will be running. Inclusion is done during a period of maximum 35 days, which include a potential 28 day long run-in period, which is initiated if the participant's medicine dose is changed in at enrollment. Baseline measurements are performed 1 to 14 days prior to randomization, DEXA scan is performed within ±14 days with regards to randomization. Eligible patients then undergo 6 months of intervention/control period according to figure 1 ("Study timeline").

Patients will be enrolled from 1st of October 2017 until 31st of January 2019. Laboratory analyses, data analyses, pathology and publication will be performed throughout 2018, 2019 and 2020.

Figure 1, Study timeline



1: Baseline examinations are done 1 to 14 days prior to randomization.
2: Run-in period of 28 days is initiated if asthma medicine is adjusted at enrollment

The study consists of 8 visits; 3 pre-interventional, 3 during intervention and 2 follow-up visits.

Table 1, clinical visit schedule

Clinical visit schedule	Screening	Run-in	Randomi-zation	Intervention			Follow-up	
Visit	100[a]	101a/101b*	102	201	202	203 **	301	302
Time (days)	-35 to -1		-8 to -1	61 ±7	122 ±7	183 ±7	274 ±7	365 ±7
Informed consent	●							
Review of inclusion and exclusion criteria	●	●						
Medical history		●						
Medication review		●						
Conversion of device[b]		●						
Adjustment of asthma medicine[c]		●						
Questionnaires								
• **Baseline Questions**		●						
• **ACQ**		●		●	●	●	●	●
• **miniAQLQ**		●				●		●
ICS titration				●	●	●	●	●
Adherence								
• **Foster score**		●		●	●	●	●	●
• **Dosage counter**		●		●	●	●	●	●
• **Control inhalation technique**		●		●	●	●	●	●
Height and weight		●				●		●
Spirometry		●		●	●	●	●	●
Methacholine[d]		(●)				(●)		
Reversibility[d]		(●)				(●)		
FeNO		●		●	●	●	●	●
Induced sputum		●				●		
Cardiopulmonary fitness test (VO2max)		●				●		
Blood test		●				●		●
Allergy test (blood test)		●						
DEXA scan[e]		●				●		
Randomization			●					

a: may be on the same day;
b: to dose counter;
c: according to adjustment algorithm;
d: Methacholine requires $FEV_1 \geq 70\%$ of predicted. If $FEV_1 < 70\%$ of predicted, reversibility test is performed instead;
e: Baseline DEXA scan is performed ±14 days after randomization.
***Note: If inhaled medicine dose is changed in dose at visit 101a, a 28 days run-in period is required, and a visit 101b is performed.**
****If subject has a moderate or severe exacerbation at visit 203, an extra visit at 7 month is required. This visit will be identical to visit 203.**

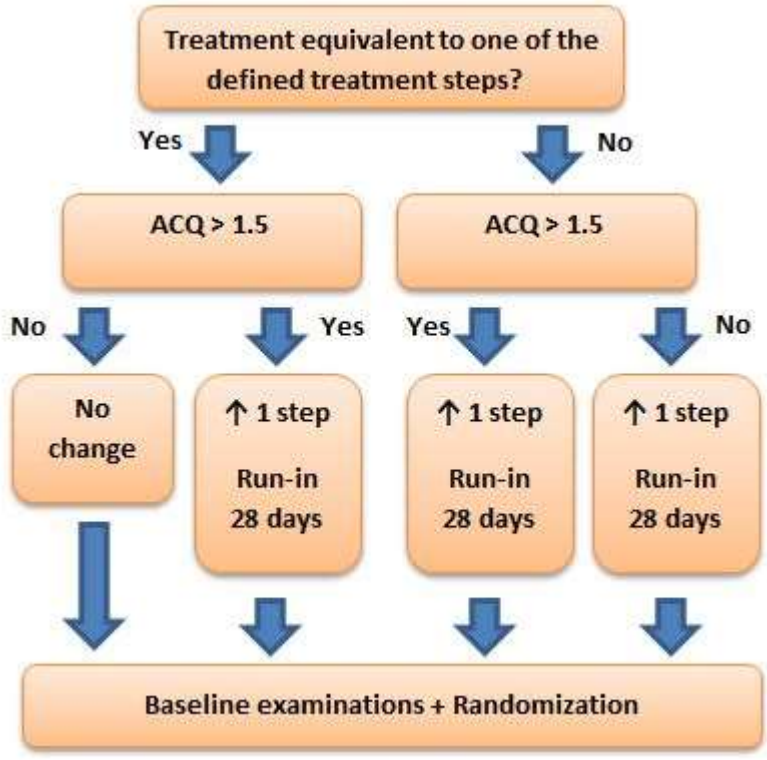
3.4

Adjustment algorithm at enrollment

Eligible subjects will at enrollment be adjusted in asthma medicine according to a pre-defined algorithm based on current treatment and asthma symptoms, figure 2. If dose is changed a 28 days run-in period is required. If using a device without dose counter, device will be converted to one with dose counter. If deemed necessary by judgement a medical doctor in the study team or by request of the participants, a device with no dose counter can be used.

Long-acting muscarinic antagonists (LAMA) and leukotriene receptor antagonists (LTRA) will be discontinued. A washout period of 5 half-lives is required before subject can be randomized (LAMA: 10 days; LTRA: 2 days).

Figure 2, adjustment algorithm at enrollment



Clinical algorithm

During the study period asthma treatment will be regulated according to pre-defined algorithm, modified from Gibson et al[12]. It's based on asthma control, assessed by Juniper Asthma Control Questionnaires (ACQ-5)[13]. Cut-off points defined the patient as either well controlled (≤1.0), partially controlled (>1.0-1.5) or uncontrolled (>1.5), table 3. If well controlled, treatment is titrated

1 step down, if uncontrolled treatment is titrated 1 step up. If partially controlled, no change in treatment occurs, table 2.

If ACQ score is >2.0 at 2 consecutive visits during intervention or follow up, or if ACQ score is> 1.5 when the participant is at treatment step 5, the participant will be referred to a (blind) specialist assessment within 4 weeks. If the blind specialist considers that it is necessary for the participant to receive another treatment during the trial period, the participant will be treated as necessary and continue in the trial. If the participant is considered unable to complete any training intervention, the participant will be discontinued. Any exacerbation is treated accordingly to international guidelines.

Table 2 – Clinical algorithm treatment steps

	Treatment
Step 1a	SABA as required
Step 1b	Budesonide 100µg twice per day
Step 2	Budesonide 200µg twice per day
Step 3	Budesonide 400µg twice per day
Step 4	Budesonide 600µg and formoterol 12 µg twice per day
Step 5	Budesonide 800µg and formoterol 24 µg twice per day

Table 3 – Algorithm for up- and down-titration of treatment during study

	ACQ score	Treatment adjustment
Uncontrolled	>1.5	↑1 step
Partially controlled	>1.0-1.5	No change
Well controlled	≤1.0	↓ 1 step

3.5

Randomization

Patients will be unequal randomized 2:1 (2 to exercise: 1 to control) by a computer-based program in random block sizes, blinded to investigator. Stratification is done by sex, ACQ-score (≤1.75, assessed on a stable treatment regime) and blood eosinophilia (≥0.15), with a total number of strata 2 x 2 x 2 = 8. Randomization is conducted by a non-investigational member of the study group.

3.6

Primary outcome measure: The proportion of participants at 6 months (visit 203) that have been down-titrated in ICS dose by at least 25%.

Secondary outcome measures:

The proportion of participants at 12 months that have been down-titrated in ICS dose by at least 25 % compared to baseline.

Change from baseline in

- Cumulated dose of ICS at 6 months
- Cumulated dose of ICS at 12 months
- Cumulated dose of LABA at 6 months
- Cumulated dose of LABA at 12 months
- Exacerbation rate
- Asthma life quality evaluated by miniAQLQ
- Airway inflammation measured by FeNO and cell count in sputum
- Systemic inflammation (hsCRP, inflammatory cytokines, bloodEOS)
- Airway hyperresponsiveness measured by methacholine test
- Lung function: FEV1 and FVC
- Cardiopulmonary fitness: Maximal oxygen consumption during an incremental bike ergometer test (VO_{2max})
- Change in fat and muscle composition (DEXA scan)

Explorative: The above-mentioned measurements, both primary and secondary, will also be carried out on subpopulations, stratified by blood eosinophilia at different cut-off values.

3.7

Asthma patients

The diagnose of asthma is based on symptoms and at least one positive asthma test the last 5 years (AHR to either mannitol or methacholine, reversibility to beta2- agonist, peak flow variation or positive eucapnic voluntary hyperventilation test) and will be confirmed by a physician at the pulmonary research unit. If no exclusion criteria and all inclusion criteria but positive asthma test is met at visit 100, reversibility test and methacholine test is conducted as planned in V101. If both tests are negative, subject will be considered as screening failure.

All participants will fill out a questionnaire at baseline (V101) with questions concerning patient's weekly activity level, smoking habits, adherence to asthma treatment and medical history.

3.8

Inclusion criteria

- Asthma
- 18-75 years
- ACQ ≥ 1 and ≤ 2.5
- On a daily dose of ICS at a minimum of 400 µg budesonide or equivalent ICS for 3 months and with no changes in asthma medicine 4 weeks prior to enrollment
- Untrained (no participation in vigorous exercise for more than 1 hour per week during the last 2 month)
- Capable of exercising on bike

Exclusion criteria

- Unable to speak and understand Danish
- Infection in the respiratory tract within 4 weeks prior to visit 100*
- Asthma exacerbation within 4 weeks prior to visit 100*
- Hospitalized for an asthma attack during the last 12 months.
- Treatment with immunotherapy within 5 T½ of the treatment drug prior to visit 100
- Initiation of allergen immunotherapy within 3 months prior to visit 100 or plan to begin therapy during study period.
- Treatment with peroral prednisolone
- Respiratory: other chronic pulmonary disease of clinically significance
- Cardiovascular: Unstable ischemic heart disease, myocardial infarction within the last 12 months, symptomatic heart failure (NYHA III-IV or EF <40%), symptomatic heart arrhythmia (documented with ECG), uncontrolled hypertension (>155/100)
- Pregnancy or breastfeeding or planned pregnancy within the next 12 months.
- Other inflammatory or metabolic diseases with the exception of rhinitis, atopy and well-controlled hypothyroidism treated with or without Eltroxin.
- Vaccination less than 2 weeks prior to any visit requiring blood samples

- Current or former smokers with > 20 pack years
- Subjects, who by investigators determination, will not be able to adhere to study protocol

* If patients are excluded due to a recent infection or exacerbation, they can undergo re-screening after a total of 4 weeks after end of exacerbation treatment/clearing the infection.

4 **Intervention**

6 month of high intensity interval training. The exercise intervention will consist of spinning for 1 hour (including a 10-minute warm up and cool down period. The 40 minutes will consist of short periods of high intensity intervals for 1-2 minutes above 80% of VO2max).

4.1

The exercise intervention

The training consists of high-intensity interval training on spinning bikes indoor. Participants meet in teams of 10-12 subjects 3 times a week for a 1-hour training session at Frederiksberg hospital. At each training session, patients will be instructed by a bachelor of physiotherapy, sports science or a Bachelor of Medicine. Patients will wear heart rate monitors, which enable continuous monitoring of their heart rate during the spinning sessions, and the responsible spinning instructor will ensure patients adherence to the training protocol.

4.2

Control group

The control group will not receive any intervention but should continue their previous level of physical activity.

5 Data collection

Data is collected during study visits and from the patient journal (see “Participant confidentiality”)
During the study, if consent is given, electronic reminders (text message and email) may be sent to participants, and data can be collected electronically prior to study visit.
Questionnaires are filled in on paper or on an electronic device directly into a secured electronic CRF, secureCRF (www.secureCRF.com; previously approved by Danish Data Protection Agency).
All source documents in paper are entered in secureCRF.
All source documents in paper are scanned/photographed and uploaded to secureCRF.

Test results (e.g. DEXA scan, spirometry, blood samples and bronchial provocation test) will be entered and uploaded to secureCRF.

6 **Outcome Assessment and risks**

6.1

Primary Outcome

Severity of symptoms is assessed with international standardized asthma control questionnaires 5-item version (ACQ-5)[1]. Asthma treatment is adjusted according to pre-defined algorithm based on ACQ-5 score, see table 2 & 3. Baseline dose is registered as the dose after adjustment of treatment at enrollment. 6 months dose is registered as the dose after adjustment according to clinical algorithm at visit 203 (6 months).

6.2

Secondary Outcomes

Respiratory questionnaires:

International standardized questionnaires will be used regarding:

- Asthma Quality of Life Questionnaire (miniAQLQ)[14]

Anthropometry and body composition*:*

- Gender, age, height (without shoes) and bodyweight (lightly dressed).
- DEXA scan at baseline and follow-up to assessment of changes in body composition.
- Risk assessment: Radiation dose is low (5-10 µSv), less than 1/100 of the dose received from natural background radiation during one year.

Fitness evaluation: At baseline and follow-up, all participants will undergo a standardized bicycle ergometer test to evaluated work capacity and maximal oxygen uptake[15].
Risk assessment: Negligible.

Exacerbation:

Severe exacerbation: Worsening of asthma symptoms (like shortness of breath, wheezing, cough or chest tightness) that requires systemic corticosteroid for at least 3 consecutive days and a need for hospitalization due to asthma or death do due to asthma.

Moderate exacerbation: occurrence of two or more of the following (1-3) and requirement for systemic corticosteroid for at least 3 consecutive days:

1. Worsening of at least one asthma symptom (shortness of breath, wheezing, cough, or chest tightness) for at least 2 consecutive days
2. Increased use of rescue inhaled bronchodilators defined by:
    a. >50% increase in SABA use and >8 puffs on 2 out of 3 consecutive days compared to baseline
    OR
    b. Night time awakenings requiring SABA use on at least 2 out of 3 consecutive nights
3. >decrease 20% in FEV1 from baseline

Mild exacerbation: The occurrence of at least one of the following without requirement of systemic corticosteroid or hospitalization:

1. Worsening of at least one asthma symptom (shortness of breath, wheezing, cough or chest tightness)
2. Increased use of rescue inhaled bronchodilators
3. >decrease 20% in FEV1 from baseline

Pulmonary function test:

Spirometry including test for reversibility for short-acting beta-2-agonist is performed with EasyOne™ without nasal clamp in accordance with international guidelines of standardized spirometry[16]. The full in- and expiratory flow is recorded.

Risk assessment: Negligible. Standard procedure in pulmonary diagnostics.

Airway hyperresponsiveness

- **Methacholine challenge test:**
  Performed as a dose-response test ad modum Yan[17]. Maximum cumulated dose is 7,368µmol. A positive test is defined as a reduction of > 20% in FEV_1 compared to baseline. Subjects with a pre-bronchodilated FEV1 < 70% will not have the test performed.
  Risk assessment: Low. Cough and shortness of breath mimicking a mild asthma attack. Standard procedure in pulmonary diagnostics.
- **Reversibility test for short-acting beta-2:**
  A pulmonary function test in accordance with international standards as described above is

initially performed. Following the pulmonary function test, a standard dose of short-acting beta-2-agonist (400µg or 1mg terbutaline) is administered and another pulmonary test is performed.

Risk assessment: Negligible. Salbutamol and terbutaline is known to cause mild side effects in the form of palpitations and unrest up to 30 minutes after administration. The test as a whole is without risk and a standard procedure in pulmonary diagnostics.

Airway inflammation:

- **Sputum sample:** Performed after provocation with nebulized saline. Collected with the aim of differential count and markers of inflammation.

  0.5-1ml will be collected at baseline and after 6 months (total of maximum 2 ml per participant) to analyse specific cytokines with relevance to asthma and inflammation, e.g. TNF alfa and IL-6.

  The sputum will be frozen at -80 degree and stored in a research biobank. The purpose of the research biobank is to store the biologic material under safe and controlled conditions until a full analysis of the collected material is possible. This procedure is chosen of economical and practical causes. The material will be pseudo anonymised in the laboratory at the Respiratory Research Unit, Bispebjerg Hospital, which complies with the regulations from the Danish Data Protection Agency.

  The material will be stored until analysis (projected at the end of year 2020 but maximally 5 years) and destroyed after analysis.

  Risk assessment: Low. Cough, throat irritation and mild shortness of breath mimicking a mild asthma attack.
- **Fraction of exhaled nitrogen (FeNO):** Measurement of fractional exhaled nitrogen oxide (FeNO). The subject inhales air without NO, followed by a 10-second exhalation. The concentration (parts per billion) of NO is measured.

  Risk assessment: Negligible. Standard procedure in pulmonary diagnostics.

Markers of systemic inflammation:

- **Standard blood sample:**

  Blood samples will be drawn from vv. cubiti with analysis of leukocytes incl. differential count, hemoglobin, thrombocytes, high-sensitivity CRP, creatinine, bilirubin, ASAT, albumin, blood sugar, Na^+, K+, IgE and RAST test for standard allergens (birch (betula),

grass (phl. Praetense) mugwort, horse, dog, cat (fel d), house-dust mites (Der p1. and Der f2) and mold (alternaria, cladosporium and aspergillus fumigatus)). In total 75 mL blood is collected in total (3 visits of 25 ml). The analyses are done by central laboratory at Bispebjerg-Frederiksberg and are destroyed upon analyses; no samples are stored for later analyses.

- **Plasma and serum concentrations of inflammatory markers**
  7 ml EDTA plasma and 7 ml serum will be collected at baseline, after 6 months and at 12 months (3 visits x 7ml x 2 = 42 ml per participant) to analyse specific cytokines with relevance to asthma and inflammation, e.g. TNF alfa, IL-6 and IL-8.
  The EDTA plasma and serum will be frozen at -80 degree and stored in a research biobank. Please see "sputum sample" for further details regarding biobank ad storage procedures. The material will be stored until analysis (projected at the end of year 2020 but maximally 5 years) and destroyed after analysis.

Risk assessment: Negligible. Pain at puncture site, minor risk of superficial hematoma. Standard procedure in general diagnostics.

Blinding assessment

At the end of each study visit, assessor is asked whether they think that the participator is in the training or control group.

7 Statistics and power calculation

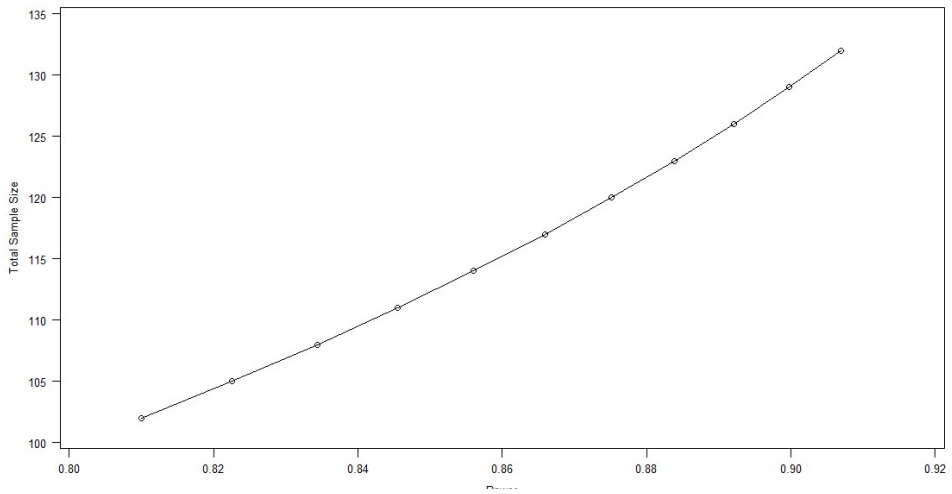
Data will be analysed using the statistical software program SPSS 23.0 (SPSS Inc., Illinois, USA).

Sample size considerations: We assume that at 6 months 10% in the control group (usual lifestyle) will be down-titrated by spontaneous (or via self-management) changes in ACQ score and that 35% of patients in the exercise group will be down-titrated. For a comparison of two independent binomial proportions using Pearson's Chi-square statistic with a Chi-square approximation with a two-sided significance level of 0.05, a total sample size of 150 assuming an allocation ratio of 1 to 2 has an approximate power of 0.941 when the proportions are 0.1 and 0.35. This corresponds to a number needed to treat (NNT) of 4 patients.

- Even if NNT is 5, a sample of 150 patients (ITT) will still have sufficient power (0.82) to detect absolute difference in proportion of patients acquiring successful down-titration of 20% (30% in exercise group vs. 10% in usual lifestyle).

- Should we not meet the a priori sample size, even a sample size of 102 will yield sufficient power to detect a difference corresponding to a NNT of 4 patients.

Figure 3, power and sample size



8 Ethical considerations

Participant withdrawal

A participant may withdraw from the study at any time without this impacting on any future investigations and/or treatments at the site, by the investigators in this study or by other staff associated with the study.

The investigator may discontinue any participant's participation for any reason, including an AE, safety concerns, or failure to comply with the protocol.
Participants will be discontinued from the study immediately if any of the following occur:

- Death.
- Other significant illness.
- Failure to adhere to the protocol.

It is important to avoid any loss to follow-up participants for the efficacy assessment and meaningful analysis of the study.

General considerations

All potential trial participants are informed, both orally and in writing, about the purpose of this trial, its process and potential risks, as well as costs and benefits of participation. In addition, the

leaflet '*Rettigheder som forsøgsperson i et sundhedsvidenskabeligt forskningsprojekt*' will be handed out. All participants are informed of their rights to withdraw from the study at any time without this impacting on any future investigations and/or treatments at any site or by some of the members of the study group. After the information is delivered, read and understood, voluntary informed consent is given by the participant by signing a consent form before study participation can take place.

It is the investigators opinion that the knowledge and potential individual benefit gained by participation in this study is commensurate with the efforts and difficulties associated with participation. Below are specific research ethics considerations related to information, consent, interventions, and outcome assessments.

Oral information

When a potential participant contacts the study, an appointment for an information interview is made. It will be stressed that the investigator is asking the participant to consider participation in the study, and that the potential trial participant has the right to bring a companion to the information interview.

The oral information is based on the written information and will be given in a language easily understood without technical or value-laden terms. The information will be given in a considerate way that is tailored to each potential trial participants. The aim is that the conversation takes place without interference. It is the responsibility of the interviewer to ensure that the potential trial participant has understood the information. The information interview is performed by the investigator or in his absence by a designated delegate. Guidelines for the oral information are given in Appendix B.

Informed consent

Consent to participation in the trial is given on the basis of the written and oral information.
An informed consent form (ICF; Appendix A) has been prepared. The form must be signed and dated by the participants prior to participation in the trial. A copy of the form is provided to the participants. The investigator or his designated delegates can receive the signed consent form. Prior to consent, it must be ensured that a potential participant has been given 24 hours to consider his or her participation.

The source documentation and CRFs will document for each participant that informed consent was obtained prior to participation in the study. The signed ICF must remain in each participant's study file and must be available for verification by study monitors at any time.

Research ethics approval

This protocol, the informed consent form, written patient information and relevant supporting information must be submitted to the ethical committee, by the Sponsor, prior to study initiation. The study will be conducted in accordance with Danish law, the Helsinki declaration, and local research ethics committee requirements.

The Sponsor is responsible for keeping the ethical committee informed of amendments or changes to the protocol, and the progress of the study, as appropriate.

Notification to the Danish Data Protection Agency

Because the study is carried out at hospital departments, it is regarded as "public" in accordance with the Data Protection Agency guidance. The study has been notified to the Data Protection Agency via the Capital Region of Copenhagen's umbrella agreement with the Data Protection Agency. The study has been approved by the Data Protection Agency (ID: BFH-2017-067)

Use of information from patient journal

By signing informed consent participators grants investigators access to obtain necessary information from the patient journal regarding your health with relevance to the study or as a part of an investigation by relevant authorities regulatory control of the study.
Participation will also include access to information regarding prescribed prescriptions and redeemed prescriptions as a part of your medication review and assessment of adherence to treatment.

Participant confidentiality

This study will be conducted under full adherence to the act on processing of personal data in current Danish legislation (*lov om behandling af personoplysninger*).

Participant medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

With the participant's permission, medical information may be shared with his or her personal physician or with other medical personnel responsible for the participant's welfare.

If the data from this study are published, the presentation format will not include names, recognizable photos, personal information or other data which compromises the anonymity of participating participants.

Retention of records

Danish regulations require that the records and documents pertaining to this study must be retained by the Investigator for 5 years after completion of the study.

Records to be retained include, but are not limited to, CRFs, consent forms, source documentation, test results, and regulatory documents.

9 Feasibility and qualifications of the research group

At Bispebjerg Respiratory Research Unit we have over the last two years conducted a large randomized controlled trial about the effects of diet and exercise in asthma including a total of 149 asthma patients. The trial was conducted in a successful collaboration with researchers and staff from the Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen. Therefore, training facilities and equipment have already been established and the planned exercise intervention has been proven to be feasible and safe. Moreover, at Bispebjerg Respiratory Research Unit we have a solid experience in conducting research within the field of asthma and exercise, and we have all necessary equipment available.

Our recent study has shown that high-intensity interval training is both feasible and safe in sedentary non-obese asthmatics[6].

10 Plans of dissemination

The study will be registered on www.clinicaltrials.gov. Results both negative, neutral and positive will be presented at congresses and in national and international peer-reviewed journals.

11 Financial support

This study is initiated and conceived by the Bispebjerg Respiratory Research Unit at Bispebjerg-Frederiksberg Hospital. The project is supported financially by Bispebjerg Respiratory Research Unit. The salary of Vibeke Backer and Morten Hostrup is internally funded. Marius Henriksen's

salary is partly guaranteed via a grant from the Oak Foundation to the Parker Institute at Bispebjerg-Frederiksberg Hospital.

The project has received funding from Bispebjerg Hospital (DKK 250.000), Bispebjerg Hospital Scientific Scholarship Fund (DKK 80.000), Lungeforeningen (DKK 90.000), Per Henriksens Fond (DKK 300.000) and Aase og Ejnar Danielsens Fond (DKK 150.000). Funding is allocated to both VIP and TAP salary as well as diagnostic procedures and equipment.
The project managers have no economical or commercial interests in the study results, be they positive or negative.
The project is not fully funded yet. The project manager will continue to apply for financial support from private and public foundations during the study period and if grants are given the Ethical Committee as well as all participating patients will be informed.

12 Remuneration

Study participants will not receive any financial support.

13 Availability of information for study subjects

If requested, participators will be informed of their test results at any time during the study period. Contact information is found in the information letter.

14 Insurance

The participants are insured by the Danish Patient Insurance Association. Financing and insurance issues are addressed in the written information material.

15 Organization and project partners

- Prof. Vibeke Backer, Dept. of Resp. Med., BBH. is the project responsible and supervisor for PhD student Anders Pitzner-Fabricius.
- MD, PhD student, Anders Pitzner-Fabricius, Dept. of Resp. Med., BBH is the project manager and investigator.
- Assistant professor, PhD, Cand.scient. Morten Nielsen will assist in planning the exercise protocol and assist on a day-to-day basis in performing the bicycle ergometer work capacity tests.
- PT, PhD, Christian Have Dall, Dept. of Physio- and Occupational Therapy, BFH, is responsible for supervising the physical exercise intervention and the development of

standard operation procedure for the bicycle ergometer work capacity test. Furthermore assisting on writing the protocol.

- Prof. Marius Henriksen, Dept. of Physio- and Occupational Therapy, BFH, is supervisor for PhD student Anders Pitzner-Fabricius.
- Medical students, Dept. of Resp. Med, BBH, will assist on carrying out visits: screening, run-in, intervention and follow-up (V100-V302).
- Physiotherapeutic students, Department of Respiratory Medicine, BBH or Department of Physio- and Occupational therapy, BFH, will assist on carrying out exercise intervention.

16 Appendix

A. Informed Consent Form
B. Participant information sheet
C. Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt
D. Recruitment material
E. Protocol résumé
F. Questionnaires: ACQ-5, mini AQLQ, Facts About You, Medical history questionnaires
G. Project responsible: Identification, authorisation and qualification

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