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ABSTRACT

Introduction Late-onset asthma in postmenopausal women is characterised by poor disease control with daily symptoms and reduced quality of life despite treatment with inhaled antiasthma therapies. These patients represent a phenotype that is characterised by low eosinophilic airway inflammation, severe symptoms, moderate obesity and poor response to inhaled antiasthma therapies, which highlights the need of identification of alternative treatment strategies. Thus, this study aims to evaluate if regular high-intensity aerobic exercise improves symptom control in postmenopausal women with asthma.

Methods and analysis This is an ongoing randomised controlled trial planning to enrol 40 postmenopausal women with late-onset asthma. Participants are randomised 1:1 either to supervised exercise training (spinning) three times per week for 12 weeks or to usual care. The primary outcome is change from baseline to follow-up in the Asthma Control Questionnaire. Secondary outcomes are changes in markers of systemic inflammation, airway inflammation, body composition and right ventricular function of the heart.

Ethics and dissemination The study is approved by the Ethics Committee in the Capital Region of Denmark nr. H-18028966 and the Danish Data Protection Agency nr. VD-2019–59. The methods used in the study are well known and have a low risk with a chance of substantial improvement in disease control in this patient group. Results are planned to be published in an international peer-reviewed medical journal regardless of outcome.

Trial registration number NCT03747211.

Strengths and limitations of this study

- This is the first randomised controlled trial designed to assess aerobic exercise training as treatment for postmenopausal women with asthma.
- The study is outcome assessor blinded which reduces the bias in interpreting the results of the examinations conducted before and after the intervention.
- The aerobic exercise intervention is supervised and monitored by trained staff at all times, which allows us to ensure sufficient adherence to the intervention.
- A limitation with the study is that it has a small sample size with specific patients with asthma, which makes the results and effects difficult to extrapolate to other patients with asthma.

BACKGROUND

Asthma is recognised as a complex and heterogeneous disease, consisting of various phenotypes with different inflammatory profiles and pathogenesis.[1–3] A large proportion of adult asthmatic patients are women, in whom symptoms manifest late in life (late-onset asthma).[4] Women with late-onset asthma above 40 years of age seldom experience remission of disease[5] and have poor disease control, often despite extensive treatment.[4 6] These women have a lower quality of life, more severe asthma,[2] more hospital admissions[7] and more extensive use of glucocorticoids and β2-agonists.[8] Pharmacotherapy of late-onset asthma in women is therefore a challenging clinical issue.[9] The influence of oestrogen on asthma is poorly understood and its influence on the immune system differs between the airways and the rest of the human body.[10] Earlier results have shown that menopausal women with asthma have increased eosinophilic infiltration of the airways.[11] In airways, the epithelial cells are influenced by oestrogen[12 13] and in vitro studies have shown that oestrogen can act as a bronchodilator.[14] In addition, in animal studies, oestrogen reduces airway epithelial cell reaction to acetylcholine significantly.[15] Further, menopause has been linked to increased asthma exacerbation frequency[13] and decreased forced vital capacity (FVC).[16] In addition, asthma has been related to

decreased right ventricular (RV) function of the heart,[17] which is potentially caused by increased pressure in the pulmonary artery induced by the obstructive respiratory pattern.[18] Life style interventions with exercise training and diet have been shown to improve asthma control in a heterogeneous sample of asthma patients and a recent meta-analysis indicated that regular exercise has a slightly positive effect on asthma control.[19 20] However, to what extent exercise training can improve asthma control and compensate for the physiological changes in postmenopausal women with late-onset asthma, is unclear. The aim of this study is to assess if regular aerobic exercise training improve symptom control in asthma and reduce airway inflammation, systemic inflammation, body composition and RV function.

METHODS AND ANALYSIS

The study is an outcome assessor-blinded, randomised controlled intervention study performed at Centre for Physical Activity Research, Rigshospitalet, Denmark. Forty postmenopausal women with late-onset asthma (>16 years at debut) are recruited from hospitals/practitioners in the region and/or by advertisement. The participants are randomised to either 12 weeks of aerobic exercise three times weekly or usual care.

Objectives

To determine whether 12 weeks of regular high-intensity aerobic exercise changes asthma control in obese, postmenopausal women with late-onset asthma.

Participants

The included patients are women aged 45–75 years and postmenopausal (defined as no menstruation for 6 months, Follicle stimulating hormone (S-FSH) >20 IE/L and P-Estradiol nmol/L<0.09), body mass index (BMI) 25–35 kg/m^2 and have an inactive lifestyle. Further, the patients should have a medical history or a current positive bronchial challenge to methacholine or mannitol, a positive reversibility test to β2-agonist, documented peak flow variation or a positive eucapnic voluntary hyperventilation test. This will be confirmed by a physician at the pulmonary research unit.

Patients screened either from the hospital-based outpatient clinics, out-side hospital outpatients clinics or via advertisement that do not meet the exclusion criteria will be met at visit 1 (table 1) where blood tests will confirm their inclusion. If tests are negative, the subject will be considered a screening failure.

Inclusion criteria

- Late-onset asthma (debut ≥16 years of age).
- Asthma Control Questionnaire (ACQ-5) ≥1.25.
- Daily treatment for asthma (Global Initiative for Asthma (GINA) level 2 and above).
- Age 45–75.
- Postmenopausal defined as no menstruation for 6 months, S-FSH >20 IE/L and P-Estradiol nmol/L<0.09.
- BMI 25–35 kg/m^2.
- Positive bronchial challenge to methacholine, mannitol or positive reversibility to β2-agonist now or historically (within 5 years of screening visit).
- Untrained (no participation in vigorous exercise for more than 1 hour per week during the last 2 months).
- Capable of exercising on a bike.

Exclusion criteria

- Unable to speak and understand Danish or English.
- Current or former smoker (>6 months cessation) with >20 years of daily smoking with 20 cigarettes per day.
- Other respiratory disease of clinical significance (including chronic obstructive pulmonary disease (COPD)).
- Unstable ischaemic heart disease, myocardial infarction within the last 12 months, symptomatic heart failure (ejection fraction (EF) <40%), symptomatic heart arrhythmia (documented with ECG), uncontrolled hypertension (>155/100).
- Any disorder that is not stable and in the opinion of the investigator could affect the safety of the subject throughout the study
- Subjects, who by investigators determination, will not be able to adhere to study protocol.

Intervention

The intervention group will undergo 12 weeks of supervised spinning three times a week for 45 min in the Department of Nutrition, Exercise and Sports, University of Copenhagen. The training will be led by trained instructors with a bachelor of sports science or a bachelor of medicine to secure homogenous quality during the complete 12 weeks. The intensity will be monitored by maximum heart rate using Polar H10 chest bands (Kempele, Finland). The training will follow a protocol regulated by maximum heart rate (HRmax) (figure 1). Participants in both groups will continue their previously prescribed pharmaceutical medication during the whole trial.

Primary outcome

- Change from baseline in ACQ-5.

Secondary outcomes

Change from baseline in:

- Bronchial hyperreactivity to methacholine.
- Airway inflammation measured by fractional exhaled nitric oxide (FeNO) and cell count in sputum.
- Systemic inflammation (hsCRP, inflammatory cytokines, blood eosinophils).
- Right diastolic and systolic heart function (including systolic pulmonary artery pressure estimated from the maximal transtricuspid regurgitant velocity).
- Heart rate variability.

Table 1 Overview of study flow

Time line	Before test day −7 to 0		Before training day 0–14			Training day 15–98	After training day 99–112	
Visit		**0***	**1**	**2**	**3**	**12 weeks**	**4**	**5**
Screening	•							
Signed informed consent form		•						
Interview regarding inclusion- and exclusion criteria			•					
Questionnaires ► ACQ ► MiniAQLQ ► HADS-score ► Nijmegen ► Morinsky			•				•	
Height and weight			•				•	
FeNO			•				•	
Blood samples			•				•	
Spirometry			•				•	
Reversibility test†			•				•	
Metacholine-test‡			•				•	
Sputum			•				•	
DEXA scan			•				•	
VO2max			•				•	
Stress echocardiography				•				•
Heart rhytm evaluation				•				•
Randomisation					•			

*Can be merged with visit 1 if signed informed consent. If more time is needed, visit 1 will be postponed minimum 24 hours.
†Only if unable to perform methacholine test.
‡Demands FEV1 ≥60% of expected, if not, spirometry with reversibility will be performed.
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; DEXA, Dual-energy X-ray absorptiometry; FeNO, fractional exhaled nitric oxide; FEV1, Forced Expiratory Volume in 1 second; HADS, Hospital Anxiety and Depression Scale; VO2max, Maximal oxygen consumption.

- Lung function: Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC).
- Maximal oxygen consumption during an incremental bike ergometer test.

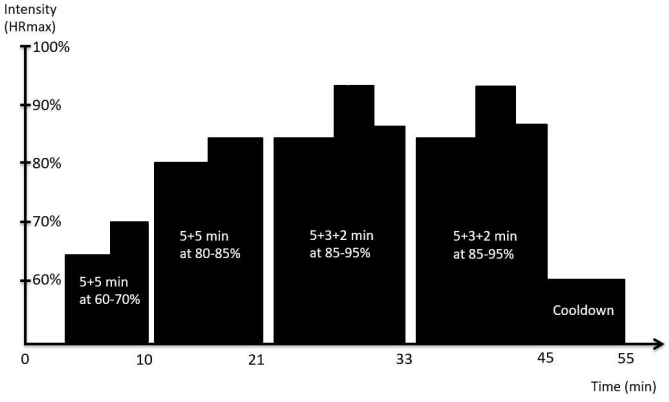

Figure 1 Training protocol displaying the intensitiy and length of each workout session. HRmax, maximum heart rate.

- Body composition (Dual-energy X-ray absorptiometry (DEXA) scan).
- Asthma life quality evaluated by Asthma Quality of Life Questionnaire (mini-AQLQ).
- Hospital Anxiety and Depression Scale (HADS).
- Nijmegen questionnaire for dysfunctional breathing.
- Morinsky Scale.

Study design

This is an outcome assessor blinded, randomised, controlled trial investigating the effect of aerobic exercise on asthma control in postmenopausal women with asthma.

The timeline of the study is as follows (table 1):

Visit 0

- Potential participants are informed about the study orally and in writing.
- The participants are given a minimum of 24 hours to consider their participation in the project before signing the informed consent form. If the patient is

ready to sign the informed consent form at Visit 0 this visit will be merged with Visit 1.

Visit 1

- Interview regarding exclusion and inclusion criteria.
- ACQ-5.
- Mini-AQLQ.
- HADS-score.
- Nijmegen questionnaire.
- Morinsky scale.
- FeNO airway inflammation.
- Blood tests.
- Spirometry (±reversibility test).
- Bronchial challenge to methacholine.
- Sputum extraction.
- Graded cycle exercise test to determine maximal oxygen consumption.

Visit 2

- Stress echocardiography (SE).
- Regular echocardiography.
- Heart monitor.

Randomisation to exercise training or usual care

Patients will be randomised 1:1 to exercise and usual care by a computer-based programme in random block sizes. Randomisation is stratified for ACQ-score (cut-off 1.75) and BMI (cut-off 30) resulting in four strata as seen below. Randomisation is conducted by a non-investigational member of the study group at the Department of Nutrition, Exercise and Sports, University of Copenhagen. Outcome assessors will remain blinded. Unblinding will only happen in case of emergency.

Strata 1: ACQ <1.75 and BMI <30.
Strata 2: ACQ <1.75 and BMI ≥30.
Strata 3: ACQ ≥1.75 and BMI ≥30.
Strata 4: ACQ ≥1.75 and BMI <30.

Measurements at baseline and follow-up

- Basic measurements
  - Weight, height and blood pressure will be measured in all patients.
- Lung function
  - Spirometry including test for reversibility for short-acting β2-agonist is performed with Jaeger Vyntus Spiro with nasal clamp in accordance with international guidelines of standardised spirometry.[21] The full inspiratory and expiratory flow is recorded.
  - Equipment: Jaeger Vyntus Pneumo, Vyaire Medical, Mettawa, Illinois, USA.
- Airway hyper-responsiveness.
  - Bronchial provocation to methacholine is performed as a dosimeter dose-response test using Jaeger Vyntus Pneumo. Maximum cumulated dose is 7368 µmol. A positive test is defined as a reduction of >20% in FEV_1 compared with baseline. Subjects with a prebronchodilated FEV1 <60% will not have the test performed but have reversibility test with β2-agonists performed instead.
  - Equipment: Vyntus APS, Vyaire Medical.
- Body composition
  - A DEXA scan is performed to assess changes in body composition. Sex, age, weight and height are registered.
  - Equipment: Lunar Prodigy Advance; GE Healthcare, Madison, Wisconsin, USA.
- Maximal oxygen consumption
  - At baseline and follow-up, all participants will undergo a standardised graded bicycle ergometer test to evaluated work capacity and maximal oxygen uptake.[22]
  - Equipment: Cosmed Quark, Rome, Italy and Monark 739E, Varberg, Sweden.
- Airway inflammation
  - Sputum sample
    - Performed after procovation with nebulised saline. Collected with the aim of differential count and markers of inflammation. 0.5–1 mL will be collected at baseline and at follow-up (total of maximum 2 mL per participant) to analyse specific cytokines with relevance to asthma and inflammation, for example, Tumor Necrosis Factor (TNF) alfa and Interleukin(IL)-6.
  - FeNO.
    - Measurement of FeNO. The subject inhales air without NO, followed by a 10 s exhalation. The concentration (parts per billion) of NO is measured. Equipment: Analyzer CLD 88 Ecomedics, Duernten, Switzerland
- Cardiac assessment
  - Echocardiography
    - Standard echocardiography (SE) performed by a cardiologist. Description of cardiac anatomy and function at relaxed state.
    - Equipment: Vivid E9 Ultrasound System, GE Vingmed Ultrasound AS, Horten, Norway.
  - SE.
    - SE will be obtained with left lateral tilt performed on a semisupine ergometer both at rest and during moderate-intensity and high-intensity exercise defined as 60% and 85%, respectively, of peak HR measured at cardiopulmonary exercise test Each stage last about 3 min depending on patients echogenicity and respiratory interference. At each stage, different image sets are acquired and stored for each set during exercise. Images are focusing on RV size and function as well as the maximal trans-tricuspid regurgitant velocity.
    - Equipment: Hardware: Vivid E9 Ultrasound System, GE Vingmed Ultrasound AS, Horten, Norway; eBike L ergometer, GE Healthcare, Horten, Norway.
    - Images will be analysed offline using EchoPAC version 113 (Ge Vingmed ultrasound as, Horten, Norway).
  - Heart rhythm monitor

- Subjects undergo a heart rate monitoring for 5 min which will record heart rate variability.
- Equipment: Finapres NOVA, Finapres Medical Systems, Enschede, Netherlands.

Withdrawal of study

Subjects can be withdrawn from the study if they do not adhere to the study protocol. If subjects wish to withdraw during the study, they are free to do so at any time.

Statistical considerations

The number of participants in each group (N=20) is based on a power calculation for the primary outcome which is ACQ score reduction ≥0.5 (SD 0.5) with 0%–20% drop-out and 80%–88% chance of detecting significant difference compared with controls. A reduction in ACQ score by 0.5 is considered clinically relevant.[23] The drop-out rate is expected to be 0%–20% based on a previous Danish exercise study with asthma patients where 16% of patients dropped out.[19]

A blinded individual will perform the statistical analysis. Mixed linear regression models will be used to estimate the effect of training versus control in primary and secondary outcome measures, as well as to assess mediator variables including changes in body composition, inflammation (in the airways or systemically) and RV function and maximal oxygen consumption. Demographic data will be analysed by descriptive statistics. χ^2 will be used for frequency distributions and Student's t-test for continuous variables. Analyses will be performed by the intention-to-treat principle with last observation carried forward in case of drop-out. The software used for statistical analysis will be R V.4.0.[24] A full statistical analysis plan will be uploaded to www.clinicaltrials.gov before data analysis.

Data will be safely collected into REDCap (Vanderbuilt University, Nashville, Tennessee, USA) hosted by Region Hovedstaden. Source data will be stored and once trial is finished double-data entry will be performed. Data will be analysed using R V.3.6.1.

Patient and public involvement

Patients are involved as participants in the current study. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy. We will distribute the results of the study to the Danish Lung Association, Asthma-Allergy Denmark and other relevant patient organisations. Further, we will spread the results among clinicians and health professionals treating adults with asthma.

Safety

Overall, the project does not contain any examinations or tests that are unusual in daily clinical work and the side effects and risk for adverse events are therefore low. All subjects will be thoroughly informed about all known risks before being asked to sign the informed consent form. All tests will be performed either by a physician or trained medical staff to minimise pain, fear and other inconveniences for the subjects. During the intervention, if any adverse events occur they will be registered and handled by an unblinded, non-investigational member of the study group.

Remuneration

None.

DISCUSSION

In asthma, there are patients that have poor symptom control despite being on high levels of inhaled corticosteroids and bronchodilating substances clearly indicating that medical therapies might not be enough to treat all patients with asthma. This study was designed with the aim to investigate if high-intensity interval training with aerobic exercise can increase symptom control in asthma.

The population in focus in this study is obese postmenopausal women with asthma with a history of or current airway hyperresponsiveness. This decision was based on a combination of current knowledge. First, menopause has been associated with negative effects on asthma such as declining lung function, increased non-type 2 inflammation and increased airway hyperresponsiveness.[10 25] Second, a cluster analysis of asthma phenotypes has described the obese woman with asthma with low levels of eosinophilic inflammation and poor response to antiasthma medication.[3] Therefore, in an era of personalised medicine, we hypothesised that this specific patient group could achieve substantial gain by an exercise intervention.

A limitation of our study is that it includes a small number of very specific participants with asthma. This makes the results difficult to interpret in the general asthma population. Further, as participants, by the interventional nature, cannot be blinded there is a risk that participants in the intervention group might act differently after randomisation compared with participants in the control group.

The intention of our study is to provide evidence for whether high-intensity interval training should be recommended to postmenopausal women with asthma. Further, we aim to explore if the possible improvements in disease control are related to objective outcomes such as airway inflammation, systemic inflammation, body composition and RV function of the heart.

Trial status

Patient recruitment commenced in February 2019 and is ongoing.

Ethics and dissemination

The study is approved by Ethics Committee of in Capital Region of Denmark nr. H-18028966 and the Danish Data Protection Agency nr. VD-2019–59. Data will be safely

stored in Epic (Sundhedsplatformen, Verona, Wisconsin, USA) hosted by Capitol Region of Denmark, REDCap (Vanderbuilt University) hosted by the Capitol Region of Denmark. Only data without personal identifiers will be extracted.

All potential trial participants are informed, both orally and in writing by trained study staff, about the purpose of this trial, its process and potential risks, as well as costs and benefits of participation. 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 (online supplemental material 1) 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.

The results of this project are expected to result in a minimum of two original research articles in internationally renowned peer-reviewed scientific journals, besides being presented at national and international meetings and conferences. Procotol amendments will be published on www.clinicaltrials.gov. Finally, the results of the project will be part of the PhD thesis.

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Contributors All authors were involved in designing the project. ESHH developed the first draft of the protocol in collaboration with VB. YH, HKR and MH read, edited and approved the final protocol version before submission. ESHH applied for approvals at the Ethics Committee and the Danish Data Protection Agency. ESHH registered the trial at ClinicalTrials.gov. YH, HKR and MH have read and approved the final version of this manuscript.

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Competing interests None declared.

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