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Non-pharmacological treatments in asthma patients with obesity

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Citation
Türk, Y. (2020, October 13). *Non-pharmacological treatments in asthma patients with obesity*. Retrieved from https://hdl.handle.net/1887/137724

Version:	Publisher's Version
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Cover Page

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Author: Türk, Y.
Title: Non-pharmacological treatments in asthma patients with obesity
Issue Date: 2020-10-13

NON-PHARMACOLOGICAL TREATMENTS IN ASTHMA PATIENTS WITH OBESITY

YASEMIN TÜRK

Non-pharmacological treatments in asthma patients with obesity

Yasemin Türk

COLOPHON

Non-pharmacological treatments in asthma patients with obesity

Y. Türk

Thesis Leiden University Medical Center

ISBN: 978-94-6361-459-7

Layout and printing: Optima Grafische Communicatie, Rotterdam, The Netherlands

The printing of this thesis was financially supported by:

Stichting Bevordering Onderzoek Franciscus

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Non-pharmacological treatments in asthma patients with obesity

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker, volgens besluit van het
College voor Promoties te verdedigen op dinsdag 13 oktober 2020 klokke 15.00 uur

door

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Voor mama en papa

As you start to walk out on the way, the way appears

Rumi (1217-1273)

TABLE OF CONTENTS

Chapter 1	General introduction and outline of the thesis	11
Part A	**Pulmonary rehabilitation in obese asthma patients**	
Chapter 2	Effect of an outpatient pulmonary rehabilitation program on exercise tolerance and asthma control in obese asthma patients *Journal of Cardiopulmonary Rehabilitation and Prevention 2017*	29
Chapter 3	High intensity training in obesity: a meta-analysis *Obesity Science & Practice 2017*	49
Chapter 4	Short-term and long-term effects of a high intensity pulmonary rehabilitation program in obese patients with asthma *European Respiratory Journal 2020*	73
Part B	**Pathophysiology of obesity related asthma**	
Chapter 5	Characterization of inflammation in visceral adipose tissue from obese asthma patients *Submitted*	99
Part C	**Bariatric surgery in morbidly obese asthma patients**	
Chapter 6	Prediction of airflow obstruction and the risk of complications in morbidly obese patients undergoing bariatric surgery *Obesity Surgery 2019*	123
Chapter 7	Pre-surgical pulmonary rehabilitation in asthma patients undergoing bariatric surgery *Obesity Surgery 2017*	135
Chapter 8	Obesity and asthma: very long-term effects of bariatric surgery on lung function and asthma control *Submitted*	149

Part D Summary

Chapter 9 Summary and general discussion 165

Addendum

Nederlandse samenvatting 203

Publications 207

Curriculum Vitae 211

1 General introduction and outline of the thesis

Yasemin Türk, Gert-Jan Braunstahl

De Nederlandse Tijdschrift voor Allergie, Astma en klinische immunologie (NTVAAKI)

1. EPIDEMIOLOGY OF ASTHMA AND OBESITY

Asthma is one of the most common chronic diseases in children and adults. Since the 1980s there has been a worldwide increase in the prevalence of asthma. Over the period 1990-2015, the number of new cases of asthma in the Netherlands doubled, and in 2017 there were an estimated 641.000 patients with asthma (1). This increase in prevalence can be attributed to various factors, including an increased awareness and improved diagnosis of asthma by physicians (1); decreased exposure to microbial pathogens; changes in living environment, such as air pollution and smoking; vitamin D deficiency; and lifestyle factors (diet and overweight) (2-5). Obesity is a global health problem associated with increased morbidity and mortality. In 2016, 49% of the Dutch population had a body mass index (BMI) $\geq$ 25 kg/m^2 and 14% of them had obesity (BMI $\geq$ 30 kg/m^2) (6, 7). Worldwide, at least 2.8 million humans die every year as a result of being overweight or obese (8). Comorbidities associated with obesity include diabetes mellitus type 2 (9, 10), cardiovascular diseases (11), osteoarthritis (12), cancer (13, 14) and pulmonary diseases, such as asthma (15-17).

2. OBESITY ASTHMA ASSOCIATION

Obesity is associated with an increased risk of developing asthma (18-20). Compared to non-obese asthmatics, asthma in the obese is often difficult to control and associated with more asthma-related hospital admissions and a decreased quality of life (21-23). In addition, obese asthmatics respond less often to inhaled corticosteroids (24, 25). Within the group of asthma patients with obesity, there are two distinct phenotypes: the "early onset, T_h2 high" and the "late onset, T_h2 low" asthma phenotype (26). In the "early onset, T_h2 high" phenotype, the asthma starts usually in childhood and is characterized by the presence of allergy and/or (eosinophilic) airway inflammation. Obesity often develops in adulthood due to frequent use of corticosteroids and/or physical inactivity. In this case, the pre-existent asthma is complicated by obesity. The "late onset, T_h2 low" asthma phenotype in patients with obesity is characterized by adult onset of asthma, lower prevalence of allergy and no (eosinophilic) airway inflammation. Especially in this group of patients there is a relative insensitivity to corticosteroids, but despite this, these patients are often treated with high doses of inhaled corticosteroids with side effects as consequence (26-28).

3. OBESITY RELATED ASTHMA

The exact pathophysiology of obesity related asthma is not yet clear, but most likely multi-factorial. Some studies report an association between obesity and sputum neutrophilia in females (29, 30), while other studies found no evidence of more airway inflammation in obese asthmatics compared to obese controls (31, 32). There are multiple mechanisms described concerning the relationship between asthma and obesity.

1. Mechanical changes in lung function. As a result of an increased mass around the chest wall and in the abdomen, a restriction and a decrease of lung compliance occurs. This results in a decreased expiratory residual volume (ERV) and a decreased functional residual capacity (FRC). A decreased ERV and FRC is associated with an expiratory airflow limitation and an increased airway resistance (15, 16, 33).

2. Comorbidities like gastro-oesophageal reflux disease (GERD) and obstructive sleep-apnea (OSA) are associated with both asthma and obesity. The prevalence of OSA is higher in normal weight patients with an uncontrolled asthma, as well as in obese patients. Obesity is a risk factor for GERD, which in turn is a risk factor for asthma (34, 35).

3. Consumption of a high fat diet ("a western diet") is associated with increased airway inflammation. In addition, it has been shown that four hours after consumption of a high fat meal, there is a significant increase in the number of neutrophils in sputum (36-38). In contrast, a reduced fat intake and increased consumption of fruit and vegetables are associated with a reduction of airway inflammation (38-41).

4. Obesity-related changes in gut microbiota may contribute to the etiology of obesity-related asthma via e.g. alterations in production of metabolites with direct effects in the lung, such as short-chain fatty acids (SCFAs); through contribution to systemic inflammation via changes in host metabolism and insulin sensitivity; or alteration of the immune system, in particular IL-17A^{+} immune cells (42). It is conceivable that obesity also has a direct effect on the lung microbiome. A higher concentration of lipids and glucose in the lung as a result of obesity might create an environment that permits some micro-organisms. In addition, atelectasis of the lower airways in obesity will create an hypoxic environment that affects bacterial survival (43, 44)

5. Obesity is associated with a low-grade systemic inflammation characterized by increased production of pro-inflammatory cytokines, like interleukin 6 (IL-6), tumour-necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-12 (IL-12) (45). This inflammation is mediated by an increase in the number of pro-inflammatory (M1)

macrophages in the visceral adipose tissue compared to normal adipose tissue that contains predominantly anti-inflammatory and regulatory (M2) macrophages (46, 47). This phenotypic switch of macrophages in visceral adipose tissue plays an important role in the development of obesity-related diseases and could also play a role in the development of asthma in obese individuals. A recent study found a higher percentage of pro-inflammatory (M1) macrophages in visceral adipose tissue of obese asthmatics compared to non-asthmatic obese subjects (48).

6. The visceral fat tissue secretes various adipokines, like leptin and adiponectin. Leptin is a hormone that plays an important role in the regulation of appetite and satiety. In addition, leptin causes upregulation of pro-inflammatory cytokines (49). Adiponectin is a hormone that is mainly involved in insulin sensitivity. It has in particular anti-inflammatory effects: it reduces the expression and release of pro-inflammatory cytokines and increases production of anti-inflammatory cytokines (50). An imbalance in the leptin/adiponectin ratio plays an important role in the development of diabetes mellitus type 2 (51). In addition, also bronchial epithelial cells express leptin (52). Furthermore, Sideleva et al. have shown that there is an increased expression of adiponectin receptor-2 and T-cadherin (binds adiponectin) in bronchial epithelial cells of obese asthma patients compared to obese controls (32). Also, an increased leptin and reduced adiponectin level was found in the BAL fluid of obese patients with asthma (32).

4. PHYSICAL (IN) ACTIVITY

Physical inactivity is not only associated with overweight and obesity, it is also an independent predictor of mortality (53). The World Health Organization recommends at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity (54). However, this is not achieved by most asthmatics. Compared to healthy controls, asthma patients make significantly less steps and spend less time at vigorous intensity activity per day. This is correlated with the level of asthma control, since asthmatic patients with worse asthma control participate less frequently in intensive physical activity (55). The majority of the adults with obesity are not able to achieve this target either due to different barriers, such as lack of motivation, lack of time and physical limitations (56-59). In addition, psychological factors like depression, anxiety and body image dissatisfaction are important limitations in people with obesity that prevent them from exercising in public (60). Moreover, obese patients with asthma have lower exercise tolerance compared to non-obese patients with asthma (61)

5. NON PHARMACOLOGICAL INTERVENTIONS IN ASTHMA AND OBESITY

Phenotyping asthma is the first important step in the treatment of asthmatics with obesity, especially to determine which patients might benefit from treatment with (higher dose) corticosteroids. Regardless of the phenotype, it is clear that obesity has a negative impact on the symptoms of asthma. That is why weight loss remains an important intervention, which is expected to result in improvement of symptoms. Different interventions are available to achieve weight loss and the appropriate intervention should be selected for each obese asthma patient based on personal characteristics. Unfortunately, the number of randomized trials with a weight loss intervention in asthma patients with obesity is limited.

5.1 Medication assisted weight loss

There are some pharmacological options for weight loss. Orlistat (tetrahydrolipstatin) binds to gastric and pancreatic lipase and decreases the absorption of triglycerides in the gastrointestinal tract by 30% (62). In the Netherlands, the use of orlistat is allowed for support of lifestyle changes in the treatment of obesity (BMI $\geq$30 kg/m^2 or BMI $\geq$ 28 + co-morbidities). Several studies have shown that the use of orlistat in addition to lifestyle intervention (diet + exercise) leads to significantly more weight reduction (2-4 kg) compared to placebo when it is used for 1-2 years. In addition, it leads to a better lipid profile and better glucose regulation (63, 64). Adverse events of orlistat are mainly gastro-intestinal, such as steatorrhoea. No data are available on the long-term effects of orlistat concerning weight loss, side effects or morbidity (64). Sibutramine inhibits the re-uptake of norepinephrine and serotonin, resulting in increased satiety and reduced food intake. It has been shown that Sibutramine in combination with a hypocaloric diet leads to significantly more weight loss compared to a hypocaloric diet with placebo (65). In the European Union, the use of Sibutramine has been banned since 2010 after it became known that subjects using Sibutramine had a higher risk of serious cardiovascular adverse events (66). In obese asthmatics, there is only one study using a combined intervention of caloric restriction and use of Sibutramine and Orlistat during 6 months. A weight loss of 7.5% was seen in the intervention group. This was equal to a decrease in BMI of 5.3 kg/m^2 compared to a decrease of 0.46 kg/m^2 in the control group (no intervention) (67). Orlistat has small effects on the short-term, but long-term effects are lacking.

5.2 Dietary and exercise intervention

In recent years, there has been increasing attention for weight loss interventions in asthmatics with obesity. A hypocaloric diet (1760 kj) during 8 weeks in asthmatic patients with a BMI $\geq$30 kg/m^2 resulted in significant weight loss, a decrease of asthma symptoms

and an improvement in lung function (FEV_1 and FVC) both at short-term and during one year of follow-up (68). The study of Scott et al. (40) was the first randomized controlled trial in obese patients with asthma comparing a dietary intervention with exercise alone and a combined dietary-exercise intervention. This study has shown that exercise alone without a dietary intervention is not effective to reduce weight or improvement of asthma symptoms. In addition, it was shown that a weight reduction of 5-10% is sufficient to result in clinically relevant improvements in asthma control and asthma related quality of life. The mean weight loss was 8.3% after 10 weeks of intervention, including a very strict caloric restriction of 885-1170 kcal/day and an exercise program with aerobic and resistance training (40). More recently, a study by Freitas et al. (69) has been published. In this study, obese asthmatics were randomized between a 3-month lifestyle intervention with or without exercise. The lifestyle intervention consisted of an informative session, a diet (caloric-restriction of 1300 kcal/day) and an exercise program (aerobic and strength) or sham-exercise (breathing exercise). The lifestyle intervention resulted in significant weight loss and improvements in asthma control, exercise capacity, lung function, airway and systemic inflammation (69). The above-mentioned studies demonstrate that a combined lifestyle intervention is effective at short term. The long-term effects of such interventions are not well known because the follow-up duration in these studies is no longer than 6 months. In general, the long-term effects of such lifestyle interventions are disappointing as most patients fall back into old habits soon. A longer follow-up of patients and the use of eHealth could probably be useful to encourage patients to maintain their diet and exercise for a longer period. However, the role of such innovative approaches in the management of asthma and obesity has not yet been investigated yet. In addition, it is not known which type of diet and exercise intervention is the most effective and safe in obese asthma patients. Although, the above-mentioned studies have included asthmatic patients with a mean BMI $\geq$ 30 kg/m^2, the proportion of patients with morbid obesity (BMI $\geq$ 40 kg/m^2) is low. The question is whether this type of lifestyle intervention is feasible and effective in this group of patients. As the intended amount of weight loss is higher, a longer intervention period with an adapted diet and exercise program may be needed. On the other hand, bariatric surgery could be an alternative treatment of these morbidly obese patients with asthma. (70).

5.3 Behavioural therapy

The goal of behavioural therapy in the treatment of obesity is to prevent relapse in an unhealthy lifestyle. A recent meta-analysis showed that behavioural treatment had positive effects on adherence to lifestyle intervention programs and physical activity in adults with obesity (71). In addition, cognitive behavioural therapy in persons with obesity is associated with significant weight loss and a reduction of eating disorders, anxiety and depression (72). In asthma patients with obesity, the effect of behavioural

therapy on weight loss and asthma control has not been investigated yet. Often, a form of behavioural therapy is used as a part of a lifestyle intervention with diet and exercise. In these studies, it is not possible to determine the contribution of behavioural therapy alone to the outcome. In a recent study, a lifestyle intervention with a hypocaloric diet and exercise was combined with cognitive behavioural therapy, using strategies such as self-monitoring, action planning and goal setting to help participants achieve weight loss and improve asthma control. Although, the intervention group had significant weight loss, there was no measurable effect on asthma control (73). Also, in this study the individual contribution of behavioural therapy cannot be determined. However, it is plausible that (cognitive) behavioural therapy can contribute to weight loss and improving asthma control by more insight and improved self-management skills at the long and short term.

5.4 Bariatric surgery

Bariatric surgery is a proven effective and sustainable treatment of morbid obesity. Procedures like "gastric sleeve" and "gastric bypass" have been performed more frequently in recent years and result in drastic weight loss with improvement of obesity-related co-morbidities, such as hypertension and type 2 diabetes mellitus (74). In addition, bariatric surgery has also been shown to improve asthma control, lung function (especially lung volumes) and bronchial hyperresponsiveness in morbidly obese patients with asthma (74-77). Furthermore, one study showed a significant improvement in peripheral airway resistance (R_5-R_{20}) after bariatric surgery in morbid obese asthmatics compared to morbid obese controls (70). This may indicate that the small airways play an important role in the pathophysiology of obesity-related asthma. Bariatric surgery results in a significant decrease of systemic inflammation, but there is no evidence for reduction of inflammation in the airways in asthma patients after bariatric surgery (70). Given these positive effects, bariatric surgery could be a solution for obese patients with asthma. In the Netherlands, bariatric surgery is only applicable in cases with morbid obesity (BMI $\geq$ 40 kg/m^2) or in subjects with a BMI above 35 kg/m^2 in combination with specific obesity-related comorbidity such as diabetes mellitus type 2, hypertension and obstructive sleep apnoea which excludes most asthma patients with a BMI between 35-40 kg/m^2 from access to this procedure. However, given the recent positive results of bariatric surgery in asthma patients, this procedure could become accessible for obese asthmatics in the near future. It is important to have the right expectations regarding the improvement in asthma symptoms. Again, the asthma phenotype is an important predictor. For example, a number of studies have shown that after bariatric surgery, bronchial hyperresponsiveness and airway resistance decrease particularly in obese asthma patients with low IgE and not in obese patients with high IgE (74, 77).

5.5 Treatment of comorbidities

Both asthma and obesity are associated with a number of co-morbidities. Obesity is a risk factor for obstructive sleep apnea (OSA), and the incidence of OSA is higher in patients with severe asthma (35). In addition, symptoms of OSA, such as fatigue and sleepiness, can impede proper rehabilitation/lifestyle intervention. Gastro-oesophageal reflux is another condition that occurs frequently in obesity, and is a risk factor for asthma (34). Early detection and treatment of these disorders could contribute to the optimal treatment of obese asthma patients.

OUTLINE AND AIM OF THIS THESIS

In this thesis, we focussed on the management of obese patients with asthma. Based on the available knowledge about the obesity and asthma relationship, and the effects of different weight loss interventions in obese asthmatics, we defined the following aims for this thesis:

1. To gain insight in the effects of exercise training in obese asthmatics and to determine the feasibility and effects of high intensity training in obese subjects
2. To design a pulmonary rehabilitation program for obese patients with suboptimal controlled asthma and to determine the effectiveness of this program in a randomized controlled trial
3. To improve our knowledge on the pathophysiology of obesity related asthma
4. To gain insight in the risks and long-term effects of bariatric surgery in morbidly obese subjects with asthma.

In **chapter 2** of this thesis the results of a retrospective observational study on the effects of pulmonary rehabilitation in obese patients with asthma are described. The improvements in asthma control and exercise capacity are compared to a group of non-obese patients with asthma. Next, a systematic review and meta-analysis on the effects of high intensity (interval) training in subjects with obesity is performed and described in **chapter 3**. With the knowledge of the effects of high intensity training in the obese, an adapted pulmonary rehabilitation program for obese asthmatics was designed. The effects of this 12-week rehabilitation program on asthma features, lung function, exercise capacity and inflammatory parameters are reported in **chapter 4.** In the second part of this thesis, we focussed on morbidly obese asthma patients. In **chapter 5,** we describe a cross-sectional study about inflammation in visceral adipose tissue of morbidly obese asthmatics compared to morbidly obese controls. In **chapter 6**, a validation study is presented about prediction of airflow obstruction and the risk of complications in morbidly obese patients undergoing bariatric surgery. In **chapter**

7, we present a case-control study with morbidly obese asthma patients participating in a 3-month pulmonary rehabilitation program before undergoing bariatric surgery. In **chapter 8,** a follow-up study is presented, evaluating the long-term effects of bariatric surgery on weight, asthma control and lung-function in morbidly obese patients with asthma and morbidly obese controls. Finally, in **chapter 9** we will reflect on, and discuss, the most important findings of this thesis. Concluding remarks and future perspectives are provided for clinical practice and future research.

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Part A

Pulmonary rehabilitation in obese asthma patients

2

Effect of an outpatient pulmonary rehabilitation program on exercise tolerance and asthma control in obese asthma patients.

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Journal of Cardiopulmonary Rehabilitation and Prevention, 2017;37:214-222

ABSTRACT

Objective: To compare the effects of an outpatient pulmonary rehabilitation (PR) program on exercise tolerance and asthma control in obese and non-obese patients with asthma.

Methods: Non-obese (body mass index [BMI] < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) patients with asthma who participated in a local multidisciplinary 12-week PR program were analyzed retrospectively. Effects of PR were assessed by changes in 6-minute walking distance (6MWD) and Asthma Control Questionnaire (ACQ).

Results: A total of 138 asthma patients were included: 53 (38.4%) obese and 85 (61.6%) non-obese. At baseline, obese patients with asthma had a lower level of exercise tolerance reflected by a lower 6MWD (525 m vs 621 m; $P < .001$). After PR, the 6MWD improved significantly in both groups (≥ 50 m in non-obese vs ≥ 45 m in obese; $P < .001$ in both groups). The improvement in 6MWD was clinically relevant in 71% of the non-obese and 60% of the obese patients. These patients had lower 6MWD ($P = .024$), higher usage of long-acting β -agonist ($P = .034$) and oral corticosteroids ($P = .033$). Asthma control also improved in both groups (Δ ACQ − 0.3 in non-obese vs Δ ACQ − 0.4 in obese; $P = .021$ and $P = .019$, respectively). Clinically relevant improvement was achieved by 46.5% of non-obese and 51.9% of obese patients with asthma. The improvements between the groups were not statistically different.

Conclusions: A standardized PR program is feasible in obese patients with asthma and they benefit as much as non-obese patients with asthma. However, there are still a large number of patients who show no clinically significant improvement. Especially patients with more severe asthma seem to benefit the most from PR.

INTRODUCTION

Epidemiological and clinical studies indicate that obesity increases the risk of asthma (1, 2) and is related to the severity of asthma (3). Compared to lean asthma patients, obese asthma patients have a lower peak flow, a greater need of inhalation medication and more often uncontrolled asthma (4-6). Physical inactivity can be an important consequence of having asthma (7). On the other hand, studies suggest also that reduced physical activity is an independent risk factor for the development of asthma (8, 9). Furthermore, physical inactivity is a major risk factor for obesity as well. Since obesity and physical inactivity are both important risk factors for disease severity of asthma, a lifestyle intervention program with a multifactorial approach could be a useful intervention in the treatment of obese asthmatics. Several studies have shown that physical training in lean asthma patients led to improvement in clinical outcomes (10-14). In theory, the multidisciplinary character of pulmonary rehabilitation (PR) provides an ideal setting to address the needs of individuals with lung disease in whom obesity is also contributing to functional limitation (15). However, only limited data are available on the benefits of PR in obese patients with asthma and on the need for obesity-specific adaptations to existing PR programs. The aim of the present study was to compare the effect of a regular outpatient PR program on exercise tolerance and asthma control in obese and non-obese patients with asthma.

METHODS

Design and Patients

This study was a retrospective cohort study. Medical records of asthma patients referred by their pulmonologist to the out-patient pulmonary rehabilitation program of the Franciscus Gasthuis in Rotterdam (The Netherlands) from January 2009 to September 2014 were analysed retrospectively. Patients between the age of 18-55 year were included based on an asthma diagnosis according to the GINA guidelines (16) and if they had completed the patient assessment before the start of PR. Patients above 55 years of age were excluded to minimize the effect of comorbidities like Chronic Obstructive Pulmonary Disease (COPD) and cardiovascular comorbidities. Patients who actively smoked were excluded from participation of the PR program.

The patient assessment prior to the start of the PR program consisted of a lung function test, a cardiopulmonary exercise test (CPET), six minute walking test (6MWT), body composition measurement and the asthma control questionnaire (ACQ). Also, all patients were seen by the pulmonary nurse for optimization of the inhalation technique. At the

end of the PR program, the 6MWT and the ACQ were repeated to evaluate the effects of PR. Patients were classified as completers if they followed at least 70% of the sessions and if there was an outtake with a 6MWT.

Pulmonary function testing

Pulmonary function testing was performed with the Vmax spirometer (Vmax Encore 22D, Carefusion) and bodybox (Vmax encore 62j, Carefusion). Only post-bronchodilator values of the forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, Total lung capacity (TLC) and residual volume (RV) were assessed. Values were expressed as a percentage of predicted (17).

Body composition

Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). Obesity was defined as a BMI equal or greater to 30 kg/m_2. Fat free mass (FFM) was measured with a bioelectrical impedance meter (Bodystat 1500, Bodystat Limited) and expressed as FFM-Index by dividing FFM by the square of height in meters (kg/m^2).

Assessment of asthma control

The level of asthma control was assessed by the Asthma Control Questionnaire (ACQ-6) (18). The ACQ is a validated standardised questionnaire for measurement of asthma control. It comprises 6 questions with different components of daytime symptoms and night time symptoms.

Exercise tests

Cardiopulmonary exercise testing was performed on an Ergoselect cyclometer (Ergoline, Bitz, Germany) using a maximal symptom limited cardiopulmonary incremental protocol according to recommendations of the ATS/ACCP guidelines (19). The six-minute walking test (6MWT) was performed indoor using a 30 m walking course. Patient preparation and measurements were performed according to the ATS/ERS statement (20).

PR program

The PR program was a multidisciplinary, out-patient program of 12 weeks. Participants took part in an indoor training session for 3 x 1 hr/week. Each session consisted of a 60 minutes work-out (30 minutes cardio/30 minutes strength training) under the supervision of a physiotherapist. Main components of training were cycling on an ergometer, walking on a treadmill, rowing on a rowing machine and muscle strength training (squats and chinlift). Every patient received an individual training scheme, the intensity and duration of each exercise were based on parameters like VO_{2max}, anaerobic

threshold and Borg scores. In general, the intensity of the training was just below the anaerobic threshold during 4 minutes alternated with high intensity (VO_{2max}) during 1 minute. Strength training was based on van Goolberg's strength rehabilitation system (KRS- Krachtrevalidatie systeem) (21). Furthermore, there were four educational sessions of 60 minutes given by the psychologist, the dietician, the social worker and the pulmonary nurse. The aim of these sessions was to gain more insight into asthma and to educate a healthier lifestyle. Individual counseling by these disciplines took place if there was an indication. Every week, the progress of the participants was discussed in a multidisciplinary team, which was led by a pulmonologist.

Statistical analyses

Differences between the patients who dropped out from the PR program and patients who completed the PR program were compared. Next, patients were divided in two groups based on their BMI (< 30 kg/m^2 and ≥ 30 kg/m^2). The baseline characteristics of the two groups (dropped-out/completed and obese/non-obese) were compared by use of chi-square test for categorical variables and the Mann Whitney U test for continuous variables with skewed distributions. Categorical data were presented as percentages and continuous variables were summarized as median values with interquartile ranges (IQR). Outcome parameters were the change of six minute walking distance (6MWD) and ACQ after PR. The change in 6MWD and ACQ (Δ = post-PR minus pre-PR values) within each group was analyzed by the Wilcoxon signed rank test for paired measurements. To compare the paired changes between the two groups, the Wilcoxon rank sum test was used. A minimal clinical important difference (MCID) of 0.5 for the ACQ and 30 m for the 6MWD was considered clinically relevant (18, 22).

We used a multiple linear regression analysis to determine the variables associated with the ACQ and 6MWD after PR. The dependent variables were the ACQ and 6MWD after the PR program; the covariables were the ACQ and 6MWD before the start of PR, BMI, VO_{2max} and FFMI. We first performed univariate regression analysis and then we analyzed the impact of the covariables on the ACQ and 6MWD after PR in enter and backward stepwise procedures. We also adjusted for interaction effects of the ACQ and 6MWD before PR with obese/non-obese. A p-value (2-sided) < 0.05 was considered to indicate a statistically significant difference in all comparisons. Correlations between different variables with BMI and 6MWD were performed by the use of Spearman correlation analyses. SPSS version 18 (IBM, Armonk, NY) was used for all statistical analysis.

RESULTS

Baseline Characteristics

A total of 627 patients were referred to PR between January 2009 and September 2014. Of the 227 patients with the diagnosis of asthma, 138 (60.8%) met the inclusion criteria of this study. Of the excluded patients, 18% did not met the GINA guidelines, 4.5% did not complete the patient assessment before the start of PR and 77.5% of the excluded patients were older than 55 years.

Of the 138 included patients, 112 (81.2%) completed the PR program. There was no differences in age, weight or BMI between the patients who dropped out or completed the PR program. However, patients who dropped out had a significantly lower vital capacity (93.5% vs. 103%, p=0.018), lower total lung capacity (93% vs. 96%, p= 0.030) and a lower 6MWD at baseline (522 m vs. 600 m, p=0.018). In addition, patients who dropped out of the PR program had significant higher ACQ scores before the start of PR compared to patients who finished the PR program (2.9 vs. 1.9, p=0.042). Fifty-three (38.4%) of the included patients had a BMI ≥ 30 kg/m^2 and were classified as obese, and 85 patients (61.6%) had a BMI < 30 kg/m2 and were classified as non-obese. There were no significant differences in baseline characteristics including lung function or smoking status between the two groups (table 1). All patients were treated with inhalation corticosteroids (ICS) and there was no difference in the use of long-acting beta-2-agonists (LABA) or other concomitant medication between the groups. Also, asthma control was comparable between obese and non-obese group before PR. However, patients in the obese group had a lower relative maximal exercise capacity compared to the non-obese group. In addition, the median 6MWD was significant higher in non-obese patients compared to their obese counterparts (Table 1).

Outcome after PR

Following the 12 weeks of PR program, both groups showed a significant increase in 6MWD (median ≥50 m [IQR 15-84 m] in the non-obese group (p< 0.001) vs. +45 m [IQR 13-77 m] in the obese group (p<0.001)) (figure 1). The improvement in obese subjects did not differ significantly from that in non-obese subjects (univariate comparison, p=0.496). The improvement in 6MWD was clinically relevant in 70.8% of the non-obese and 60.4% of the obese patients (p=0.378). Patients who did achieve the MCID of ≥30 m had a significant lower 6MWD (p=0.024), higher usage of LABA (p=0.034) and oral corticosteroids (p=0.033) at baseline (table 2). Subgroup analysis showed that obese patients who improved ≥ 30 m (n=26) had a significant lower relative VO_{2max}, a lower 6MWD and a higher Borg score for dyspnea compared with obese patients without clinically relevant improvement (n=17) (table S1, table S2). Multiple linear regression analysis showed that

of the variables BMI, VO_{2max}, ACQ (before PR) and 6MWD (before PR), only 6MWD (before PR) was an independent predictor of 6MWD after PR (β=0.699; 95% CI 0.578-0.820, p< 0.001); R^2=0.78, p< 0.001).

Table 1. Baseline characteristics of study participants[a]

	Non-obese asthma (n=85)	Obese asthma (n= 53)	p-value
Age (y)	42 [33-50]	45 [39.5-50.5]	0.211
Female/male (%)	65.8/34.2	71.7/28.3	0.476
Weight (kg)	75.1 [65.0-81.5]	103.6 [89.8-113.5]	**<0.001**
BMI (kg/m^2)	25.4 [23.2-28.0]	35.0 [32.0-36.8]	**<0.001**
FFMI (kg/m^2)	16.0 [14.7-17.2]	18.9 [17.6-21.0]	**<0.001**
Allergic/non-allergic/unknown (%)	70.6/24.7/4.7	60.4/34.0/5.6	0.459
Current smokers/ former smokers/never smokers (%)	0/41.2/58.8	0/47.2/52.8	0.490
Medication use n (%)			
o ICS	85 (100%)	53 (100%)	
o LABA	75 (88.2%)	47 (90.4%)	0.696
o SABA	17 (20.0%)	12 (23.1%)	0.669
o Anticholinergic	34 (40.0%))	27 (51.9%)	0.173
o Oral corticosteroids	6 (7.1%)	3 (5.8%)	0.767
FEV_1 (% predicted)	90 [80-102.5]	90 [77.5-97.5]	0.684
FEV_1/FVC (%)	78 [71-82]	78 [71-83]	0.868
TLC (% predicted)	99 [89.0-109.0]	95 [89.8-107.3]	0.343
RV/TLC	31.0 [24.8-35.7]	30.4 [25.0-35.0]	0.957
PI_{max} (% predicted)	111 [97.0-128.0]	109 [95.0-131.5]	0.784
Relative VO_{2max} (% predicted)	69.5 [57.1-80.1]	50.8 [43.2-59.1]	**<0.001**
Absolute VO_{2max} (% predicted)	76.0 [65.0-92.0]	82.0 [68.0-94.0]	0.412
6MWD (m)	621.0 [546.0-685.0]	525.0 [455.0-597.5]	**<0.001**
Borg dyspnea rating[b]	4.0 [3.0-5.0]	5.0 [3.0-7.0]	0.079
Borg fatigue rating[c]	4.0 [3.0-5.0]	4.0 [3.0-7.0]	0.125
ACQ score	1.9 [1.4-2.8]	2.2 [1.5-3.3]	0.144

Abbreviations: ACQ, Asthma Control Questionnaire; BMI: body mass index; FEV_1, forced expiratory volume in 1 second; FFMI, fat-free mass index; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; 6MWD, 6-minute walk distance; PI_{max}, maximal inspiratory pressure; RV/TLC, ratio between residual volume and total lung capacity; SABA, short acting β-agonist; TLC, total lung capacity; VO2max, maximal oxygen uptake;

[a]Continuous variables are reported as median [interquartile range] and categorical data are reported as noted.

[b]Dyspnea score after 6-minute walk test

[c]Fatigue score after 6-minute walk test

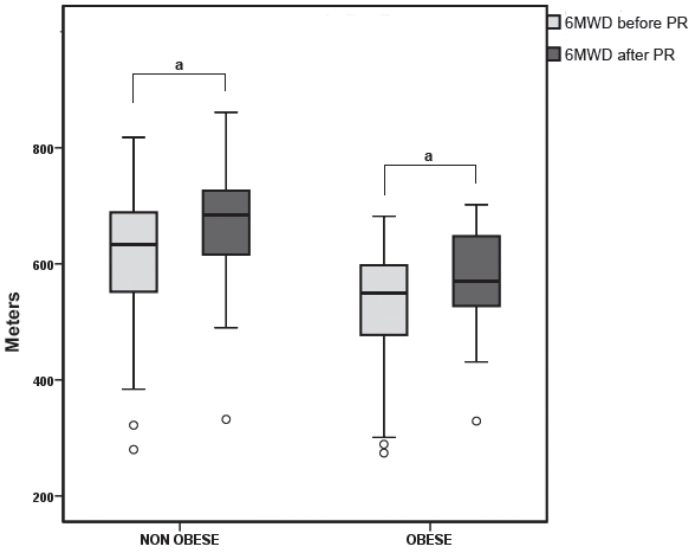

Figure 1. Change in 6MWD after PR for both groups in meters. Box represents the median 6MWD with the IQR. Whiskers represent the highest and lowest data within 1.5 IQR of the lower and upper quartiles. IQR indicates interquartile range; 6MWD, 6-minute walk distance; PR, pulmonary rehabilitation. a $P < .001$.

Pre- and a post-ACQ scores were available from 70 of the 112 patients who completed the PR program (63% of the non-obese and 61% of the obese group). The median ACQ before PR was 2.17 (IQR 1.42-3.24) in the obese and 1.83 (IQR 1.3-2.6) in the non-obese group. After PR, ACQ improved significantly in both groups (ΔACQ -0.4, p= 0.019 in the obese and ΔACQ -0.3, p=0.021 in the non-obese; figure 2). A MCID of 0.5 in ACQ was achieved by 20 of the 43 non-obese (46.5%) and 14 of the 27 obese patients with asthma (51.9%, p=0.546). There were no differences in patient-related problems (physical, exacerbations and psychological) during PR between patients with and without clinically relevant improvement in the 6MWD (table S3) and ACQ (table S4). At the end of the PR, there was no significant difference in the ACQ between the two groups (figure 3; univariate comparison p=0.944). Multiple linear regression analysis showed that of the included variables, only ACQ (before PR) was a significant predictor of ACQ (after PR) (β=0.821; 95% CI 0.619-1.022, $p < 0.001$; R^2=0.47, p<0.001).

Association between BMI and clinical parameters

There was no significant correlation between the BMI and FEV_1 (r=-0.158, p=0.063), but inverse correlations were found for BMI with the 6MWD (r=-0.521, p<0.001) and the relative VO_{2max} (r=-0.568, p< 0.001) (figure 4). There were also no significant correlations between the BMI and ACQ or improvements in ACQ and 6MWD.

Table 2. Characteristics of patients with and without clinical significant improvement in 6MWD (≥30 m)

	Δ 6MWD <30 m (n=38)	Δ 6MWD ≥30 m (n=72)	p-value
Age (y)	43.5 [37.5-47.0]	45.5 [37.0-51.0]	0.212
Female/male (%)	71.1/28.9	70.8/29.2	0.981
Weight (kg)	79.2 [64.6-105.0]	83.3 [73.9-95.7]	0.416
BMI (kg/m^2)	29.0 [23.4-34.3]	28.8 [25.7-33.2]	0.631
FFMI (kg/m^2)	16.7 [15.1-19.4]	17.4 [15.7-18.8]	0.711
Allergic/non-allergic/unknown (%)	65.8/28.9/5.3	66.7/26.4/6.9	0.917
Current smokers/ former smokers/never smokers (%)	2.6/47.4/50	0/41.7/58.3	0.302
Medication use n (%)			
o ICS	38 (100%)	72 (100%)	0.466
o LABA	32 (84.2%)	69 (95.8%)	**0.034**
o SABA	9 (23.7%)	13 (18.1%)	0.483
o Anticholinergic	14 (36.8%)	29 (40.3%)	0.725
o Oral corticosteroids	0 (0%)	8 (1.1%)	**0.033**
FEV_1 (% predicted)	94.5 [87.0-104.3]	88.0 [72.5-101.0]	0.090
FEV_1/FVC (%)	77 [72-83.3]	77 [66.8-82.0]	0.403
TLC (% predicted)	102.5 [90.5-111.3]	98.0 [89.0-108.0]	0.216
RV/TLC	29.0 [25.4-32.5]	32.0 [26.4-36.77]	0.100
PI_{max} (% predicted)	109 [91.5-126]	109 [91.5-126]	0.634
Relative VO_{2max} (% predicted)	63.7 [52.1-77.3]	61.6 [48.7-61.6]	0.451
Absolute VO_{2max} (% predicted)	80.5 [66.0-94.0]	79.5 [67.8-94.5]	0.955
6MWD (m)	619 [550-688]	596 [482-639]	**0.024**
6MWD (% predicted)	85 [80-90]	80 [70-87]	**0.009**
Borg dyspnea[b]	4.0 [3.0-5.0]	4.0 [3.0-7.0]	0.235
Borg fatigue[c]	4.0 [3.0-5.0]	4.0 [3.0-6.0]	0.332
ACQ score	1.8 [1.3-3.0]	2.1 [1.6-2.7]	0.263

Abbreviations: ACQ, Asthma Control Questionnaire; BMI, body mass index; Δ, delta or change; FEV_1, forced expiratory volume in 1 second; FFMI, fat-free mass index; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; 6MWD, 6-minute walk distance; PI_{max}, maximal inspiratory pressure; RV/TLC, ratio between residual volume and total lung capacity; SABA, short acting β-agonist; TLC, total lung capacity; VO_{2max}, maximal oxygen uptake;

[a]Continuous variables are reported as median [interquartile range] and categorical data are reported as noted.

[b]Dyspnea score after 6-minute walk test

[c]Fatigue score after 6-minute walk test

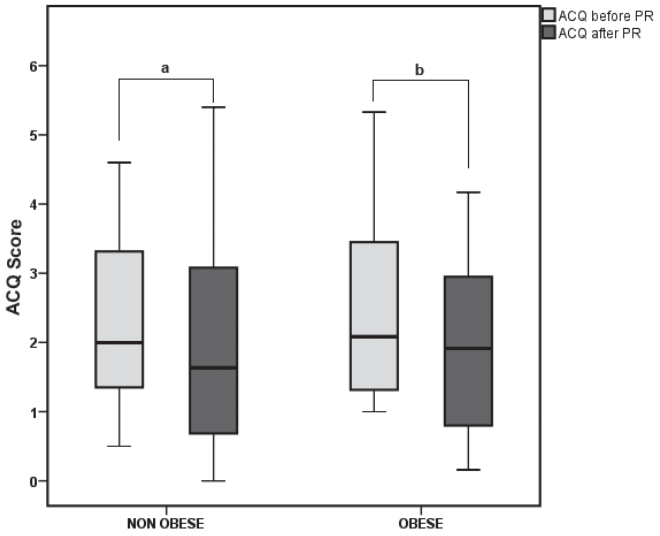

Figure 2. Improvement of ACQ after PR for both groups. Box represents the median ACQ with the IQR. Whiskers represent the highest and lowest data within 1.5 IQR of the lower and upper quartiles. ACQ indicates Asthma Control Questionnaire, IQR indicates interquartile range; PR, pulmonary rehabilitation. a $P = .021$; b $P = .019$.

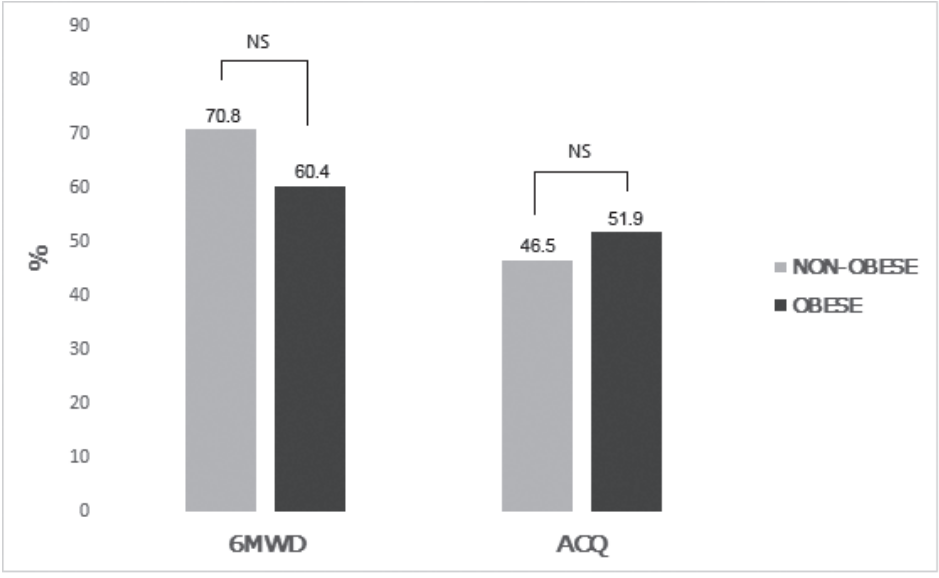

Figure 3. Percentage of patients with a clinical relevant improvement in 6MWD and the ACQ score. ACQ indicates Asthma Control Questionnaire; 6MWD, 6-minute walk distance.

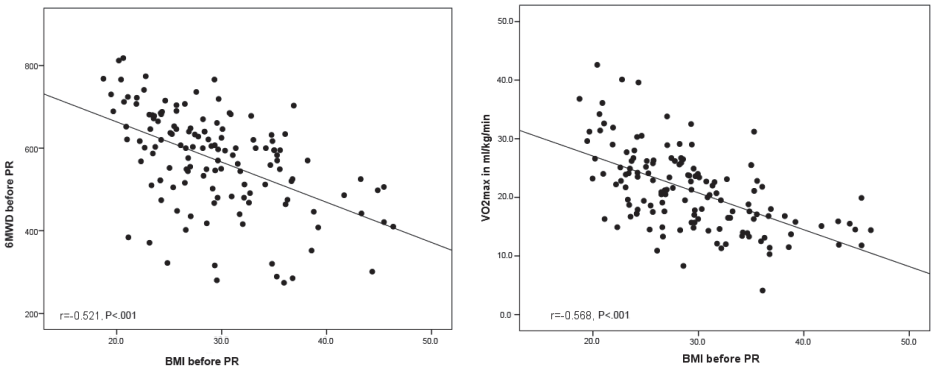

Figure 4. Correlations between BMI with baseline 6MWD (a) and VO_{2max} (b) in the study population ($P <$ .001). BMI indicates body mass index; 6MWD, 6-minute walk distance; PR, pulmonary rehabilitation; VO_{2max} , maximal oxygen uptake.

Association between 6MWD and clinical parameters

There was a correlation between the baseline FEV_1 with the 6MWD at baseline (r=0.481, p<0.001). The VO_{2max} correlated significantly with baseline 6MWD (r=0.505, p< 0.001). The ACQ correlated weakly with the 6MWD (r =-0.359, p< 0.001) (figure 5). ΔACQ and Δ6MWD were not correlated (r=-0.102, p=0.407).

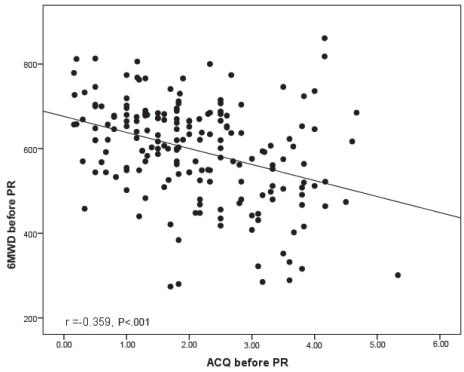

Figure 5. Correlation between asthma control (ACQ) and 6MWD ($P < .001$). ACQ indicates Asthma Control Questionnaire; 6MWD, 6-minute walk distance; PR, pulmonary rehabilitation.

DISCUSSION

In this retrospective, observational study, we studied the effects of a 12-week outpatient PR program in obese and non-obese patients with asthma. Both groups showed significant improvements in functional exercise performance and asthma control. The results of this study suggest that a multidisciplinary PR program is equally effective in obese

and non-obese asthmatics. Despite the increasing insights in the effectiveness of PR in patients with chronic obstructive pulmonary disease, data on asthma and especially on patients with obesity and asthma are sparse. This is surprising as these patients are often very symptomatic and pose a challenge in medical management. In the present study, baseline values of patients with and without obesity were not significantly different with regard to age, lung function and medication usage. Still, obese patients with asthma had a lower level of exercise tolerance reflected by a lower 6MWD and VO_{2max} at baseline compared with non-obese patients with asthma. This is consistent with previous results in obese and normal-weight people with asthma and is most likely due to limitations in exercise, lower levels of cardiopulmonary fitness and a sedentary lifestyle (23-26) . The inverse correlation between the BMI with the 6MWD and VO_{2max} in our study supports the conclusion that obesity contributes to exercise intolerance in patients with asthma. Indeed, there was no significant difference in lung function between the groups and there was no association between baseline FEV_1 and 6MWD indicating that patients with a good lung function (FEV1 >90% pred) such as those in the present study, are not limited by chronic airflow limitation. Rather, the difference in exercise tolerance is explained by BMI.

Despite the difference in exercise capacity at baseline, obese patients were able to achieve the same amount of improvement as non-obese patients. Also, the average improvement in 6MWD was above the threshold of 30 m, which has been accepted as the MCID for adult patients with chronic respiratory diseases (22). When analysing individual data, the majority (60%) of the obese and (70%) non-obese patients showed an improvement greater than the MCID. Interestingly, these were the patients with a shorter 6MWD at baseline and a higher usage of LABA and oral corticosteroids. This finding implies that especially patients with more severe asthma benefit from PR. Subgroup analysis in obese patients confirmed this conclusion.

Remarkably, the level of asthma control in obese patients did not differ from that of non-obese patients. The reason for this could be that in general, only patients with uncontrolled or severe asthma are referred for PR. Also, the use of anticholinergic inhalation medication on top of high-dose inhaled corticosteroids and LABA was high among the study group indicating that the majority were more severe (GINA 4) patients with asthma. Asthma control significantly improved in both groups. However, the average improvement was below the minimally important difference of 0.5 in GINA classification. Fifty-two percent of the obese and 47% of the non-obese patients had a clinically relevant improvement in asthma control. However, failure to improve ACQ above the MCID of 0.5 in almost 50% of the patients cannot be interpreted without more informa-

tion on medication usage after PR, but the retrospective nature of this study cannot answer this question.

Previous studies in lean patients with asthma have shown clear improvements in FEV_1 (27), exercise capacity (27-29), asthma control (27-29) and quality of life (29, 30) after an exercise program. Moreover, one study showed a significant reduction in the number of emergency department visits in the year after the PR program (31). The above-mentioned studies as well as the present data confirm that exercise training is effective to regain cardiopulmonary fitness and seem also effective to improve asthma control in suboptimally controlled patients with asthma. Importantly, the present study extends these findings to patients with obesity and asthma.

An important question is whether weight reduction is an important factor for a positive outcome of these programs. A study by Scott et al. demonstrated that even modest weight loss (5%-10% of body weight) is sufficient to improve asthma control, lung function and quality of life in obese adults with asthma (32). In the present study, the BMI was significantly inversely associated with the 6MWD and the 6MWD was associated with ACQ. This finding implies that, in addition to cardiopulmonary fitness, weight reduction might be an important goal of treatment for obese patients with asthma during a rehabilitation program. Also, which type of exercise program (endurance or high-intensity/interval) is more effective to optimize weight reduction and clinical benefits in obese patients with asthma needs to be investigated. Unfortunately, data on weight loss were not available in our study population.

Of the 138 patients in this study, 26 patients did not complete the PR program (18.8%). This dropout rate is within the range of 10-32% which has been described in several studies (15). The most frequent reasons for dropping out were exacerbations and lack of motivation. Interestingly, patients who dropped out of the program had a lower 6MWD and a higher ACQ before starting the program. It is conceivable that patients with unstable asthma and lower baseline exercise capacity are more prone to develop exacerbations during PR and dropout. The dropout ratio was not different between patients with and without obesity.

Our study has some limitations. ACQ results could not be obtained for all patients. Only 62.5% of the patients had a pre- and post ACQ administered. This could be the reason that we were unable to demonstrate clinical improvements in ACQ after rehabilitation. We excluded a selection bias as we found no difference in baseline parameters between patients with and without ACQ results. In addition, there was no data available about inflammatory markers and the amount of weight loss at the end of the rehabilitation

program. Furthermore, we do not have information on maintenance of the benefits after rehabilitation, which is an indication for lifestyle change and might differ between obese and non-obese patients with asthma.

CONCLUSION

Despite the inherent limitations of this retrospective study, our results suggest that a standardized PR program is effective to regain cardiopulmonary fitness and improve asthma control in suboptimally controlled patients with asthma. Importantly, the present study extends these findings to patients with obesity and asthma. However, there is still a large proportion of patients who shows no clinical significant improvement. For these patients, an adapted PR program with emphasis on weight loss and self-management strategies could probably be beneficial to improve the effects on exercise tolerance and asthma control.

ACKNOWLEDGEMENTS

We thank dr. E. Birnie for his help in statistical analysis.

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SUPPLEMENT

Table S1. Subgroup analysis of obese patients with and without minimal clinically relevant improvement in 6MWD[a]

	Δ6MWD <30 m (n = 17)	Δ6MWD ≥30 m (n = 26)	p-value
Relative VO_{2max} %	58.6 [50.7-68.0]	49.6 [43.0-58.1]	.027
6MWD, m	570 [525-616]	502 [453-595]	.048
Borg dyspnea rating[b]	4 [1.5-5.5]	5 [4-7]	.045

Abbreviations: m, meters; VO_{2max}, maximal oxygen uptake; 6MWD, 6-minute walk distance.
[a]Data are reported as median [interquartile range].
[b]Recorded at the end of the 6-minute walk test.

Table S2. Subgroup analysis of non-obese patients with and without minimal clinically relevant improvement in 6MWD[a]

	Δ6MWD <30 m (n = 20)	Δ6MWD ≥30 m (n = 45)	p-value
Weight, kg	71.3 [60.9-77.4]	76.3 [69.8-84.5]	.026
6MWD, m	681.5 [595-711]	607 [545-657]	.042
Borg fatigue rating[b]	5 [4.0-6.8]	4 [3-5]	.045

Abbreviations: Δ, delta or change; m, meters; 6MWD: 6 minute walking distance.
[a]Data are reported as median [interquartile range].
[b]Recorded at the end of the 6-minute walk test.

Table S3. Patient-related problems during PR[a]

	Δ6MWD <30 m	Δ6MWD≥30 m	p-value[b]
PR without problems	62.9	72.4	.372
Physical problems/injuries	14.3	15.7	.848
Asthma exacerbation	8.6	4.3	.372
Psychological issues	11.4	9.9	.803

Abbreviations: Δ, delta or change; m, meters; PR, pulmonary rehabilitation; 6MWD, 6-minute walk distance.
[a]Data are reported as percentages.
[b]Chi-square test used.

Table S4. Patient-related problems during PR[a]

	ΔACQ <0.5	ΔACQ ≥0.5	p-value[b]
PR without problems	64.9	79.3	0.198
Physical problems/injuries	18.9	17.2	0.861
Asthma exacerbation	10.8	3.4	0.262
Psychological issues	8.1	3.3	0.412

Abbreviations: Δ, delta or change; ACQ, Asthma Control Questionnaire; PR, pulmonary rehabilitation.
[a]Data are reported as percentages.
[b]Chi-square test used.

3 High intensity training in obesity- a meta-analysis

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Obes Sci Pract. 2017 May 29;3(3):258-271

ABSTRACT

Introduction: High Intensity training (HIT) is a time-effective alternative to traditional exercise programs in adults with obesity, but the superiority in terms of improving cardiopulmonary fitness and weight loss has not been demonstrated.

Objective: to determine the effectiveness of HIT on cardiopulmonary fitness and body composition in adults with obesity compared to traditional (high volume continuous) exercise.

Methods: A systematic search of the main health science databases was conducted for randomized controlled trials comparing HIT with traditional forms of exercise in people with obesity. Eighteen studies were included in the meta-analysis. The (unstandardized) mean difference of each outcome parameters was calculated and pooled with the random effects model.

Results: HIT resulted in greater improvement of cardiopulmonary fitness (VO_{2max}) (MD 1.83, 95% CI 0.70, 2.96, $p<0.005$; $I^2=31\%$) and a greater reduction of %body fat (MD -1.69, 95% CI -3.10, -0.27, $p=0.02$, $I^2=30\%$) compared to traditional exercise. Overall effect for BMI was not different between HIT and traditional exercise.

Conclusion: Training at high intensity is superior to improve cardiopulmonary fitness and to reduce %body fat in adults with obesity compared to traditional exercise. Future studies are needed to design specific HIT programs for the obese with regard to optimal effect and long-term adherence.

INTRODUCTION

Physical inactivity is one of the major factors associated with obesity, and a low physical fitness is an independent risk factor for mortality. Exercise is an effective strategy to reduce weight and to improve health (1). The World Health Organization recommends at least 150 minutes of moderate intensity, or at least 75 minutes of vigorous-intensity physical activity for healthy adults in a week (2). However, the majority of the adults with obesity are not able to achieve this target due to different barriers, such as lack of motivation, lack of time and physical limitations (3-6). In addition, psychological factors like depression, anxiety and body image dissatisfaction are important limitations in people with obesity to perform exercise in public (7).

High intensity training (HIT) is a time-effective alternative to traditional exercise programs which mostly involves a low to moderate intensity training of long duration. HIT is defined as exercise performed at an intensity of > 65% of maximal capacity (8). In general, HIT is often performed with intensities above 80% of maximal capacity and therefore an interval training is often used in order to maintain the exercise performance (8). High Intensity Interval Training (HIIT), a specific form of HIT, is characterized by brief repetitions of high intensity exercise (30s-min) alternated with periods of rest or low-intensity exercise (1-5 min) (9, 10). Recent studies showed that HIIT is effective to increase cardiopulmonary fitness (11, 12) and to improve insulin sensitivity (12). Also, several studies have shown similar or better results with regard to weight reduction after a HIIT intervention compared to high volume, continuous training (13-15). Traditionally for weight loss, a medium intensity, high volume training is advised to increase fat oxidation. HIIT can effectuate weight reduction by promoting fat oxidation in a shorter time period, but also mechanisms like increased post exercise fat oxidation and a decreased post exercise appetite could play a role (15). Besides, some studies showed that HIIT is perceived to be more enjoyable than moderate intensity continuous exercise, also in the obese (16, 17). This may improve the adherence to exercise and promote health benefit over a longer period.

Up until now, the superiority of HIT in terms of improving cardiopulmonary fitness or weight reduction compared to moderate intensity continuous training has not been shown yet in persons with obesity. Most of the studies demonstrating weight reduction with HIT are not performed in an obese study population and there is a lot of variation in exercise protocols used in these studies. Therefore, it is currently not possible to make recommendations on the optimal type of exercise in adults with obesity. The aim of this review and meta-analysis was to determine the effectiveness of HIT on cardiopulmonary fitness and body composition in adults with obesity compared to traditional forms of

exercise (lower intensity, high volume continuous). Secondly, we were interested in the effect of HIIT compared to traditional forms of exercise on these outcomes.

METHODS

This review is based on PRISMA Statement for reporting systematic reviews and meta-analysis of studies that evaluate health care interventions (18).

Search strategy

A systematic search of the main health science databases (i.e. PubMed, Embase, Medline, Cochrane and Pedro) was conducted on 30 November 2015 and on 31 January 2017. The following search terms and matching synonyms were used: obesity, obese, high intensity, interval, exercise training and clinical trial. The full search strategy in each database can be found in the supplemental file (S1).

Inclusion and exclusion criteria

For this review, randomized controlled trials published after the year 2000 were included. Studies were included if the mean Body Mass Index (BMI) of the study population was above 30 kg/m^2 and if the participants were adults between 18 and 60 years. At least one of the intervention groups in the studies must have performed high intensity (interval) training (HIT or HIIT), while the control group must have performed medium or low intensity (continuous) training or normal level of physical activity. At least one of the following outcome parameters must have been reported: maximal oxygen uptake (VO_{2max}) or any of the following body composition parameters: BMI, fat mass (%), waist circumference, fat free mass, fat free mass index. Trials must have been written in English or Dutch. Studies were excluded if the details of the exercise intervention were lacking; the participations of the studies had any significant cardiovascular of neurological co-morbidity; there was any significant co-intervention (psychological, drugs or nutritional) and if the duration of the intervention was shorter than 2 weeks.

Outcome measures

The primary outcome parameter was the maximal Oxygen Uptake (VO_{2max}) in ml/kg/min. Secondary outcome parameters were body weight (kg), Body Mass Index (BMI) (kg/m^2), waist circumference (cm) and fat mass (%).

Selection of Studies

Two authors (YT, WT) screened the articles for inclusion by using the title and abstracts. Abstracts were excluded based on the study design, age and BMI of the study popula-

tion. Next, the full text of the selected articles was screened by those two researchers for inclusion based on study design, patient characteristics, intervention and outcomes. If there was a disagreement between these two authors, the third researcher (MK) made the definitive decision. The reference list of all relevant articles was screened for eligible studies for this review.

Risk management

Risk of bias for each article was assessed by two reviewers (YT and WT) independently. The recommendations in the Cochrane handbook of systematic reviews of interventions were used Authors used the risk of bias tool in Review Manager 5 (version RevMan 5.3; https://tech.cochrane.org/revman) software and evaluated the risk as "low risk", "unclear risk" or "high risk" for each domain (selection bias, performance bias, detection bias, attrition bias and reporting bias). Disagreements were resolved by consensus between the reviewers.

Data extraction and management

Following data were extracted from the included studies: publication year, journal, study site, study design, objectives, methods of analysis, size of study population, gender, age, type of intervention, intensity and volume of exercise training, duration of the intervention and study, VO_{2max} (before-after), BMI (before-after), body weight (before-after), waist circumference (before-after) and percentage body fat (before-after). RevMan 5.3 was used for data management. Only 4 articles reported the change from baseline with the corresponding standard deviations of the change for different outcomes. Calculation of standard deviations of the change in other articles was not possible because of missing standard error, t- and p-values. Because of the heterogeneity in time points (baseline-final value measurement), imputation of standard deviations of the change was not recommended (Cochrane Handbook for Systematic Reviews of Interventions). Therefore, a comparison of the final measurements was used, which in randomized controlled trials estimates the same effect as the comparison of changes from baseline (19). Data were extracted from the articles. The (unstandardized) mean difference of each outcome parameters was calculated and pooled with the random effects model (19).

Heterogeneity

Heterogeneity was expected in the size and characteristics of the study populations (age and gender) and in the characteristics of the interventions, such as the type of exercise, the intensity, frequency and the total intervention period. To determine the heterogeneity across the studies, the Chi^2 and I^2 tests of RevMan 5.3 were used (20). Heterogeneity was interpreted as not important when I^2 was between 0% to 40%, moderate when I^2 was 30% to 60%, substantial when I^2 was 50%-90% and considerable when I^2 was 75% to

100%. For the Chi^2 test, a p-value of 0.10 was used to determine statistical significance in heterogeneity (19).

Subgroup analysis

Subgroup analyses were performed for HIIT (interval only) for each outcome parameter if there was sufficient data available. Additionally, subgroup analysis was performed for HIT compared to medium- or low intensity exercise training and compared to normal level of physical activity.

Sensitivity analysis

A sensitivity analysis was conducted by excluding studies with an intervention period shorter than 4 weeks. In addition, sensitivity analysis was performed by excluding studies with less than 20 participants from the analysis.

Meta-regression

If there were significant results, meta-regression analysis was performed to determine the impact of study characteristics (duration of the intervention period, intensity, intervals, repetitions, baseline BMI, age, gender and publication year) on the difference in VO_{2max} and body composition (%body fat) between the HIT and traditional interventions. Meta-regression analyses were performed in Stata v14.2 using the 'metareg' procedure taking the individual study as unit of analysis. For VO_{2max}, adjusted effect sizes are reported. For % body fat, univariable ('crude') effect sizes are displayed.

Meta-regression analysis to evaluate the impact of study characteristics on the before/after changes of VO_{2max} and % body fat within the HIT/HIIT groups could not be performed because the estimated standard error of the mean before/after change in these variables was usually not reported.

RESULTS

Results of the search

There were 4251 records identified from the initial search of electronic databases. Two additional articles were identified through other sources. After removing the duplicates, 1865 titles were left for screening. From this list, the full text of 81 relevant articles were reviewed in detail. Finally, 18 articles were included in the meta-analysis (Figure 1).

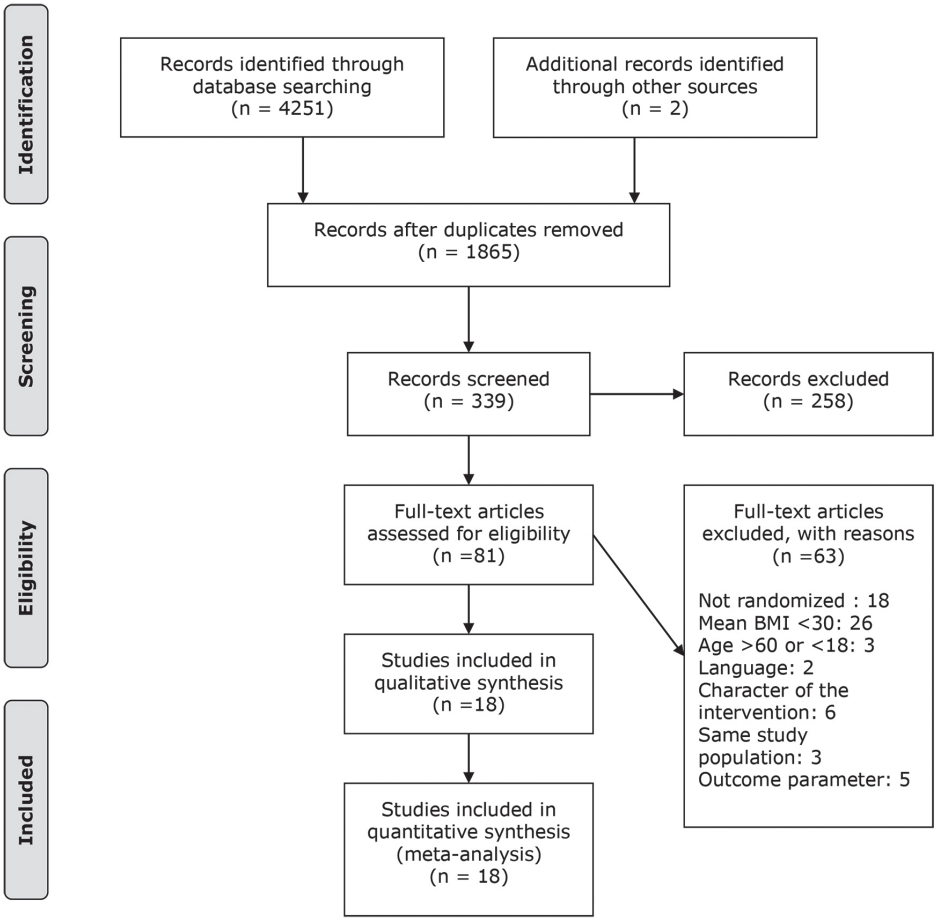

Figure 1: Flow diagram of screening and selection of articles for review.

Risk of bias in included studies

The overall quality of the included studies was low (Figure 2). Details about the randomization process and allocation concealment were lacking in almost all studies, so the risk of bias was unclear. Only 3 studies reported a blinded assessment of the outcomes (21-23). Also in 4 studies, the number of participants was low, ranging from 12-18, with the risk of overestimation or underestimation of the effect on outcome parameters (21, 24-26). In most studies, there was not enough information to determine reporting bias (Figure 2 and 3, S2).

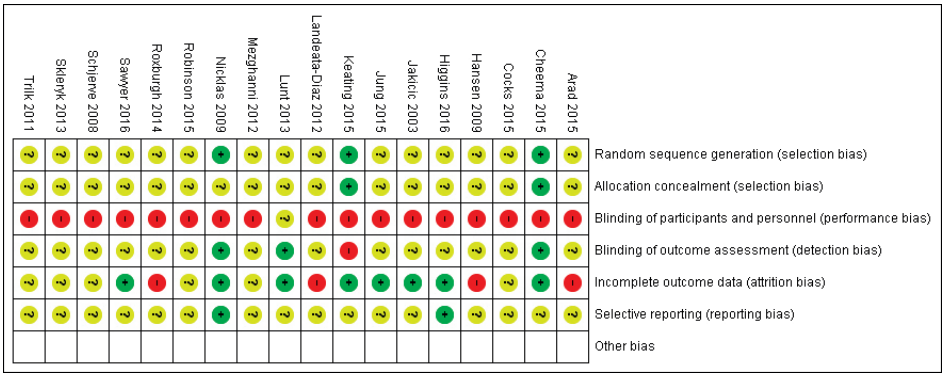

Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

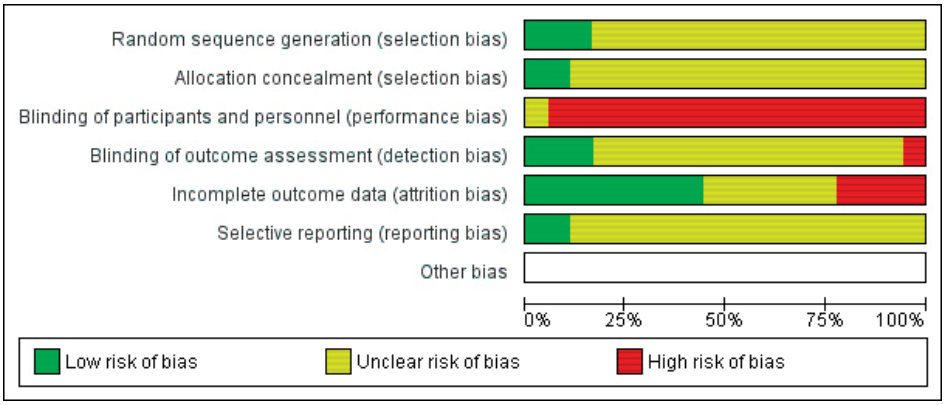

Figure 3: Risk of bias graph. Review authors' judgement about each risk of bias item presented as percentages across all included studies.

Characteristics of the included studies

The characteristics of the 18 included studies are summarized in Table 1. A total of 854 participants were randomized in these studies. The sample size differed between 12 and 201 participants. All studies were published between 2003 and 2016. The mean age of the included patients was between 24 and 59 year and the mean BMI range was between 30-38 kg/m^2. In all included studies, obesity was defined as a BMI equal or greater to 30 kg/m^2. Twelve studies excluded participants with diabetes (I and II) (21, 24, 26-35), and 13 studies excluded patients with hypertension and cardiac comorbidity (21, 23, 24, 26, 28-30, 32-37) . One study did not provide information about the presence of comorbidities (25).

Characteristics of the interventions

Details of the exercise interventions in each study are summarized in Table 1. Twelve studies compared HIIT with lower intensity exercise or normal level of physical activity (21, 22, 24-28, 30, 35-37). Six studies compared the effect of a continuous HIT with lower intensity exercise training (29, 31, 38) or normal level of physical activity (23, 32, 33). In two studies, there was a diet intervention included in both the intervention and control group, so the intensity of the exercise was the only difference between these groups (23, 32). In the majority of the studies, participants trained 3 to 5 times a week, and the duration of the interventions varied from 2 weeks to 6 months. Different exercise modalities were cycling (24-28, 30-32, 34-36, 38), walking/running (22, 23, 29, 30, 33, 34, 36-38) and boxing (21). There was considerable variation in the used HIIT protocols. The number of repetitions varied from 4 to 12 repetitions, with intervals of 10s to 4 min. The intensity of the exercise varied from 70-100% of the maximal heart rate (HR_{max}) (21, 22, 26, 27, 30, 37), 90-100% of VO_{2max} (36) or 85-200% of W_{max} (24, 34) . Three studies performed "all out" sprints against a resistance equivalent to 0.05 kg/body mass (25, 28, 35). The intensity of continuous HIT was 60-75% of VO_{2max} (31, 38) or 70-80% of HR_{max} (23, 29, 32, 33) . Adherence to the intervention program was above 75% in 10 of the 18 studies (21, 23, 25, 29-32, 34, 36, 38). One study reported a lower adherence rate of 59% (22); one study excluded patients with an attendance of < 70% from analysis (28), and in the other 6 studies, no information was provided about adherence (24, 26, 27, 33, 35, 37). Three of the 18 studies reported adverse events related to the intensity of the exercise. In the study of Lunt et al. three participants had developed injuries in the group with maximal volitional interval training. No injuries occurred in the group with aerobic interval training or walking (22). In the study of Nicklas et al., one patient in the vigorous intensity vs. 4 patients in the moderate intensity group discontinued exercising because of time problems (2) or injuries (3) (23). In the study of Keating et al. during exercise a syncopal episode occurred in one patient in the high intensity and one patients in the low intensity group (31).

Measurements

Anthropometric parameters such as height and weight were measured in a standardized way in all studies. Cardiopulmonary fitness was measured by determining the maximal oxygen uptake (VO_{2max}) either by an incremental cycling test (24-28, 30-32, 34, 35, 38) or by the use of a treadmill for maximal exercise (21-23, 29, 36, 37). Different protocols were used for exercise testing (39, 40) but mainly a load-incremental protocol was used until volitional exhaustion and/or reaching >85% age-predicted heart rate and/or plateau of VO_{2max} and/or a drop of the pedaling rate < 50/rpm. Body composition was measured by a bioelectrical impedance (33) or a dual energy x-ray absorptiometry (DXA) (23, 24, 26-28, 35, 37, 38). In one study, the % body fat was computed from six skinfold sites using validated equations (21).

Table 1: Overview of the characteristics of included studies. Data are presented in means ±SD.

Study	N	Age (y)	BMI (kg/m^2)	Training	Intensity	Duration	Control	Outcome VO2max (ml.min.kg)	Outcome BMI (kg/m^2)
Arad et al. 2015 (27)	28 female	HIIT: 29 ± 4 CON: 30 ±7	HIIT: 32.5 ±3.6 CON: 32.1 ±3.2	HIIT (cycling; 24 min) (3/week)	6 min warm-up 50%HRR 4x30-60s 75-90% HRR 5 min cool-down	14 weeks	Normal level of physical activity	HIIT: from 23.1±4.9 to 24.9±5.5 CON: from 19.7 ±6.3 to 20.9 ±4.6	HIIT: from 32.5±3.6 to 32.7 ±3.8 CON: from 32.1±3.2 to 31.6 ±3.6
Cheema et al. 2015 (21)	12 7: female 5: male	39 ±17	HIIT: 32.0±5.9 CON: 30.8±2.6	HIIT (Boxing; 50 min) (4/week)	5 min warm up HIIT 2:1 >75% HRR vs rest/pacing	12 weeks	50 min brisk walking (4/week)	HIIT: from 27.9 ±2.4 to 32.5 ±5.0 CON: from 29.0 ±6.4 to 28.8 ±8.0	HIIT: from 32.0±5.9 to 30.5 ±4.0 CON: from 30.8 ±2.6 to 30.7 ±3.0
Cocks et al. 2015 (24)	16 male	SIT: 24 ±5.7 MICT:26±5.7	SIT: 35.8 ±4.2 MICT: 33.7±4.2	SIT (cycling) (5/week)	2 min warm up (50W) 30s 200% Wmax /120s 30W 4 to 7 intervals	12 sessions	40-60 min continuous cycling -65% VO2peak (5/week)	SIT: from 33.9 ±3.4 to 36.3 ±4.5 MICT: 35.1 ±4.2 to 39.8 ±7.6	SIT: from 35.8±4.2 to 35.7 ±4.2 MICT: 33.7±4.2 to 33.1±4.5
Hansen et al. 2009 (38)	50 male	59 ±8	HIT: 32.1±4.5 LIT: 32.7±3.9	HIT (walking, cycling, cross-country ski-type exercise) (3/week)	40 min continuous at 75% VO2peak	6 months	55 min continuous at 50% VO2peak	HIT: from 20.8 ±5.5 to 24.7 ±6 LIT: from 20.9 ±5 to 23.5 ±5.5	HIT: from 32.1±4.5 to 31.4 ±4.5 LIT: from 32.7 ± 4 to 32.3 ±4.5
Higgins et al 2016 (20)	60 female	20.4 ±1.5	30.3 ±4.5	SIT (cycle ergometer) (3/week)	4 min warm-up 30 s 'all out" sprints, 4 min active recovery. 5 repetitions in week 1-2, 6 repetitions in week 3-4 and 7 repetitions in week 5-6	6 weeks	20-30 min cycling at 60-70% Heart rate reserve	SIT: from 29.1 ±4.8 to 33.2 ± 4.4 MICT: from 26.9 ±4.5 to 28.8 ± 4.3	
Jakicic et al. 2003 (29)	201 female	HI/HI: 38.3 ±5.4 MI/HI: 36.8±5.3	HI: 32.8 ±3.9 MI: 32.2 ±3.9	High intensity/ high duration (treadmill) (5/week)		12 months	Moderate intensity/high duration (5/week)	HI: from 20.2±2.9 to 24.5±4.8 MI: from 19.4±3.2 to 22.1±4.0	HI: from 32.9 ±3.9 to 29.5 ±4.8 MI: from 32.3 ±3.9 to 29.2 ±4.8

Table 1: Overview of the characteristics of included studies. Data are presented in means ±SD. (*continued*)

Study	N	Age (y)	BMI (kg/m^2)	Training	Intensity	Duration	Control	Outcome VO2max (ml.min.kg)	Outcome BMI (kg/m^2)
Jung et al. 2015 (30)	32 27:female 5:male	51 ±10	32.9 ±6.3	HIIT (25 min) (walking,elliptical machine, treadmill or cycling) (3/week)	3 min warm up 10x1 min 90% HRpeak 2 min cool-down	10 days + 4 weeks	20-50 min continuous 65% HRpeak	HIIT: from 20.7 ±3.3 to 22.6 ±4.1 MICT: from 20.8 ±5.2 to 22.0 ±4.6	HIIT: from 29.8 ±5.5 to 29.9 ±5.1 MICT: from 32.1 ±4.1 to 31.9 ±3.7
Keating et al. 2015 (31)	48	43.6 ±3.0	33.4 ±1.3	HI (cycling) (3/week)	30-45 min 60-70% VO2peak	8 weeks	Low to moderate intensity, high volume (Brisk walking) 45-60 min 50% VO2peak	HI: from 21.9 ±4.8 to 24.9 ±5.5 LO: from 24.9 ±3.5 to 27.2 ±2.8	HI: from 36.3 ±5.9 to 35.8± 5.9 LO: from 33.9 ±3.1 to 33.4 ±3.1
Landaeta-Diaz et al. 2012 (32)	45 30: female 15: male	MeD: 57.2 ±4.4 MeDE: 59.05 ±5.5	MeD: 38.44 ±6.5 MeDE: 37.05 ±3.22	MeDE (diet +exercise) (ergometer) (3/week)	30 min 80% HRmax	12 weeks	Diet only- calori restriction (500kcal/day)	MeDE: from 18.87 ±5.59 to 27.31 ±4.70 MeD: from 19.99 ±5.72 to 22.38 ± 6.98	MeDE: from 37.05±3.22 to 33.79±3.21 MeD: from 38.44 ±6.5 to 36.35 ±6.12
Lunt et al. 2013 (22)	49 36:female 13:male	WALK: 46.3 ±5.4 AIT: 48.2 ±5.6 MVIT: 50.3 ±8.0	WALK: 32.7 ±4.3 AIT: 32.1 ±3.1 MVIT: 32.4 ±2.9	AIT: aerobic interval training (walking) MVIT: maximal volitional intensity training (3/week)	AIT: 4min HIIT (85-95% HRmax)/3 min walking 4 repetitions (40 min) MVIT: 30 s volitional intensity/4 min walking 3-6 repititions (25-40 min) 10 min warming up 5 min cool-down	12 weeks	WALK: 10 min warming up 5 min cool down 33 min walk (65-75% HRpeak)	AIT: from 24.2 ±4.8 to 25.6 ±4.8 MVIT: from 25.0 ±2.8 to 25.2 ±3.4 WALK: from 26.5 ±5.3 to 25.2 ±3.6	AIT: from 32.1 ±3.1 to 32.1 ±3.0 MVIT: from 32.4 ±2.9 to 32.3 ±2.9 WALK: from 32.4 ±2.9 to 32.3 ±2.9

Table 1: Overview of the characteristics of included studies. Data are presented in means ±SD. (*continued*)

Study	N	Age (y)	BMI (kg/m^2)	Training	Intensity	Duration	Control	Outcome VO2max (ml.min.kg)	Outcome BMI (kg/m^2)
Mezghanni et al 2012 (33)	31 female	25.2 ±4.8	G75: 32.9 ±1.8 G50: 34.1 ±3.6 CON: 33.2 ±1.8	High intensity aerobic training (walking and jogging)	G75: 20-55 min 75% HRR	12 weeks	Moderate intensity aerobic training G50: 20-55min 50% HRR OR Control		G75: from 32.9 ±1.8 to 30.5 ±2.4 G50: from 34.1 ±3.6 to 32.9 ±3.8 CON: from 33.2 ±1.8 to 33.3±1.7
Nicklas et al. 2009 (23)	112 female	CR: 58.4 ±6.0 CR+MI: 57.7 ±5.5 CR+HI: 59.0 ±5.0	CR: 33.9 ±4.0 CR+MI: 33.7 ±3.5 CR+HI: 32.9 ±3.7	Caloric restriction + high intensity exercise (treadmill) (3/week)	3-5 min warm up CR+HI: 70-75%HRR	20 weeks	CR+MI: 45-50%HRR OR CR only	CR+HI: +4.1 ± 3.7 CR+MI: +2.5 ±2.6 CR only: +2.0 ±2.6	
Robinson et al. 2015 (34)	39	52±10	HIIT: 32.9± 6.6 MICT: 31.4 ± 4.1	HIIT (cycle, treadmill, elliptical)	HIIT: 3 min warm up 4x 1:1 85-90% Wpeak/20% Wpeak to 10x 1:185-90% Wpeak / 20% Wpeak Cooldown (32.5% Wpeak)	2 weeks	20-50 min of continuous activity at 32.5% Wpeak	HIIT: from 20.4 ±3.4 to 21.9 ±4.0 MICT: from 20.6 ±4.9 to 22.1 ±4.7	HIIT: from 32.9 ±6.6 to 32.6 ±6.7 MICT: from 31.4 ±4.1 to 31.3 ±4.0
Roxburgh et al 2014 (36)	29 19: female 10: male	36.3 ± 6.9	CMIET+HIIT: 30.7± 6.3 CMIET: 29.6± 4.7 Control: 29.2 ±4.2	CMIET+ single bout of HIIT (treadmill and cycling) (5/week)	4 sessions CMIET +1 session HIIT: 60s 100%VO2max -150 s recovery 8-12 repetitions	12 weeks	CMIET: 15 min walking and 15 min cycling (45-60%HRR) Control: normal activity level. No exercise	CMIET+HIIT: from 32.7 ±9.2 to 36.0±11.5 CMIET: from 33.2±4.0 to 34.5 ±6.1 CON: from 30±4.6 to 28.3±6.5	CMIET+HIIT: from 30.7 ±6.3 to 30.6±6.1 CMIET: from 29.6±4.7 to 29.4±4.7 CON: from 29.2 ±4.2 to 29.5±4.4

Table 1: Overview of the characteristics of included studies. Data are presented in means ±SD. (*continued*)

Study	N	Age (y)	BMI (kg/m^2)	Training	Intensity	Duration	Control	Outcome VO2max (ml.min.kg)	Outcome BMI (kg/m^2)
Sawyer et al. 2016 (26)	18 9: female 9: male	HIT: 35.6 ±8.9 MICT: 34.8 ±7.7	HIIT: 37.4 ±6.2 MICT: 34.5 ±3.2	HIIT (cycle ergometer) (3/week)	5 min warm-up (50-60% HRmax) 10x 1 min intervals (90-95% HRmax) 5 min cool-down (50-60% HRmax)	8 weeks	5 min warm-up (50-60% HRmax) 30 min cycling at 70-75% of HRmax 5 min cool-down (50-60% HRmax	HIIT: from 20.3 ±4.9 to 24.4 ±5.9 MICT: from 22.4 ±3.6 to 25.5 ±4.5	HIIT: from 37.4 ±6.2 to 37.4 ±6.1 MICT: from 34.5 ±3.2 to 34.5 ±3.2
Schjerve et al. 2008 (37)	40 32: female 8: male	Strength: 46.2 ± 10.6 Moderate intensity: 44.4 ±7.9 High intensity: 46.9±7.9	Strength: 34.5±5.05 Moderate intensity: 36.7±5.05 High intensity: 36.6±4.49	HIIT (treadmill, walking and running) (3/week)	10 min warm up 50-60% HRmax 4x4 min 85-95% + 3 min interval walking 50-60% HRmax 5 min cool down	12 weeks	Moderate intensity: 47 min walking 60-70% HRmax Strength training: 15 min warm up 40-50% HRmax 4x5 90% 1RM		
Skleryk et al. 2013 (25)	16 male	38.7±5.5	33.7±5.7	Sprint interval training (SIT) (ergometer) (6 sessions)	8-12x10 s 'all out' sprints	2 weeks	Traditional exercise recommendations (TER) 30 min 65% VO2max (10 sessions)	SIT: from 29.7 ±3.7 to 29.3±5.3 TER: from 26.3±5.7 to 26.3±6.2	SIT: from 32.2±5.9 to 32.2±5.9 TER: from 35.2±5.1 to 35.2±5.1
Trilk et al. 2011 (35)	28 female	SIT: 30.1±6.8 CON: 31.4±5.5	SIT: 35.7±6.3 CON: 34.6±5.9	Sprint interval training (SIT) (ergometer) (3/week)	SIT: 4 min warm up 30 s sprint against resistance (0.05kg/kg) 4 min active recovery (low RPM at 0% body mass)	4 weeks	Normal level of physical activity	SIT: from 21.6±4.12 to 24.5±4.12 CON: from 20.5±3.4 to 20.4±3.0	

Abbreviations: HIIT (High intensity interval training), CON (control), SIT (sprint interval training), MICT (medium intensity continuous training), HI (high intensity), LI (low intensity), MeD (Mediterranean diet), MeDE (Mediterranean diet with exercise), AIT (aerobic interval training), MVIT (maximal volitional intensity training), WALK (walking exercise), CR (caloric restriction), CR+MI (caloric restriction + medium intensity exercise), CR+HI (caloric restriction +high intensity exercise), CMIET (continuous medium intensity exercise training), TER (traditional exercise recommendations)

Outcome VO_{2max}

Fifteen studies reported VO_{2max} as an outcome parameter. Compared to traditional exercise, HIT was significantly more effective to improve VO_{2max} (MD 1.83, 95% CI 0.70, 2.96, p<0.005; I^2=31%) (Figure 4). In addition, comparing HIIT with traditional exercise revealed a significant effect in favour of HIIT (MD=1.79, 95% CI 0.21, 3.36, p=0.03; I^2=38%) (Figure 5). Continuous HIT showed a statistical significant effect for VO_{2max} (MD 1.68, 95% CI 0.10, 3.27, p=0.04; I^2=25%).

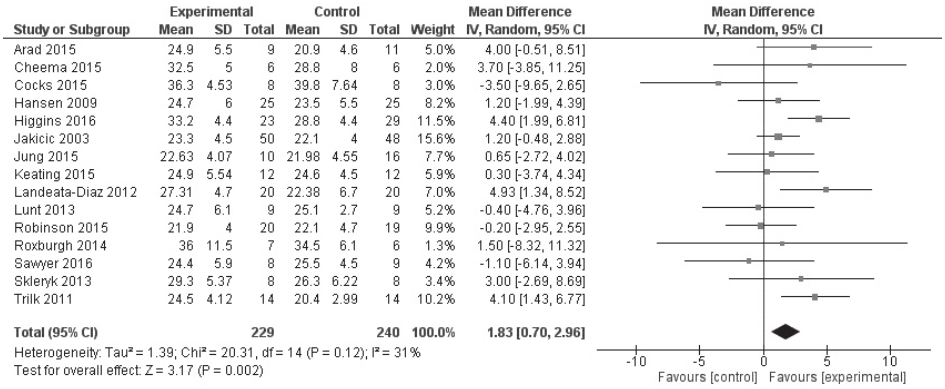

Figure 4: Forest plot of comparison: HIT vs. traditional exercise. Outcome: Maximal Oxygen Uptake (VO_{2max})

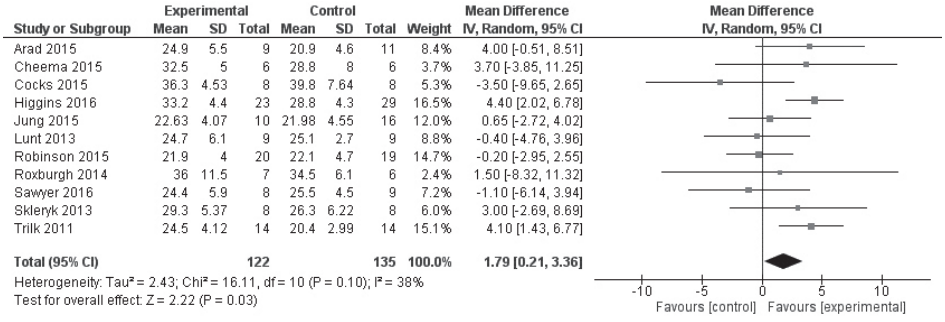

Figure 5: Forest plot of comparison: HIIT vs. traditional exercise. Outcome: Maximal Oxygen Uptake (VO_{2max})

Outcome body composition

The overall effect for BMI, body weight, waist circumference was not different between HIT and traditional exercise (Table 2a). However, HIT resulted in a significant reduction in the percentage of body fat compared to traditional exercise (MD -1.69, 95% CI -3.10, -0.27, p=0.02, I^2=30%) (Figure 6). In addition, comparing HIIT with traditional exercise revealed a significant effect for the percentage of body fat in favour of HIIT (MD -2.01, 95% CI -3.75, -0.30, p=0.02, I^2=0%) (Table 2b).

Table 2a: Effect of HIT vs. lower intensity exercise on cardiopulmonary fitness (VO_{2max}) and body composition.

	Study (n)	Participants (n)	MD (IV, Random, 95% CI)	p-value	I^2
VO_{2max} (ml/kg/min)	15	469	1.83 [0.70, 2.96]	<0.05	31%
BMI (kg/m^2)	15	437	0.20 [-1.10, 1.50]	0.76	91%
Body weight (kg)	12	386	-1.18 [-4.16, 1.80]	0.44	0%
Body fat (%)	10	296	-1.69 [-3.10, -0.27]	0.02	30%
Waist circumference (cm)	8	253	-1.04 [-4.54, 2.45]	0.56	27%

Table 2b: Effect of HIIT vs. lower intensity exercise on cardiopulmonary fitness (VO_{2max}) and body composition.

	Study (n)	Participants (n)	MD (IV, Random, 95% CI)	p-value	I^2
VO_{2max} (ml/kg/min)	11	257	1.79 [0.21, 3.36]	0.03	38%
BMI (kg/m^2)	9	177	0.37 [-1.44, 2.18]	0.69	70%
Body weight (kg)	7	153	-0.42 [-5.30, 4.47]	0.87	7%
Body fat (%)	7	157	-2.01 [-3.73, -0.30]	0.02	0%
Waist circumference (cm)	5	111	-1.63 [-6.37, 3.10]	0.87	7%

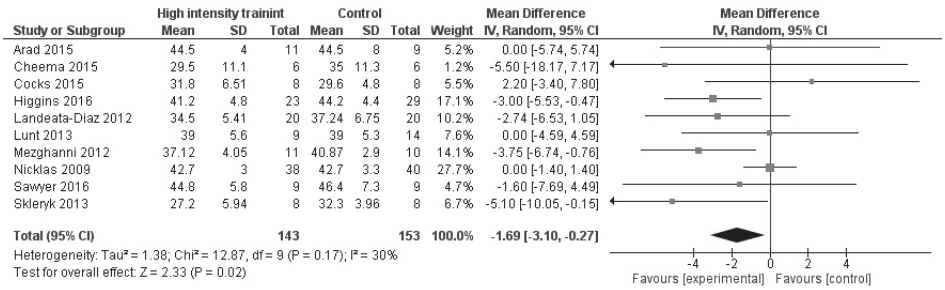

Figure 6: Forest plot of comparison: HIT vs. traditional exercise. Outcome: %body fat

Subgroup analysis

Subgroup analysis for HIT compared to baseline physical activity revealed a significant effect for VO_{2max} in favour of HIT (MD 4.32, 95% CI 2.39, 6.26, p<0.005;I^2=0%). Also, HIT compared to medium intensity training showed a significant effect for VO_{2max} in favour of HIT (MD 1.20, 95% CI 0.12, 2.28, p=0.03, I^2=11%).

Sensitivity analysis

Sensitivity analysis by excluding studies with an intervention period shorter than 4 weeks did not change the results for VO_{2max} or other outcomes (25, 34). Also, excluding studies with less than 20 participants did not change the results for VO_{2max} or other outcomes (21, 24-26).

Meta-regression

Duration of the intervention period (VO_{2max}: β=0.014, p=0.979; %body fat: β=0.16, p=0.132), intensity of intervention (VO_{2max}: β=-1.34, p=0.602; %body fat: β=-0.11, p=0.887), intervals (VO_{2max}: β=-0.04, p=0.372; %body fat: β=0.01, p=0.290), number of repetitions (VO_{2max}: β=-0.203, p=0.763; %body fat: β=-0.39, p=0.262) and baseline BMI (VO_{2max}: β= -0.66, p=0.087; %body fat: β=0.12, p=0.708) were not significantly associated with the treatment effects for VO_{2max} and %body fat between HIT and traditional intervention. In addition, studies with a younger study population (VO_{2max}: β=-0.06, p=0.721; %body fat: β=0.049 , p=0.192), male study population (VO_{2max}: β= 1.93, p=0.237; %body fat: β= 0.06, p=0.960) and recent studies (VO_{2max}: β=-4.15, p=0.093; %body fat: β=0.46 p=0.766) were not associated with the treatment effects for VO_{2max} and %body fat.

DISCUSSION

In this review and meta-analysis, the effectiveness of high intensity training in terms of cardiopulmonary fitness and body composition was compared to other forms of exercise in adults with obesity. Based on the results of this meta-analysis we can conclude that training at high intensity is a better method to improve cardiopulmonary fitness in the obese population than traditional, lower intensity continuous training. In addition, when high intensity interval training was compared with other forms of exercise, we found a significant better improvement of VO_{2max}.

To our knowledge, this is the first meta-analysis comparing high intensity training with other forms of exercise in adults with obesity. Previous studies in normal weight adults (BMI < 25 kg/m^2) showed significant improvements in cardiopulmonary fitness (11) after an HIIT intervention compared to medium intensity continuous training (41). In a randomized controlled trial in overweight patients with metabolic syndrome, Tjonna et al. showed a significant higher increase in VO_{2max} after HIIT compared to continuous moderate exercise (CME) (35% vs. 16%). Moreover, HIIT was superior compared to CME in reducing risk factors for metabolic syndrome, such as reduction in blood glucose and lipogenesis in adipose tissue and enhancing endothelial function. There was no difference between HIIT and CME groups with regard to weight reduction (14). Different mechanisms underlying the increase of VO_{2max} in HIIT are an increased ATP generation by phosphocreatine degradation during HIIT and muscle glycogenolysis (15, 42), improvement in vascular/endothelial function (43), an increase in cardiac output by enhanced cardiac contractility and an increased muscle oxidative capacity by upregulation of mitochondrial activity (10, 44). However, it is unclear whether these adaptations are different in the people with obesity. With regard to body composition, this meta-

analysis showed a significant reduction in the percentage of body fat in favour of HIT compared to traditional exercise. Moreover, HIIT showed the same effect compared to lower intensity continuous exercise. This finding implies a direct effect of high intensity (interval) training on fat oxidation, and was confirmed by a previous study of Trapp et al. who showed significantly more reduction in subcutaneous fat in young healthy women who performed HIIT (3/week, 15 weeks) compared to a continuous exercise training (13). However, in the present meta-analysis, there was no difference in the amount of weight loss, BMI or waist circumference between HIT or traditional exercise. This may be explained by the absence of an accompanying significant dietary intervention. For example, in a randomized controlled trial with asthma patients with obesity, Scott et al. showed that after 10 weeks of either dietary intervention, exercise intervention or combined dietary/exercise invention, only patients who received dietary or combined intervention did have a statistically significant amount of weight loss (45). This study emphasises the importance of a dietary intervention on top of exercise. However, in this meta-analysis, studies with diet as an intervention were excluded, because the aim was to focus on the effect of HIT. Another issue is that the most included studies did not provide data on equal energy expenditure between HIT and traditional exercise forms. Only one study controlled this well, showing that sprint interval training resulted to a greater decrease of fat mass and led to a nearly 2-fold greater increase in VO_{2max} compared to medium intensity continuous training with equal exercise energy expenditure (28). Another possibility for the absence of positive effects on BMI is that the variable duration of the exercise intervention could have influenced the results. However, excluding articles with an intervention period of <4 weeks did not change the results. A recent meta-analysis of Jelleyman et al. demonstrated that HIIT was associated with modest weight loss (-1.3 kg, $p<0.001$) compared to a non-exercising control group, but not compared to continuous training. However, the primary aim of the mentioned study was to investigate the effect of HIIT on glucose regulation (46).

Although this review shows that high intensity (interval) training has favorable effects on cardiopulmonary fitness and body composition in adults with obesity, the results should be interpreted with caution. An important limitation is that most included studies only reported the pre- and post-intervention parameters, but not the change from baseline, or the corresponding 95% CI or p-values of that change. Therefore, we were only able to compare post-intervention values. Although, only randomized controlled trials were included, there were some imbalances in baseline values between the intervention and control groups in some of the studies. The small sample sizes in these studies could be the reason for these imbalances and this could result in a bias. Nevertheless, excluding studies with small sample sizes from analysis did not change the results. Secondly, the primary outcome in some studies was different from VO_{2max} and body composition.

Moreover, small size studies may be underpowered to show a significant effect on these parameters. Different methods were used to determine outcome parameters which could lead to variation heterogeneity in outcomes and outcome assessment. Also, the risk of bias was unclear in most domains, especially with regard to selection bias (randomization/allocation) and reporting bias. In addition, excluding comorbidities like diabetes and cardiovascular problems in these studies could result in an important selection bias. However, in this review and meta-analyses we were able to summarize the available data about high intensity (interval) exercise intervention in the obese population.

There are some issues that should be considered about high intensity exercise in the obese. Performing exercise at high intensity is very demanding and could be a potential risk for knee- and other injuries in the obese. However, only three of the 18 included studies reported adverse events related to the intensity of the exercise. Also, 13 of the 18 studies excluded patients with hypertension and cardiac comorbidity, conditions that are usually present in the obese population. VO_{2max} is recognized as one of the best predictors of mortality among cardiac patients and several studies have noted that high intensity interval training is safe and effective in cardiac patients (47, 48). Moreover, some studies reported that HIIT results in greater improvements in VO_{2max} compared to moderate intensity continuous training (47, 49-51). Another issue is the motivation for an exercise program in persons with obesity. Depression, a negative body image and embarrassment are factors that can influence the decision to participate in an exercise program. Therefore, attention to these psychological should be given in addition to exercise training in this group of patients (7). In the included studies, most of the exercises were performed on a cycle ergometer or on a treadmill. Little is known about the effect or risk of other exercise modalities, like running (outdoor) or swimming. Future studies are needed to investigate which type of HIT is most suitable for the obese with regard to side effects, risk of injuries, but also with regard to long-term adherence and effects. In addition, patients with obesity and with different comorbidities (cardiovascular, pulmonary, diabetes) should be included in these kind of studies to investigate the feasibility and effects in this group of patients. In conclusion, HIT is, 1) superior to traditional exercise in improving cardiopulmonary fitness, which is an important indicator of health, 2) superior to traditional exercise in reducing the percentage of body fat 3) feasible and well-tolerated in persons with obesity. Larger, well-designed randomized controlled trials are required to confirm the findings and to design optimal (HIT) training programs for the obese population.

ACKNOWLEDGEMENTS

We thank J.W. Schoones (Walaeus Library, Leiden University Medical Center, Leiden, The Netherlands) for his help in performing the search. We thank E. Birnie (Franciscus Gasthuis, Rotterdam, The Netherlands) for his help in statistical analysis.

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4

Short-term and long-term effect of a high intensity pulmonary rehabilitation program in obese patients with asthma: a randomized controlled trial

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European Respiratory Journal. 2020;56(1):1901820.

ABSTRACT

Objective: To determine the short-term and long-term effects of a high intensity pulmonary rehabilitation (PR) program on asthma control, body composition, lung function and exercise capacity in obese asthma patients.

Methods: Patients with obesity (BMI $\geq$ 30 kg/m^2) and suboptimal controlled asthma (Asthma Control Questionnaire (ACQ) $\geq$ 0.75) were randomly assigned to a 3-month pulmonary rehabilitation program (PR only), pulmonary rehabilitation program with the use of an internet based self-management support program (PR+SMS) or usual care. The PR program included high intensity interval training, nutritional intervention and psychological group sessions. Patients in the usual care group were advised to lose weight and to exercise. The primary outcome was the difference of change of ACQ between PR only and PR+SMS after 3 months. Total follow-up was 12 months.

Results: Thirty-four patients were included in the study (14 PR only, 9 PR+SMS, 11 control). Compared to patients in usual care, patients in the PR only group had a significant reduction in BMI and significant improvements in asthma control, exercise capacity and aerobic capacity after 3 months. These improvements persisted during 12 months of follow-up. No difference in ACQ between PR+SMS and PR only groups were observed. However, users of the SMS program had a significant lower BMI after 12 months compared to subjects in the PR only group.

Conclusion: A high intensity pulmonary rehabilitation program provides sustained improvements in asthma control, body composition and exercise capacity in obese asthmatics that are not optimally controlled and, therefore, should be considered in the treatment of these patients.

INTRODUCTION

Obesity is associated with an increased risk of asthma, and asthma in patients with obesity is difficult to control (1-3). Physical inactivity is an independent risk factor for severe asthma (4, 5). Both asthma and obesity are associated with a decreased level of physical activity (5, 6). In a previous study, we demonstrated that obese adults with asthma have a lower exercise capacity compared to normal weight adults with asthma. Nevertheless, obese asthmatics were able to show similar improvements in exercise capacity and asthma control compared to non-obese asthmatics after a 12-week pulmonary rehabilitation (PR) program. Still, a large group of obese asthmatics had no improvements from this PR program, which may indicate that there is need for a different approach in this group of patients (7). In recent years, there has been increasing attention for lifestyle interventions in asthmatics with obesity. Until now, the few published studies show that a weight loss program with exercise and dietary restriction improves asthma control and the quality of life of obese asthma patients at short term (8, 9). However, information on long-term results of such programs are still lacking. Studies in this field are urgently needed, not only to demonstrate feasibility and long-term effectiveness, but also to determine the effects of different exercise modalities. High intensity interval training (HIIT) is feasible in obese subjects and was found to be superior to medium intensity continuous training in improving cardiopulmonary fitness (VO_{2max}) and in decreasing % body fat (10). However, the feasibility and effectiveness of HIIT have not yet been investigated in obese subjects with suboptimal controlled asthma. In addition, data about the use of an e-health program as a part of PR programs to improve long-term effectiveness is lacking. Therefore, we designed a 3-month PR program consisting of a combination of HIIT, a dietary intervention and a psychological intervention. In this pragmatic randomized trial, we investigated both short-term and long-term effects of this integrated PR program with and without the use of an internet-based self-management program on body composition, aerobic capacity, lung function and asthma-related outcomes compared to usual asthma care in patients with obesity and suboptimal controlled asthma.

METHODS

Study design

This single-centre pragmatic randomized controlled trial was conducted at the Franciscus Gasthuis & Vlietland, Rotterdam, a non-academic teaching hospital, the Netherlands. Patients were recruited from the pulmonology outpatient clinic between January 2014 and December 2016. Eligible subjects were randomly assigned to one of the intervention groups or control group: 1) pulmonary rehabilitation only (PR only), 2) pulmonary

rehabilitation with online self-management support (PR+SMS), 3) usual care. There was no blinding. For randomization details, see supplemental file (S1). This study was approved by the local medical research ethics committee (Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o; NL46602.101.13) (Netherlands Trial Registry number NTR4322).

Study patients

Subjects between 18 and 55 years were included if they fulfilled the criteria for obesity (BMI $\geq$30 kg/m^2) and had a suboptimal controlled asthma (asthma control questionnaire score (ACQ) $\geq$ 0.75) despite optimal inhalation therapy (inhalation corticosteroid and a long-acting B-agonist). Asthma was diagnosed according to the GINA guidelines (11). Exclusion criteria are included in the supplemental file (S2)

Intervention

The PR groups (PR only and PR+SMS) participated in a 12-week PR intervention program including exercise training, nutritional intervention and psychological group sessions. The exercise training was a high-intensity interval training session of 40-60 minutes (intensity around 90% of VO_{2max}), 3 times a week under the supervision of a physiotherapist (Supplemental file S3). In addition, participants were prescribed a caloric diet of approximately 1500 kcal/day with a balanced intake of macronutrients. They were supervised by a dietician (3 clinical visits + 3 phone calls during 12 weeks). During these visits, a healthy lifestyle was promoted and patients were educated in a healthy diet. Psychological counseling took place during 4 group sessions (1 hour). These sessions focused on behavioral modification and motivational strategies. Subjects who were randomized to PR+SMS participated in the same program but additionally used the internet based self-management tool 'PatientCoach' (www.patientcoach.lumc.nl). For details about this program, see supplemental file S4. Subjects who were randomized to PR+SMS group used the PatientCoach program during 3 months of PR and 12 months of follow-up. Subjects in the usual care group were advised to lose weight and to exercise. Total follow-up time was 1 year and all study participants were regularly seen every 3 months for assessment.

Outcomes

The primary outcome parameter was the difference of change of ACQ between PR+SMS group and PR only group after 3 months of intervention. Secondary outcomes were ACQ at 3 months between both PR groups and the usual care group, ACQ at 12 months, asthma related quality of life (AQLQ), lung function, physical activity level, exercise capacity, body composition, airway and systemic inflammation and exacerbation rate

at 3 and 12 months of follow-up between the PR only and control groups and between the PR+SMS and PR groups.

Assessments

Asthma control and asthma related quality of life were assessed by the validated asthma control questionnaire (ACQ) and the asthma quality of life questionnaire (AQLQ) (12, 13). Pulmonary function was measured with standard spirometry (Vmax Encore 22D, Carefusion) and bodybox (Vmax encore 62j, Carefusion) according to the American Thoracic Society (ATS) / European Respiratory Society guidelines (ERS) (14). Aerobic capacity (VO_{2max}) was measured with a cardiopulmonary exercise test (CPET) according to the ATS/ACCP guidelines (15). For a detailed description of all assessments and blood/sputum analysis see supplemental file S5 (16-23).

Statistics

Assuming an mean±SD effect size (difference of ΔACQ at 3 months) between PR+SMS and PR only groups of 0.5 ± 0.35, randomization ratio 1:1:1, and adjustment for 20% drop out, at least 3x12 patients had to be included in the study. See supplemental file S6 for descriptives and statistical analysis within the groups. Effectiveness of the pulmonary rehabilitation program was studied by comparing outcome parameters of the PR only group versus control group. The added value of the online self-management program was studied by comparing the PR only and PR+SMS groups. The data of the randomized subjects were analysed according to the intention to treat principle. For the comparisons of the primary and secondary outcomes between groups at 3 months, linear regression models were used with the randomization group, gender and the baseline variable as independent variables. Long-term (12 months) effectiveness for continuous measures was evaluated with repeated measurements analyses, with the outcome measure of interest as dependent variable, and the baseline value, time, group and gender as covariables (linear mixed model, covariance structure: unstructured). To analyze the effect of BMI on asthma control (ACQ), asthma quality of life (AQLQ), functional residual capacity (FRC) and VO_{2max} at 3 months and 12 months, we included ΔBMI in the regression analysis and BMI in the linear mixed model. Exacerbations at three months were analyzed as proportions of at least one exacerbation per patient, and tested with the binomial test. Long-term (12 months) effectiveness for number of exacerbations was modeled with Generalized Estimation Equations, with the number of exacerbations as dependent variable and the baseline value, time and group as covariables (distribution: Poisson, link: Log). The beta coefficients of the poisson model were transformed in rate ratios by exponentiating the beta of the model and the confidence intervals. IBM SPSS version 22 was used for all statistical analysis. Given the exploratory character of the

study, p-values were not adjusted for multiple testing. A p-value (two-sided) < 0.05 was considered to indicate a statistically significant difference in all comparisons.

RESULTS

Participants

A total of 112 subjects were screened for eligibility and 34 patients were randomized. Twenty-three subjects were randomly allocated to the intervention groups (14 PR only and 9 PR+SMS) and 11 subjects in the control group. Three subjects withdrew informed consent: one control patient just after randomization, and two patients in the PR+SMS group during the PR program. Eventually 31 subjects were included in the intention-to-treat analysis (Figure 1). Baseline characteristics of the three groups are presented in table 1. Participants had a class II obesity (mean±SD BMI 36.24 ± 4.46 kg/m^2) and

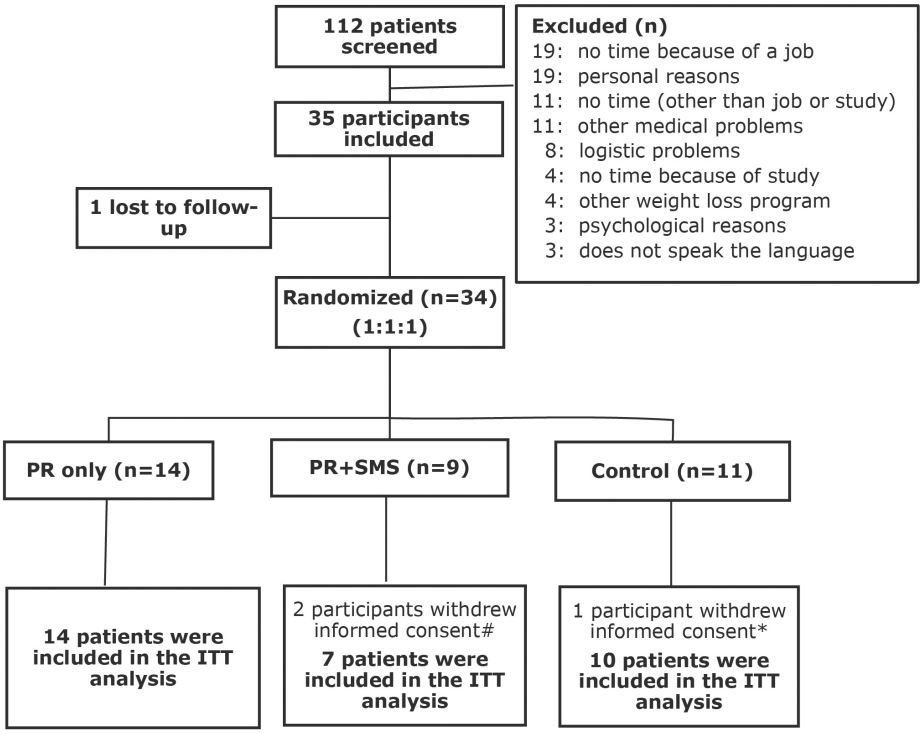

Figure 1: Diagram of inclusion and randomization of study participants. #: during the pulmonary rehabilitation program; *: after randomization.

a low physical fitness (VO_{2max} 18.25 ± 4.64 ml/kg/min). All patients were using inhaled corticosteroids (ICS) and a long-acting B_2 agonist (LABA). In addition, 39% of the patients were using a leukotriene receptor antagonist (LTRA) and 23% were using a long-acting muscarinic antagonist (LAMA). Based on the criteria of the GINA guidelines of 2019 (FeNO, serum and sputum eosinophils) the majority (77%) of the study participants had a type 2 asthma. Median ACQ was 2.0 [IQR 1.5-2.5] and 74% of the participants had an uncontrolled asthma (ACQ ≥ 1.5) at the time of randomization.

Table 1: baseline characteristics of study participants in three groups: pulmonary rehabilitation only (PR only), pulmonary rehabilitation + self-management support (PR+SMS) and control.

	PR only (n=14)	PR+SMS (n=7)	Control (n=10)	p-value
Age (y)	41.57 ± 9.73	41.57 ± 12.54	41.90 ± 8.58	0.996
Gender (%female)	71.43	57.14	90.00	0.298
Weight (kg)	103.25 ± 17.76	106.33 ± 10.87	100.68 ± 17.56	0.786
BMI (kg/m^2)	36.72 ± 4.79	36.82 ± 4.96	35.16 ± 3.86	0.664
Fat mass (%)	44.67 ± 5.90	39.60 ± 11.80	44.1 ± 4.5	0.330
Waist (cm)	109.07 ± 13.75	114.29 ± 8.83	107.00 ± 10.51	0.458
Diabetes (%)	7.14	28.57	0.00	0.133
Hypertension (%)	14.29	0.00	30.00	0.246
PD_{20} (mg)	0.12 [0.06-1.59]	0.28 [0.07-0.28]	0.22 [0.04-0.47]	0.784
FEV_1 (%)	86.93 ± 9.35	95.86 ± 11.74	82.4 ± 16.17	0.105
FEV_1/FVC	76.86 ± 8.88	78.71 ± 6.79	74.30 ± 8.97	0.565
RV (%)	78.92 ± 15.47	85.43 ± 20.55	86.80 ± 17.86	0.528
TLC (%)	66.00 ± 14.30	68.29 ± 11.94	91.10± 8.57	0.262
RV/TLC (%)	27.00 ± 5.52	26.57 ± 4.93	30.60 ± 6.24	0.245
FRC (%)	66.0 ± 14.30	68.86 ± 11.94	72.30 ± 18.14	0.621
Fe_{NO} (ppb)	18.0 [10.5-25.0]	17.0 [16.0-25.0]	17.0 [8.5-26.0]	0.895
VO_{2max} (%)	51.07 ± 17.66	60.57 ± 16.46	56.50 ± 11.27	0.405
ACQ	2.17 [1.46-2.50]	1.67 [1.17-1.83]	2.09 [1.50-2.68]	0.333
AQLQ	4.77 [4.33-5.43]	4.40 [4.13-5.33]	4.47 [3.47-5.00]	0.668
6MWD (m)	578.17 ± 75.70	605.78 ± 55.95	587.30 ± 72.95	0.733
Steps	5997 [4024-8048]	5616 [4306-6080]	7413 [2962-8155]	0.421
PAL	1.48 ± 0.16	1.43 ± 0.09	1.47 ± 0.14	0.815

Data are presented as mean±SD or median [interquartile range], unless otherwise stated. BMI: body mass index; PD20: doses of methacholine (mg) leading 20% reduction in forced expiratory volume in 1 s (FEV1); FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; RV/TLC: ratio between residual volume and total lung capacity; FRC: functional residual capacity; FeNO: fractionated exhaled nitric oxide; VO2max: maximal oxygen uptake; ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; 6MWD: 6-min walking distance; PAL: physical activity level.

Intervention

The median compliance rate to the PR (PR only and PR+SMS) program was 85.7% [IQR 72.0-94.4%]. Four patients had a compliance rate < 50%. Two of these patients withdrew from the physical training program because of knee problems originated during the training. One patient was diagnosed with a neurological disorder during the intervention period and one patient participated very irregularly to the program for unknown reasons. Generally, HIIT was well tolerated by the participants. The most frequent complaint of patients was muscle aches in the first weeks of the training.

Changes in outcomes at 3 months within groups

The outcomes in each group are presented in table 2. In both PR only and PR+SMS groups, there was a significant reduction in weight, BMI and %fat mass after 3 months of PR. Waist circumference only decreased significantly in the PR+SMS group. No reduction

Table 2: Parameters at baseline and changes within groups after 3 months.

	Baseline	**Change within groups after 3 months**	**p-value** PR vs control PR+SMS vs PR
ACQ			
Control	2.09 [1.50-2.68]	-0.25 [-0.66-0.63]	
PR only	2.17 [1.46-2.50]	-0.67 [-1.42-0.00]**	0.113
PR+SMS	1.67 [1.17-1.83]	-0.66 [-1.17,-0.33]**	0.620
AQLQ			
Control	4.47 [3.47-5.00]	0.12 [-0.26-0.62]	
PR only	4.77 [4.33-5.43]	0.20 [-0.33-0.84]	0.758
PR+SMS	4.40 [4.13-5.33]	1.47 [-0.40-1.74]	0.384
Weight (kg)			
Control	100.7 [17.56]	- 0.1 [1.7]	
PR only	103.3 [17.76]	- 4.9 [4.9]**	**0.028**
PR+SMS	106.3 [10.87]	-10.9 [8.4]**	0.091
BMI (kg/m^2)			
Control	35.2 [3.9]	0.25 [0.65]	
PR only	36.7 [4.8]	-1.81 [1.79]**	**0.010**
PR+SMS	36.8 [5.0]	-3.62 [2.73]**	0.152
Waist circumference (cm)			
Control	107.0 [10.5]	4.67 [11.96]	
PR only	109.1 [13.7]	- 3.68 [7.23]	0.173
PR+SMS	114.3 [8.8]	-12.14 [9.84]**	0.107
Fat mass (%)			
Control	44.1 [4.5]	-0.33 [1.75]	
PR only	44.7 [5.9]	-1.41 [1.36]**	**0.015**
PR+SMS	39.6 [11.8]	-2.01 [3.86]**	0.326
FEV$_1$ (%)			
Control	82.4 [16.2]	-0.22 [7.5]	
PR only	86.9 [9.4]	1.0 [6.2]	0.351
PR+SMS	95.9 [11.7]	2.5 [7.8]	0.808

Table 2: Parameters at baseline and changes within groups after 3 months. (*continued*)

	Baseline	Change within groups after 3 months	p-value PR vs control PR+SMS vs PR
FRC (%)			
Control	72.3 [18.1]	- 1.4 [8.8]	
PR only	66.0 [14.3]	9.2 [8.1]*	**0.017**
PR+SMS	68.3 [11.9]	10.2 [10.5]	0.943
ERV (l)			
Control	0.45 [0.22]	0.04 [0.16]	
PR only	0.42 [0.18]	0.22 [0.16]*	**0.033**
PR+SMS	0.53 [0.23]	0.31 [0.47]	0.783
FeNO (ppb)			
Control	17.0 [8.5-26.0]	-0.5 [-14.8-4.0]	
PR only	18.0 [10.5-25.0]	-0.5 [-3.3-3.3]	0.113
PR+SMS	17.0 [16.0-25.0]	0.5 [-7.3-6.5]	0.875
VO_{2max} (%)			
Control	56.5 [11.3]	- 0.1 [10.5]	
PR only	51.1 [17.7]	+13.2 [9.2]*	**0.029**
PR+SMS	60.6 [11.3]	+11.2 [13.5]	0.678
6MWD (m)			
Control	587 [73]	-14 [51]	
PR only	578 [76]	52 [40]*	0.080
PR+SMS	606 [56]	63 [40]**	0.627
Steps (n)			
Control	7413 [2962-8155]	1281 [-65-4036]	
PR only	5997 [4024-8048]	1008 [70-2994]	0.100
PR+SMS	5616 [4306-6080]	3097 [1785-4740]**	0.181
PAL			
Control	1.47 [0.14]	0.04 [0.08]	
PR only	1.48 [0.16]	0.00 [0.18]	0.429
PR+SMS	1.43 [0.09]	0.11 [0.08]**	0.367
Sputum eosinophills (%)			
Control	0.65 [0.50-2.90]	1.20 [0.25-3.05]	
PR only	0.65 [0.05-4.30]	-0.15 [-2.40-1.13]	0.270
PR+SMS	0.90 [0.23-4.05]	0.00 [-0.83-1.05]	0.680
Sputum neutrophills (%)			
Control	49.4 [39.6-57.2]	- 7.2 [-49.1- -7.2]	
PR only	37.2 [28.4-51.0]	- 3.6 [-33.5-35.9]	0.828
PR+SMS	29.6 [23.4-57.9]	15.1 [-9.8-22.4]	0.852

Data are presented as median [interquartile range] or mean±SD, unless otherwise stated. PR only: pulmonary rehabilitation only; PR+SMS: pulmonary rehabilitation+self-management support; ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; BMI: body mass index; FEV1: forced expiratory volume in 1 s; FRC: functional residual capacity; ERV: expiratory reserve volume; FeNO: exhaled nitric oxide fraction; VO2max: maximal oxygen uptake; 6MWD: 6 min walking distance; PAL: physical activity level. Stated p-values are for difference between PR only versus control and PR+SMS versus PR only groups (ANOVA). Differences within groups tested with the paired samples Student's t-test or Wilcoxon matched pairs test. *: $p \leq 0.005$ versus baseline; **: $p \leq 0.05$ versus baseline.

was observed in any of these parameters in the usual care group. Significant improvements in asthma control was observed in both intervention groups after 3 months of PR (median ΔACQ -0.67 for PR only and -0.66 for PR+SMS), whereas no significant improvement was seen in the usual care group (median ΔACQ -0.25) (figure 2). The median improvements in both groups were above the minimal clinically important difference (MCID) of 0.5. There was an increase in functional residual capacity (FRC) in the PR only group, and a trend was observed in the PR+SMS group. There were no significant improvements in dynamic lung function parameters, such as FEV_1 and FVC. Aerobic capacity (VO_{2max}) improved only significantly in the PR only group and a trend was observed in the PR+SMS group. There was an improvement in 6MWD in both PR only and PR+SMS groups. The activity level only improved in the PR+SMS group (table 2).

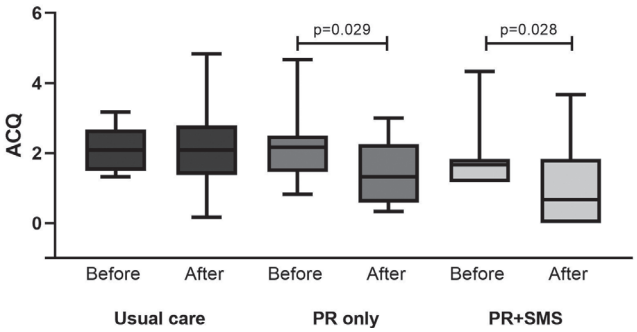

Figure 2: Changes in asthma control (Asthma Control Questionnaire (ACQ)) in each group after 3 months. Data are presented as median (interquartile ranges); p-value for ANOVA.

Outcomes in pulmonary rehabilitation (PR only) versus usual care groups

Subjects in the PR only group had a significantly greater reduction in weight (β=-2.193 CI [-4.116; -0.271], p=0.028), BMI (β=-0.986 CI [-1.70; 0.273], p=0.010) and %fat mass (β = -1.633 CI [-2.888; -0.377], p=0.015) compared to the usual care group at 3 months and these improvements in body composition persisted during 12 months of FU (table 2, 3 and figure 3). At 3 months, there were no differences in asthma control or asthma quality of life between the PR only and usual care group, but during 12 months of FU ACQ was significantly lower in the PR only group compared to the usual care group (β=-1.06 CI [-1.84; -0.27], p=0.011). In addition, there was a significant increase in function residual capacity (FRC) and expiratory reserve volume (ERV) in the PR only group compared to the usual care group at 3 months. However, these improvements were not significantly different after 12 months of FU. Exercise capacity (VO_{2max} and 6MWD) improved significantly in the PR only group after 3 months of PR and these improvements persisted during 12 months of FU. Delta BMI was only significantly associated with improvement in FRC (β=-4.13 CI [-6.24; -2,01], p=0.001), but not with ACQ (β=0.005 CI [-0.396; 0.406, p=0.979), ACLQ (β=-0.20 CI [-0.60; 0.19], p=0.288) and VO_{2max} (β=-1.00 CI [-6.25; 4.25],

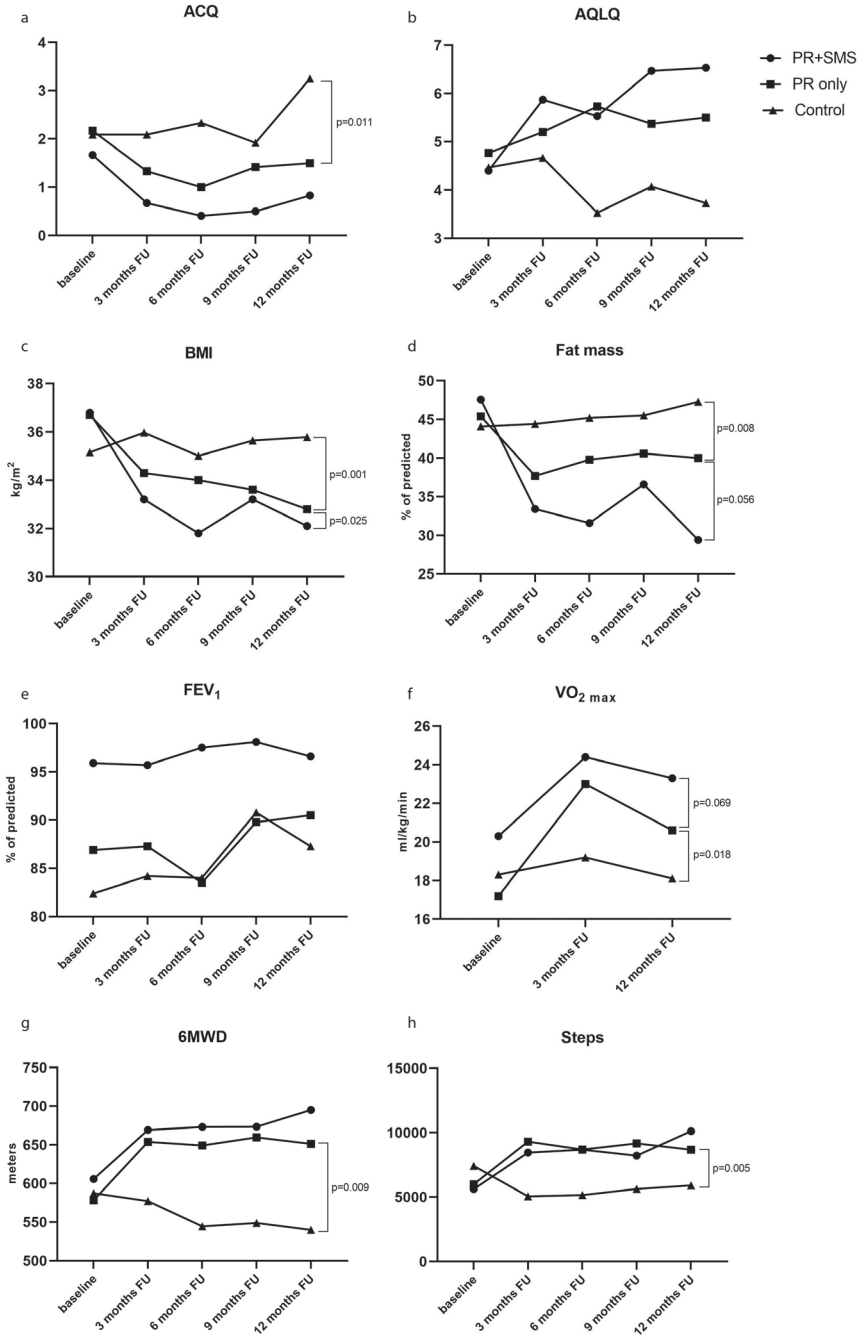

Figure 3: Changes over time in a) Asthma Control Questionnaire (ACQ), b) asthma-related quality of life (AQLQ), c) body mass index (BMI), d) fat mass, e) forced expiratory volume in 1 s (FEV_1), f) maximum exercise capacity (VO_{2max}), g) 6-min walk distance (6MWD), h) steps. Dots present mean or median values. p-value for difference between groups over time (repeated measurements (mixed model)).

Table 3: Change after 12 months.

	Change at 12 months vs baseline within groups	Mean difference between the groups over time* β-coefficient (95% CI)	p-value
ACQ			
Control	0.91 [-0.49-2.50]		
PR only	-0.59 [-1.62-0.22]	-1.06 [-1.84- -0.27]	**0.011**
PR+SMS	-1.05 [-0.84- -1.87]	-0.34 [-0.95-0.27]	0.252
AQLQ			
Control	-0.14 [-0.62-1.37]		
PR only	0.59 [-0.46-1.93]	0.28 [-0.65-1.22]	0.537
PR+SMS	0.60 [-0.44-2.50]	0.32 [-0.64-1.29]	0.483
BMI			
Control	0.78 [1.29]		
PR only	-2.15 [2.85]	-2.25 [-3.38- -1.11]	**0.001**
PR+SMS	-4.90 [6.11]	-2.27 [-4.20- -0.35]	**0.025**
Waist circumference (cm)			
Control	-0.33 [3.33]		
PR only	-4.88 [7.77]	-3.25 [-8.86-2.35]	0.239
PR+SMS	-12.5 [17.87]	-7.07 [-15.91-1.78]	0.109
Fat mass (%)			
Control	1.80 [1.11]		
PR only	-3.62 [4.41]	-2.63 [-4.42- -0.84]	**0.008**
PR+SMS	-6.30 [8.44]	-2.03 [-4.13-0.07]	0.056
FEV1 (%)			
Control	1.43 [6.32]		
PR only	4.50 [10.49]	0.24 [-5.40-5.87]	0.931
PR+SMS	0.00 [6.67]	3.37 [-4.41-11.14]	0.368
FRC (%)			
Control	8.83 [26.32]		
PR only	7.38 [13.50]	12.2 [7.91-16.5]	**<0.001**
PR+SMS	10.8 [5.89]	1.37 [-6.64-9.38]	0.702
VO_{2max} (%)			
Control	1.33 [14.07]		
PR only	11.7 [15.65]	12.04 [1.99-22.08]	**0.022**
PR+SMS	7.50 [3.70]	-7.83 [-19.58-3.92]	0.174
6MWD (m)			
Control	-40.38 [53.99]		
PR only	40.29 [53.52]	58.0 [16.9-99.1]	**0.009**
PR+SMS	81.40 [59.45]	10.5 [-25.98-46.91]	0.539
Steps			
Control	987 [-1621-5747]		
PR only	5591 [3480-4491]	3200 [1256-5144]	**0.005**
PR+SMS	902 [-282-2080]	740 [-1614-3095]	0.388

Data are presented as median [interquartile range] or mean±SD, unless otherwise stated. PR only: pulmonary rehabilitation only; PR+SMS: pulmonary rehabilitation+self-management support; ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; BMI: body mass index; FEV1: forced expiratory volume in 1 s; FRC: functional residual capacity; VO2max: maximal oxygen uptake; 6MWD: 6 min walking distance. p-value for difference between PR only versus control and PR+SMS versus PR only groups over time (repeated measurements (mixed model)). *: effect sizes adjusted for time, parameter baseline value and gender.

p=0.685) at 3 months. However, we found a trend for significant association of BMI with FRC (β=-0.61 CI [-1.23; 0.01], p=0.054) and VO_{2max} (β=-1.17 [-2.38; 0.037], p=0.057) at 12 months, but no association with ACQ (β=-0.03 [-0.12; 0.05], p=0.412) and AQLQ (β=-0.01 [-0.09; 0.77], p=0.901) were found. We observed no significant changes in the amount of daily steps or physical activity level at 3 months, but subjects in the PR only group had significant higher amount of daily steps compared to the subjects in the usual care group after 12 months of FU (β= 3200 CI [1256; 5144], p=0.005) (table 2, 3 and figure 3). There were no differences observed in airway inflammation (FeNO, sputum eosinophils and sputum neutrophils) between PR only and usual care groups after 3 and during 12 months of FU. However, there was a significant decrease in serum leptin levels in the PR only group compared to the control group after 3 months and during 12 months of FU (table 4). This decrease in serum leptin was significantly associated with reduction in BMI (β= 9.37 CI [4.60; 14.12], p=0.001).

Outcomes in pulmonary rehabilitation group *with* versus *without* the use of the online self-management support (PR only vs PR+SMS)

No differences were found in weight or body composition between PR only and PR+SMS groups at 3 months (table 2). However, during 12 months of FU, patients in the PR+SMS group had a significant lower weight (β=-6.23 CI [-11.3; -1.12;], p=0.021) and BMI (β=-2.27 CI [-4.20; 0.35], p=0.025) compared to subjects in the PR only group. In addition, there was a trend for a lower %fat mass in the PR+SMS group (β=-2.03 CI [-4.13; 0.07], p=0.056) (table 3, figure 3). No statistically significant differences were observed in changes of ACQ, AQLQ, lung function, exercise capacity (VO_{2max} and 6MWD) or activity level (PAL or daily steps) between PR+SMS and PR only group at 3 months and during 12 months of FU. We did not find any difference in FeNO, sputum eosinophils or neutrophils between these groups at 3 months and during 12 month of FU. Serum leptin levels decreased significantly more in the PR only group compared to the PR+SMS group at 3 months (β= 19.5 CI [5.65; 33.35], p=0.009) and this difference persisted during 12 months of FU (β= 20.66 CI [7.10; 34.21], p=0.006). However, we observed no differences in any of other inflammatory markers at 3 months or 12 months of follow-up (table 4).

Exacerbations

No difference in the proportion of patients with an asthma exacerbation during the 3 months intervention period were found between the PR only group and the control group (16.7% vs. 55.6%, p=0.16). In addition, no difference in the proportion of patients with an exacerbation was observed in PR+SMS vs PR only group. During the 12 months of follow-up, a higher rate of exacerbations was observed in the control group compared to the PR only group (β (poisson rate)=0.839 CI [0.116; 1.563], p=0.023; RR 2.314 CI [1.123; 4.773]) whereas no significant difference in exacerbation rate was seen between

PR+SMS group and the PR only group (β (poisson rate)=0.319 CI [-0.811; 1.449], p=0.580; RR 1.376 CI [0.444; 4.259]).

Table 4: Change of systemic inflammatory markers after 3 months and 12 months.

	Baseline	Change within groups after 3 months	P-value (1)	Mean difference between the groups over time* β-coefficient (95% CI)	p-value (2)
Leptin (ng/ml)					
Control	71.0 [49.0-103.0]	-3.0 [-10.5-3.3]		0.0 [-16.0-15.0]	
PR only	77.5 [47.3- 98.3]	-27 [-37- -16]‡	**0.001**	-7.0 [-42.0-20.0]	**0.018**
PR+SMS	17.5 [8.5-100.0]	-2.5 [-6.5-2.3]	**0.009**	-5.0 [-11.0-1.5]	**0.006**
Adiponectin (µg/ml)					
Control	39.0 [18.5-53.0]	-9.0 [-28.8-9.8]		-4.0 [-27.0-7.0]	
PR only	34.0 [17.8-103.8]	-6.0 [-15.0-22.0]	0.228	0.0 [-22.0-37.0]	0.384
PR+SMS	41.5 [22.8-102.8]	-14.0 [-37.8-21.3]	0.541	-13.0 [-56.0- -14.5]	0.361
hsCRP (ng/ml)					
Control	8672 [1653-27145]	6.0 [-1351-542]		-301 [10911-313]	
PR only	3209 [1657-8069]	-222 [-1136-1699]	0.802	-899 [-1947- -260]	0.462
PR+SMS	7837 [1070-22397]	-1800 [-11597- -569]‡	0.758	-1677 [-4760-3322]	0.415
Pentraxin (pg/ml)					
Control	361.9 [297.1-424.2]	30.1 [2.3-104.4]		78.1 [52.9-376.4]	
PR only	431.7 [364.3-514.5]	25.4 [-54.3-223.1]	0.645	23.2 [-126.5-218.1]	0.830
PR+SMS	378.8 [226.2-579.1]	90.6 [-0.33-300]	0.249	121.4 [121.4-336.7]	0.149
Eosinophills (10^9 cells/l)					
Control	0.20 [0.10-0.25]	0.0 [-0.10-0.00]		0.0 [-0.08-0.00]	
PR only	0.30 [0.10-0.50]	0.0 [-0.20-0.04]	0.987	-0.01 [-0.06-0.12]	0.636
PR+SMS	0.20 [0.10-0.40]	-0.05 [-0.13-0.10]	0.465	-0.07 [-0.15-0.00]	0.684
Leucocytes (10^9 cells/l)					
Control	6.95 [5.83-8.10]	0.5 [-1.3-1.7]		0.3 [-1.0-1.8]	
PR only	6.15 [5.40-8.05]	0.3 [-0.6-1.5]	0.722	0.1 [-1.4-0.4]	0.126
PR+SMS	8.70 [6.60-9.70]	0.3 [-1.7-1.1]	0.955	-0.3 [-0.9-0.6]	0.544

Data are presented as median [interquartile range], unless otherwise stated. hsCRP: high sensitivity C-reactive protein. p-value(1) for difference between PR only vs control or PR+SMS vs. PR only groups at 3 months (ANOVA); *) effect sizes adjusted for time, parameter baseline value and gender. p-value(2) for difference between PR only vs control and PR+SMS vs PR only groups at 12 months (Repeated measurements); ‡ $p \leq 0.05$ vs. baseline (Significance estimated by regression analysis of log-transformed inflammatory markers

DISCUSSION

In this pragmatic study, we investigated the short and long-term effects of a 3-months high intensity pulmonary rehabilitation program in obese patients with suboptimal controlled asthma. The majority of the patients had an uncontrolled type 2 asthma (GINA 4) and a low aerobic capacity at the time of inclusion. Nevertheless, high intensity interval training in this group of patients was found to be feasible. Moreover, this short-term PR-program resulted in a clinically relevant improvement of asthma control and marked

improvements in body composition, aerobic capacity, and lung function in a short period of three months. More importantly, the positive effects on asthma control (ACQ), BMI, exercise capacity and physical activity persisted during the 12 months of follow-up period. Although, we did not find any difference in the primary outcome: asthma control, between the PR only and PR+SMS groups at 3 months, we demonstrated that adding an internet-based self-management program on top of the PR program results in better weight management over time. The outcomes of this study emphasize the feasibility and the importance of lifestyle modification in this particular group of patients.

Despite the relevance of weight loss in asthmatics with obesity, there are only few randomized controlled trials available about weight loss interventions in these patients (24, 25). The first studies included only dietary interventions (26) or diet combined with weight loss medication (27). Although these interventions resulted in a significant weight loss and improvements in asthma symptoms at short-term, information on the persistence of these effects over a long period was lacking. The study of Scott et al. (8) was the first randomized study comparing a combined dietary and exercise intervention with diet or exercise alone. This study demonstrated that exercise alone had no effect on weight loss or asthma symptoms, and that a combined diet/exercise intervention should be the choice in obese asthmatics (8). However, in this study, not only obese, but also overweight subjects were included and the level of asthma control was better compared to that in the present study (ACQ 1.36 vs 2.0). The mean weight loss was 8.3% after 10 weeks of intervention, including a very strict caloric restriction of 885-1170 kcal/day and an exercise program with aerobic and resistance training. In contrast, Ma et al. (28) found modest weight loss (5% and 4%) after 6 and 12 months of lifestyle intervention, including a dietary restriction of 1200 kcal/day and at least 150 min of moderate intensity physical activity/week in 330 obese adults with uncontrolled asthma. The effects on asthma control were disappointing. The authors concluded that a weight loss of 10% or greater may be required for a clinically significant improvement in asthma outcomes (28). More recently, Freitas et al. demonstrated that a 3-month weight loss program with caloric restriction of approximately 1300 kcal/day, aerobic and resistance training results in significant improvements in body composition, asthma control, aerobic capacity, lung function, airway and systemic inflammation in obese adults with asthma (9). In the present study, a less strict caloric restriction of 1500 kcal/day combined with high intensity interval training (intensity ±90% of VO_{2max}) resulted in a mean weight loss of 5% in the PR only group and 12% in the PR+SMS group at 3 months, with persistent improvements in asthma control, BMI and exercise capacity in the majority of patients at 12 months.

Obesity is characterized by low-grade systemic inflammation with increased production of pro-inflammatory cytokines. In this study, we did not find any reduction in pro-

inflammatory cytokines, like Hs-CRP or Pentraxin, but we have demonstrated that there was a decrease in serum leptin levels in participants immediately after the PR program and during 12 months of FU. This decrease in serum leptin appeared strongly associated with the persistent decrease of BMI during 12 months of follow-up in the PR only group.

Although an intervention period of 3 months may appear short to achieve a lifestyle change, we have demonstrated that a short-term well-designed multidisciplinary PR program could result in long-term benefits. The positive effects on weight, aerobic capacity and symptoms could encourage patients to maintain their diet and exercise for a longer period. In addition, the use of an internet-based self-management program during and after the PR-program could be supportive for long-term adherence. As we have showed in the present study, compared to non-users, users of the SMS program on average had a significant lower BMI after 12 months of FU. The role of such innovative approaches in the management of asthma and obesity should be further explored (29-31).

The implementation of the new HIIT exercise program was well tolerated and successful in this group of patients who are limited by their weight as well as by their asthma. In addition, the rate of exacerbations was not higher in the intervention group, indicating that HIIT did not negatively affect asthma control. To our knowledge, this is the first study showing that HIIT is feasible in obese persons with suboptimal controlled asthma. Furthermore, it has been shown that HIIT is perceived to be more pleasant than moderate intensity continuous exercise (32). This may improve the adherence to exercise and promote health benefit over a longer period.

Another important issue is the cost-effectiveness of such rehabilitation programs. The cost of a 3-month rehabilitation program is approximately €3000,- p.p. The costs of an exacerbation varies between €500-3000,- depending on the extra visits, ER visits and the requirement of a clinical admission. So depending on the severity of the exacerbations and the long-lasting effect of the program, PR could ultimately be cost-effective. In the Netherlands this program is therefore only available for more severe, uncontrolled patients. However, the present study was not designed or powered to calculate cost-effectiveness.

Our study has some limitations. Firstly, this study comprises a relatively small sample (figure 1). It was very difficult to recruit suitable candidates for this study. Most eligible patients were unable to participate because of work or other reasons. Despite small group-sizes, our explorative study suggests that PR is effective and that SMS contributes to maintaining long-term effects. A larger study is needed to corroborate these results

with sufficient power. Our study participants were predominantly female, and able and motivated to participate in this program which could have resulted in a selection bias. However, in this kind of studies, motivation for participation is an important requirement for success. In addition, diets were not tailored to each patients, which could be a pitfall. This could explain the differences in weight loss between the patients, especially male patients could have lost much more weight with this amount of caloric restriction. However, our diet was less strict compared with other studies (8, 9). Finally, we have used an integrated pulmonary rehabilitation program, and were unable to determine the contribution of the four individual components of this program to the outcome. We have shown that the reduction of BMI is especially associated with improvements in lung function, but not with the improvement of asthma control. This indicates that it is not "just a matter of weight loss", but that the other components of the PR program, like exercise and psychological intervention are probably at least equally important to achieve improvements in asthma control.

The present study, despite its limitations, is the first demonstrating that a short-term multidisciplinary PR program with HIIT and the use of an internet based self-management program is feasible and effective at both short and long term, in suboptimal controlled asthmatics with obesity. Such well-designed PR programs should be considered in the treatment of obese asthmatics.

ACKNOWLEDGEMENTS

We wish to thank all employees of the departments of physiotherapy, dietetics, medical psychology, lung function and department of clinical chemistry at the Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands. We are grateful for the help of A. van Schadewijk and A.C. van der Linden (Leiden University Medical Center, Leiden, the Netherlands) in the analysis of serum markers of systemic inflammation

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SUPPLEMENT

S1 Randomization

For randomization, a research randomization program was used (http://www.randomizer.org/form.htm). Randomisation was not stratified. Patients were randomly assigned in a 1:1:1 ratio using a computer-generated permuted-block scheme. Allocation took place by an independent researcher after written consent had been obtained from all subjects and baseline data were collected, ensuring concealment of allocation.

S2 Exclusion criteria

Exclusion criteria were: current smoking or a smoking history of $\geq$ 10 pack years; asthma exacerbation (need of antibiotics/oral corticosteroids) in 6 weeks before inclusion; COPD or other pulmonary pathology apart from asthma, except for adequately treated OSAS with a Apnea Hypopnea Index < 5.0; and any significant orthopaedic of neurologic problems that reduce mobility or cooperation with physical training.

S3 Exercise training program

Training was performed three times per week for twelve weeks. Each training session was divided into four parts: the warming-up, stretching, the exercises and the cooling down. Between each part, the patients had thirty seconds rest and were allowed to drink some water. The warming up consisted of a seven-exercises routine, each exercise was thirty seconds. The routine was repeated 3 times. The intensity was progressive and patients were asked to reach a seven at the 10-grade Borg scale. The stretching consisted of ten minutes full-body stretching exercises, and aimed to improve the range of motion of joints, to prepare the body for the training and to prevent injuries. The number of sets completed in the exercises was increased during the first seven weeks. The patients started with three sets of four exercises. Each exercise was a bodyweight exercise and lasted 45 seconds. Between each series the patients had thirty seconds rest and they were allowed to drink some water. At the end of week seven (training 21 sessions) patients reached six set training session of four exercises. In each training session the patients were asked to maintain the intensity during the workout close to 90% of their VO_{2max} or to reach at least a seven at the 10-grade Borg scale.

The cooling down was also five minutes at the end of the training session. It consisted of full body exercises to return vital parameters to resting rate such as heart rate and breath before leaving the facility. During the cooling down there was no intensity target.

S4 Internet based self-management program "PatientCoach"

This program offers components for goal setting, tailored information, social forum and an e-consult option with health care professionals. In addition, the PatientCoach system includes modules for self-monitoring asthma control (ACQ), weight, lung function, feedback, medication plan, reminders and alerts. Furthermore, physical activity was monitored by an automated internet-based accelerometer (Fitbit, www.fitbit.com).

S5 Assessments

Body composition

Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). Obesity was defined as a BMI equal or greater to 30 kg/m^2. Fat mass (FM) and fat free mass (FFM) was measured with a bioelectrical impedance meter (Bodystat 1500, Bodystat Limited) and expressed as % of predicted. Metabolic syndrome was diagnosed according to the National Cholesterol Education Program's Adult treatment Panel III report (NCEP ATP-III) criteria (18).

Asthma control and asthma quality of life

Asthma control was assessed by the validated asthma control questionnaire (ACQ). It comprises 6 questions with different components of daytime symptoms and night time symptoms (14). Asthma related quality of life was measured with the validated asthma quality of life questionnaire (AQLQ) (15). For both questionnaires, a change of > 0.5 is considered as clinically relevant (14,15). An asthma exacerbation was defined as worsening of symptoms with need for oral corticosteroids and/or antibiotics)

Lung function

Pulmonary function was measured with standard spirometry (Vmax Encore 22D, Carefusion) and bodybox (Vmax encore 62j, Carefusion) according to the American Thoracic Society (ATS) / European Respiratory Society guidelines (ERS). Post-bronchodilator values were expressed as a percentage of predicted (16) . Methacholine challenge test was used to measure bronchial hyperresponsiveness (PD20). Fractional exhaled nitric oxide (Fe_{NO}) was measured with the Niox-Flex (Aerocrine AB, Sweden) at a constant flow rate of 50 ml/s and expressed as parts per billion in accordance with the guidelines of the American Thoracic Society and European Respiratory Society (19).

Exercise capacity

Aerobic capacity (VO_{2max}) was measured with a cardiopulmonary exercise test (CPET) performed on an Ergoselect cyclometer (Ergoline, Bitz, Germany) using a maximal symptom limited cardiopulmonary incremental protocol according to the recommendations

of the ATS/ACCP guidelines (17). The six-minute walking distance (6MWD) was measured by the six-minute walking test (6MWT), performed indoor using a 30 m walking course . Patient instruction and measurements were performed according to the ATS/ERS statement (25).

Daily activity

Daily activity such as daily steps and physical activity level (PAL) was measured with a portable movemonitor (DynaPort MoveMonitor, McRoberts, The Hague, The Netherlands), attached to the lower back by a belt. Participants were instructed to wear the movemonitor during 7 days at all times, except during water-related activities (20).

Blood sampling and analysis

Blood samples were obtained by venapuncture, and laboratory measurements were performed according to standard procedures by the department of Clinical Chemistry. For the analysis of serum markers of systemic inflammation, serum aliquots were frozen at -80°C and analysed in bulk. The Meso Scale Discovery Platform (Meso Scale Discovery, Gaitherburg, MD) was used to detect leptin, adiponectin and high sensitivity (hs)-CRP. Serum Pentraxin was analyzed using a commercial ELISA (Hycult Biotech (HBT)).

Sputum induction and analysis

Sputum induction with hypertonic saline (4.5%) and processing was performed by a validated method according to the guidelines (21-23). An ultrasonic nebulizer (Klava) with a two-way non-rebreathing valve (Hans Rudolph) and an output of 2 ml/min was used for induction. Before start and during the procedure, spirometry (Vmax Encore 22D, Carefusion) was performed to assess the lung function at baseline and during sputum induction. Pre-treatment with salbutamol 400 µg was given in order to prevent excessive bronchoconstriction. The expectorated sputum was kept at 4°C and processed immediately after collection to obtain cells and supernatant. For sputum processing, the whole sample was mixed with the same volume of sputolysin reagent (DTT), then placed in a shaking water bath of 37°C for 15 minutes for homogenization. After this, the sample was filtered through a 100 µm filter and centrifuged (1500 rpm;10 min). The supernatant was removed and was stored at -80°C. The cell pellet was resuspended in PBS/1% (w/v) human serum albumin (HSA). Total cell counts were determined with a Bürker Haemocytometer and cell viability was assessed using the by trypan blue exclusion method. Cytospins were made and stained with May-Grünwald-Giemsa. Differential cell counts were performed by counting at least 400 non-squamous sputum cells. Samples with more than 80% squamous cells were excluded from analysis (21-24).

S6 Statistical analysis

Baseline variables were summarized as mean±SD for continuous variables with normal distributions, median (interquartile range) for continuous variables with skewed distributions, and n (%) for categorical variables. The 3 and 12 months differences within groups were summarized as mean±SD or median (IQR) depending on the shape of the distribution and tested with the paired Student's t-test or the nonparametric Wilcoxon matched pairs test, respectively.

Part B

Pathophysiology of obesity related asthma

5 Characterization of inflammation in visceral adipose tissue from obese asthma patients

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Submitted

ABSTRACT

Objective: To quantify adipose tissue inflammation in morbidly obese asthmatics and obese controls and to correlate this with clinical asthma parameters and with systemic inflammation markers to determine whether adipose tissue inflammation plays a role in the pathology of asthma in the obese.

Methods: Visceral adipose tissue (VAT) was collected from obese patients with and without asthma (n=36 vs. n=50) undergoing bariatric surgery. Immunohistochemistry was performed to identify mast cells, total ($CD68^+$), M1 ($CD11c^+CD68^+$) and M2 ($CD206^+CD68^+$) macrophages. In addition, "crown-like structures" (CLS) were counted, and mRNA expression of leptin, adiponectin and IL-6 in VAT was assessed by RT-PCR. Serum markers of systemic inflammation were measured by ELISA.

Results: No differences were observed in numbers of macrophages, mast cells and leptin, adiponectin and IL-6 mRNA expression in VAT of morbidly obese asthmatics and morbidly obese controls. Solitary macrophages in VAT expressed CD206 reminiscent of a M2 phenotype, and only macrophages in CLS expressed M1 marker CD11c. However, no differences in the number of CLS were detected. Obese subjects with uncontrolled asthma had higher serum IL-6 and hs-CRP levels compared to obese controls, and serum IL-6 was associated with bronchial hyperreactivity.

Conclusion: No evidence for increased inflammation in adipose tissue was found between morbidly obese asthmatics and morbidly obese controls. Uncontrolled asthma in the obese is associated with increased systemic inflammation. However, no evidence for a contribution of VAT to this systemic inflammation was found.

INTRODUCTION

Obesity related asthma is increasingly recognized as a distinct phenotype (1). This phenotype is usually characterized by adult-onset of symptoms, female predominance, high symptom expression and relative insensitivity to corticosteroids. Th2-related inflammation in the airways of patients with obesity related asthma is rare, and this phenotype of asthma seems rather to be characterized by non-eosinophilic airway inflammation (2, 3). Some studies reported an association between obesity and sputum neutrophilia in female (4, 5), while other studies found no evidence of airway inflammation in obese asthmatics compared to obese controls (6, 7). Until now, the exact pathophysiology of obesity related asthma is not fully understood, but it is likely that multiple mechanisms are involved. Mechanisms that have been implicated include mechanical changes of the lung with a decrease in functional residual capacity (FRC) and expiratory residual volume (ERV); asthma-related comorbidity like gastro-oesophageal reflux disease (GERD) and obstructive sleep-apnoea (OSA); increase in systemic oxidative stress; dietary factors and decrease in physical activity; an imbalance in leptin/adiponectin ratio; changes in gut microbiota; and systemic inflammation (8, 9).

Obesity is characterized by a low-grade systemic inflammation with increased production of pro-inflammatory cytokines, like interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α) (6, 10). This inflammation is mediated by recruitment and classical activation of macrophages in the obese visceral adipose tissue (11). Classically or M1 activated macrophages produce pro-inflammatory cytokines (IL-1β, IL-6, IL-12, IL-23 and TNF-α), reactive oxygen species (ROS) and metalloproteinases (12, 13). Visceral fat tissue in lean state is characterized by the presence of alternatively or M2-activated macrophages (14). This type of activated macrophages is considered to largely serve an anti-inflammatory/pro-repair function, and develops after exposure to mediators such as IL-4 and IL-13, M-CSF, corticosteroids or immune complexes, among others. They play important roles in Th2 responses and parasite defences. In addition, they can contribute to resolution of inflammation and tissue repair with increased production of anti-inflammatory mediators (IL-1Ra, IL-10, transforming growth factor (TGF- β)) (15).

In obesity, the recruitment and activation of macrophages toward a pro-inflammatory state in visceral fat tissue is a result of local hypoxia due to hypertrophy of adipocytes. It is thought that adipocyte cell death leads to accumulation of Adipose Tissue Macrophages (ATMs) around the adipocyte, forming so-called "crown-like" structures to scavenge cell debris and free lipid droplets (11, 14, 16-18). This "phenotypic" switch of macrophages is linked to insulin resistance, cardiovascular diseases, and other obesity related comorbidities (19-22). There are few recent studies available linking

pro-inflammatory macrophages in adipose tissue with asthma. The study of Sideleva *et al*. found increased macrophage infiltration and an increased expression of leptin in visceral adipose tissue of obese subjects with asthma compared to obese controls (7). In a study of Periyalil *et al*., higher percentages of M1 macrophages in visceral adipose tissue of obese asthmatics compared to obese controls were reported (23). However, the role of adipose tissue inflammation and systemic inflammation in the pathology of obesity-related asthma still needs to be explored.

The objective of the present study was to quantify adipose tissue inflammation in morbidly obese asthmatics and morbidly obese controls and to correlate this with clinical asthma parameters and with markers of systemic inflammation to determine whether adipose tissue inflammation plays a role in the pathology of asthma in morbidly obese subjects.

METHODS

Study design

A cross-sectional study was performed to characterize adipose tissue inflammation in morbidly obese patients with and without asthma. This study is a part of a larger longitudinal study from which previously results were published (6, 24, 25).

Study population

Morbidly obese adults with and without asthma who were screened preoperatively for bariatric surgery were included in this study. Subjects were between 18 and 50 years of age, and had a Body Mass Index (BMI) of 35 kg/m^2 or more. Asthma was diagnosed according to GINA guidelines (26). Patients were excluded if they had a history of smoking more than 10 pack years or if they were currently smoking more than 10 cigarettes a day; were using oral corticosteroids; had a recent exacerbation of asthma ($\leq$ 4 weeks); were unable to perform pulmonary function tests; or had other pulmonary disease than asthma. Written informed consent was obtained from all subjects and the local ethics committee (Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam) approved the study protocol (Netherlands Trial Register 3204).

Clinical assessment

Pulmonary function tests (spirometry, exhaled Nitric Oxide (Fe_{NO}), diffusion capacity and Methacholine provocation test) and skin-prick tests were performed during two visits before bariatric surgery. Asthma symptoms were assessed by the asthma control Questionnaire (ACQ) (27) and the mini Asthma Quality of Life Questionnaire (AQLQ) (28).

Metabolic syndrome was diagnosed according to the National Cholesterol Education Program's Adult treatment Panel III report (NCEP ATP-III) criteria when ≥3 of the following 5 risk factors were present: abdominal obesity, an elevated level of serum triglycerides, low serum of high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, and high serum glucose level or treatment for any of these disorders (29). Further details about assessments are described in a previous study (24).

Blood sampling

Most laboratory measurements were performed according to standard procedures by our Department of Clinical Chemistry. Plasma-cholesterol, HDL-cholesterol, glucose and triglycerides were measured using LX-20 and DxC analyzers (Beckman Coulter, Miami, FL, USA). LDL-cholesterol was calculated using the Friedewald formula. Blood cell counts and 5-part leukocyte differentiation were determined automatically using LH750 or DxH800 analyzers (Beckman Coulter). Serum samples were obtained before bariatric surgery, and stored at -80°C. Serum markers of systemic inflammation were assessed using the Meso Scale Discovery Platform (Meso Scale Discovery, Gaitherburg, MD), for IL-6, IL-8, high sensitivity (hs)-CRP, TNF-α, GM-CSF, leptin and adiponectin. Lower and upper limit of detection were respectively 0.7-2500 pg/ml, 0.6-2500 pg/ml, 0.05-142 µg/ml, 0.8-2500 pg/ml, 0.61-2500 pg/ml, 0.2-100 ng/ml and 0.064-1000 µg/ml. All values that were below or above the lower or upper limit of detection of the assay, were arbitrarily set at these limits. These data on systemic inflammation in these study group have been published before (6). We repeated the statistical analysis of the data from the subgroup of patients who were included in the present study.

Adipose tissue sampling and analysis

Visceral adipose tissue (VAT) was obtained during bariatric surgery and fixed in formalin. After embedding in paraffin, 4 µm slices were cut. Immunohistochemistry was performed to identify mast cells (AA1 [tryptase]$^+$) and macrophages (CD68$^+$). Double staining for M1 (CD11c$^+$CD68$^+$) and M2 (CD206$^+$CD68$^+$) macrophages was performed. The primary antibodies were mouse-anti human CD68 (1:250, clone PG-M1, DAKO), rabbit-anti human CD11c (1:50, Abcam) and rabbit-anti human CD206 (1:1000, Abcam). As secondary antibodies Dako-envision+system-HRP Anti Rabbit and BrightVision poly AP-anti-Mouse were used. VECTORNovaRED substrate kit for peroxidase and VECTOR BCIP/NBT subtrate kit for alkaline phosphatase served as chromogens. Details about the color staining procedures are described in supplemental file (S1). Both solitary CD68 positive and double positive (CD11c$^+$CD68$^+$ or CD206$^+$CD68$^+$) cells were counted and expressed as positive cells per area of adipose tissue section. The number of "crown-like structures" (CLS) was counted and expressed in CLS/area. Crowns were defined as three or more CD68 positive cells surrounding an adipocyte. Quantitative RT-PCR was

performed to measure normalised mRNA expression of leptin, adiponectin and IL-6 in VAT, using the relative standard curve method. RPL13A served as a reference gene. The assays were performed on a Bio-rad CFX Realtime PCR system with the use of IQ SYBRGreen supermix (Bio-rad, Hercules, CA, USA). Primer sequences are shown in table 1.

Table 1: Primer pairs used for RT-PCR

Name	Forward	Reverse
Human leptin	5'AATGCATTGGGGAACCCTGT3'	5'AGGAGACTGACTGCGTGTGT3'
Human adiponectin	5'ACTGCAACATTCCTGGGCTG3'	5'GGAGGCCTGGTCCACATTAT3'
Human IL-6	5'CAGAGCTGTGCAGATGAGTACA3'	5'GATGAGTTGTCATGTCCTGCA3'
Human RPL13A	5'AAGGTGGTGGTCGTACGCTGTG3'	5'CGGGAAGGGTTGGTGTTCATCC3'

Statistical analysis

Categorical data were presented as percentages and continuous variables were summarized as median values with interquartile ranges (IQR). Differences between groups were analysed with the independent samples test (Mann Whitney U test). Differences were considered significant when $p<0.05$. Correlations between inflammatory markers in adipose tissue and blood with clinical variables were performed by the use of Spearman correlation analyses. Statistical analysis was performed with PASW statistics 25.

RESULTS

Baseline characteristics are shown in table 2. A total of 86 patients were included in the original study (24). Of these, 79 participants (31 morbidly obese asthmatics, 48 morbidly obese controls), had sufficient visceral fat tissue available for analysis. As expected, obese asthmatics had a lower FEV_1 (85.6% vs. 97.0%, $p<0.001$), a lower PD20 (0.37 vs 1.80 mg, $p <0.001$), a higher asthma control questionnaire score (ACQ 1.14 vs. 0.29, $p<0.001$) and a lower asthma related quality of life (AQLQ 5.80 vs. 6.57, $p <0.005$). There were no differences in baseline eosinophil counts, but there was a trend for a higher leukocyte count in obese asthmatics (table 2). Although, there was no difference in BMI between morbidly obese asthmatics and controls, morbidly obese asthmatics had a significant higher abdominal circumference (132.5 vs. 127 cm, $p=0.042$), and a higher level of serum triglycerides (1.18 vs 0.88 $x10^9$/l, $p=0.014$).

Systemic inflammation

In line with our previous findings in the complete patient group (6), also in this subset of the original cohort we found that morbidly obese asthmatics had statistical significant higher serum IL-6 levels compared to morbidly obese controls (0.71 vs. 0.70 pg/ml,

Table 2: Baseline characteristics.

	Morbidly obese asthmatics (n=31)	Morbidly obese controls (n=48)	p-value
Gender (% female)	77.4	81.3	0.679
Age (years)	32.0 [26.0-43.0]	38.0 [28.3-44.0]	0.350
Weight (kg)	127.4 [115.8-146.8]	126.0 [114.2-147.3]	0.637
BMI (kg/m^2)	44.8 [41.0-49.4]	43.0 [40.8-48.0]	0.393
Abdominal circumference (cm)	132.5 [123.1-140.8]	127.0 [119.0-134.5]	**0.044**
Smoking (%never/ever/current)	54.8/16.1/29.1	70.8/16.7/12.5	0.161
Diabetes (%)	3.2	16.7	0.066
Leucocyte count (10^9/l)	8.8 [7.5-10.3]	8.0 [7.1-9.0]	**0.044**
Eosinophils (10^9/l))	0.1 [0.0-0.2]	0.1 [0.0-0.1]	0.256
Total cholesterol	5.1 [4.4-5.9]	5.0 [4.4-5.6]	0.786
Triglycerides	1.2 [0.9-1.9]	0.9 [0.6-1.3]	**0.011**
HDL cholesterol	1.10 [1.00-1.30]	1.3 [1.00-1.5]	0.096
FEV_1 (% predicted, pre)	86.0 [76.0-97.0]	97.5 [89.0-106.8]	**<0.001**
PD20 (methacholine, mg)	0.37 [0.09-1.09]	1.80 [1.80-1.80]	**<0.001**
TLC (%predicted)	95.0 [87.0-102.0]	95.0 [86.5-101.0]	0.904
ACQ	1.14 [0.59-1.70]	0.29 [0.00-0.68]	**<0.001**
AQLQ	5.80 [4.97-6.27]	6.60 [5.47-6.87]	**<0.005**

Data are presented as median [interquartile range]. Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; PD20, cumulative doses of methacholine leading to 20% decrease in FEV_1; TLC, total lung capacity; ACQ, Asthma Control Questionnaire; AQLQ, Asthma quality of Life Questionnaire.

p=0.009). However, the absolute difference between the groups was very small and not clinically relevant. There was no significant difference between other markers of systemic inflammation (hs-CRP, leptin, adiponectin, GM-CSF and TNF-α) between morbidly obese asthmatics and controls (table 3).

Table 3. Markers of systemic inflammation.

	Morbidly obese asthmatics (n=31)	Morbidly obese controls (n=48)	p-value
hs-CRP (µg/ml)	34.27 [23.58-56.57]	31.52 [15.84-58.56]	0.441
Leptin (ng/ml)	68.66 [36.91-94.05]	68.34 [38.09-88.20]	0.734
Adiponectin (µg/ml)	12.00 [9.73-16.40]	13.99 [10.46-16.13]	0.334
GM-CSF (pg/ml)	0.61 [0.61-0.61]	0.61 [0.61-0.61]	0.161
IL-6 (pg/ml)	0.71 [0.70-0.97]	0.70 [0.70-0.70]	**0.009**
IL-8 (pg/ml)	3.86 [3.08-5.33]	3.88 [3.13-5.24]	0.739
TNF-α (pg/ml)	0.80 [0.80-0.80]	0.80 [0.80-0.80]	0.772

Data are presented as median [interquartile range]. hs-CRP, high-sensitivity C-reactive protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-6, interleukin 6; IL-8, interleukin 8; TNF-α, tumour necrosis factor-alpha.

Adipose tissue

There was no difference in the amount and size of fat cells between these groups (Figure 1a+b). In addition, there was no difference in the total number of mast cells and macrophages in adipose tissue of obese asthmatics and obese controls (Figure 1c+d). Interestingly, solitary macrophages in VAT expressed the M2 marker CD206, and only macrophages in "crown-like structures" expressed the M1 marker CD11c (Figure 2a+b). However, comparing the area of CLS or the CLS/M2 ratio between the groups revealed no differences between controls and asthmatics (Figure 1e). In addition, leptin, adiponectin

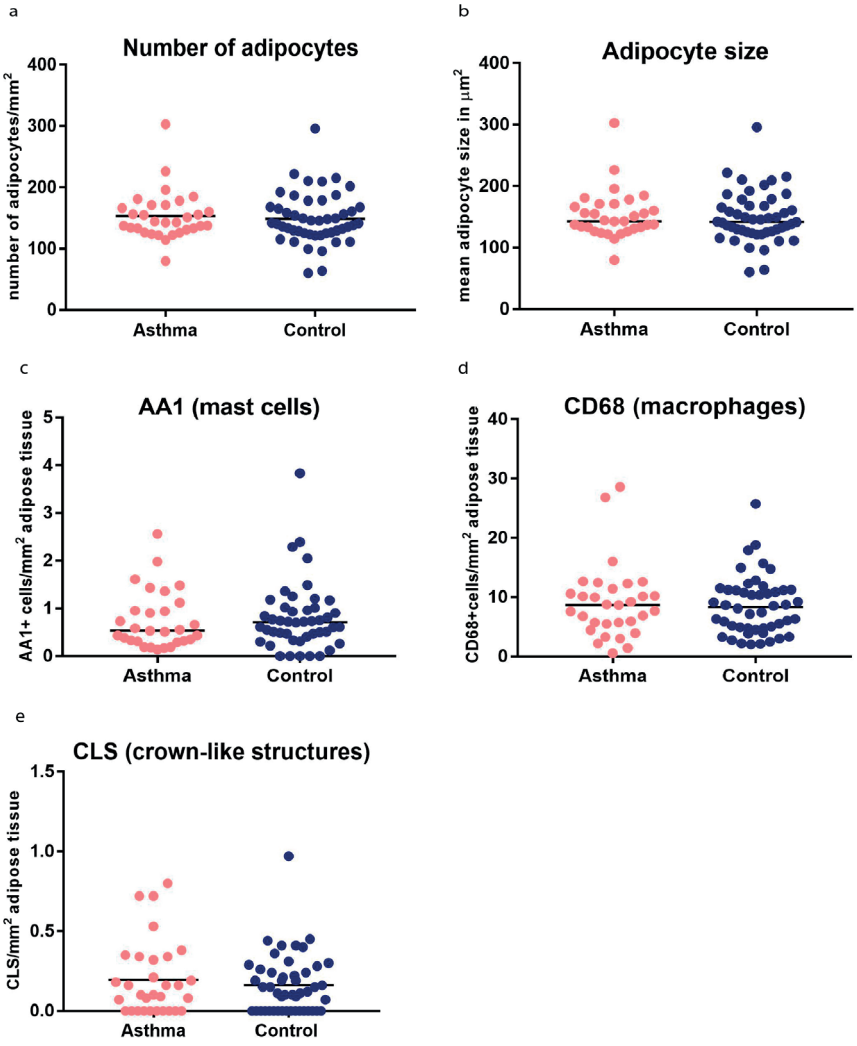

Figure 1: Number of a) adipocytes; b) size of adipocytes c) mast cells (AA1; tryptase$^+$); d) macrophages (CD68$^+$); and e) number of crown-like structures (CLS) in adipose tissue of obese asthmatics and obese controls. Horizontal bar represents the median values.

and IL-6 mRNA expression in VAT did not differ between obese patients with asthma and obese controls (Figure 3).

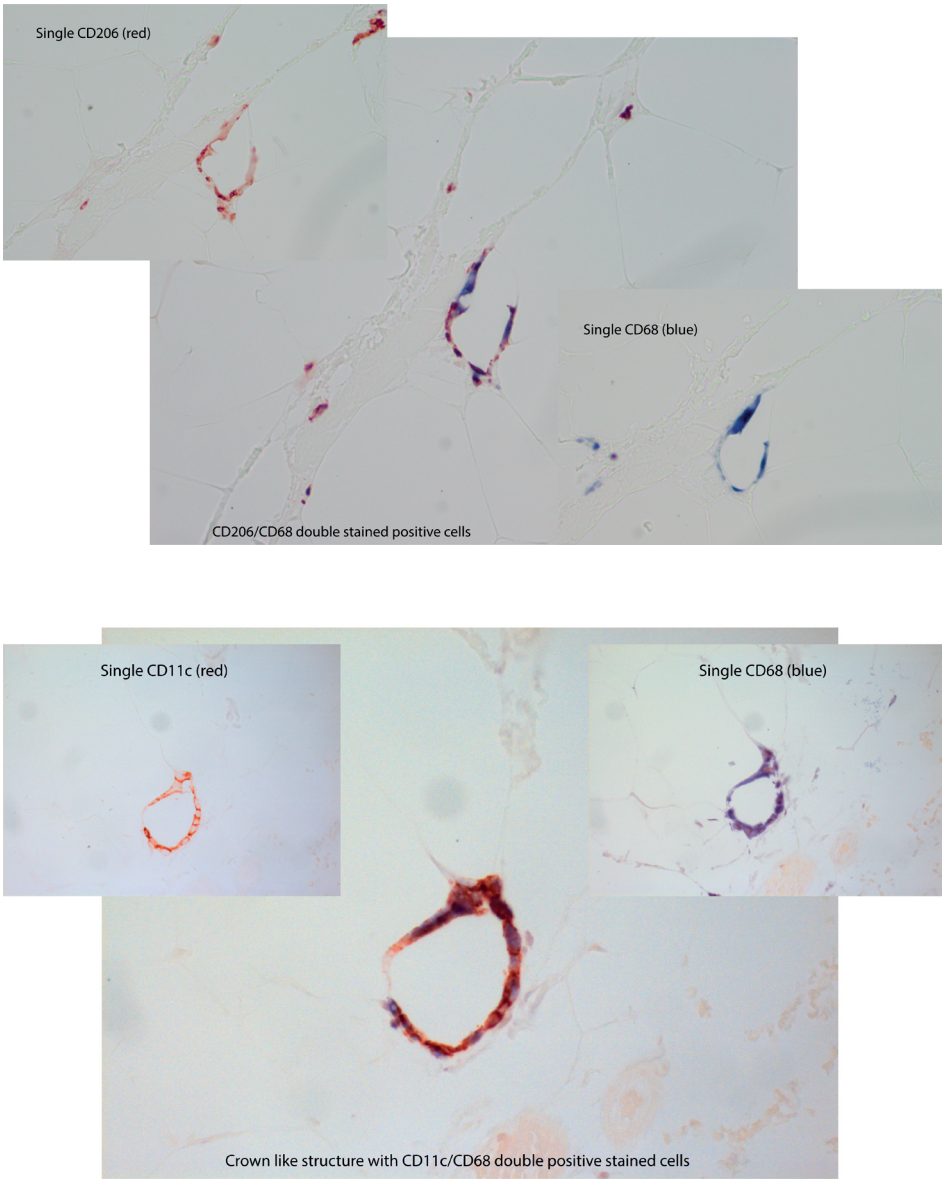

Figure 2: a) Solitary adipose tissue macrophages (ATMs) expressing CD68 (blue) and the M2 marker CD206 (red); b) Macrophages in "crown-like structure" expressing CD68 (blue) and the M1 marker CD11c (red)

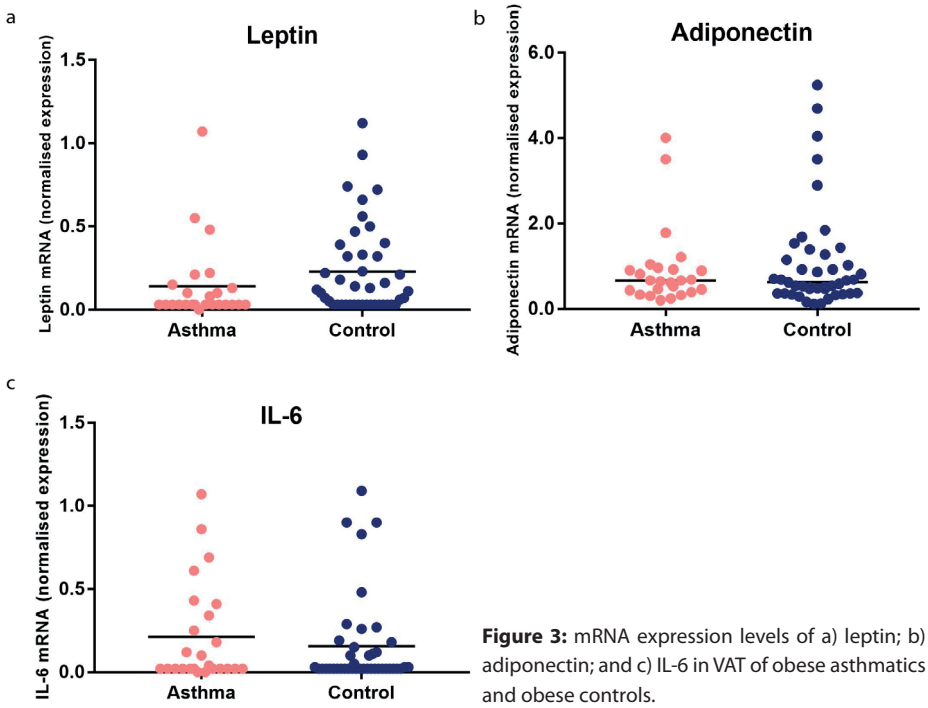

Figure 3: mRNA expression levels of a) leptin; b) adiponectin; and c) IL-6 in VAT of obese asthmatics and obese controls.

Subgroup analysis in asthmatics

Asthma subjects with uncontrolled asthma (ACQ ≥1.5) (n=8) had significant lower serum levels of adiponectin (9.6 [8.7-10.9] µg/ml vs. 14.0 [10.5-16.8] µg/ml, p=0.010) and higher levels of hsCRP (57.5 [34.8-91.6] vs. 30.7 [20.2-46.3] µg/ml, p=0.048) compared to asthmatics with controlled asthma. No difference in expression levels of leptin, adiponectin and IL-6 in adipose tissue were observed between asthma subjects with controlled and uncontrolled asthma. When we compared uncontrolled asthmatics with controls, we found significantly higher serum levels of IL-6 (0.9 [0.7-1.0] pg/ml vs. 0.70 [0.70-0.72] pg/ml, p=0.005), hsCRP (57.5 [34.8-91.6] µg/ml vs. 31.5 [15.8-58.6] µg/ml, p=0.023) and lower serum levels of adiponectin (9.6 [8.7-10.9] µg/ml vs. 14.0 [10.5-16.1] µg/ml, p=0.007) in asthmatics. No differences in expression levels of these cytokines in adipose tissue were observed between uncontrolled asthmatics and controls.

Metabolic syndrome

The percentage of subjects with metabolic syndrome was the same between obese patients with and without asthma. Subjects with metabolic syndrome had significantly more solitary macrophages and CLS per area of adipose tissue compared to subjects without metabolic syndrome (p=0.036; p=0.013 resp.). However, no difference in mRNA

expression of IL-6, leptin and adiponectin in adipose tissue were observed between subjects with and without metabolic syndrome.

Correlations between adipose tissue, systemic inflammation and clinical parameters

We found a correlation between abdominal circumference and the expression of leptin in VAT (r=0.531, p =0.011) (figure 4). There was a positive correlation between the number of solitary macrophages and the number of CLS per area in adipose tissue (r=0.554, p<0.001). A higher abdominal circumference was associated with worse asthma control (r=0.246, p=0.040) and a lower FEV_1 (% predicted) (r=-0.271, p=0.018). However, these correlations were weak. Interestingly, a higher serum IL-6 was significantly associated with bronchial hyperresponsiveness (PD20) (r=-0.342, p=0.002). There were no associations found with any of the inflammation markers in VAT with bronchial hyperresponsiveness (PD20).

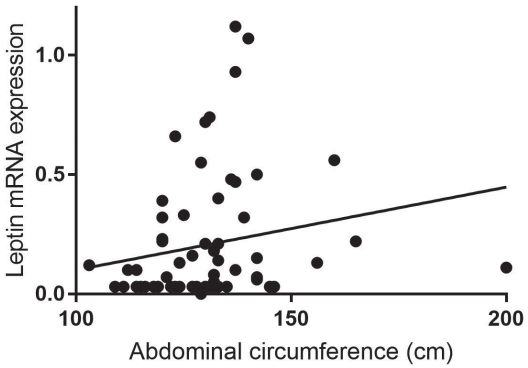

Figure 4: Correlations between abdominal circumference and mRNA (normalised expression) levels of leptin (r=0.531, p=0.011).

DISCUSSION

In both our previous analysis and in the subgroup analysis of the subjects selected for the present study we found that obese subjects with uncontrolled asthma had significantly higher serum levels of IL-6, hs-CRP and lower serum levels of adiponectin compared to obese controls (6). These findings indicate that uncontrolled asthma is associated with systemic inflammation. However, when we compared the total group of asthma patients with controls, no difference in systemic inflammation was found. More importantly, we found no differences in the numbers of macrophages (CD68), crown like structures, mast cells and mRNA expression levels of IL-6, adiponectin and leptin in VAT of obese asthmatics compared to obese controls. We found no associations with any of

the adipose tissue inflammation markers and lung function (FEV_1) or asthma control. The findings of this study are consistent with our previous findings on inflammation in lung tissue in which no differences were observed in submucosal cell counts of eosinophils, neutrophils, mast cells, macrophages, B-cells and T cells in bronchial biopsies of morbidly obese asthmatics compared to obese controls (6).

Our findings are not fully in line with the outcomes of other recently published studies. The group of Periyalil et al. used flow cytometry and observed a higher percentage of M1 ATMs (CD11c+, $CD206^{med}$) in VAT of obese asthmatics. Moreover, the percentage of M1 macrophages was associated with macrophage counts in sputum and a lower FEV_1 (23). The study of Sideleva et al. showed increased macrophage infiltration and an increased expression of leptin in visceral adipose tissue of obese subjects with asthma compared to obese controls. They found no evidence of increased airway inflammation in obese asthmatics, but airway epithelial cells of asthmatics had higher expression of adiponectin receptor-2 and T-cadherin (that also binds adiponectin). In addition, leptin levels were higher and adiponectin levels were lower in BAL of obese asthmatics, suggesting a direct link between these metabolic parameters and the airways. Moreover, airway reactivity was found to be significantly associated with visceral fat leptin expression (7). In the present study, we found no associations with any of the adipose tissue inflammation markers with airway hyperreactivity, but there was a significant association between serum IL-6 and bronchial hyperreactivity indicating that systemic inflammation and IL-6 may play a role in the pathophysiology of asthma in the obese.

In the before mentioned studies, as well as in the present study, included subjects were comparable: pre-dominantly female with morbid obesity and late onset asthma with no eosinophilic or neutrophilic airway inflammation. However, there were methodological differences that may explain the differences. Using immunohistochemistry, we were able to identify both M1 and M2 macrophages in human adipose tissue. Interestingly, macrophages in adipose tissue of obese subjects were mainly of a CD206+ M2 phenotype, and only macrophages in crown-like structures were expressing the M1 marker CD11c+, which constituted a very small proportion of ATMs. Although this finding is in apparent contrast with most experimental data in mice, it is in line with previous studies in human adipose tissue. Spencer et al. showed that compared to lean adipose tissue, obese adipose tissue contains more CLS, and that the majority of macrophages were not organized in CLS and were associated with fibrosis. They showed that macrophages in CLS were predominantly CD11+ M1, but most other macrophages were CD206+ M2 (30). Boulier et al. found that ATMs that accumulate in fat mass exhibit a CD206+ M2 phenotype rather than a CD11c+ M1 phenotype (31) and Fjeldborg et al. showed elevated numbers of macrophages with a preponderance of M2 (CD206/CD14) and lower

expression of M1 markers (MCP-1/CD14, IL6/CD14) in adipose tissue of obese subjects (16). Finally, some studies have reported that ATMs can express both M1 and M2 markers, and that CD206+ M2 macrophages are capable of producing pro-inflammatory mediators (11, 32). Therefore, ATMs are heterogeneous and results may depend on different methodological techniques and markers used. Results of different studies should therefore be interpreted with caution and the markers used should be clearly noted as recently advised by Murray et al (33).

Adipose tissue and systemic inflammation are known to be associated with insulin insensitivity, diabetes type II and other features of metabolic syndrome (34, 35), but their role in asthma needs to be explored. Interestingly, in the present study obese asthmatics had a higher abdominal circumference and increased level of triglycerides, as compared to obese controls, both markers of metabolic syndrome, but the percentage of subjects with metabolic syndrome was not different between obese asthmatics and obese controls. Adipose tissue of subjects with metabolic syndrome had more CD68+ macrophages and CLS (CD11c+ M1 macrophages) compared to subject without metabolic syndrome. In addition, abdominal circumference was associated with expression of leptin in VAT. Negative correlations were found between abdominal circumference with both asthma control and FEV_1. Although these correlations were weak, it is in line with previous published data showing that metabolic syndrome is associated with impaired lung function and more severe asthma (36-38).

A recent study by Peters et al. showed that obese asthmatics with high systemic IL-6 levels were more likely to have hypertension and leucocytosis, which are features of metabolic dysfunction. In addition, systemic IL-6 inflammation was associated with severe asthma in both obese and non-obese asthmatics with metabolic dysfunction (39). This indicates that IL-6 is a marker of metabolic dysfunction and may play a causal role in the severity of asthma. Despite the higher levels of systemic IL-6 in obese subjects with uncontrolled asthma compared to obese controls and the association between systemic IL-6 and airway hyperreactivity in the present study, there was no association between systemic IL-6 expression and lung function or asthma control. An explanation for this could be that the majority of included subjects had mild to moderate asthma, diagnosed during pre-operative screening for bariatric surgery. This is also confirmed by the fact that we did not find differences in serum IL-6 levels between controlled asthmatics and controls.

Another limitation of our study is the lack of fat tissue for analysis after weight loss by bariatric surgery, which could have provided more insight to inflammatory processes in adipose tissue in both asthmatics and non-asthmatics. In addition, we were not able to perform qualitative double staining of M1 and M2 macrophages in bronchial tissue due

to technical problems, which could provide more details about the role of macrophage subsets in the airways of obese asthmatics. In addition, we could not do flow cytometry due to the lack of fresh material. Furthermore, due to the cross-sectional study design, we cannot prove causal relationships between inflammatory markers and clinical parameters in obese asthma.

Despite the limitations in this study, we were able to confirm that VAT of the obese is characterized by mainly CD206+ M2 macrophages. In addition, we have shown that uncontrolled asthma in the obese is associated with increased systemic inflammation. However, we were unable to show evidence for increased inflammation in adipose tissue as a source of this increased systemic inflammation in obese asthmatics. Future research in this field could provide more insight in the links between adipose tissue inflammation, metabolic syndrome and the pathophysiology of asthma in the obese.

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SUPPLEMENT

S1

Details about the staining procedure:

We performed the double staining according to the protocol as described by Vector laboratories (https://vectorlabs.com/discovery-through-color/multiple-antigen-labeling-sub-section).

We selected a combination of Vector Nova Red as a peroxidase substrate, and BCIP/NBT as substrate for alkaline phosphatase. We first performed the single stainings for all the antibodies, and next tested several combinations of substrates and varied the order in which we applied the antibodies and the substrates. We finally selected the combination that gave similar results as the single stainings. Both secondary antibody complexes were raised in goat (goat anti-rabbit- EnVision -HRP and goat anti-mouse Polyvision-AP), which also diminishes the change of crossreactivity.

For CD11c/CD68 the optimized procedure was as follows:

- Antigen retrieval pH=9.0
- Incubation with anti-CD11c (rabbit), followed by anti-rabbit -HRP Envision complex
- Substrate development with Novared (red)
- Incubation with anti-CD68 (mouse), followed by anti-mouse-AP Polyvision complex
- Substrate development with BCIP/NBT (blue)

No counterstaining was applied

For CD206/CD68 the optimized procedure was as follows:

- Antigen retrieval pH=9.0
- Incubation with rabbit anti-CD206 and mouse anti-CD68 simultaneously
- Incubation with anti-rabbit-HRP Envision complex
- Incubation with anti-mouse-AP Polyvision complex
- Substrate development with BCIP/NBT (blue)
- Substrate development with Novared (red)

No counterstaining was applied

Supplementary figures

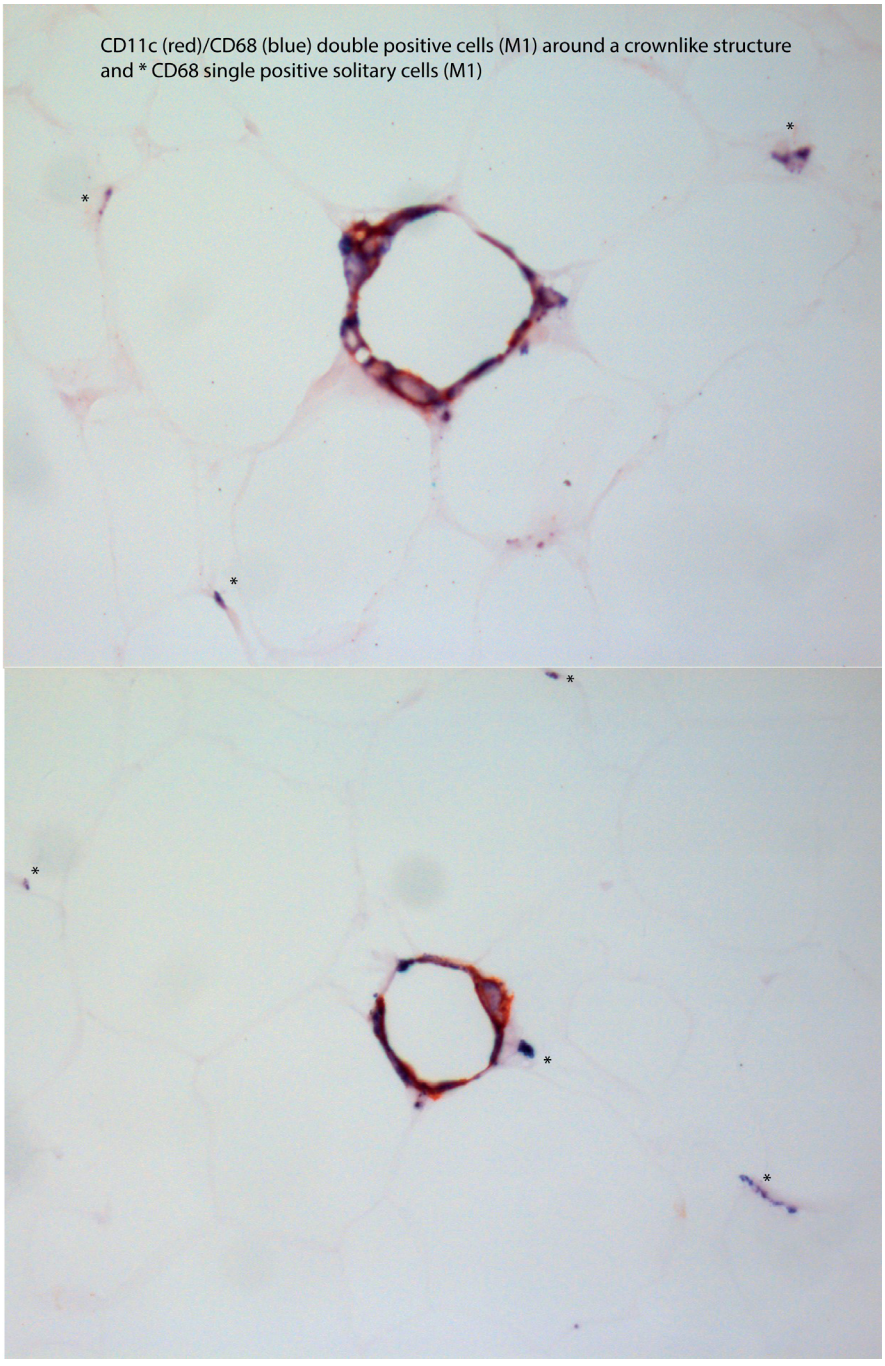

Figure S1a: Adipose tissue with CD11c (red)/CD68 (blue) double positive cells (M1) around a crown-like structure and CD68 single positive solitary cells (M2) (*)

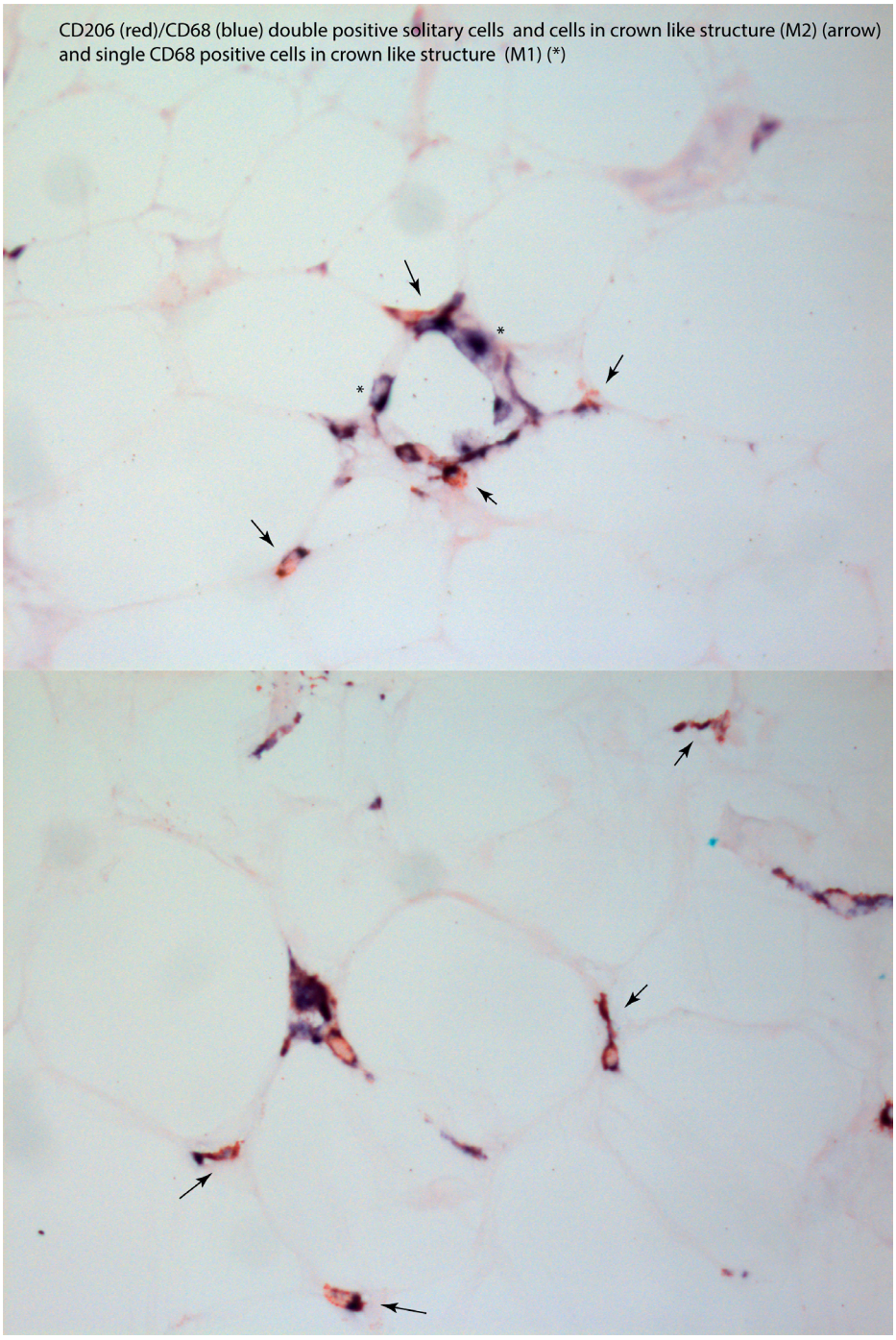

Figure S1b: Adipose tissue with CD206 (red)/CD68 (blue) double positive solitary cells and cells in crown-like structure (M2) (arrow) and CD68 single positive cells in crown-like structure (M1) (*)

Part C

Bariatric surgery in morbidly obese asthma patients

6 Prediction of airflow obstruction and the risk of complications in morbidly obese patients undergoing bariatric surgery

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Obesity Surgery. 2019 Sep;29(9):3076-3080

ABSTRACT

Morbidly obese subjects with airflow obstruction who underwent laparoscopic bariatric surgery appear to have the greatest risk to develop complications. In a retrospective cohort study, we identified a waist circumference ≥ 120 cm, smoking history ≥ 5PY and history of obstructive lung disease as statistically significant predictors of airflow obstruction. The resulting algorithm, aimed to identify subjects with airflow obstruction before bariatric surgery, was validated in a prospective study. The algorithm was found to be effective in identifying patients with low risk of airflow obstruction (negative predictive value 94.7%). Airflow obstruction, however, was not associated with postoperative complications as we expected. In contrast, inspiratory capacity and the Epworth Sleepiness scale were more promising predictors for postoperative complications in subjects undergoing bariatric surgery.

INTRODUCTION

Bariatric surgery is the only longstanding effective treatment of morbid obesity. However, patients undergoing bariatric surgery may develop post-operative complications. Pulmonary complications such as pneumonia and respiratory failure account for one fifth of the morbidity after bariatric surgery (1). Hamoui et al. demonstrated that vital capacity was independently predictive of post-operative complications and they concluded that pre-operative pulmonary function testing is useful to predict complications of bariatric surgery through open laparotomy (2). We previously demonstrated that subjects with obstructive pulmonary function had a threefold risk of complications after laparoscopic bariatric surgery (3). This underlines that pre-operative pulmonary function testing might also be useful to assess a patient's post-operative complication risk. With the increasing number of laparoscopic bariatric procedures, it is important to determine whether a pre-operative lung function is necessary in every patient. A screening algorithm to identify patients with high risk of obstructive lung function and complications will be useful in the clinic to select those who should perform a pre-operative lung function test. The present study had two aims: 1) to develop a screening algorithm for prediction of obstructive lung function; 2) to validate this algorithm in morbidly obese patients undergoing bariatric surgery.

METHODS

This study consisted of a retrospective part and a prospective part. The aim of the retrospective study was to develop a screening algorithm. The aim of the prospective part was to validate this algorithm in patients who underwent a preoperative screening program for bariatric surgery in the Franciscus Gasthuis in Rotterdam, the Netherlands. Eligibility criteria for bariatric surgery, assessments during this study and the details about the bariatric surgery are shown in supplemental file (S1). All participating subjects gave informed consent. This study was approved by the local medical research ethics committee (Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o; protocol 2013/17)

Methods and statistics retrospective cohort

In the retrospective part, patients were included between October 2009 and March 2012. Data from a previous study was used for developing a screening algorithm in this study (3). All subjects performed spirometry and were seen by a pulmonologist before admission to bariatric surgery. The primary endpoint was a significant obstructive lung function (either FEV_1 increase after salbutamol 400 µg of ≥12% and 200 ml or FEV_1/FVC

ratio <0.7) with a need for medication (Inhalation corticosteroid (ICS with or without short-acting or long-acting β-agonists (SABA or LABA)) prescription.

Patients were divided into groups with and without medication prescription after consultation. Unadjusted between-group comparisons were performed using Student's t test or the chi-square test and the Mann Whitney U test for nonparametric comparisons. Multiple logistic regression analysis (stepwise backward procedure) was used to assess the relationship between pre-operative factors and the risk of medication prescription adjusted for other co-variables. Baseline variables associated with complications in univariate analysis were examined in the logistic regression analysis. Age and gender were added to the regression analysis. All analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, Illinois, USA). A two-sided $p<0.05$ was considered a statistically significant result.

Methods and statistics prospective cohort

Between April 2015 and December 2017, we performed a longitudinal cohort study comprising candidates for laparoscopic bariatric surgery. All subjects were screened with the 1-1-2 screening algorithm (1 point for waist circumference $\geq$ 120 cm, 1 point for smoking history $\geq$5PY and 2 points for a history of obstructive lung disease). A cut-off point of 2 was used to identify subjects with a low risk of obstructive lung function (<2) and subjects with a high risk of obstructive lung function ($\geq$ 2). All subjects performed spirometry. Patients were contacted by telephone after 7 and 30 days after bariatric surgery and postoperative complications were scored with a standardized question form. In addition, medical records of patients were screened for complications. Complications were divided into pulmonary, surgical, infectious or other complications.

Sensitivity and specificity were calculated for obstructive lung function. Primary outcome was the negative predictive value (NPV) of the 1-1-2 prediction score for obstructive lung function. NPV>= 0.87 was considered as valid to use the algorithm as a predictive triage test. To assess which baseline values were associated with complications, baseline values were compared between subjects with and without complications with Student's t test or the Chi-square test and the Mann Whitney U test for nonparametric comparisons. In the subgroup with a 1-1-2- score $\geq$ 2, a multiple logistic regression analysis (backward) was used to assess the relationship between preoperative factors and the risk of complications adjusted for other co-variables. Baseline variables associated with complications in univariate analysis were examined in the logistic regression analysis.

RESULTS

Retrospective cohort

A total of 769 patients was included (mean BMI 45.4 kg/m2, M:F 1:4). In 105 patients (13.7%) medication was prescribed before bariatric surgery after consultation with the pulmonologist. Baseline characteristics showed that subjects with medication prescription (ICS with or without SABA or LABA) were older (40.6 vs. 42.4 years, p=0.012), had a larger abdominal circumference (131.3 vs. 135.2 cm, p=0.028) and more pack years (8.1 vs. 12.4 years, p=0.012). Furthermore, they more often had a history of asthma or COPD (14.4 vs. 49.5%, p<0.001), and were already using inhalation medication (17.4 vs. 47.6%, p<0.001).

Regression analysis

After adjustment for age, gender, and the use of inhalation medication, it was shown that an abdominal circumference of >120 cm (OR 2.6), >5 pack years smoking (OR 1.9) and the history of asthma or COPD (OR 5.5) were significant predictors for a significant airflow obstruction requiring inhaler medication. From these parameters, a predictive 1-1-2 algorithm was deducted giving 1 point for an abdominal circumference of >120 cm, 1 point for >5 pack years of smoking and 2 points for a history of asthma or COPD. The area under the curve was 0.728. A cut off point of 2 gave a sensitivity of 0.702 and a specificity of 0.658.

Results prospective cohort

A total of 250 patients was included of whom 152 subjects had a 1-1-2 algorithm score <2 (61%) and 98 subjects $\geq$ 2 (39%). The 1-1-2 algorithm provided a NPV of 94.7% for prediction of obstructive lung function, which was considered as valid. Prognostic accuracy was 64.7%, sensitivity 68.0% and specificity 64.3% for airflow obstruction. Prognostic accuracy of 1-1-2 algorithm was 46.2%, sensitivity 35.9% and specificity 57.4% for all perioperative complications.

Complications could be assessed in 195 patients (78.3%). Fifty-four patients could not be contacted by telephone. There were in total 54 complications in 52 patients (27.7%) until 30 days after bariatric surgery: 15 surgical (7.7%), 14 infectious (7.2%), 9 pulmonary (4.6%) and 16 other complications (8.2%) (table 1).

There were 13 re-admissions (6.7%) (table 1). Re-laparoscopy was performed in 1 patient, re-laparotomy was performed in 3 patients (hematoma (1x), active bleeding (2x)) and echo-guided puncture of an abscess in 1 patient. There were no fatal complications.

Table 1: Postoperative complications

	Frequency
Pulmonary complications	9 (4.6%)
• Respiratory tract infection	7
• Asthma/COPD exacerbation	2
Surgical complications	15 (7.7%)
• Hematoma (intra-abdominal)*	7
• Active bleeding (intra-abdominal)****	4
• Spleen injury*	1
• Anastomotic leak**	2
• Stenosis*	1
Infectious complications	14 (7.2%)
• Urinary tract infection	2
• Wound/abdominal wall infection	8
• Infected hematoma*	1
• Phlebitis	1
• Gastro-intestinal infection*	1
• Unknown	1
Other complications	16 (8.2%)
• Deep venous thrombosis	1
• Post-operative abdominal pain	6
• Dysphagia	1
• Dehydration	3
• Hypotension	2
• Hypertension	1
• Constipation*	1
• Arterial occlusion*	1

*Complications that resulted in re-admission in hospital

Patients with complications had a lower mean FEV_1 (89% vs 93.5%, p=0.049), a lower vital capacity (VC) (99% vs 104%, p=0.027) and a lower inspiratory capacity (IC) (115% vs 124%, p=0.037) (Table 2 and 3). Despite the lower FEV_1 in patients with complications, the sensitivity of obstructive lung function (FEV1/FVC < 0.70 and/or Δ FEV1 12%+200 cc) for total complications as well as pulmonary complications was low (sensitivity 7.8% (AUC 0.553) and 7.9% (AUC 0.555) respectively). Interestingly, subjects with complications had a trend for a higher score on Epworth Sleepiness Scale (ESS), suggesting a higher occurrence of OSAS in the group with complications (table 2).

After logistic regression analysis, adjusting for age, gender and BMI, not airway obstruction, but IC (OR 0.91) and ESS (OR 1.5) remained significant predictors of total post-operative complications (AUC 0.796). For pulmonary complications, only ESS remained a significant predictor (OR 1.5).

Table 2: Baseline characteristics of patients with and without complications

	Patients with complications (n=52)	Patients without complications (n=143)	p-value
Age (years)	43.7 ± 9.8	40.6 ± 11.6	0.092
Weight (kg)	122.2 ± 17.3	124.3 ± 17.7	0.459
BMI (kg/m2)	42.0 ± 4.6	43.4 ± 4.8	0.074
Waist circumference (cm)	126.7 ± 11.8	129.9 ± 13.0	0.121
Gender (% female)	82.7	82.5	0.977
Smoking status			0.758
Never (%)	36.5	40.6	
Former (%)	38.5	39.2	
Active (%)	25.0	20.2	
Comorbidity			
Diabetes Mellitus (%)	11.5	14.8	0.574
Hypertension (%)	34.6	25.2	0.193
Hypercholesterolemia (%)	23.1	14.0	0.130
Asthma (%)	9.6	10.5	0.859
COPD (%)	1.9	0.7	0.453
ACQ (median)	0.0 [0.0-0.5]	0.0 [0.0-0.33]	0.292
AQLQ (median)	6.6 [6.1-7.0]	6.8 [6.3-7.0]	0.342
ESS (median)	3.0 [1.0-7.0]	2.0 [1.0-4.0]	0.075
GERDQ (median)	6.0 [6.0-7.0]	6.0 [6.0-7.0]	0.776
Surgery			
ASA (median)	3.0 [3.0-3.0]	3.0 [3.0-3.0]	0.603
Operation (% gastric bypass)	67.3	58.0	0.242
Operation duration (min)	60.8 ± 20.0	59.1 ± 20.5	0.615
Admission duration (hours)	28 [26-52]	27 [26-28.5]	**0.013**

Data are presented as mean±SD or median [interquartile range], unless otherwise stated. BMI, body mass index; COPD, chronic obstructive pulmonary disease; ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; ESS, Epworth Sleepiness Scale; GERDQ, gastroesophageal reflux disease questionnaire; ASA, American Society of Anesthesiologists Classification

Table 3: Pulmonary function tests

	Patients with complications (n=52)	Patients without complications (n=143)	p-value
FEV_1 (% predicted)	89.0 ± 14.6	93.5 ± 13.7	**0.049**
FVC (% predicted)	97.0 ± 14.2	100.7 ±14.0	0.108
FEV_1/FVC (% predicted)	78.3 ± 6.9	79.6 ± 7.9	0.339
VC (% predicted)	98.6 ± 14.0	103.6 ± 14.0	**0.027**
IC (% predicted)	115.0 ± 18.7	124.2 ± 16.2	**0.037**
ERV (liter)	0.59 ± 0.30	0.56 ± 0.31	0.621

Data are presented as mean±SD. FEV_1, forced expiratory volume in 1 second; FVC, Forced vital capacity; VC, vital capacity; IC, inspiratory capacity; ERV, expiratory reserve volume

DISCUSSION

In the present study, we aimed to develop a screening tool to predict airway obstruction in morbidly obese subjects undergoing bariatric surgery. With a high negative predictive value, the 1-1-2 algorithm appeared to be useful to rule out patients with low risk of obstructive lung function. However, in the prospective analysis we have shown that an obstructive lung function is not associated with more postoperative complications in morbidly obese subjects. With the introduction of laparoscopic bariatric surgery, the rate of pulmonary complications is significant lower as shown by *Masoomi et al.* They demonstrated that the greatest rate of acute respiratory failure was observed after open gastric bypass surgery, and that this rate was much lower after laparoscopic bariatric surgery (4). In the present study, we have shown that the rate of pulmonary complications was the lowest compared to other complications and there were no cases of respiratory failure. This may be due to improved anesthesia techniques and increased experience with laparoscopic techniques by surgeons. In addition, post-operative complications may be reduced effectively by the standardized pre- and postoperative care of bariatric patients, such as adequate analgesia; early mobilization of patients from bed; the use of low-moleculair weight heparin to prevent trombo-embolic events and use of proton pump inhibitors. However, compared to other studies in this field the rate of pulmonary complications and total complications in the present study may seem high. For example, in a prospective study of 1055 patients who underwent elective non-thoracic surgery, the rate of pulmonary complications was 2.7% within 7 days of surgery (5). In contrast to our study, the included patients were not particularly obese and the complications included respiratory failure, pneumonia and atelectasis. In our study, the mean BMI was above 40 kg/m^2, but the pulmonary complications were mild and did not result in hospital admission. In a review about prediction of postoperative pulmonary complications in patients undergoing non-thoracic surgery, the incidence of pulmonary complications varied from 2 to 19%. This variation could be the result of different definitions for pulmonary complications. Furthermore, hypercapnia and reduced spirometry values were not associated with postoperative pulmonary complications in this review (6). In another study in obese patients undergoing bariatric surgery, the rate of respiratory postoperative complications was 7.5%, including O_2 desaturation, symptomatic atelectasis, productive cough, dyspnea, pneumonia and pulmonary thromboembolism. They found that the rate of pulmonary complications were higher in subjects with a restrictive lung function, rather than airflow limitation. In addition, they showed that not lung function, but OSAS is the only independent predictor of pulmonary complications in patients undergoing bariatric surgery (7). In our study, inspiratory capacity and not airflow limitation, seems to be a better marker for post-operative complications. Furthermore, we have shown that ESS, a symptom score for sleepiness, is the only sig-

nificant predictor of pulmonary complications in the obese. Although, the percentage of subjects with previously diagnosed OSAS was low in the present study, sleepiness and OSAS could play a role in developing peri-operative complications as shown by Clavellina-Gaytán et al. (7) and should therefore be treated before surgery.

Limitations of this study are: different time intervals between the retrospective and prospective cohort; 20% loss to follow-up in the prospective cohort and the fact that the study was not primarily powered to predict complications. In addition, we only performed spirometry and did not measure lung volumes in the body box. Obesity often results in a decreased expiratory residual volume (ERV) and a decreased functional residual capacity (FRC) as a result of increased mass around the chest wall and in the abdomen. In the present study, the median ERV measured with spirometry was indeed decreased compared to a non-obese population. It is possible that lung volumes (FVC, IC) are better predictors of peri-operative complications as the result of the present study suggest. Another limitation is that in the obese patient not only pulmonary physiology, but multiple mechanisms like cardiovascular and hormonal factors are involved in the risk of post-operative complications.

In conclusion, the 1-1-2 algorithm is useful to rule out patients with low risk of obstructive lung function. However, not airflow obstruction, but inspiratory capacity and ESS seem better predictors of (pulmonary) complications in morbidly obese subjects undergoing bariatric surgery.

ACKNOWLEDGEMENTS

We are grateful for the help of all the staff in the Respiratory Laboratory and members of the Bariatric Surgery Team at Franciscus Gasthuis & Vlietland.

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SUPPLEMENT

Eligibility criteria

Eligibility criteria for bariatric surgery were: age between 18 and 60 years, body mass index (BMI) either $\geq$40 or $\geq$35 kg/m^2 combined with the presence of comorbidity such as diabetes mellitus, hypertension or proven obstructive sleep apnea syndrome (OSAS).

Assessments

Prior to surgery, all subjects underwent physical examinations that included routine assessment of anthropometry and pulmonary function. Height and weight were measured wearing light clothes and no shoes. Body mass index was calculated as weight (in kg) divided by height (in m squared). Abdominal circumference was measured directly to the body surface midway between the lower rib margin and the ileac crest. Fat free mass and fat weight (in kg and % body weight) were measured using electrical impedance analysis (Bodystat 1500, Bodystat Ltd, British Isles). The presence of comorbidities was defined as follows: diabetes mellitus, hypertension or hyperlipidemia all by the use of medication, the presence of the metabolic syndrome according to the NCEP-ATP-III criteria, the diagnosis of asthma and COPD after consultation with a pulmonologist and pulmonary function tests, as described below. The Epworth Sleepiness Scale questionnaire was used to assess OSAS, and the GERD-Questionnaire for gastro-esophageal reflux disease (GERD).

Pulmonary function tests

Spirometry was performed with Vmax spirometer (Vmax SensorMedics Viasys, type Encore 20/22/229/62 Encore, Cardinal Health, USA) before and after 400 µg of inhaled salbutamol, with subjects in a sitting position and nose clips in place according to the American Thoracic Society / European Respiratory Society statement. All values obtained were related to height, age and gender and expressed as percentage of their predicted value (reference ERS 1993). The pulmonary function test results are shown as pre-bronchodilator values unless otherwise indicated. The degree of reversibility in FEV_1, which indicates a diagnosis of asthma is generally accepted as ≥12% and 200 ml from the pre-bronchodilator value ($\Delta FEV_1 \geq 12\%$).

7

Pre-surgical pulmonary rehabilitation in asthma patients undergoing bariatric surgery

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Obesity Surgery, 2017 Nov;27(11):3055-3060

ABSTRACT

This pilot study was performed to investigate the feasibility of pre-surgical pulmonary rehabilitation (PR) in morbidly obese patients with uncontrolled asthma, undergoing bariatric surgery. Four morbidly obese female patients with asthma participated in a 12-week PR program (exercise, diet and psychological intervention) before undergoing bariatric surgery, and the outcomes were compared to a matched group of 7 female controls (bariatric surgery only). In patients who participated in PR, asthma control and asthma quality of life improved dramatically after 3 months of PR. Besides, asthma control was better at the moment of surgery. The results of this pilot study show that PR is feasible in morbidly obese asthmatics and should be considered for a selected group of patients uncontrolled asthma before undergoing bariatric surgery.

INTRODUCTION

Epidemiological studies have shown that obesity increases the risk of developing asthma, and that asthma in obese people is often associated with more symptoms, a lower peak flow and a higher need of inhalation medication (1). In a previous study, we have demonstrated that bariatric surgery has a proven beneficial effect on symptoms and lung function in morbidly obese patients with asthma (2). However, surgery has risk of complications, especially in patients with pulmonary diseases (3). Furthermore, bariatric surgery does solve the problem of overeating, but it does not address other important issues like behaviour or lifestyle. Lifestyle and especially exercise is an important factor in both managing obesity and asthma. Therefore, a debate has emerged whether lifestyle intervention before bariatric surgery can improve the outcomes of bariatric surgery and can decrease the risk of complications in morbidly obese patients with asthma. Pulmonary rehabilitation (PR) can be seen as a life-style intervention (4), that is especially suited for patients with obesity-related respiratory disorders and individuals with lung disease in whom obesity is also contributing to functional limitation. Nevertheless, data on the effect of PR in obese patients with respiratory disorders are limited. Therefore, we performed a pilot study to investigate the feasibility of pre-surgical pulmonary rehabilitation aimed to improve the outcomes of bariatric surgery in morbidly obese patients with uncontrolled asthma.

MATERIALS AND METHODS

Study design

We performed an explorative case-control study in which we compared morbidly obese female patients with asthma participating in a 12-week PR program before undergoing bariatric surgery with a matched subgroup of our previous study (2). This subgroup consisted of morbidly obese female patients with uncontrolled asthma (ACQ >1.5) who did undergo bariatric surgery without PR before. We compared lung function (FEV_1), Body Mass Index (BMI), asthma control and asthma quality of life. In the patients that underwent PR before bariatric surgery also exercise capacity was measured. The total follow-up of the study was 6 months after bariatric surgery.

Study population

The study population consisted of morbidly obese subjects (Body Mass Index (BMI) > 40 kg/m^2) with proven asthma. Asthma diagnosis was based on the presence of symptoms and reversible airway obstruction or bronchial hyperresponsiveness. Patients were be-

tween 18 and 55 years old and had uncontrolled asthma (Asthma Control Questionnaire (ACQ) score of $\geq$ 1.5) after maximal treatment.

Intervention

The PR program consisted of 12 weeks of outpatient training, which took place three times a week during 40-60 minutes. Exercise training was based on a High Intensity Interval Training (HIIT) protocol, and was supervised by a physiotherapist. Participants were allowed to have an intake of maximal 1500 kcal/day. There were 4 clinical visits and 3 phone consultations with the dietician. Psychological counseling took place during 4 group sessions of 1 hour. These sessions focused on behavioral modification and motivational strategies. After 12 weeks of rehabilitation, patients underwent laparoscopic bariatric surgery: either a gastric sleeve gastrectomy or a Roux-and-Y gastric bypass surgery. Controls underwent laparoscopic bariatric surgery without participating in a PR program before. All subjects underwent pre-operative screening and consultation of the internist, psychologist and dietician as a part of standard bariatric care. All candidates were required to lose weight before surgery. In addition, they followed a low-carbohydrate diet during 2 weeks before the planned bariatric surgery to reduce the size of the liver, so the surgery could be performed more easily.

Outcomes

Outcomes measured in cases and controls were; the asthma symptom score (ACQ), asthma quality of life (AQLQ), BMI, lung function (FEV1) and complications. Outcomes measured in the cases only were exercise capacity (6 minute walking distance (6MWD), Maximal Oxygen Uptake (VO_{2max})) and daily step count.

Assessments

See supplementary material for a detailed description of the questionnaires, lung function tests and exercise tests. Briefly, validated questionnaires were used to assess asthma control and asthma related quality of life (5, 6). Exercise capacity was measured by a 6 minute walking test and a cardiopulmonary exercise test (7, 8). Lung function, bronchial hyperresponsiveness (PD20) and Fractional exhaled nitric oxide (FeNO) were measured according to ERS/ATS recommendations (9, 10). All complications within 90 days of bariatric surgery were scored.

Data presentation

Categorical data were presented as percentages and continuous variables were summarized as median values with interquartile ranges (IQR). No statistical analysis was performed due to the low sample size. Follow-up was completed until 6 months post-surgery.

RESULTS

Patient characteristics

Four cases and seven controls were included in the study. Baseline characteristics are shown in table 1. Both cases and controls were morbidly obese (median BMI > 40 kg/m^2). Patients who participated in PR before bariatric surgery were older (44 vs 30 year), had a lower FEV_1 (73.5% vs 96%) and a worse asthma control (ACQ 2.23 vs 1.86) compared to controls.

Table 1: Baseline characteristics of cases (PR before BS) and controls (BS=bariatric surgery).

	PR before BS (n=4)	BS (n=7)
Age (y)	44 [28-48]	30 [25-46]
BMI (kg/m^2)	44.75 [41.0-45.59]	45.87 [44.32-52.22]
Waist circumference (cm)	134.5 [116.3-141.5]	131.0 [121-152.25]
FFMI	22.06 [20.44-22.65]	21.64 [20.24-24.24]
FEV_1 (%)	73.5 [58.3-95.5]	96.0 [86.0-107.0]
FVC (%)	102.0 [85.75-115.3]	97.0 [92.0-116.0]
FRC (%)	68.0 [58.00-105.0]	64.5 [52.25-89.50]
RV (%)	96.0 [77.50-119.75]	89.5 [88.25-105.0]
FeNO (ppb)	24.0 [6.0-66.75]	12.0 [8.0-12.0]
EO (x10^9/l)	0.30 [0.25-0.30]	0.10 [0.0-0.10]
ACQ	2.23 [1.66-2.96]	1.86 [1.71-2.43]
AQLQ	3.79 [2.75-5.27]	4.27 [3.93-5.07]
Daily steps	6901 [6144-8160]	5705 [3347-7584]
VO_{2max} (ml/kg/min)	14.30 [12.15-19.98]	
VO_{2max} (%)	43.0 [35.25-55.25]	
6MWD (m)	509 [486-545]	
6MWD (%)	81.87 [69.23-90.05]	

All variables are presented as medians with the interquartile range. BMI, body mass index (weight (kg)/ height^2 (cm)); FFMI, fat free mass index (kg/m^2); FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; FRC, forced residual capacity; RV, residual volume; FeNO, fractional exhaled nitric oxide (ppb); EO, eosinophil's x10^9/l; ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; VO_2max, maximal oxygen uptake; 6MWD, 6-min walking distance.

Outcomes after 3 months of PR

All four cases completed 3 months of PR. The median adherence rate was 80.6% [77.3-91.3]. There were no adverse events related to the exercise training or other interventions of PR. In all patients, asthma control improved dramatically (median ACQ from 2.23 to 0.59) after 12 weeks of PR. Importantly, this improvement was above the minimal clinical

importance difference (MCID) of ≥ 0.5. Besides, the increase in asthma related quality of life (AQLQ) was also clinically relevant. There was a decrease in median BMI (Δ-1.39 kg/m^2). Exercise tolerance measured with the 6-minute walking test and cardiopulmonary exercise test improved in all patients (table 2). The median improvement of 6MWD was above the MCID of 30 m (7).

Table 2: Outcomes in cases (PR before BS) (n=4).

	Baseline (n=4)	After PR (n=4)	3 months after BS (n=4)	6 months after BS (n=4)
BMI (kg/m^2)	44.8 [41.0-45.6]	42.7 [39.6-44.1]	35.4 [30.9-39.3]	30.0 [28.1-35.0]
Waist circumference (cm)	134.5 [116.3-141.5]	118.5 [111.8-120.3]	94.0 [89.8-111.0]	94.0 [89.8-111.0]
ACQ	2.23 [1.66-2.96]	0.59 [0.04-2.13]	0.83 [0.21-0.96]	0.75 [0.08-1.29]
AQLQ	3.79 [2.75-5.27]	5.12 [3.98-6.10]	6.30 [5.78-6.82]	6.20 [5.39-6.82]
FEV_1 (%)	73.5 [58.3-95.5]	74.0 [59.8-87.5]	76.0 [51.3-88.8]	85.0 [59.0-92.3]
FRC (%)	68 [58-105]	80 [76-80]	103 [67-137]	102 [79-136]
Daily steps	6901 [6144-8160]	5305 [4584-5305]	6283 [4176-10357]	8336 [6067-8336]
VO_{2max}	14.3 [12.15-16.98]	15.4 [13.1-15.4]		
6MWD (m)	509 [486.3-544.5]	541 [531-541]	567 [524-629]	571 [561-621]

All variables are presented as medians [interquartile range]. BMI, body mass index (weight (kg)/height^2 (cm)); ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; FEV_1, forced expiratory volume in 1 s; FRC, forced residual capacity; VO_2max, maximal oxygen uptake; 6MWD, 6-min walking distance.

Bariatric surgery

Cases underwent bariatric surgery within 2 weeks after the last PR session. Compared to controls, cases had better-controlled asthma at the moment of surgery (figure 1a). A gastric bypass surgery was performed in three cases and one control, and a gastric sleeve surgery was performed in 1 case and 6 controls. In the group of cases, 1 patient developed a productive cough the day after (gastric bypass) surgery and received a treatment with antibiotics and corticosteroids. The same patient underwent a re-surgery within 30 days after the initial surgery because of an anastomotic leakage. After this re-surgery, she was admitted to the intensive care unit (ICU) because she developed a respiratory failure as a result of aspiration pneumonia. After 1 week of treatment in the ICU she was able to recover in the surgery ward and was discharged from hospital in good condition. Other cases did not have any complications from the surgery. There were no complications of the surgery in the group of controls.

Outcomes 3 and 6 months after bariatric surgery

Three months after bariatric surgery both in cases and controls ACQ was improved compared to baseline. Although there was some increase in ACQ in cases at 3 months, ACQ

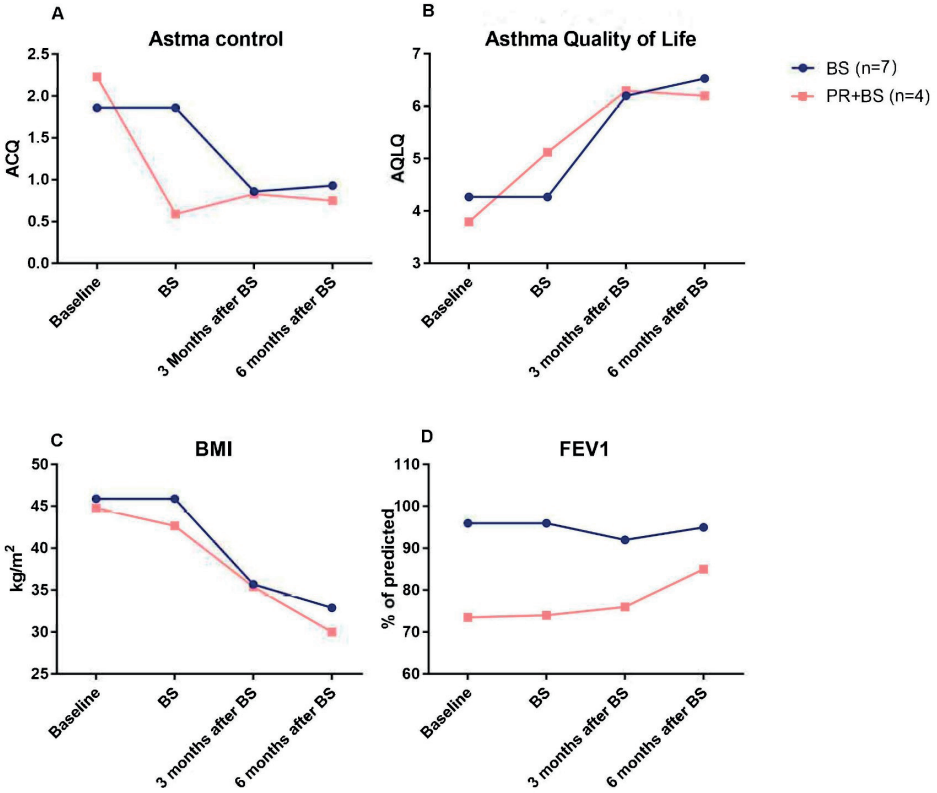

Figure 1: (A) Asthma control (ACQ), (B) Asthma quality of life (AQLQ), (C) Body mass index (BMI) and (D) Forced expiratory volume in 1 s (FEV_1) before and after bariatric surgery in morbidly obese patients with and without pre-surgical pulmonary rehabilitation (PR+BS vs. BS).

remained significant lower until 6 months in both groups compared to baseline (figure 1a). Both in cases and controls, AQLQ improved after bariatric surgery (figure 1b). Also, there was a large decrease in BMI (figure1c). In cases, there was a gradual improvement of lung FEV_1, but no improvement was seen in FEV_1 in controls (figure 1d). Exercise tolerance (6MWD) improved further in cases at 3 and 6 months after bariatric surgery and this improvement was clinically relevant (figure 2). However, there was no marked increase in the daily step count (table 2).

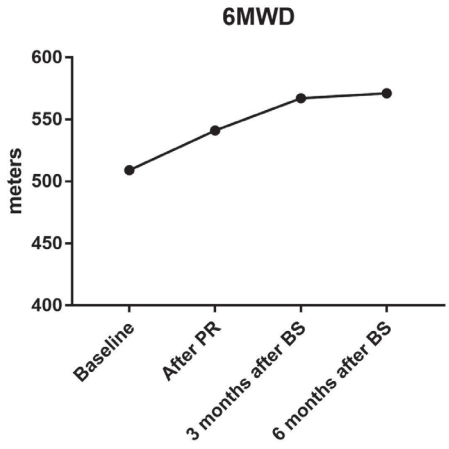

Figure 2: Six-minute walking distance (6MWD) in morbidly obese patients who participated in PR before bariatric surgery.

Table 3: Outcomes in controls (BS only) (n=7).

	Baseline (n=7)	3 months after BS (n=7)	6 months after BS (n=7)
BMI (kg/m^2)	45.9 [44.3-52.2]	35.7 [34.5-48.8]	32.9 [30.1-43.8]
Waist circumference (cm)	131.0 [121.0-152.3]	109.0 [107.0-136.0]	99.0 [92.0-118.0]
ACQ	1.86 [1.71-2.43]	0.86 [0.21-1.61]	0.93 [0.11-1.04]
AQLQ	4.27 [3.93-5.07]	6.20 [5.45-6.60]	6.13 [5.90-6.33]
FEV_1 (%)	96.0 [86.0-107.0]	92.0 [83.0-93.0]	95.0 [77.0-103.0]

All variables are presented as median [interquartile range]. Abbreviations BMI, body mass index (weight (kg)/height^2 (cm)); ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; FEV_1, forced expiratory volume in 1s; FRC, forced residual capacity.

DISCUSSION

In this explorative study, we included four female obese asthma patients participating in a 3-month pulmonary rehabilitation program before undergoing bariatric surgery. In these patients, we have seen improvements in asthma control, asthma quality of life, VO_{2max} and 6MWD after 3 months of PR. Furthermore, there was a decrease in the median BMI before undergoing bariatric surgery. Importantly, these improvements were clinically relevant. Besides, during 6 months of follow-up after bariatric surgery, the improvements in ACQ, AQLQ and 6MWD persisted. Compared to a matched subgroup of seven female patients from our previous study who did not participate in a PR program before bariatric surgery, patients who participated in PR were older and had a lower FEV_1 and a less controlled asthma. Still, PR was effective to improve asthma control and exercise tolerance before bariatric surgery. Although, we were not able to show reductions in complications in this study, we assume that a better asthma control before surgery could

result in lower rate of complications. The results of this case-control study suggest that a PR program is feasible and could be beneficial for a selected group of obese patients with uncontrolled asthma before undergoing bariatric surgery.

There is very limited data available about the effect of PR in morbidly obese asthma patients. In a randomized controlled trial with obese asthmatics, Scott et al. showed that after 10 weeks of either dietary intervention or combined dietary/exercise invention, patients had a significant amount of weight loss. Besides, modest weight loss (5-10% of body weight) was sufficient to improve asthma control, lung function and quality of life in obese adults with asthma (11). Another recent study showed clinical improvements in asthma control, greater weight loss and improvements in aerobic fitness after a 3 months weight loss program combined with exercise in obese asthmatics (12). However, patients included in these studies were not morbidly obese as in the present study. Studies about PR in morbidly obese patients with respiratory disorders before undergoing (bariatric) surgery are lacking. Nevertheless, such studies are highly relevant because these patients have an increased risk for developing complications after surgery. A recent randomized controlled trial by Baillot et al. showed that pre-surgical exercise training is feasible in subjects with obesity awaiting bariatric surgery. They showed improvement of physical fitness and social interactions after 12 weeks of training compared to controls, without any difference in weight loss. Post-surgical data are not available in this study (13). A RCT by Kalarchian et al., investigating the impact of pre-surgical lifestyle intervention on weight loss at 6, 12 and 24 months after bariatric surgery showed no difference compared to usual care. In addition, they found no effects on post-surgical complications. A limitation of this study is that there were no data available about other outcomes like physical activity or quality of life (14). Another recent study showed that exercise counseling and using pedometers are effective to increase physical activity during the preoperative period up to 6.5 months after bariatric surgery (15). None of these studies have included subjects with asthma or other respiratory disorders.

In the present study, we showed that the improvements of ACQ, AQLQ and 6MWD after PR persisted until 6 months after bariatric surgery. However, there were no differences in the amount of improvements of ACQ and AQLQ after bariatric surgery between patients who performed PR or not.

Despite the small sample size and the descriptive nature of this study, the results suggest that PR is feasible in morbidly obese asthmatics and should be considered for a selected group of patients uncontrolled asthma before undergoing bariatric surgery. Well-designed randomized controlled trials are needed to confirm these results and the effect on post-surgical complications.

ACKNOWLEDGMENTS

We thank departments of physiotherapy, psychology and dietetics with their contribution to this study.

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SUPPLEMENT

Exclusion criteria

Patients were excluded if they had any significant orthopaedic of neurological problems, COPD or other pulmonary pathology apart from asthma, except for adequate treated OSAS with a Apnea Hypopnea Index (AHI) <5; if they had an asthma exacerbation in 6 weeks prior to screening requiring a course of oral steroids or antibiotics; if they were on maintenance therapy with oral corticosteroids, current smokers or > 10 pack years; and if they participated in a PR program in the last 2 years before this study.

Measurements

The asthma control questionnaire (ACQ) was used to assess the level of asthma control. The ACQ is a validated standardised questionnaire for measurement of asthma control. It comprises 6 questions with different components of daytime symptoms and nighttime symptoms (6). The asthma quality of life questionnaire (AQLQ) was used to assess quality of life (5). The movement monitor (Microberts, DynaPort move-monitor) was used to evaluate daily steps.

Exercise capacity was assessed by a six-minute walking test (6MWT), and the incremental cardiopulmonary exercise test (CPET) was assessed using an electronically braked cycle ergometer according to the ERS/ATS recommendations (7, 8).

Lung function was measured by spirometry (Vmax SensorMedics Viasys, type 6200 Encore, 229/6200 Encore, 22 Encore, Cardinal Health, USA.) before and after 400 µg of inhaled salbutamol, according to the American Thoracic Society / European Respiratory Society guidelines. All values were expressed as percentage of their predicted value (10). A PD_{20} methacholine provocation test was performed to determine bronchial hyperreactivity. Asthma diagnosis was based on a history of typical respiratory symptoms and a FEV_1 improvement of > 12% (of the % predicted value) and > 200 mL or PD_{20} methacholine > 1.76 mg, according to the GINA guidelines (10).

Fractional exhaled nitric oxide (FeNO) was measured at a constant flow rate of 50 mL/s and expressed as parts per billion in accordance with the guidelines of the American Thoracic Society (ATS) and European Respiratory Society (ERS). FeNO measurements were performed with the Niox-Flex (Aerocrine AB, Sweden) (9). Anthropometric measurements such as BMI, hip/waist ratio were measured according to standard guidelines.

8 Obesity and asthma: very long-term effects of bariatric surgery on lung function and asthma control

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Submitted

ABSTRACT

Bariatric surgery has a proven beneficial effect on asthma symptoms, lungfunction and quality of life in obese patients with asthma up to 12 months following surgery. In a prospective follow-up study, we aimed to determine the very long-term effects of bariatric surgery in this population. Obese subjects with asthma included in the OBAS 1.0 study where invited for follow-up at 8 years after bariatric surgery. Although there was an increased BMI in both asthmatic and non-asthmatic subjects 8 years after bariatric surgery, the improvements in asthma control, asthma quality of life and small airway function persisted in asthmatic subjects. These results emphasize the importance of weight loss by bariatric surgery in the treatment of morbid obesity related asthma.

INTRODUCTION

Obesity is associated with an increased risk of developing asthma in adulthood (1). This obesity-related asthma phenotype is difficult to control and less responsive to standard asthma therapy (2-4). The pathophysiology of this phenotype is not fully understood, and various studies have described multiple mechanisms (5-7). Weight loss by bariatric surgery in morbidly obese subjects with asthma has been shown effective to improve lung function, asthma control and to reduce airway hyperreactivity on the short term (up to 12 months) (8, 9). In the present study, we show the long-term effects of bariatric surgery on asthma control, lung function and BMI, eight years after bariatric surgery in a previously studied cohort (8).

METHODS

Study design

This prospective follow-up study (OBAS 1.1) was conducted at the Franciscus Gasthuis & Vlietland, Rotterdam, between November 2017 and June 2018. All participating subjects gave written informed consent. Results of OBAS 1.0 study have been reported before (8). The study protocol was approved by the local research ethics committee (Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam e.o. #2017-69; Netherlands Trial Register number NL.62822.101.17).

Study patients

In the OBAS 1.0 study, there were 3 groups of patients included: obese patients with asthma who underwent bariatric surgery (BS+A), obese patients without asthma who underwent bariatric surgery (BS-A) and obese patients with asthma who did not undergo bariatric surgery (NBS+A). Subjects who participated in OBAS 1.0 study and completed the 12 months' follow-up were invited to participate in the 8 years' follow-up study. Patients were excluded if they were pregnant or if they were in the asthma control group without bariatric surgery and had undergone bariatric surgery within the last 8 years. Inclusion- and exclusion criteria in OBAS 1.0 have been reported elsewhere (8).

Outcomes

The primary endpoint was the score change in the asthma control questionnaire (ACQ) and asthma quality of life questionnaire (AQLQ) between 12 months and 8 years of follow-up after bariatric surgery. Secondary study parameters were lung function, airway resistance, physical activity and obesity parameters.

Assessments

Description of pulmonary function tests (spirometry, lung volumes, exhaled nitric oxide, impulse oscillometry), questionnaires (Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ)), measurements of physical activity and laboratory tests were described elsewhere (8).

Statistics

Paired data for scale variables are expressed as median (min-max), and categorical variables are expressed as percentages. For the comparison between the three groups at baseline, the kruskall wallis test for scaled data or the Chi-square or Fisher exact test were used. For all groups, 12-month follow-up data were compared with 8-year follow-up data, using the related-samples Wilcoxon rank test. The impact of bariatric surgery and asthma respectively on the outcomes over time (baseline- 12 months FU- 8 years FU) was studied using repeated measurements analysis (linear mixed modelling) including the baseline parameter value, time, asthma (yes/no), bariatric surgery (yes/no) and interaction effects asthma x time, bariatric surgery x time as covariates (covariance structure: unstructured). For the impact of BMI on ACQ, AQLQ and lung function, BMI was included as covariable instead of bariatric surgery in the repeated measurements analysis. All analyses were performed using SPSS V25.0 software. Results were evaluated at 95% CI at a two-sided significance threshold of $p<0.05$.

RESULTS

Of the 78 patients who completed the 12 months' follow-up (OBAS 1.0 study), 22 subjects (6 NBS+A, 9 BS+A and 7 BS-A) were willing to participate and 17 subjects attended the follow-up visit. Five patients were not able to attend the visit, but did fill in the questionnaires (ACQ, AQLQ) and answered the questions of the case report form by telephone. Baseline characteristics of included patients at baseline and 8 years of FU are described in table 1. The use of inhaled corticosteroids was lower in the BS+A group compared to the NBS+A group.

Comparing baseline characteristics of patients who participated in the OBAS 1.1 follow-up study and patients who did not participate, revealed that patients who were included in the follow-up study had statistically significant lower BMI and a worse asthma control and quality of life at baseline (8 years ago) compared to patients who did not participate in the follow-up study. There were no significant differences in gender, age, lung function, use of corticosteroids, smoking status and age of onset of asthma.

Table 1: Characteristics of the included patients.

	Baseline			8 years FU		
	NBS+A (n=12)	**BS+A (n=27)**	**BS-A (n=39)**	**NBS+A (n=6)**	**BS+A (n=9)**	**BS-A (n=7)**
Gender (% female)	91.7	74.1	82.1	83.3	77.8	100.0
Age (years)	33 (20-45)	36 (19-48)	39 (18-50)	41 (28-53)	49 (33-56)	54 (45-54)
Smoking status						
Never smoked (%)	75.0	55.6	71.8	83.3	50.0	50.0
Smoked in history (%)	16.7	11.1	17.9	16.7	12.5	33.3
Current smoker (%)	8.3	33.3	10.3	0.0	37.5	16.7
Age of onset of asthma (% as child)	75	33	n.a.	66.7	33.3	n.a.
Inhaled corticosteroids (%)	21.4	17.2	6.8	66.7	11.1	0.0

Variables are presented as median (min-max) unless otherwise stated.

The main findings of the study are summarized in table 2 and figure 2.

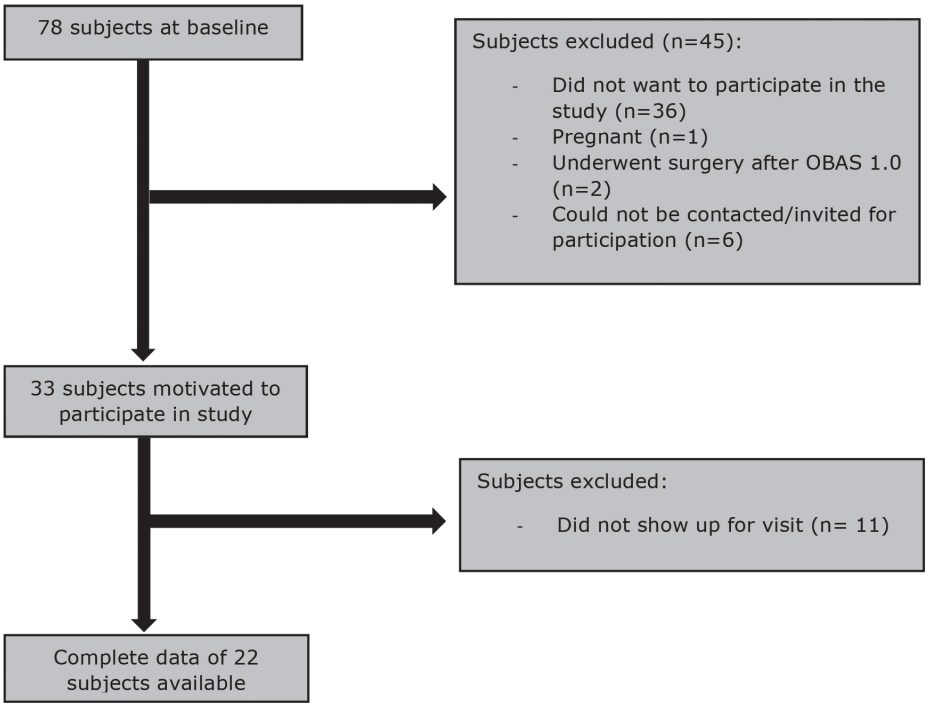

Figure 1: Study profile

Table 2: Effects of bariatric surgery on 12 months and 8 years of follow-up

GROUP	NBSA+				BS+A				BS-A			
	Baseline (n= 12)	**12-months FU (n=12)**	**8-years FU (n=6)**	**p-value[1]**	**Baseline (n= 27)**	**12-months FU (n=27)**	**8-years FU (n=9)**	**p-value[1]**	**Baseline (n=39)**	**12-months FU (n=39)**	**8-years FU (n=7)**	**p-value[1]**
Weight (kg)	103 (82-133)	107 (82-136)	103 (98-118)	0.173	130 (101-202)	88 (68-144)*	89 (69-131)	0.108	126 (94-199)	80 (63-123)*	85 (79-105)	0.028
BMI (kg/m2)	35.6 (30.9-53.9)	36.2 (31.8-55.0)	35.5 (32.7-38.7)	0.116	45.1 (38.1-63.8)	30.2 (23.9-43.4)*	32.3 (24.0-36,4)	0.025	43.1 (35.6-58.6)	29.0 (22.1-44.2)*	33.0 (27.0-35.1)	0.028
Abdominal circumference (cm)	119 (102-155)	113 (95-135)	111 (43-120)	0.500	133 (112-165)	99 (90-142)*	97 (84-131)	0.733	127 (103-200)	93 (19-122)*	88 (79-104)	0.893
FFM	56.3 (43.0-70.9)	56.0 (42.7-67.9)	58.2 (51.7-71.9)	0.043	61.2 (47.8-100.5)	49.0 (41.5-79.12)*	48.6 (43.8-76.1)	0.866	62.0 (47.2-74.7)	52.1 (35.5-98.0)*	47.5 (45.7-58.1)	0.144
FFMI	19.5 (16.7-22.8)	18.8 (17.3-23.6)	19.2 (18.1-22.2)	0.043	21.5 (17.1-31.0)	17.8 (15.6-22.9)*	18.2 (15.3-19.8)	0.204	21.5 (17.4-26.5)	18.4 (14.6-24.0)*	17.7 (15.6-19.4)	0.068
Fat mass (%)	43.5 (24.5-59.5)	43.5 (26.2-59.8)	43.3 (28.0-46.4)	0.144	50.9 (37.6-70.4)	36.0 (19.9-52.0)*	42.9 (31.3-47.0)	0.018	50.7 (31.1-59.1)	33.3 (13.1-76.0)*	42.2 (30.8-45.9)	0.068
Fat weight (kg)	45.1 (27.6-79.0)	43.3 (29.2-81.0)	42.5 (33.1-51.8)	0.043	68.1 (44.5-134.4)	31.3 (14.2-67.60)*	39.6 (22.0-45.4)	0.063	62.3 (32-100)	25.0 (9.0-6-.5)*	35.9 (26.1-44.7)	0.068
Steps (n)	7191 (3307-9587)	4964 (2021-12176)	4613 (2061-10083)	0.317	4964 (2021-12176)	8312 (3030-12910)*	5977 (3192-9106)	0.465	4613 (2061-10083)	8094 (2031-11114)*	4614 (2566-9402)	0.593
ACQ[2]	1.7 (0.3-2.6)	1.0 (0.3-2.0)*	0.6 (0.3-1.9)	0.248	1.1 (0.4-2.9)	0.4 (0.0-1.9)*	0.7 (0.0-2.0)	0.075	0.3 (0.0-2.9)	0.0 (0.0-1.0)	0.0 (0.0-0.6)	0.99
AQLQ[3]	5.3 (0.0-6.7)	5.8 (3.4-6.7)	5.8 (5.3-6.1)	0.116	5.6 (3.7-6.8)	6.7 (3.0-7.0)*	6.2 (4.8-7.0)	0.030	6.3 (0.0-7.0)	6.9 (5.7-7.0)*	7.0 (5.6-7.0)	0.715
Spirometry												
FEV1, pre (% predicted)	91 (45-106)	81 (71-117)	91 (79-108)	0.141	86 (66-119)	95 (67-119)*	102 (77-116)	0.089	97 (73-125)	106 (75-134)*	106 (87-122)	0.893
FEV1, post (% predicted)	98 (49-106)	88 (70-118)	96 (83-112)	0.138	93 (75-118)	100 (79-117)*	119 (76-121)	0.046	101 (75-129)	108 (80-139)*	111 (90-124)	0.892
FVC, pre (% predicted)	103 (64-118)	103 (77-131)	107 (83-119)	0.138	97 (75-126)	105 (75-131)*	120 (78-133)	0.075	105 (77-144)	109 (87-149)*	124 (98-141)	0.345
FVC, post (% predicted)	104 (62-120)	106 (78-131)	105 (85-121)	0.138	99 (74-126)	107 (77-123)*	121 (76-136)	0.115	105 (78-141)	107 (84-149)*	126 (100-140)	0.223
FEV1/FVC, pre (%)	79 (61-90)	78 (63-83)	78 (69-83)	0.588	76 (63-92)	77 (57-92)	73 (64-86)	0.683	81 (66-93)	83 (73-99)*	76 (69-79)	0.269

Table 2: Effects of bariatric surgery on 12 months and 8 years of follow-up (*continued*)

GROUP	NBSA+				BS+A				BS-A			
	Baseline (n= 12)	**12-months FU (n=12)**	**8-years FU (n=6)**	**p-value[1]**	**Baseline (n= 27)**	**12-months FU (n=27)**	**8-years FU (n=9)**	**p-value[1]**	**Baseline (n=39)**	**12-months FU (n=39)**	**8-years FU (n=7)**	**p-value[1]**
FEV1/FVC, post (%)	83 (69-91)	78 (66-86)	80 (74-85)	0.276	80 (67-94)	81 (69-94)	78 (72-86)	0.498	84 (68-94)	87 (77-98)*	77 (72-82)	0.042
RV, post (% predicted)	80 (74-92)	80 (51-105)	75 (64-99)	0.498	74 (39-126)	84 (40-115)	89 (55-109)	0.207	74 (47-118)	84 (43-137)*	72 (58-104)	0.500
TLC, post (% predicted)	93 (77-109)	97 (74-107)	97 (80-102)	0.465	97 (83-106)	102 (79-115)*	106 (70-114)	0.673	95 (75-114)	100 (81-122)*	105 (85-115)	0.715
FRC, post (% predicted)	68 (54-90)	69 (40-87)	63 (52-80)	0.080	59 (40-95)	91 (53-135)*	102 (55-118)	0.933	64 (41-88)	94 (59-145)*	75 (53-117)	0.343
RV/TLC, post (%)	27 (20-36)	23 (18-40)	26 (15-34)	0.077	22 (10-41)	25 (13-36)	27 (14-37)	0.596	25 (14-41)	28 (11-40)*	23 (21-33)	0.498
FeNO (ppb)	16 (7-96)	15 (8-58)	21 (6-69)	0.416	16 (8-45)	15 (8-36)	19 (11-33)	0.345	16 (7-53)	15 (5-67)	18 (8-21)	0.144
IOS												
R5 (kpa/s)	0.58 (0.24-1.11)	0.62 (0.29-0.86)	0.41 (0.31-0.70)	0.500	0.69 (0.42-1.39)	0.42 (0.26-0.80)*	0.35 (0.24-0.67)	0.866	0.58 (0.17-0.97)	0.35 (0.17-0.68)*	0.38 (0.25-0.718)	0.225
R20 (kpa/s)	0.44 (0.20-0.65)	0.40 (0.21-0.64)	0.29 (25-0.60)	0.138	0.45 (0.27-1.03)	0.32 (0.20-0.61)*	0.31 (0.19-0.38)	0.735	0.43 (0.18-0.68)	0.27 (0.14-0.57)*	0.32 (0.24-0.46)	0.138
R5-R20 (kpa/s)	0.18 (0.04-0.62)	0.20 (0.07-0.27)	0.10 (0.05-0.25)	0.225	0.25 (0.06-0.66)	0.07 (0.01-0.19)*	0.05 (0.03-0.24)	0.345	0.17 (-0.01-0.48)	0.07 (0.01-0.17)*	0.10 (0.01-0.26)	0.893
Fres (Hz)	17.3 (9.2-30.4)	17.6 (10.9-24.8)	13.6 (9.5-21.7)	0.043	22.7 (10.5-29.0)	11.9 (5.9-23.1)*	10.0 (8.47-24.45)	0.612	18.5 (8.4-28.7)	11.2 (7.4-19.0)*	14.24 (8.50-24.82)	0.080

Data are presented as median (min-max)

* $p<0.05$ for the comparison baseline versus 12 months follow up within each group

[1]p-value for the comparison between 12 month follow up and 8 years follow up within each group

[2]scores of the Asthma Control Questionnaire range from 0 to 6, with lower scores indicating better asthma control

[3]scores of the Asthma Quality of Life Questionnaire range from 1 to 7, with higher scores indicating better asthma-specific quality of life

NBS+A, no bariatric surgery and asthma group; BS+A, bariatric surgery and asthma group; BS-A, bariatric surgery without asthma group; BMI, body mass index; FFM, fat free mass; FFMI, fat free mass index; ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; FEV1: forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; FRC, functional residual capacity; FeNO, exhaled nitric oxide; IOS, impulse oscillometry

Asthma control and asthma quality of life

After 8 years of follow-up, the improvements in ACQ persisted in all groups. However, in the BS+A group, there was a trend for a lower median ACQ after 8 years compared to 12 months, but the difference was not clinically relevant ((Δ ACQ 0.30 vs MCID of 0.5). In addition, the median AQLQ after 8 years was significantly lower in the BS+A group compared to 12 months (6.2 vs 6.7, p=0.030). However, the median change was not clinically relevant (Δ AQLQ -0.34 vs MCID of 0.5) (table 2).

Asthmatics had still a higher ACQ (β=0.82 CI [0.22; 1.43], p=0.011) and a lower AQLQ score (β =-0.87 CI [-1.60; -0.14], p=0.023) compared to non-asthmatics during 8 years FU after bariatric surgery. No difference in ACQ and AQLQ was observed between asthmatics who underwent bariatric surgery and asthmatics who did not (ACQ: β=-0.43 CI [-1.2; 0.35], p=0.255) (AQLQ: β=0.11 [-0.69; 0.91], p=0.780) (figure 2 a+b). BMI was associated with both ACQ and AQLQ during follow-up, but differences were small (for ACQ β= 0.04 CI [0.02; 0.06], p<0.001, for AQLQ β= -0.04 CI [-0.07; -0.009], p=0.013).

Lung function

After 8 years, the median FEV_1 (post) in BS+A group was significantly higher compared to the median FEV_1 at 12 months. In addition, the median FEV_1 in the BS+A group was higher compared to NBS+A group during 12 months of FU (β-11.28 (-20.34; -2.21), p=0.020) whereas no difference in FEV_1 was observed between BS+A and BS-A groups (figure 2c). A higher BMI was associated with a lower FEV_1 (β -0.59 (-0.97; -0.21), p=0.003). A significant lower FEV_1/FVC (post) was found in the BS-A group after 8 years compared to 12 months of FU. No difference was observed in changes of FEV_1/FVC between both bariatric (β=-1.20 CI (-3.89;1.49), p=0.344) and asthma groups (β=-0.09 CI (-2.09; 1.09), p=0.924) over time (figure 2d). No significant association was found between BMI and FEV_1/FVC (β=-0.14 CI (-0.29; 0.02), p=0.080). The improvement in small airway function (R_5-R_{20}) in both bariatric groups in the first 12 months following surgery persisted during 8 years of FU. Moreover, the R_5-R_{20} in asthmatic subjects who underwent bariatric surgery was significantly lower during 8 years of FU compared to asthmatics who did not undergo bariatric surgery (β=-0.08 CI (-0.16; 0.00), p=0.041) (figure 2e). In addition, R_5-R_{20} was associated with BMI (β=0.006 CI (0.004; 0.008), p<0.001)

Body composition and physical activity

After 8 years, median BMI was higher compared to 12 months FU in both bariatric groups (table 2). However, this increase did not reach the baseline BMI before surgery. In the non-asthmatic group (BS-A), a significant higher weight and a trend for higher percentage of fat mass was found. There was no difference in BMI over time between both bariatric groups (β=-0.66 CI (-4.14; 2.80), p=0.691). In the asthmatic group, we

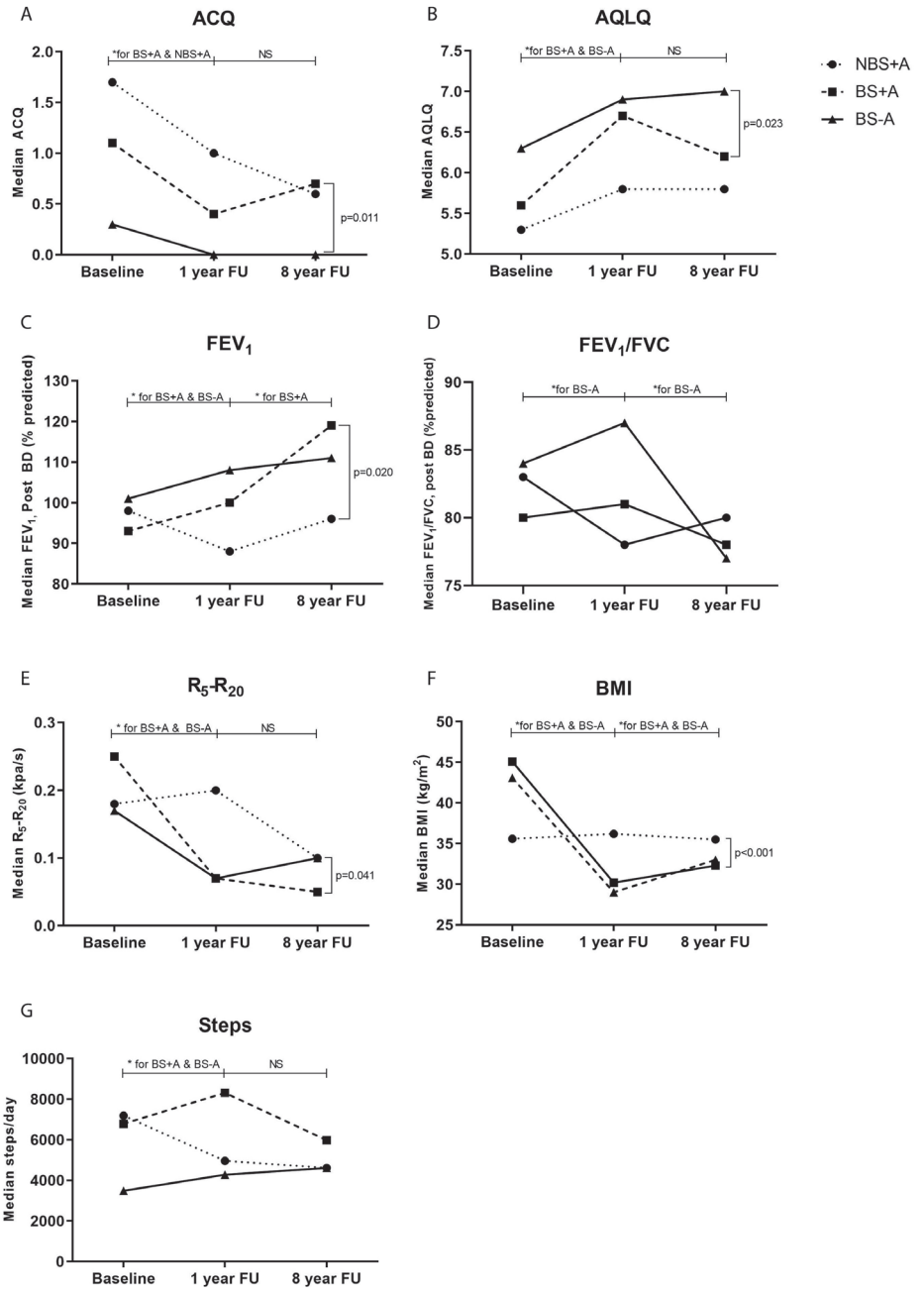

Figure 2: Effect of weight loss by bariatric surgery on asthma-related outcomes in 3 groups (NBS+A: no bariatric surgery and asthma group (circles); BS+A: bariatric surgery and asthma group (squares); BS-A: bariatric surgery without asthma group (triangles)). The p-values refer to differences between groups over time, obtained with repeated measurements analysis with results adjusted for time, asthma (yes/no), bariatric surgery (yes/no) and interaction effects asthma x time, bariatric surgery x time covariables. Only significant p-values are shown.

found a higher percentage of fat mass, but the median weight was not different at 8 year vs. 12 months of FU. Asthmatics who underwent bariatric surgery had a persisted lower BMI during 8 years FU compared to asthmatics who did not undergo bariatric surgery (β=-12.35 CI [-15.93; -8.77], p<0.001) (figure 2f).

There was a significant increase in the total number of daily steps in both bariatric groups at 12 months of follow up. At 8 years the median of total dialy steps in both bariatric groups was lower compared to 12 months of FU. However, this difference was not statistically significant. In addition, we found no statistical differences in the total number of steps between both bariatric and asthma groups during 8 years of FU in the multivariate analysis (figure 2g).

DISCUSSION

We have demonstrated that the positive effects of bariatric surgery on most asthma-related outcomes in morbidly obese patients with asthma persist over years. In both bariatric groups there was an increase in median BMI after 8 years, but this increase did not reach the baseline BMI by far. Although there was a trend for decrease of asthma control and a statistically significant decrease of asthma-related quality of life in the BS+A group, these were not clinically relevant. Another important finding is that despite the increase in BMI, the improvement in small airway function (R_5-R_{20}) in the BS+A and BS-A groups persisted after 8 years of FU. Our results contribute to the very limited knowledge about the long-term effects of bariatric surgery in morbidly obese subjects with asthma. A study by Hewitt et al. evaluated the long-term effects of bariatric surgery on pulmonary function and the status of asthma (10). After 5 years of follow-up, they reported considerable improvements in asthma symptoms in 48% of the patients. However, the asthma diagnosis as well as the evaluation of symptoms were based on self-reports, without objective measurements. Another study by Maniscalco et al. (11) found significant improvements in asthma control after one and 5 years of bariatric surgery in asthmatic patients compared to asthmatics who did not undergo bariatric surgery. In contrast to the present study, they found a sustained decrease in BMI between 1 year and 5 years of FU after bariatric surgery. The improvements in FEV_1 and FVC in asthmatics who underwent bariatric surgery, however, were only significant after 5 years of FU. In the present study, both FEV_1, FVC and lung volumes (RV, TLC, FRC, RV/TLC) were better after 12 months in both asthmatic and non-asthmatic bariatric groups, and the improvements persisted over the years. In fact, the median FEV_1 (post) in the BS+A group was significantly higher at 8 years FU compared to 12 months FU. No significant improvement in FEV_1/FVC was found in the asthmatic group (BS+A), indicating that

bariatric surgery does not influence obstruction of the larger airways on the long term in this group of patients. A recently published meta-analysis confirmed this finding (12). Interestingly, the FEV_1/FVC in the non-asthmatic group decreased after 8 years FU. Despite the significant increase in BMI, BMI was not associated with FEV_1/FVC. In contrast, our study shows a sustained improvement in R_5-R_{20}, a marker of small airway function, in the BS+A group. Given the significant correlation of R_5-R_{20} with BMI, it is likely that the small airways play an important role in obesity related asthma. The strength of the present study was that we have included an obese post-surgery control group of subjects without asthma, as well as an obese control group with asthma who did not undergo bariatric surgery. Study limitations were: 1) some patients could not be contacted due to outdated patient details; 2) the low participation rate, of the 33 patients who initially consented to participation, only 17 patients showed up. We have shown that participants of the OBAS 1.1 follow-up study were patients with a lower BMI at baseline and a worse asthma control and quality of life compared to the participants of the initial OBAS 1.0 study. This could have resulted in a bias; 3) we did not perform a methacholine provocation test to measure bronchial hyperreactivity, 4) there were differences between the asthma groups at baseline, for example the use of inhaled corticosteroids was lower in the BS+A group compared to the NBS+A group. The reason for this is that most subjects in the BS+A group were diagnosed with asthma during the pre-operative screening for bariatric surgery and in general had milder disease. Despite the inherent limitations, this is the first study on the very long-term effects of bariatric surgery in morbidly obese subjects with asthma and without asthma. Sustained improvements in lung function, asthma control and the peripheral small airway function were found in asthma patients 8 years after bariatric surgery. All findings together emphasize the importance of weight loss by bariatric surgery in the treatment of obesity related asthma.

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Part D

Summary

9 Summary and general discussion

OVERVIEW

In ancient times, asthma was already recognized in many cultures, such as the Chinese, Egyptian, Hebrew, Greek and Roman culture (1). Hippocrates (460-377 BC) was the first to use the term "asthma" which is derived from the Greek word "asthmaino" (αστημαινω) and means "panting", indicating that any patient with breathlessness was asthmatic (2). In the following centuries, the pathophysiology of asthma and the relationship with environmental factors and lifestyle became clearer. Already in the 12th century, treatment of asthma included rest, avoidance of opium, good personal and environmental hygiene and a healthy diet (3). Asthma now is defined as a heterogeneous disease with different phenotypes with variability in clinical symptoms, etiology and even a different treatment (4-6). Obesity is one of the lifestyle-related risk factors for developing asthma, and the so-called "obesity related asthma" is recognized as a distinct phenotype of asthma (7). As obesity has reached epidemic proportions globally, also the number of asthma patients with obesity has increased over years (8, 9). Optimal treatment of obese asthma patients is challenging as these patients are very symptomatic, respond less often to standard asthma therapy and have other contributing co-morbidities (10, 11). In this thesis, we performed a series of studies aimed to provide insight in the management of obese patients with asthma and to evaluate the effects of weight loss interventions like pulmonary rehabilitation and bariatric surgery. Additionally, we aimed to improve our knowledge about the pathophysiology of obesity-related asthma.

MAIN FINDINGS

In **chapter 1**, an overview of the obesity-asthma association is presented. We emphasized the presence of two obesity-asthma phenotypes: the "early onset, T_h2 high" (classic asthma in the obese patient) and the "late onset, T_h2 low" (obese subject who develop asthma in adulthood) asthma phenotype (12). These phenotypes might need a different approach for treatment as the first phenotype should be treated with corticosteroids and may benefit from weight loss, but the second phenotype is often resistant to treatment with corticosteroids and might rather benefit from weight loss. We described that both obesity and asthma are associated with reduced level of physical activity. Finally, we reviewed the different interventions for weight loss in obese asthmatics and we indicated the lack of knowledge about the optimal weight loss strategy in these patients. In **chapter two**, the effects of a standardized 12-week outpatient pulmonary rehabilitation (PR) program was investigated in obese (BMI $\geq$ 30) and non-obese (BMI $<$ 30) patients with asthma. Although, obese asthmatics had a significantly lower level of exercise capacity at baseline, they were able to achieve the same improvements in

exercise capacity as non-obese asthmatics. The average improvement in asthma control was statistically significant in both groups but it was below the minimally important difference of 0.5 (13). In addition, we have shown that having an uncontrolled asthma is not a barrier to participate in PR; in fact patients with more severe asthma did have more benefit from PR in our study. However, important limitations of this retrospective observational study were the absence of data about weight loss and the intensity of physical training, and the fact that ACQ results could not be obtained in all patients. Furthermore, we have shown that there is a large proportion of obese asthma patients who did not show clinical significant improvement. These subjects may benefit from an adapted PR program with emphasis on weight loss, exercise and self-management strategies. In **chapter 3**, we presented a meta-analysis of randomized trials to determine the effectiveness of high intensity (interval) training on cardiopulmonary fitness and body composition in adults with obesity (BMI $\geq$30) compared to traditional (high volume, continuous) exercise. Although the included studies were heterogeneous with small sample sizes, we were able to show that high intensity training is superior to traditional exercise in improving cardiopulmonary fitness (VO_{2max}) and reducing the percentage of body fat. More importantly, we have shown that training at high intensity is feasible and well-tolerated in persons with obesity. The suboptimal results for asthma control in the retrospective study described in **chapter 2** and the feasibility of high intensity training (HIT) in the obese with better outcomes for cardiopulmonary fitness and fat percentage described in **chapter 3** motivated us to design an adapted pulmonary rehabilitation program for obese asthmatics. This 12-week pulmonary rehabilitation program consisted of a multi-disciplinary approach with the following components: 1) dietary intervention, with a caloric restriction of approximately 1500 kcal/day, supervised by a dietician, 2) exercise intervention with high intensity interval training (HIIT) of 40-60 minutes (intensity ± 90% VO_{2max}), 3x a week with supervision of a physiotherapist, 3) psychological counselling during 4 group sessions with focus on behavioural modification and motivational strategies, and 4) E-health, using an internet based self-management program during 12 weeks of rehabilitation and during 12 months of follow-up. In **chapter 4,** we investigated the effectiveness of this newly designed rehabilitation program in a randomized controlled trial. Obese subjects with suboptimal controlled asthma were randomized in three groups: 1) rehabilitation program, 2) rehabilitation program with the use of E-health, or 3) usual care. After 3 months of intervention, there was a clinically relevant improvement in asthma control and marked improvements in body composition, aerobic capacity and lung function in patients who participated in the pulmonary rehabilitation program. More importantly, the positive effects on asthma control, BMI, exercise capacity persisted after 12 months of follow-up. This is an important addition to the current knowledge, because long-term effects of such lifestyle interventions were lacking (14, 15) (16). Moreover, we proved that high intensity interval training (HIIT) is

feasible in obese persons with suboptimal controlled asthma. We also demonstrated that the use of E-health in the form of an internet-based self-management program on top of this PR program and during follow-up resulted in even better weight management over time. The outcomes of this study emphasize the feasibility and the importance of lifestyle modification in this particular group of patients. However, some limitations of this study must be addressed. Firstly, this study included a very small sample size and participants were mainly female. This could result in a bias because of the anatomical and hormonal differences in female and male. Another important limitation is that patients with a BMI > 45 kg/m^2 were excluded from the study. The reason for this was the assumption that these morbidly obese patients could not perform HIIT without risk of injuries. An alternative treatment for these patients could be bariatric surgery (17).

Asthma in these morbidly obese (BMI > 45 kg/m^2) patients is usually characterized by adult-onset of symptoms, female predominance, high symptom expression and relative insensitivity for corticosteroids. This so-called "obesity-related asthma" is characterized by a non-eosinophilic airway inflammation. Although some studies reported an associated with sputum neutrophilia (18, 19), other studies found no evidence of airway inflammation in obese asthmatics at all (20, 21). The exact pathophysiology of obesity related asthma is unknown, but different mechanisms have been implicated as described in **chapter 1**. One of these mechanisms is the low-grade systemic inflammation characterized by increased production of pro-inflammatory cytokines, like interleukin 6 (IL-6) and tumour necrosis factor-alpha (TNF-α). As a result of obesity, there is an increased recruitment and activation of macrophages in visceral adipose tissue towards a pro-inflammatory (M1) state with production of pro-inflammatory cytokines (22). There are few recent studies linking pro-inflammatory macrophages in visceral adipose tissue with asthma (21, 23). In **chapter 5**, we performed a cross sectional study to characterize adipose tissue inflammation in morbidly obese patients with and without asthma. Contrary to our hypothesis, we found no evidence for increased adipose tissue inflammation in morbidly obese asthmatics compared to obese controls.

Bariatric surgery is considered as the only longstanding effective treatment of morbid obesity. In a previous study, it was shown that obese subjects with airflow obstruction who underwent laparoscopic bariatric surgery had the greatest risk to develop complications (24). A waist circumference ≥ 120 cm, smoking history ≥5 PY and history of obstructive lung disease were identified as statistically significant predictors of airflow obstruction. The resulting algorithm, aimed to identify subjects with airflow obstruction before bariatric surgery, was validated in a prospective study in **chapter 6.** Although, the algorithm was found to be effective in identifying patients with low risk of airflow obstruction (negative predictive value 94.7%), no association was found between

airflow obstruction and postoperative complications. In **chapter 7** we described a case-control study with 4 female morbidly obese asthma patients participating in a 3-month pulmonary rehabilitation program before undergoing bariatric surgery. The rehabilitation program was the same described in **chapter 4.** Compared to a matched subgroup (n=7) of morbidly obese asthma patients who did not participate in a PR program before bariatric surgery, the participants were older, had a lower FEV_1 and a less controlled asthma. Still, it was feasible to participate in PR and perform HIIT. They had clinically relevant improvements in asthma control, asthma quality of life and exercise capacity and a decrease in BMI after 3 months of PR and before bariatric surgery. The improvements persisted during 6 months of follow-up after bariatric surgery. The outcome of bariatric surgery on patients who participated in PR was not different from patients who did not participate in PR. Due to the small and descriptive character of this study we were not able to show reduction in complications, but it is plausible that improved asthma control and a better exercise capacity can reduce the risk of complications in this group of patients. Furthermore, it could be helpful to improve the physical activity level after bariatric surgery. However, we are not able to make a statement about this based on this study. Studies about PR in morbidly obese patients with respiratory disorders before undergoing (bariatric) surgery are lacking. Despite the lack of sufficient evidence, we suggest that a pre-operative PR program should be considered in morbidly obese patients with suboptimally controlled asthma.

In **chapter 8,** we describe a follow-up study of a previous study of morbidly obese subjects with and without asthma who underwent bariatric surgery. We have shown that the improvements in asthma control, asthma quality of life, lung function and especially airway resistance (R_5-R_{20}) in subjects with asthma persisted 8 years after surgery. Until now, there are only two other studies evaluating the 5-year outcome of bariatric surgery in morbidly obese asthmatics. One study showed improvement of FEV_1 and 48% of the asthmatic patients had no asthma symptoms 5 year post-operatively (25). Another study demonstrated persistent improvement of FEV_1 and asthma control after 5 years of bariatric surgery in patients with asthma (26). The added value of our study is that we have shown that the improvement in airway resistance persisted in obese asthma patients after 8 years of follow-up. This indicates a persistent improvement in small airway function. All findings together emphasize the importance of weight loss by bariatric surgery in the treatment of obesity related asthma.

Based on the main findings of my thesis, I will discuss three main topics. First, I will describe the pathophysiology and possible mechanisms in the obesity-asthma link. Secondly, I will focus on different aspects, challenges and gaps of lifestyle interventions

in obese asthma. Finally, I will make some suggestions for follow-up and maintaining long-term effects of lifestyle interventions in obese asthma patients.

THE OBESITY ASTHMA LINK

Obesity is associated with an increased risk of developing asthma and asthma in the obese is more often difficult to control. As we have described in **chapter 1**, there are at least two phenotypes that can be distinguished in obese patients with asthma (7, 27, 28). The first phenotype is the obese subject with an early onset, allergic or eosinophilic asthma ("early onset, T_h2 high") (classic asthma in the obese patient). The pathophysiology of this phenotype is often characterized by a chronic, T_h2 -related airway inflammation with the release of cytokines such as IL-4, IL-5, IL-9 and IL-13 leading to an inflammatory cascade with promotion of IgE production and recruitment of mast cells and eosinophils (29). In this group of patients, obesity develops at older age, sometimes as a result of frequent use of corticosteroids and/or physical inactivity. Asthma in these obese patients does not remit when they lose weight, even though symptoms and medication use may improve. In this phenotype, obesity complicates the pre-existing asthma, most likely by the same multiple mechanisms that have been implicated as causative for the second phenotype: "obesity related asthma". This second phenotype is characterized by a late onset, non-allergic, non-eosinophilic asthma ("late onset, T_h2 low") (obese subject who develop asthma in adulthood). The asthma frequently resolves with sufficient weight loss (17, 30). The different mechanisms implicated for the obesity-asthma association have been discussed shortly in chapter 1.

Genetic predisposition

Firstly, it is known that obesity and asthma share some genetic predisposition. In a large twin study, it was reported that the covariation between obesity and asthma is predominantly caused by shared genetic risk factors for both conditions (31). In addition, this study provided evidence that a common set of genes increases the susceptibility for both asthma and obesity. This analysis showed that approximately 8% of the genetic component of obesity is shared with asthma and genetic variations in specific regions of the human genome have been identified as being related to both obesity and asthma (31). For example, the gene on chromosome 5q31–q32 that codes for the adrenergic β_2-receptor, has also effect on the sympathetic nervous system activity and is therefore important in regulating not only the airway tone but also the resting metabolic rate (28, 32). A polymorphism of the gene encoding TNF-α is associated with both asthma (33) and obesity (34, 35). The gene (NR3C1) that codes for the glucocorticoid receptor (also on chromosome 5q31–q32) is related to both asthma and obesity (36). Polymorphism of

this gene is associated with asthma (37) and genetic variations in the glucocorticoid receptor has impact on obesity and especially on the accumulation of abdominal visceral fat (36, 38, 39). So, subjects with specific variations in the glucocorticoid receptor are at risk for developing both asthma and obesity. Genetic predisposition may partly explain why some obese subjects develop asthma and some do not. Therefore, more insight into these genetic influences of the obesity-asthma association is needed.

Effects of obesity on lung function

Another important hypothesis in the obesity-asthma link is the mechanical effects of obesity on lung function. Due to accumulation of subcutaneous fat around the chest wall and visceral fat in the abdomen, a restriction and a decrease of lung compliance develops. This results in a significantly decrease of functional residual capacity (FRC) and a decrease of expiratory reserve volume (ERV) (40, 41). It is well established that breathing at low lung volumes is associated with increased bronchial hyperresponsiveness (42-44). This can be explained by different factors such as reductions in the outward tethering forces that the parenchyma exerts on the airways to which it is attached (43) and increased airway narrowing as a results of enhanced airway smooth muscle shortening (42). Another factor is increased closure of the peripheral airways due to tidal breathing close to the closing volume (45, 46), especially on the supine position, leading to airflow limitation and increased peripheral airway resistance (47). As a result, the lung will become "hyperresponsive" and more "asthma-like" as a result of compression of the chest wall by fat mass. This raises the question whether the term "asthma" is appropriate to use for this obesity-related airway disease. However, according to the GINA guideline, asthma is a heterogeneous disease that is usually but not always characterized by a chronic airway inflammation. It is defined by the presence of variable respiratory symptoms and a variable expiratory airflow limitation. Moreover, the guideline emphasize that there are different types of asthma, with different underlying disease processes, such as obesity (48). An important question is why only some obese individuals develop asthma, when all of them have a reduction in lung volumes? Firstly, it is possible that asthma may arise in obese individuals with airways that already are more compliant than average (49). One study in subjects with obesity related asthma and obese controls showed that asthmatics had larger values of peripheral elastance than controls before weight loss, and after weight loss, the peripheral elastance was decreased by 60% in those with asthma, but only 27% in the control subjects (50). This finding implicates that compared to obese controls, obese subjects who develop asthma have unusually collapsible airways that become compromised in case of reduction of lung volumes by obesity (49). Secondly, the variation in distribution of adipose tissue in the body could play an important role in the extent to which the lung volumes decrease. Individuals with central adiposity (abdomen, mediastinum) might be expected to have more lung

compression and increased airway hyperresponsiveness than individuals with more peripherally storage of adipose tissue (tighs, buttocks). Some studies have shown that central obesity is a risk factor for late onset asthma even after adjusting for BMI (51-53). However, the dose-response relationship between the amount and distribution of adipose tissue and the mechanical changes are not completely known. It is likely that the amount and distribution of adipose tissue is one of the factors that is playing a role in the development of asthma in the obese.

In chapter 4, we have shown that after 3 months of pulmonary rehabilitation, there was a significant increase in FRC and ERV in obese asthmatics. In addition, there are several studies showing a significant decrease of bronchial hyperresponsiveness and airway resistance after weight loss by bariatric surgery in morbidly obese subjects (17, 54). Interestingly, this occurs particularly in subjects with Th2-low asthma and not in subjects with Th2-high asthma (55) indicating that altered lung function resulting from obesity is playing especially an important role in late-onset, obesity-related asthma. More importantly, in **chapter 8**, we have shown that the improvement in peripheral airway function after bariatric surgery persists after 8 years of follow-up in obese asthmatic patients.

The role of metabolic syndrome

It is well known that visceral adipose tissue is metabolic active. Normal visceral adipose tissue contains predominantly anti-inflammatory and regulatory M2 macrophages (56). In the obese state, there is recruitment and activation of adipose tissue macrophages (ATMs) towards a pro-inflammatory state (M1 activation) (22). M1 macrophages, forming crown-like structures in adipose tissue, produce pro-inflammatory cytokines (IL-1β, IL-6, IL-12, IL-23 and TNF-α), reactive oxygen species (ROS) and metalloproteinases (22, 57). Adipose tissue and systemic inflammation are known to be associated with insulin insensitivity, diabetes type II and other features of metabolic syndrome (58, 59). Metabolic syndrome is defined by a set of clinical characteristics including abdominal obesity, hyperglycemia, hypertriglyceridemia, hypertension, and low high-density lipoprotein cholesterol levels (60). In **chapter 5**, we have shown that visceral adipose tissue (VAT) of subjects with the metabolic syndrome had more CD68+ macrophages and crown-like structures (CD11c+ M1 macrophages) compared to subjects without the metabolic syndrome. Abdominal circumference was also significantly associated with expression of leptin in VAT. Although the percentage of subjects with metabolic syndrome was not different between obese asthmatics and obese controls in our study, obese asthmatics had a higher abdominal circumference and increased levels of triglycerides, both markers of metabolic syndrome. We also have shown negative correlations between abdominal circumference and asthma control and as well as FEV_1. These findings are in line with other studies showing that metabolic syndrome is associated with impaired lung

function (61) and more severe asthma (62-64). It is plausible that metabolic syndrome is associated with asthma through obesity and the induction of systemic inflammation. However, other features of metabolic syndrome may also affect airway function. For example, hyperinsulinemia can increase airway smooth muscle contractility and can induce bronchial hyperreactivity (65). Interestingly, a recent retrospective study reported that metformin use was associated with improved asthma outcomes among subjects with both diabetes and asthma (66). In addition, dyslipidemia is associated with lung function impairment and bronchial hyperreactivity by activation of the innate immune system and greater systemic inflammation (67, 68). In a recent study, it was shown that obese asthmatics with high systemic IL-6 levels were more likely to have features of metabolic syndrome. Moreover, systemic IL-6 was associated with severe asthma in both obese and non-obese asthmatics with metabolic dysfunction (69). In another study, is has been shown that obese asthmatics with metabolic syndrome have less benefit from weight loss by surgery. Subjects with metabolic syndrome at baseline and during follow up after surgery had the highest risk of losing asthma control at subsequent visits, even after adjusting for weight at each visit (70). These findings suggest that metabolic syndrome is associated with asthma control independent of weight loss and contributes to the hypothesis that metabolic syndrome affects airway function/asthma control via a different pathway than obesity only.

Adipose tissue inflammation

Independent from the effect of metabolic syndrome on asthma, the question is whether obese asthma patients have more adipose tissue inflammation than obese controls? To investigate this, we performed a cross sectional study to characterize adipose tissue inflammation in morbidly obese asthmatics and morbidly obese controls and to correlate this with markers of systemic inflammation and clinical parameters **(chapter 5)**. We found that obese subjects with asthma had significantly higher levels of serum IL-6 compared to obese controls, and serum IL-6 was significantly associated with bronchial hyperresponsiveness. In addition, uncontrolled asthmatics had higher levels of hs-CRP and lower levels of adiponectin compared to controlled asthmatics. These findings indicate that (uncontrolled) asthma is indeed associated with increased systemic inflammation. To our surprise, we found no differences in the numbers of adipose tissue macrophages (ATMs), crown-like structures (M1 macrophages), mast cells and mRNA expression levels of IL-6, adiponectin and leptin, in VAT of obese asthmatics compared to obese controls. We also found no associations with any of the adipose tissue inflammation markers and lung function (FEV_1) or asthma control. So, we were unable to show evidence for increased inflammation in adipose tissue as a source of increased systemic inflammation in obese asthmatics. This finding is in line with our previous finding on inflammation in lung tissue in which no differences were observed in submucosal cell counts of eosino-

phils, neutrophils, mast cells, macrophages, B or T cells in bronchial biopsies of morbidly obese asthmatics compared to obese controls (20). However, an important limitation in our study was that most of the patients had well controlled, mild asthma. However, our findings are not in line with the outcomes of recent published studies. The group of Periyalil et al. used flow cytometry and observed a higher percentage of M1 ATMs in VAT of obese asthmatics. Moreover, the percentage of M1 macrophages was associated with macrophage counts in sputum and a lower FEV_1 (71). The study of Sideleva et al. showed increased macrophage infiltration and an increased expression of leptin in visceral adipose tissue of obese subjects with asthma compared to obese controls. They found no evidence of increased airway inflammation in obese asthmatics, but airway epithelial cells of asthmatics had higher expression of adiponectin receptor-2 and T-cadherin (that also binds adiponectin). In addition, leptin levels were higher and adiponectin levels were lower in BAL of obese asthmatics, suggesting a direct link between these metabolic parameters and the airways. Moreover, airway reactivity was found to be significantly associated with visceral fat leptin expression (21). The inconsistencies between these studies indicate that more research is needed to provide increased insight in the links between visceral adipose tissue inflammation, metabolic syndrome and the development of asthma in the obese.

In **chapter 4**, we have shown a significant decrease of serum leptin levels in obese asthmatics after weight loss by 3 months of pulmonary rehabilitation program, including dietary, exercise and psychological intervention. In the control group, no change was observed. This decrease in leptin level persisted during 12 months of follow-up and was associated with the persistent weight loss during follow-up in this group of patients. Despite the reduction of systemic inflammation, we did not observe any change in airway inflammation, such as Fe_{NO}, sputum eosinophils or sputum neutrophils in this group of patients. However, one recent study compared dietary intervention versus exercise plus dietary intervention and found significant reduction of systemic inflammation (e.g. IL-6, leptin, IL-4, adiponectin, IL-10) and Fe_{NO} with exercise plus dietary intervention, but it is not clear if it this was related to exercise or the weight loss (72). Another study by Scott et al showed a decrease in neutrophilic airway inflammation following weight loss in women (73). Weight loss by bariatric surgery is associated with significant reduction in systemic inflammation, but not with airway inflammation (17). Bariatric surgery has been shown effective to reduce adipose tissue inflammation by loss of fat mass, reduction of the adipocyte size, shift in distribution of fat from visceral to subcutaneous compartment, increase of insulin sensitivity, alteration of adipokine secretion and decrease of adipose inflammation as well as systemic inflammatory markers (74).

Other mechanisms

As discussed in **chapter 1**, there are other important potential mechanisms that have been linked to obesity-related asthma. The occurrence of obesity-related comorbidities, like gastro-esophageal reflux and OSAS are associated with asthma. Especially OSAS is associated with metabolic syndrome and could be an important trigger for uncontrolled asthma in the obese (75).

A high fat diet is associated with airway inflammation (76-78) and animal studies suggest that a high fat diet increases the number of innate lymphoid cells in the lung and can induce both innate airway hyperresponsiveness and allergic airway inflammation through an IL-1β pathway (79). In contrast, a reduced fat diet is associated with reduction of airway inflammation (78). Also, vitamin D deficiency may be a risk factor for the development of both obesity and asthma. Obesity is associated with decreased circulating levels of vitamin D (80) and there is growing literature on the association between vitamin D deficiency and the severity of asthma and corticosteroid resistance (81). The effect of vitamin D supplements on asthma in the obese is not known. One study showed a significant increase in vitamin D levels after 3 months of weight loss program with exercise in obese asthma patients, but the correlation with improvements in clinical parameters remained unclear (72). Importantly, bariatric surgery is associated with reduced vitamin D levels and supplementation of this vitamin is required after bariatric surgery (82).

Dietary changes can also lead to alterations in gut microbiotica and this may also affect the development of asthma in the obese. Obese diet contains typically low fiber and high fat. Low fiber intake is associated with changes in gut microbiota and circulating levels of short-chain fatty acids (SCFAs). The *Bacteroidetes* bacteria, a major producer of SCFA, is reduced in the gut in obesity and in the lungs in asthma (83, 84). It is conceivable that obesity also has a direct effect on the lung microbiome. A higher concentration of lipids and glucose in the lung as a result of obesity might create an environment that permits some micro-organisms (85, 86). Exercise results in better glucose regulation and seems to have an effect in restoration of gut microbiota homeostasis in patients with type II diabetes. It is probable that changing gut microbiotica by exercise, diet or bariatric surgery can result in changes in lung tissue through release of e.g. SCFA, may impact on the lung microbiota and cause a better asthma control (87).

LIFESTYLE MANAGEMENT IN OBESITY AND ASTHMA

Lifestyle management has become an important topic in recent years. There is a lot of attention from newspapers, magazines, television and social media. Many types of weight loss diets and different forms of exercise interventions are recommended. Meanwhile, an entire industry has been formed with creative diets and exercise programs. It is however not known which type of intervention is the most "effective" or "healthy". Especially for obese persons with a medical condition, such as an uncontrolled asthma, it is difficult to find the most suitable intervention due to limitations associated with this medical condition. In **chapter 1**, we have reviewed the available literature on weight loss interventions in obese asthma patients. As we have addressed, there is limited data available on this topic, but in recent years there have been few studies published on this (14-16, 73, 88, 89). In **chapter 4**, we have shown that a multidisciplinary weight loss intervention program is feasible and effective in obese asthmatics. In this study, we have chosen for a pulmonary rehabilitation program with a combined dietary and exercise intervention as well as psychological counseling. The pulmonary rehabilitation program was in a hospital setting and group based. An important limitation of this kind of design is that we are not able to determine the contribution of each individual component of the rehabilitation program. So, which component of the intervention is the most contributing factor in weight loss or improving asthma control?

Dietary intervention

The first question is: what kind of diet should be recommended for weight loss in obese persons with asthma? In our study in **chapter 4**, but also in many other weight loss studies, a hypocaloric diet with a balanced intake of macronutrients (30% fat, 10-15% protein and 60-65% carbohydrate) was used. In healthy people with a BMI between 28 to 40 kg/m^2, a hypocaloric diet with a reduction of approximately 600 kcal of the usual daily caloric intake appears to be effective to reach a weight reduction of ± 5 kg in 1 year (90). In addition, some studies have shown that a change in macronutrient composition such as a lower consumption of carbohydrates and a higher intake of proteins (e.g. Atkins like), is associated with significant greater reduction in body weight compared to a low-fat diet at the short term (6 months), but at 12 months the difference in weight loss between these dietary approaches was negligible in most studies (91-95). Also, low-fat dietary interventions do not lead to greater weight loss when compared to higher fat dietary interventions of similar intensity (96). In a meta-analysis with comparison of different diet programs in overweight and obese adults, it was shown that all treatments were superior to no diet intervention at 6 months of follow-up. Compared to no diet, both the low-carbohydrate diets and the low-fat diets were associated with an estimated weight loss of 8 kg at 6-month follow-up and 7 kg at 12-month follow-up. The weight

loss differences between individual diets were minimal (97). Another popular diet is the Paleolithic nutritional pattern. This dietary pattern is characterized by intake of food of our Paleolithic, pre-agricultural ancestors. It includes mainly lean meats, fish, fruits, vegetables, nuts and seeds. Intake of dairy products, grains, sugar and legumes are not allowed in the Paleolithic diet (98). A recent meta-analysis of four randomized controlled trials demonstrated that compared to other dietary patterns, a Paleolithic diet resulted in improvements in several components of the metabolic syndrome (waist circumference, triglycerides and blood pressure). The relative low content of carbohydrates and salt in this diet could be beneficial for subjects with metabolic syndrome (99). However, the long-term effects and adverse events of this diet, and the effect compared to other low-carbohydrate diets, should be investigated first. Also the effectiveness of specific dietary patterns in asthma, such as a "Mediterranean diet" characterized by high intake of antioxidants, the use of vitamin and mineral supplements (vitamin C, E, calcium, magnesium, selenium) or high intake of fatty acids or caffeine has not been proven (100). The weight loss differences between the diets are small and mainly based on caloric restriction, either by reduction of fat or carbohydrates. So, the recommendation of any diet should be made individually for every patient who should be able to adhere to the diet in order to lose weight. There are important patient-related factors predicting the success of a dietary intervention. For example, people who are overweight can be classified on the basis of their eating behavior, such as emotional eaters, restrained eaters and external eaters. Each type requires a specific approach. In addition, lack of knowledge, motivation or insight in illness are important determinants of weight loss. Proper guidance by a dietitian who responds to this in the right way is important to achieve and maintain effect (101-103).

The role of exercise

The study of Scott et al published in 2013, showed that exercise alone does not result in significant weight loss (1.8%) or in better asthma control. The mean weight loss after a 10 week intervention with diet including caloric restriction of 885-1170 kcal/day was 8.5% and after a combined diet-exercise intervention 8.3% (73). Also, in previous studies in healthy obese subjects, the contribution of exercise without dieting in weight loss appeared to be modest (104). On the other hand, exercise provides conservation of fat free mass (FFM) during weight loss by dieting (73, 104, 105). Although, the effect of exercise on initial weight loss may be limited, it could play a role in maintaining weight loss over time. Indeed, there are studies showing that exercise has an important role in prevention of weight gain (106-110), but the results are inconsistent given the outcome of a recent systematic review of randomized controlled trials showing no improvement of weight loss maintenance with exercise (111). Another systematic review in which observational studies as well as non-randomized and randomized trials were included,

showed however that a large volume of physical activity was associated with less weight gain with or without prior weight reduction. However, this outcome was mainly based on the outcomes of observational studies and non-randomized trials. When analyzing randomized controlled trials in this review, the preventive effect of prescribed exercise training on weight loss maintenance was modest (weighted mean weight regain with exercise was 0.28 kg/months vs 0.33 kg/month without exercise) (112). The inconsistency between studies and the lack of effects of exercise in weight loss maintenance in most intervention studies could probably be explained by the use of BMI or %of weight loss as a measurement for successful weight reduction. Given the fact that exercise can result in conservation of muscle mass which is heavier than fat mass, using parameters like %fat mass or waist circumference could be more appropriate. Another explanation could be the strong variation in the volume, type and timing of the exercise intervention. So, how much exercise is needed for weight loss maintenance? Based on the results of observational studies, it seemed that an increase of energy expenditure of physical activity of approximately 1500-2000 kcal/week is associated with improved weight maintenance (112). This is more than most randomized controlled trials achieved. Other studies argue that a physical activity level above 200 minutes/week is effective to prevent weight gain after successful weight loss (113). It is possible that there is a threshold of exercise/physical activity that needs to be reached to have an effect on weight loss or maintenance. Another question is what kind of exercise is the most effective or suitable for obese persons with a pulmonary limitation? Based on the existing literature, it is currently not possible to make recommendations on the optimal type of exercise in adults with obesity. Traditionally, moderate intensity aerobic exercise is applied in the management of obesity in order to achieve weight loss. There are several studies available examining the effects of different aerobic exercise modalities on weight loss outcomes. However, the heterogeneity of these studies; with different exercise modalities (e.g. walking, cycling, jogging, swimming), different frequency and intensity of exercise is an important limitation to make conclusions about the optimal type of exercise. Based on studies and meta-analysis on this field, we can conclude that a moderate to high-intensity aerobic exercise, conducted at a frequency of at least three times per week, and without a diet, is effective to lose approximately 2-3% of the initial weight within 6 months. Low-intensity walking and habitual activity like increasing daily step counts appear to be effective in reducing 1-1.5% of the initial weight at 3-6 months (114). In contrast, resistance training alone seems not effective for significant weight loss, but it is effective in improving body composition by preservation or increasing fat free mass (115). **In chapter 3**, the effectiveness of high intensity (interval) training (HIIT) was compared to other forms of exercise in adults with obesity. In this meta-analysis we showed that HIIT is superior to moderate intensity continuous training (MICT) in improving cardiopulmonary fitness (VO_{2max}). This is also confirmed by previous studies in normal

weight adults (116, 117). HIIT also appeared to be superior to moderate intensity continuous training (MICT) in reducing risk factors for metabolic syndrome, such as reducing blood glucose and blood pressure in obese subjects and improving vascular function in patients with cardiovascular disorders (118-120). In addition, we have shown that HIIT leads to a significant reduction in the percentage of body fat compared to MICT. This finding implies a direct effect of high intensity (interval) training on fat oxidation, and was confirmed by a previous study of Trapp et al. who showed significantly more reduction in subcutaneous fat in young healthy women who performed HIIT (3/week, 15 weeks) compared to a continuous exercise training (121). However, in our meta-analysis, there was no difference in the amount of weight loss, BMI or waist circumference between HI(I)T or MICT. Two other recent meta-analyses comparing HIIT and MICT in obese adults found modest improvements in body composition, but no significant difference for any body composition measure between these two exercise modalities (122, 123). In addition, one of these studies found that HIIT is superior to MICT in improving cardiopulmonary fitness (VO_{2max}) after correction for the time spent for exercise (123). So, based on these studies we can assume that HIIT is at least equally or even more effective than MICT. Time is an important barrier for physical activity in (obese) adults (124). The fact that HIIT is less time consuming, makes it a good alternative for MICT. Besides, some studies showed that HIIT is perceived to be more enjoyable than moderate intensity continuous exercise, also in the obese (125, 126). This may improve the adherence to exercise and promote health benefit over a longer period. Despite these positive effects, there are some issues that should be considered regarding high intensity exercise in the obese with a pulmonary limitation. Most studies investigating the effects of HIIT excluded subjects with hypertension and cardiac comorbidity, conditions that are usually present in the obese population. On the other hand, several studies have noted that high intensity interval training is safe and effective in cardiac patients (127, 128). Performing exercise at high intensity is very demanding and could be a potential risk for knee- and other injuries in the obese. In **chapter 4**, we have demonstrated that HIIT was well tolerated and successful in obese patients who were limited by their weight as well as their asthma. Only 2 patients had to withdraw because of knee-problems. In addition, the rate of exacerbations was not higher in the intervention group, indicating that HIIT did not negatively affect asthma control. Our study is, to our knowledge, the first study showing that HIIT is feasible in obese persons with suboptimal controlled asthma. However, future studies are needed to investigate which type of HIIT is most suitable for the obese with regard to side effects, risk of injuries, but also with regard to long-term adherence and effects. In addition, obese patients with different comorbidities (cardiovascular, pulmonary, diabetes) should be included in this kind of studies to investigate the feasibility and effects in this group of patients. There is no consensus about the optimal frequency of the exercise intervention. In most intervention studies, the frequency of

the exercise intervention is 3 times a week (18, 72, 122). In my opinion, to achieve a healthy lifestyle pattern for a long period, it is important to exercise on a regular basis and three times a week seems effective to achieve this goal. Regardless of the optimal type and frequency of exercise, it is well known that exercise is associated with reduced asthma exacerbations (129). Therefore, exercise on a regularly basis should be recommended for every asthma patient.

Psychological counselling

Psychological counselling or "behavioural therapy" has already become an important component of a lifestyle intervention in the treatment of obesity. It is effective to improve the adherence to lifestyle intervention programs and physical activity in adults with obesity (130). Cognitive behavioural therapy in obese subjects is also associated with reduction of eating disorders, anxiety and depression (131). It is well established that asthma is also associated with anxiety and depression (132) and cognitive behavioural therapy has proven to be effective to reduce anxiety in asthma patients as well (133). Also important is the positive effect of cognitive behavioural therapy in smoking cessation in obese subjects (134). Smoking is associated with poor asthma control and corticosteroid insensitivity, which can result in use of higher dosage of inhalation corticosteroids (135). It is therefore important to stimulate patients to quit smoking. In addition, having an eating disorder, depression or other comorbidities can form a serious barrier to lose weight effectively for obese asthma patients. Therefore, psychological therapy should be included in each weight loss intervention of pulmonary rehabilitation program. Often, a form of behavioural therapy is used as a part of a lifestyle intervention with diet and exercise. In **chapter 4**, psychological intervention was a part of the pulmonary rehabilitation program in obese asthmatics. Psychological counselling took place during 4 group sessions and focused on behavioral modification and motivational strategies. Despite the fact that we found significant improvements in clinical outcomes, it is not possible to determine the contribution of behavioural therapy alone to the outcomes. Although, there is no clear evidence for the effectivity of such therapies in clinical outcomes of weight loss interventions in obese asthma patients, it is plausible that (cognitive) behavioural therapy can contribute to weight loss and improving asthma control by more providing insight and improved self-management skills on the long- and short-term.

Group- vs. individual based lifestyle intervention

Studies have indicated that group-based treatment of obesity results in greater weight loss compared to individual treatments (136, 137). Suggested explanations for this higher efficacy of group-based approaches include social support, empathy, competition between participants and role-modeling for an healthy lifestyle (138-140). The

interaction among the participants can promote positive lifestyle changes by verbal communication, social learning, emotional activation and physiological activation (139, 140). The effect of the group size on weight loss or other healthy lifestyle patterns is less clear. One randomized controlled trial examining the effects of group size on weight loss showed that participants in smaller groups (12 members) had ± 3 kg greater weight loss than participants in a larger group (30 members) (138). However, other studies did not confirm this finding (141, 142). The logistics and the costs of individual of small group delivered treatments results in a search for alternative formats for both weight loss as well as asthma management. Internet-based programs or a combination of an online format with face-to-face component of the intervention in larger groups could be effective and could increase cost-effectiveness of such lifestyle programs (142). In our study, described in **chapter 4,** a small proportion of the participants used a format with a combination of a small group-delivered pulmonary rehabilitation program with the combination of an internet-based self-management program. The online self-management program was used during 3 months of pulmonary rehabilitation and during 1 year of follow-up. The clinical outcomes, such as the improvement in asthma control, lung function, aerobic capacity and body composition at the short term did not differ from participants who did not use the online self-management program. However, in the long term, the users of the online self-management program had significantly lower BMI than non-users. It is important that the effect of such innovative formats is investigated in larger groups of patients.

Pulmonary rehabilitation or lifestyle intervention at home vs. at the hospital

In **chapter 4** and in **chapter 7**, we described a pulmonary rehabilitation program for obese patients with suboptimal controlled asthma. The pulmonary rehabilitation program was conducted at the hospital with the supervision of a physiotherapist. Reasons for us to choose for a hospital setting were: 1) safety of performing HIIT in suboptimal controlled, obese asthmatics. No other studies were available about HIIT in this group of patients who are at risk for injuries and pulmonary problems; 2) ability to monitor and increase adherence to the exercise program, dietary and psychological sessions. However, an important limitation of a hospital setting is the limited access for a broader patient population due to higher costs, distance to the hospital and the unavailability of programs in the evening. In our study in **chapter 4**, 112 patients fulfilled the inclusion criteria but only 34 were able to participate. The remaining patients could not comply due to other duties, like a full-time job and care for children. A home-based program could be an ideal alternative for this group of patients. There are few studies available about home-based pulmonary rehabilitation in asthma patients showing positive results regarding aerobic capacity and lung function (143, 144). However, the small sample sizes and the lack of a control group are important limitations to interpret the results of

these studies. There is one randomized controlled trial that is currently investigating home-based telerehabilitation vs. traditionally center-based pulmonary rehabilitation for people with chronic respiratory disease (145). Obesity is associated with multiple comorbidities, such as cardiovascular diseases, diabetes and osteoarthritis. I would suggest, for obese patients with such comorbidities and suboptimally controlled asthma, to participate in a pulmonary rehabilitation program or lifestyle program in a controlled setting. This could be a hospital, but also an outpatient pulmonary rehabilitation program in a pulmonary rehabilitation center. Guidance by a specialized physiotherapist is of great importance.

Patient related factors for successful weight loss

The outcome of a specific weight loss or lifestyle intervention program differs for every patient. There are patients with successful weight loss, improvements in physical activity and other clinical parameters; patients with no success at all; and patients with initial success but a relapse after a time period. This also points to the fact that successful weight loss is not just a matter of dieting and exercising, but more of a complex system with multiple factors involved. Identifying characteristics of patients that predict weight loss and maintenance is essential to improve effectiveness and to offer the optimal type of intervention for every individual patient. So, which factors determine the success rate of a weight loss program? In one study, previous dieting, low self-motivation and body size dissatisfaction were found as negative predictors of weight outcomes on the short-term (146). This was confirmed by other studies (147, 148). An older age, race (white over negroid), fewer self-implemented weight loss attempts, greater exercise self-efficacy, greater dietary restraint, fewer fat-related dietary behaviors were found to independent predictors of successful weight loss with the lifestyle program in diabetic patients (147). In contrast, initial weight loss seems to be a strong predictor of weight loss maintenance (149, 150). Other factors associated with weight maintenance are internal motivation to lose weight, having a physically active lifestyle, a regular eating pattern, social support, better coping strategies, ability to handle stress and more psychological strength and stability (150, 151). Interestingly, a study in asthma patients participating in a weight loss program, showed that individuals with more severe asthma (poorer asthma quality of life and a lower FEV_1/FVC) were more successful in achieving weight loss. In addition, male sex was associated with greater weight loss, and reducing emotional eating was associated with greater weight loss in women (152). **In chapter 2**, we have demonstrated that especially patients with more severe asthma had clinically relevant improvements in exercise capacity. In **chapter 4**, we have demonstrated that the majority of the participants had an uncontrolled asthma before the start of the rehabilitation program. Despite this, the pulmonary rehabilitation program resulted in clinically relevant improvement of asthma control and marked improvements in body composition,

aerobic capacity, and lung function. These studies emphasize that severe asthma is not a barrier for successful participation in such lifestyle programs. The finding that male sex is associated with greater weight loss is interesting and should be further explored. In our study, the percentage of male participants was low and although we have the impression that male participants had better outcomes in body composition, exercise capacity and asthma control, we cannot make conclusions on this based on our studies. Other important determinants of obesity and physical activity are the socio-economic status and education level. A low education level, low social and socioeconomic status are associated with a higher BMI (153, 154) and adults with a higher education level and a higher socioeconomic status tend to engage in physical activity more frequently (155). Moreover, chronic exposure to stress could contribute to the development of obesity and can have a negative impact on successful weight loss (156). It is important to gain more knowledge about the determinants of successful lifestyle change and maintenance to select the appropriate intervention and follow-up for obese asthma patients.

Bariatric surgery

Bariatric surgery is considered as the only longstanding effective treatment of morbid obesity. There is an increase in the number of bariatric surgery procedures being performed every year (157). The switch from open procedures to laparoscopic procedures and the growing experience in these surgeries have resulted in a decrease in complications (158). The role of spirometry as pre-operative screening for pulmonary complications of bariatric surgery remains therefore controversial. **In chapter 6**, we have demonstrated that the rate of pulmonary complications was the lowest compared with other complications in morbidly obese patients undergoing bariatric surgery. In addition, the pulmonary complications were mild and there were no cases of respiratory failure in our cohort. More importantly, we have shown that inspiratory capacity and not airflow limitation is associated with post-operative complications in this group of patients. The Epworth Sleepiness Scale (ESS), a symptom score for sleepiness, was found to be the only predictor of pulmonary complications in the obese. Our findings are in line with other studies in this field showing that a restrictive lung function and the presence of OSAS are more reliable factors to predict post-operative complications in the obese (159). Therefore, routine pre-operative spirometry seems not indicated in this group of patients.

Although airflow limitation is not associated with post-operative complications, patients with an uncontrolled obstructive airway disease will be prone to develop complications. Optimization of asthma control before every surgery is therefore recommended. The fact that morbidly obese subjects have often multiple comorbidities, and a low cardiorespiratory fitness, does increase their risk for complications. In addition, when these

patients are smoking, the risk of developing postoperative complications is even higher (160). Furthermore, bariatric surgery does solve the problem of overeating, but is it unclear whether bariatric surgery has an positive impact on physical fitness and lifestyle behavior (161, 162). It is even described that weight loss by bariatric surgery reduces aerobic capacity due to muscle mass loss (163). Asthma is also associated with reduced physical activity and this is even correlated to the level of asthma control (164). So, there should be attention for lifestyle (weight loss and smoking cessation) and improving cardiorespiratory fitness before and after bariatric surgery. In **chapter 2**, we have demonstrated that obese asthmatics have lower exercise capacity compared to non-obese patients with asthma. In **chapter 7,** a pilot study is presented of four morbidly obese patients with uncontrolled asthma who participated in a 3-month high intensity pulmonary rehabilitation program before undergoing bariatric surgery. Although, it concerns a small group of patients, we have shown that high intensity interval training is also feasible in a selected group of morbidly obese patients with asthma. We have seen clinically relevant improvements in asthma control and aerobic capacity after 3 months and before surgery, and these improvements persisted during 6 months of follow-up. Although we were not able to show reductions in complications in this study, it is conceivable that a better asthma control before bariatric surgery results in lower rate of complications. Long-term effects of such pre-surgical interventions in morbidly obese asthmatics are lacking. In non-asthmatic patients, it has been shown that bariatric surgery complemented by a pre- and postoperative lifestyle change program leads to improvement in physical activity, cardiopulmonary fitness and enhanced weight loss up to 24 months after bariatric surgery (162, 165, 166). In my opinion, pre-surgical lifestyle intervention should be a part of the bariatric procedure in every morbidly obese patient. Morbidly obese patients with a pulmonary condition, such as an uncontrolled asthma, should participate in a pulmonary rehabilitation program before bariatric surgery, not only to optimize asthma control and physical fitness before surgery, but also to learn symptom management, enhance weight loss and to incorporate physical activity in their lives to reduce exacerbations, cardiovascular comorbidity and health care costs on the long-term. Ideally, the effects of such programs should be investigated in large randomized controlled trials. However, the limited financial resources in research limits the design and implementation of these type of studies.

Bariatric surgery of morbidly obese asthma patients has been shown effective to improve asthma control and to reduce airway hyperreactivity (14, 17). In the Netherlands, bariatric surgery is only applicable in cases with morbid obesity (body mass index (BMI) $\geq$ 40 kg/m^2) or in subjects with a BMI above 35 kg/m^2 in combination with specific obesity-related comorbidity, which excludes most asthma patients with a BMI between 35-40 kg/m^2 from access to this procedure. In the next guideline update, asthma will be

included as one of the comorbidities so that asthma patients will be eligible for bariatric surgery from a BMI level of 35 kg/m^2. However, it is important for the clinician to consider when to refer asthma patients for bariatric surgery. As noted before, every obese patient with suboptimal controlled asthma should be encouraged to lose weight and to participate in exercise. Pulmonary rehabilitation is an ideal setting to initiate a change in lifestyle in obese asthma patients. As described in this thesis, this rehabilitation program should include not only physical exercise, but also dietary intervention and psychological support with the supervision of a multidisciplinary team. It has already been shown that a weight loss of 5-10% is sufficient to achieve improvements in asthma control, lung function and quality of life in obese adults with asthma (73). However, in morbidly obese asthma patients (BMI >40 kg/m^2) the amount of weight loss that is needed to reduce asthma symptoms may be higher. In addition, there may be physical conditions that limit morbidly obese patients to follow a diet or perform exercise. Bariatric surgery should be considered in these patients. Bariatric surgery will be particularly effective in the obese with a late-onset, obesity-related asthma (55). In these patients, the asthma often resolves following bariatric surgery. Therefore, it is important to have the right expectations regarding the improvement in asthma symptoms in early onset, Th2-high asthma. Although, symptoms may improve, asthma will often persist, and patients should continue their inhalation corticosteroids.

LONG-TERM EFFECTS AND FOLLOW-UP

The most challenging issue in lifestyle interventions is maintaining long-term effects. From the available literature, it is known that the effects of dietary or exercise interventions decrease over time, mainly because of lack of compliance (167). In contrast, bariatric surgery results in a larger and prolonged effect on weight loss, which increases the popularity of this intervention. In **chapter 8**, we have shown that the positive effects of bariatric surgery on asthma control, asthma quality of life and lung function in morbidly obese asthmatics persist during 8 years of follow-up. This study is one of the first investigating long-term effects of bariatric surgery in morbidly obese subjects with asthma. Also described in this thesis, both pulmonary rehabilitation and lifestyle intervention in obese asthmatics are associated with improvements in asthma symptoms, quality of life and exercise capacity at the short-term. However, studies with a long follow-up period are lacking. Most studies have a follow-up of three to six months after intervention (72, 73). In our study, described in **chapter 4,** we had a follow-up period of 12 months. We have shown that a multidisciplinary pulmonary rehabilitation (PR) program of 3 months resulted in sustained improvements in asthma control, body composition and exercise capacity during 12 months in obese patients with suboptimally controlled asthma. More

importantly, patients who participated in PR had a lower rate of exacerbations during 12 months of follow-up. Outside the methodological limitations of our study, a reduction in exacerbation rate is a very important finding as asthma exacerbations are associated with serious morbidity, mortality and increased health care costs (168). Therefore, exacerbation rate could be used as a marker of success for these interventions. It is important to increase the long-term effects of such pulmonary rehabilitation programs in these patients. The goal should be a change of lifestyle into a healthy pattern to maintain health benefits over time. However, lifestyle changes do require intensive guidance within a multidisciplinary team to evaluate and select the optimal approach for each individual to achieve maximal effect. Another challenge is the follow-up of patients after finishing the pulmonary rehabilitation program. Regularly follow-up visits with the physician or pulmonary nurse could be effective to monitor adherence and gives opportunity to intervene in case of relapse to old habits. A disadvantage of this method is that it is very time consuming and expensive. The use of e-health could be an ideal alternative for this to follow-up of these patients. E-health is already used in asthma care and it is associated with improved asthma control and quality of life (169, 170). Using e-health as a tool to increase adherence to a healthy lifestyle pattern and to monitor the effects on asthma control, physical activity, medication use, and exacerbation rate could be very effective as a part of pulmonary rehabilitation or lifestyle intervention. In this thesis, we have shown in **chapter 4** that users of an online self-management program during pulmonary rehabilitation and during 12 months of follow-up had better weight management over time. Although, the study included a small number of subjects, we have shown that using an internet based self-management tool is feasible in a group of obese subjects with suboptimally controlled asthma. In addition to using e-health as add-on for pulmonary rehabilitation, it is conceivable that e-health can be used as a tool for home-rehabilitation. This could be achieved by e.g. using mobile-apps for a step-by-step rehabilitation plan, and monitoring efficacy by using modules for diet, physical activity, lung function and questionnaires and online feedback by professionals on this. Moreover, social media could play an important role in forming patient platforms, share evidence-based knowledge and advise about healthy lifestyle and asthma. Not every patient will be able to use this kind of technology and for those a more conservative approach will be adequate. However, in this technology era, the use of e-health in healthcare is unavoidable and further research should be encouraged to determine the ideal conditions with respect to the practice of e-health in the treatment of obese patients with asthma.

CONCLUDING REMARKS

The studies in this thesis show the relevance of non-pharmacological interventions in the treatment of obese patients with asthma. It is important to recognize that the interaction between obesity and asthma is complex and multifactorial. More insight in the pathogenesis of airway disease in obesity is essential to develop treatment strategies to prevent and to treat this type of asthma in the obese. Future studies should focus on the sub-phenotyping of the obese asthma patients, based on pathophysiological and immunological mechanisms. The role of adipose tissue distribution and inflammation in the development of asthma should be further explored. Despite more systemic inflammation in obese asthmatics, we found no evidence for more adipose tissue inflammation compared to obese controls. We found associations between visceral adipose tissue inflammation with the metabolic syndrome, and associations of the metabolic syndrome with airway function and asthma. Therefore, the links between visceral adipose tissue inflammation, metabolic syndrome and asthma should be investigated. The role of early-life factors involved in establishing the microbiome, asthma- and obesity-associated alterations of the microbiome, hormonal factors and gender differences in the development of asthma in the obese are other important issues to be addressed in future studies.

Based on the studies in this thesis we can conclude that weight loss either by a lifestyle intervention program or bariatric surgery is effective to improve clinical outcomes in asthma. Currently, bariatric surgery is only applicable in asthma patients with morbid obesity (BMI above 40 kg/m^2). It is associated with sustained weight loss, improved asthma control, reduced bronchial hyperreactivity and reduced airway resistance over a long follow-up period. To improve asthma control and aerobic capacity before surgery and to initiate a lifestyle change, I advocate that every patient with uncontrolled asthma should participate in a pulmonary rehabilitation program before surgery. In the obese asthmatic patients with a BMI between 30 and 40 kg/m^2, a short-term multidisciplinary pulmonary rehabilitation program with a combined dietary intervention, high intensity interval training and psychological intervention is effective to improve body composition, aerobic capacity and clinical outcomes. A more important finding is that some improvements persist during 12 months of follow-up, indicating that a successful change of lifestyle is possible. Future studies should focus on the optimization and implementation of the rehabilitation/lifestyle intervention program for obese asthmatics. Moreover, strategies should be designed to optimize adherence and increase the long-term effects of these interventions in the obese asthma patients.

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Nederlandse samenvatting

Publications

Curriculum vitae

NEDERLANDSE SAMENVATTING

Astma werd reeds in de oudheid herkend als een luchtwegziekte. Hippocrates (460-377 v.Chr.) beschreef als eerste de term "astma" dat is afgeleid van het Griekse woord "asthmaino" (αστημαινω) wat "hijgen" betekent. In de daaropvolgende eeuwen werd de pathofysiologie van astma en de relatie met omgevingsfactoren en leefstijl steeds duidelijker. Al in de 12e eeuw omvatte de behandeling van astma rust, het vermijden van opium, goede persoonlijke en omgevingshygiëne en een gezond dieet. Lange tijd werd astma gezien als één ziekte, klassiek gekenmerkt door aanwezigheid van allergie en een chronische eosinofiele ontsteking van de luchtwegen (T_h2 inflammatie). Behandeling met inhalatiecorticosteroïden (ontstekingsremmers) vormt derhalve nog steeds de hoeksteen van de behandeling van astma. Heden wordt astma echter gedefinieerd als een heterogene ziekte, wat betekent dat er verschillende vormen van astma zijn, ook wel astma fenotypes genoemd. Elk fenotype wordt gekenmerkt door een ander ziekteproces dat deels op een andere manier behandeld zou moeten worden. Obesitas (BMI $\geq$30 kg/m^2) is een risicofactor voor het ontwikkelen van astma en het zogenaamde "obesitas-gerelateerde astma" wordt erkend als een van de fenotypes van astma. Aangezien obesitas inmiddels een wereldwijde epidemie is geworden, is ook het aantal astmapatiënten met obesitas in de loop der jaren flink toegenomen. De behandeling van astmapatiënten met obesitas is vaak een uitdaging, omdat deze patiënten meer klachten hebben, minder goed reageren op standaard astmatherapie (inhalatiecorticosteroïden) en andere bijdragende chronische ziekten (comorbiditeiten) hebben. In dit proefschrift presenteren we een aantal studies die we hebben uitgevoerd om inzicht te krijgen in de behandelingsmogelijkheden van astmapatiënten met obesitas en om de effecten van gewichtsverlies door middel van longrevalidatie en bariatrische chirurgie te onderzoeken.

In **hoofdstuk 1** hebben we een overzicht gegeven van de associatie tussen obesitas en astma. Verschillende mechanismen die een rol zouden kunnen spelen in deze associatie zijn o.a. veranderingen in de longfunctie, genetische factoren, het bestaan van astma gerelateerde comorbiditeiten, een hoog vetgehalte in het dieet, veranderingen in het darm microbioom en veranderingen in het vetweefsel gevolgd door meer ontsteking in het bloed (systemische inflammatie). We hebben benadrukt dat het belangrijk is om allereerst het fenotype van astma in deze groep patiënten met obesitas te bepalen. Er zijn twee fenotypes te onderscheiden. Ten eerste heb je obese patiënten met klassiek astma, vaak ontstaan op de kinderleeftijd en gekenmerkt door de aanwezigheid van een allergie en een eosinofiele luchtwegontsteking (early onset, T_h2 high fenotype). Obesitas compliceert in dit geval de pre-existente astma (eerst astma, daarna obesitas). Deze patiënten zullen primair gebaat zijn met behandeling d.m.v. inhalatiecorticosteroïden

op geleide van de ontstekingsmarkers. Alhoewel gewichtsverlies de klachten van de astma kan verminderen, is het stoppen van inhalatiecorticosteroïden bij dit fenotype van astma, vaak niet mogelijk en niet aan te raden. Het obesitas-gerelateerde astma fenotype kenmerkt zich daarentegen door weinig (eosinofiele) luchtwegontsteking (late onset, T_h2 low). Het ontstaat typisch op de volwassen leeftijd ten gevolge van obesitas (eerst obesitas, daarna astma). Behandeling met inhalatiecorticosteroïden is vaak niet effectief bij deze patiënten, zij hebben met name baat bij gewichtsverlies. Daarnaast hebben we beschreven dat zowel obesitas als astma geassocieerd zijn met een verminderde lichamelijke activiteit. Ten slotte hebben we de verschillende mogelijke interventies voor gewichtsverlies bij obese astmapatiënten besproken, zoals medicamenteuze interventies, dieet en beweeginterventies, gedragstherapie en bariatrische chirurgie.

In **hoofdstuk 2** hebben we in een retrospectieve studie het effect van een 12-weken longrevalidatie programma onderzocht bij astmapatiënten met en zonder obesitas (BMI $\geq$30 kg/m^2). Astmapatiënten met obesitas bleken bij aanvang van het programma een significant lagere inspanningscapaciteit te hebben. Desondanks waren ze in staat om na 12 weken dezelfde verbeteringen in inspanningscapaciteit te bereiken als astmapatiënten zonder obesitas. De gemiddelde verbetering in astmacontrole was statistisch significant in beide groepen, maar lag onder de grens van klinische relevantie. Daarbij had een groot aantal astmapatiënten met obesitas geen klinisch significante verbetering in de astmacontrole.

In **hoofdstuk 3** presenteren we een meta-analyse van gerandomiseerde studies om het effect te bepalen van hoge intensiteit (interval) training (HIT) op de maximale zuurstofopname capaciteit (VO_{2max}) wat een maat is voor conditie, en op het percentage lichaamsvet bij volwassenen met obesitas (BMI $\geq$30 kg/m^2) in vergelijking met traditionele vormen van training met matige intensiteit. Alhoewel de beschikbare studies vrij heterogeen waren, met een klein aantal proefpersonen, konden we met deze meta-analyse aantonen dat (interval) training met een hoge intensiteit superieur is aan traditionele training bij het verbeteren van conditie en het verminderen van het percentage lichaamsvet bij volwassenen met obesitas. Een andere belangrijke bevinding was dat training met hoge intensiteit ook goed mogelijk is bij personen met obesitas.

Op basis van de beschreven resultaten in **hoofdstuk 2 en 3** hebben we een aangepast longrevalidatieprogramma samengesteld voor astmapatiënten met obesitas. Dit multidisciplinaire longrevalidatieprogramma van 12 weken bestond uit de volgende componenten: 1) dieetinterventie, met een caloriebeperking van ongeveer 1500 kcal / dag, dit werd begeleid door een diëtist, 2) beweeginterventie met intervaltraining met hoge intensiteit (HIIT) van 40-60 minuten (intensiteit $\pm$ 90% VO_{2max}), 3x per week met

supervisie van een fysiotherapeut, 3) psychologische begeleiding tijdens 4 groepssessies met focus op gedragsverandering en motivatie, en 4) het gebruik van een online zelfmanagement programma gedurende 12 weken longrevalidatie en gedurende 12 maanden follow-up. In **hoofdstuk 4** hebben we het effect van dit longrevalidatieprogramma onderzocht in een gerandomiseerde studie. Obese patiënten met suboptimaal gecontroleerd astma werden gerandomiseerd in drie groepen: 1) longrevalidatieprogramma, 2) longrevalidatieprogramma met gebruik van een online zelfmanagement programma, of 3) standaard zorg (optimale astmamedicatie met advies om af te vallen en te sporten). Na 3 maanden longrevalidatie was er een significante afname van het gewicht, BMI en percentage lichaamsvet ten opzichte van de groep met standaard zorg. Daarbij was er een klinisch relevante verbetering in astmacontrole, inspanningscapaciteit en longfunctie bij patiënten die deelnamen aan het longrevalidatieprogramma. De positieve uitkomsten op de astmacontrole, BMI en inspanningscapaciteit bleven bestaan na 12 maanden follow-up. Dit is een belangrijke bevinding gezien gegevens over de langetermijneffecten van dergelijke longrevalidatie programma's tot dusver ontbraken. Daarnaast hadden personen die het online zelfmanagement programma hadden gebruikt, een lagere BMI na 12 maanden follow-up ten opzichte van personen die het longrevalidatie programma hadden gevolgd zonder het online zelfmanagement programma. Bovendien hebben we laten zien dat hoge intensiteit intervaltraining (HIIT) mogelijk is bij obese personen met suboptimaal gecontroleerd astma. Deze studie laat zien dat leefstijlaanpassingen middels een longrevalidatieprogramma haalbaar en belangrijk is bij deze specifieke groep patiënten.

Zoals eerder genoemd, kenmerkt het obesitas- gerelateerde astma fenotype zich door weinig luchtwegontsteking. Het pathofysiologisch mechanisme van dit astma fenotype is meest waarschijnlijk multifactorieel waarbij de exacte rol van het vetweefsel nog onbekend is. Dit vetweefsel is de bron van een laaggradige systemische ontsteking met toegenomen productie van pro-inflammatoire cytokines. Deze ontsteking wordt gemedieerd door een toename van het aantal pro-inflammatoire (M1) macrofagen in het viscerale vetweefsel ten opzichte van het normaal vetweefsel dat overwegend anti-inflammatoire (M2) macrofagen bevat. Deze fenotypeswitch van macrofagen in het vetweefsel speelt een belangrijke rol bij de ontwikkeling van obesitas-gerelateerde aandoeningen en er zijn een aantal studies die pro-inflammatoire macrofagen in het visceraal vetweefsel ook linken met astma. In **hoofdstuk 5** hebben we daarom het vetweefsel van morbide obese personen met en zonder astma vergeleken. Ondanks dat er aanwijzingen zijn dat astma gepaard gaat met meer systemische ontsteking, hebben wij geen bewijs gevonden voor meer ontsteking in het vetweefsel van obese personen met en zonder astma.

Bariatrische chirurgie wordt beschouwd als de enige effectieve behandeling van morbide obesitas (BMI ≥40 kg/m^2) met een langdurig effect. In een retrospectieve studie bleek dat morbide obese personen met een obstructieve longfunctie het meeste risico hadden op complicaties van laparoscopische bariatrische chirurgie. Een buikomtrek van >120 cm, rookhistorie van >5 pakjaren en een voorgeschiedenis met een obstructieve longziekte zoals astma en COPD werden geïdentificeerd als significante voorspellers van een obstructieve longfunctie bij deze groep patiënten. Het predictiemodel dat werd ontwikkeld met deze parameters met het doel om personen met luchtwegobstructie te identificeren werd in een prospectieve studie in **hoofdstuk 6** onderzocht. Het predictiemodel blijkt effectief in het identificeren van personen met een laag risico op luchtwegobstructie. Er werd echter geen verband gevonden tussen luchtwegobstructie en het optreden van postoperatieve complicaties na laparoscopische bariatrische chirurgie.

In **hoofdstuk 7** beschrijven we een case-control studie met 4 morbide obese patiënten met een suboptimaal gecontroleerd astma die deelnemen aan een longrevalidatie programma gedurende 3 maanden vooraf aan bariatrische chirurgie. Dit longrevalidatie programma is vergelijkbaar met het longrevalidatie programma beschreven in hoofdstuk 4. In vergelijking met een gematchte controlegroep van morbide obese astmapatiënten die geen longrevalidatie programma hebben gevolgd voorafgaand aan bariatrische chirurgie, hadden deze 4 patiënten een hogere leeftijd, een lagere FEV_1 en een minder goed gecontroleerd astma. Desondanks was het mogelijk om deel te nemen aan dit intensieve longrevalidatie programma met hoge intensiteit interval training (HIIT). De deelnemers hadden een klinisch relevante verbetering in astma controle, kwaliteit van leven en inspanningscapaciteit en een significante afname van de BMI na 3 maanden longrevalidatie voor de bariatrische chirurgie. Na 6 maanden follow-up waren deze effecten nog steeds zichtbaar. We zagen geen verschillen in de uitkomsten van de bariatrische chirurgie tussen patiënten die wel of niet hadden deelgenomen aan longrevalidatie en vanwege een klein aantal patiënten in deze beschrijvende studie konden we geen analyse doen naar verschillen in postoperatieve complicaties. Het is echter aannemelijk dat een verbeterde astmacontrole en conditie vooraf aan bariatrische chirurgie het risico op complicaties bij deze patiënten vermindert. Alhoewel we geen grote uitspraken kunnen doen aan de hand van deze kleine studie, lijkt het ons zeer verstandig om alle morbide obese patiënten met suboptimaal gecontroleerd astma te verwijzen voor longrevalidatie vooraf aan bariatrische chirurgie.

In **hoofdstuk 8** bespreken we de resultaten van een studie naar de lange-termijn effecten van bariatrische chirurgie bij morbide obese personen met en zonder astma. We zagen dat 8 jaar na bariatrische chirurgie, de gemiddelde BMI in beide groepen

toegenomen was ten opzichte van 1 jaar na bariatrische chirurgie. Echter, deze toename was minimaal ten opzichte van het verschil met de BMI voorafgaand aan de bariatrische chirurgie. Ondanks deze kleine toename in BMI zagen we dat de verbeteringen in astmacontrole, kwaliteit van leven en longfunctie nog steeds aanhouden. Een andere belangrijke bevinding was dat de verbetering van de functie van de kleine luchtwegen (R5-R20) in de morbide obese personen met en zonder astma nog steeds aanwezig is na 8 jaar follow-up. Deze studie benadrukt het belang van gewichtsverlies door bariatrische chirurgie bij de behandeling van obesitas gerelateerd astma.

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CURRICULUM VITAE

Yasemin Türk was born on December 13th 1987 in Bergen op Zoom, the Netherlands. In 2006 she graduated from high school at the Regionale Scholengemeenschap 't Rijks. The same year she started medical school at the Erasmus University in Rotterdam from which she obtained the degree of medical doctor in September 2012. After her graduation, she worked as a resident (ANIOS) at the department of pulmonology in the Franciscus Gasthuis and in April 2013 she started with her PhD project "Obesity and Asthma" under the supervision of prof. dr. P.S. Hiemstra, prof. dr. C. Taube (Leiden University Medical Centre) and dr. Braunstahl (Franciscus Gasthuis & Vlietland). The results of this project are presented in this thesis. In February 2017 she started with her residency training in Internal medicine under the supervision of A.P. Rietveld and Y. Schrama, followed by her specialty training in Pulmonology at the Franciscus Gasthuis & Vlietland, supervised by dr. J.C.C.M in 't Veen.