Summary and general discussion
SUMMARY AND GENERAL DISCUSSION

Obesity has historically been viewed as a sign of wealth and prosperity. However, obesity is not a medical disorder that started with the industrial revolution, since already Hippocrates wrote that “Corpulence is not only a disease itself, but the harbinger of others”\(^{(1)}\). The current epidemic of obesity has revealed various co-morbidities associated with obesity. Asthma is one these co-morbidities which are associated with obesity, and is the focus of the research described in the present thesis. The main topic of this thesis is whether the relationship between obesity and asthma is causal or that obesity and asthma are two co-incidental diseases in the same person.

**Main findings**

In **chapter 2** we have shown that both overdiagnosis as well as underdiagnosis of asthma occur in the morbidly obese. A diagnosis of asthma based on symptoms alone is unreliable in the morbidly obese, and pulmonary function testing is an essential part of the diagnosis of asthma in the morbidly obese\(^{(2)}\).

As overdiagnosis of asthma cannot fully explain the interplay between obesity and asthma, we explored other explanations. In **chapter 3** all possible known explanations were discussed. As a new explanation the metabolic syndrome was suggested\(^{(3)}\). To investigate whether the metabolic syndrome might explain the relationship between obesity and asthma, we explored in **chapter 4** the relationship between airflow obstruction (FEV\(_1\)/FVC) – an essential component of the diagnosis of asthma – and the metabolic syndrome. This study showed a small, but statistically significant, difference in eosinophils and FEV\(_1\)/FVC between subjects with and without the metabolic syndrome\(^{(4)}\). After correction for other variables, an association between blood eosinophils and FEV\(_1\)/FVC remained. Although the differences we have found were relatively small, it might support our hypothesis that the presence of the metabolic syndrome may influence lung function impairment, through the induction of systemic inflammation, in particular, mediated by blood eosinophils.

We therefore investigated in **chapter 5** characteristics of bronchial biopsies from morbidly obese asthma patients and morbidly obese controls. We were surprised to find that despite evidence for systemic inflammation, which seemed to be related to the level of asthma control, there was no evidence for bronchial inflammation in the morbidly obese as shown e.g. by the absence of increased numbers of eosinophils or neutrophils\(^{(5)}\).

Bariatric surgery is considered a definitive solution for morbid obesity, as weight loss is permanent in contrast to dieting, which is most often a temporary solution. In **chapter 6** we have shown that subjects with complications within 30 days of bariatric surgery more often have airflow reversibility or airflow obstruction\(^{(6)}\). Therefore, as symptoms indicative of airway disease are often unreliable in the morbidly obese – as already
discussed in chapter 2 - , pulmonary function tests should routinely be part of the pre-operative risk assessment.

In chapter 7 we extensively looked at both clinical, physiological, systemic and bronchial mucosal inflammatory parameters before and after bariatric surgery in morbidly obese asthma subjects and morbidly obese control subjects. Although we found no improvement in our primary endpoint FEV₁/FVC, we did find improvement in asthma control, quality of life, medication use and PD₂₀ methacholine. The significant improvement of R₅-R₂₀ (peripheral airway function) after bariatric surgery, which was associated with BMI, ACQ and PD₂₀, suggests that peripheral airways play a major role in the relationship between obesity and asthma. Finally, bariatric surgery also decreased markers of systemic inflammation, and mast cell counts in bronchial submucosa of obese asthma subjects. Collectively these findings emphasize that weight loss as achieved by bariatric surgery should be a cornerstone in the treatment of morbidly obese asthma patients.

Based on my main findings, this discussion is subdivided into three main topics. First, I will discuss the pitfalls concerning the diagnosis of asthma, especially in the morbidly obese. Then, I will describe bronchial and systemic inflammation in the morbidly obese. Thereafter I will address bariatric surgery in the morbidly obese, and will especially focus on the therapeutic effect of bariatric surgery in morbidly obese asthma patients.

**Diagnosis of asthma in the morbidly obese**
The first step to investigate the possible causal relationship between asthma and obesity, is to be sure that the diagnosis of asthma is correct. According to the latest Global Initiative for Asthma (GINA) definition of 2014, asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Although the GINA guidelines are clear in stating that besides symptoms, also objective measurements of variable expiratory airflow limitation are necessary for the diagnosis of asthma - implying that lung function testing is mandatory for the diagnosis of asthma - in daily practice the diagnosis of asthma is often made only on the basis of symptoms. Especially within the morbidly obese population, this symptom-based approach has been proven to be of limited value. Morbidly obese do often have dyspnea and the diagnostic challenge is to distinguish dyspnea resulting from overweight and dyspnea due to asthma. In chapter 2 we have shown that both overdiagnosis as well as underdiagnosis of asthma occur in the morbidly obese. A diagnosis of asthma based on symptoms alone is unreliable in the morbidly obese patient population, and pulmonary function testing is an essential part in the diagnostic progress of asthma in the morbidly obese. 
To our knowledge, this is the first study that not only focuses on overdiagnosis but also on underdiagnosis of asthma in this patient population. Underdiagnosis of asthma can lead to undertreatment, increased morbidity and eventually possible death. On the other hand, overdiagnosis leads to overtreatment with possible risk of side-effects of the inhaled corticosteroids and high health costs. It can be argued that the use of inhaled corticosteroids (ICS) can influence the results of the provocation test\(^9\), however stopping of ICS use is a possibility to correct for this. Many clinicians are reluctant to do this, but we have shown that it can be done in most morbidly obese (asthmatic) patients without complications (ref; unpublished observations).

Many of the population-based studies use a physician-diagnosis of asthma. The question thus arises, whether this physician diagnosis of asthma is correct, especially in the morbidly obese. However, as a result of the inclusion method of our study in chapter 2, we cannot make any statement on the frequency of underdiagnosis or overdiagnosis in the total morbidly obese population. So, it is still unclear whether overdiagnosis of asthma truly explains the relationship between obesity and asthma. Further research in a cross-sectional study in the general population in which all subjects undergo spirometry and bronchial provocation testing could answer this question.

**Bronchial and systemic inflammation in the morbidly obese**

As overdiagnosis of asthma cannot fully explain the interplay between obesity and asthma, we explored other explanations. In **chapter 3** all possible known explanations are discussed.

"Obese asthma" may be a unique phenotype of asthma, characterized by decreased lung volumes, greater symptoms for a given degree of lung function impairment, destabilization or lack of asthma control, lack of eosinophilic inflammation and a different response to controller medication. Therefore, the clinical evaluation of an obese patient with asthma must require a more rigorous and objective approach. Whether this relationship is really causal or represents parallel co-morbidities is unclear. In animal models, there is an increasing amount of evidence for the role of adipokines derived from fat tissue in the relationship between obesity and asthma. These adipokines cause a low grade systemic inflammation, which might cause or enhance bronchial inflammation. The data are conflicting in humans. However, the fact that weight loss improves asthma control and normalizes the concentration of adipokines in the circulation implies that there must be some role for adipokines in the relationship between obesity and asthma.

A hypothesis not discussed in chapter 3, is the effect of gut microbiota on asthma and obesity. The modern dietary pattern with reduced fiber content is associated with changes in gut microbiota biodiversity, which is a risk factor for allergy and obesity\(^{10}\). The gut microbiota and the microbiome (collective genetic material of gut microbiota) are important in normal immune development. A disruption of the gut microbiota
increases immune and metabolic dysregulation, and increases the risk of obesity and asthma. The changing gut microbiota is linked to inflammation through increased CRP, TNFα and IL-6\(^{(11)}\). The hygiene hypothesis states that excessive cleaning and reduced pathogen exposure contribute to inadequate immune responses\(^{(12)}\). A link can be seen with the gut microbiota which can be influenced by diet and antibiotics use, and some state that the hygiene theory should be rewritten into the “microflora hypothesis”\(^{(13)}\). This hypothesis postulated that disturbances in gut microbiota lead to underdeveloped microbiota, which impair proper maturation of the immune system leading to allergic hypersensitivity and asthma. But also obesity is influenced by altered gut microbiota. In obese subjects the gut barrier is altered leading to higher plasma lipopolysaccharide levels which trigger low grade inflammation and insulin resistance\(^{(14)}\). Because the notion that gut microbiota affects obesity and asthma is a recent insight, we have not performed any research on this subject yet.

Another explanation how obesity can influence asthma is the metabolic syndrome (mentioned in chapter 3). Since obesity is a component of the metabolic syndrome and the metabolic syndrome also includes systemic inflammation, it is to be expected that there is a relationship between metabolic syndrome and asthma. The few data that are available show that there is no relationship between metabolic syndrome and asthma, but there is one between the metabolic syndrome and asthma-like symptoms.

To investigate whether the metabolic syndrome might explain the relationship between obesity and asthma, we explored in chapter 4 the relationship between airflow obstruction (FEV\(_1\)/FVC) – an essential component of the diagnosis of asthma – and the metabolic syndrome. This study showed a small, but statistically significant, difference in eosinophils and FEV\(_1\)/FVC between subjects with and without the metabolic syndrome\(^{(4)}\). After correction for other variables, an association between blood eosinophils and FEV\(_1\)/FVC remained. Although the differences we have found were relatively small, it might support our hypothesis that the presence of the metabolic syndrome may influence lung function impairment, through the induction of systemic inflammation, in particular, mediated by blood eosinophils.

Insulin resistance, another part of the metabolic syndrome, might also help to explain the relationship between obesity and asthma. Hyperinsulinemia may lead to changes in the lung characteristics of asthma via growth factor-like effects\(^{(15)}\). A vagally mediated bronchoconstrictor effect of hyperinsulinemia has also been described\(^{(16)}\). A study in healthy adults has found an association between insulin resistance and bronchial hyperresponsiveness\(^{(17)}\). We however, found that only hypertension – as one of the five components of the metabolic syndrome – was associated with FEV\(_1\)/FVC and furthermore, we did not test bronchial hyperresponsiveness.
After we had found more circumstantial evidence that systemic inflammation might explain the relationship between asthma and obesity, we investigated whether this systemic inflammation also leads to local bronchial inflammation. As bronchial inflammation is considered a key component of asthma, if bronchial inflammation in present in the morbidly obese asthma subject, it would argue for a causal relationship between obesity and asthma.

Whereas other studies tried to investigate this bronchial inflammation by bronchial lavage or bronchial brushes, it can be argued whether they truly investigated bronchial inflammation. There might be a difference in the inflammatory cell population within the airway epithelium (as investigated by lavage, brushes or bronchial biopsies) and that in submucosa (as investigated by bronchial biopsies). We therefore investigated in chapter 5 characteristics of bronchial biopsies from morbidly obese asthma patients and morbidly obese controls.

As we found in chapter 4 that increased numbers or circulating eosinophils could be a specific manifestation of the systemic inflammation associated with the metabolic syndrome, it could be expected that asthma in the morbidly obese is also an eosinophil driven disease as it is known to be in many lean atopic asthma subjects. However, there is large debate in literature about the nature of the inflammation in obese asthma subjects. Asthma in the obese has been characterized as a specific phenotype, with a female predominance, late on-set and not eosinophilic\(^{18}\).

We were surprised to find that despite evidence for systemic inflammation, which seemed to be related to the level of asthma control, there was no evidence for bronchial inflammation in the morbidly obese, characterized by increased numbers of eosinophils or neutrophils\(^{5}\). Despite one part of the morbidly obese study population was diagnosed as having asthma, while the other part of the morbidly obese study population had no asthma, there was no difference in any of the components of bronchial inflammation studies with the exception of CD8 positive T-cells. Both groups had the same degree of obesity, had no differences in lung function, or prevalence of the metabolic syndrome. A good explanation why one group has asthma and the other not, despite the fact that there is no difference in bronchial inflammation remains a question to be elucidated.

Our data suggest that asthma in our cohort is not driven by a classical T\(_{h2}\)-mediated mechanism and probably needs to be regarded as a distinct phenotype of the disease, not related to significant detectable inflammatory responses in the airway walls. Possibly asthma in the *morbidly obese* – as were the subjects of our studies – constitutes a specific phenotype, which is distinct from asthma in *obese* subjects. Desai *et al.*\(^{19}\), who investigated obese asthma subjects (mean BMI 36 kg/m\(^2\) versus mean BMI 44 kg/m\(^2\) in our study), did find an elevated bronchial submucosal eosinophil number as compared to lean controls and lean asthmatics. Others discuss that the lack of airway eosinophils could be altered trafficking of these cells from the vasculature or interstitium into the
airspace rather than a unique inflammatory phenotype per se\(^{(20)}\). While others state that the location of the eosinophils within specific tissues may directly affect their function\(^{(21)}\). Additionally, we also found no evidence for neutrophil-dominated bronchial inflammation, as has been shown in an obese asthma group by Scott\(^{(22)}\).

Furthermore our study was the first to compare bronchial biopsies from morbidly obese asthma subjects to morbidly obese controls. Previous studies compared obese asthmatics with lean asthmatics, and found differences. It should be kept in mind that these differences can also be attributed to obesity rather than asthma.

As the classical Th2-mediated mechanism seems not to be present in the morbidly obese with asthma, other mechanisms could be active. Another cell type of interest are the macrophages. Blood monocytes and adipose tissue macrophages in obesity demonstrate a classical M1 activation. Lugogo \textit{et al} compared macrophages of 42 obese subjects with asthma with 46 obese subjects without asthma, and found that alveolar macrophages in obese asthmatics demonstrate an exaggerated response to the proinflammatory effect of leptin\(^{(23)}\). Furthermore, Fernandez has showed that in obese asthmatics the efferocytosis (the process by which macrophages ingest and clear apoptotic cells) of blood monocytes and airway macrophages in obese asthmatics was 40% lower as compared to lean asthmatics. Although we found no differences in the number of macrophages in the bronchial tissue between morbidly obese asthmatics and morbidly obese controls, of course there could have been a difference in macrophage function. Further research should also focus on macrophages in the fat tissue, and whether these macrophages in the fat tissue also influence systemic inflammation and thereby bronchial inflammation.

Th\(_{17}\) cells, developmentally distinct from Th\(_{1}\) and Th\(_{2}\) cells, could also play a role in the relationship between obesity and asthma, as IL-17A – produced by Th\(_{17}\) cells, but also by other cell types – is required for the development of bronchial hyperresponsiveness in obese mice\(^{(24)}\). Furthermore, Mathews \textit{et al}. have recently shown that the increases in IL-17A precedes the development of bronchial hyperresponsiveness by several weeks in mice\(^{(25)}\), suggesting that obesity and asthma are not two co-incidental diseases. Data on IL-17A in obese humans with asthma is rare, and it also was not a subject of our research.

Air pollution is now mentioned as a novel risk factor for the development of obesity\(^{(26)}\) and asthma, and research is now focusing on bronchial inflammation caused by air pollution\(^{(27)}\). Endocrine-disrupting chemical (EDC) are chemicals that can disrupt adipogenesis and energy balance. Air pollution can induce obesity via a systemic inflammatory pathway that targets adipocytes\(^{(28)}\). Many EDCs are highly lipophilic and therefore accumulate in the fat tissue, where they can release proinflammatory signals but also may cause adipocyte proliferation and differentiation. This seems quite plausible, and might explain the exploding prevalence of obesity in the last decades, other than excess caloric intake, sedentary lifestyle or genetic susceptibility. However, it is now also stated
that obese individuals are more vulnerable to develop asthma due to exposure to air pollutants than lean individuals. In a study with 148 children with persistent asthma, the association between indoor particulate matter less than 2.5 µm in mean aerodynamic diameter (PM$_{2.5}$) and nitrogen dioxide (NO$_2$) levels and respiratory symptoms were examined. Overweight children were more susceptible to pulmonary effects of PM$_{2.5}$ and NO$_2$\(^{(29)}\). This does not answer whether it is asthma or obesity that made the children more susceptible to EDCs. In a mouse study by Shore et al, obese mice inhaled greater doses of air pollutant ozone in the lungs than normal weight mice because of higher breathing frequency, accompanied by greater airway hyperresponsiveness and greater cellular inflammation\(^{(27)}\). This is not in line with our results of bronchial tissue inflammation, as discussed in chapter 5, where we found no difference in cellular inflammation between obese subjects with or without asthma. This might be explained by the fact that there might be an association between air pollutants and asthma or obesity, but this is not a causal relationship. Further research on air pollution is needed.

Since we found no difference in bronchial inflammation between obese asthma subjects and obese controls, it can be argued that the definition of asthma as a syndrome characterized by airway hyper-responsiveness, inflammation and clinical symptoms, as presented in the GINA guidelines, is perhaps not applicable to the morbidly obese. In the present study, all asthma subjects had symptoms, reversible airway obstruction or increased bronchial hyper-reactivity. In contrast, in majority of patients no airway inflammation could be detected. This further strengthens the concept of a different asthma phenotype, whereas the phenotype observed in the present study has no distinct inflammatory changes in the airways. This phenomenon probably explains why these patients have such a poor response to anti-inflammatory medication. Weight loss seems to be the most important therapeutic goal, although further research on this subject is needed.

**Bariatric surgery**

Bariatric surgery is considered a definitive solution for morbidly obesity. In line with the worldwide epidemic of obesity, the number of bariatric surgery procedures being performed is increasing every year, with a 22-fold increase between 1996 en 2008\(^{(30)}\). The prevention of complications of bariatric surgery is of great importance, especially since surgery is elective and complications are difficult to treat in this group of morbidly obese patients. As we have shown in chapter 4 that morbidly obese subjects with the metabolic syndrome have a slight, but statistically significant, increase in airflow obstruction, we wondered whether subjects with more airflow obstruction or airflow reversibility, had more complications after bariatric surgery. In chapter 6 we have shown that subjects with complications within 30 days of bariatric surgery more often have airflow reversibility or airflow obstruction\(^{(6)}\). Therefore, as symptoms are often unreliable
in the morbidly obese – as already discussed in chapter 2 - , pulmonary function tests should routinely be part of the preoperative risk assessment. Generally, laparoscopic bariatric surgery is safe, but randomized prospective studies are needed to investigate whether abnormal pulmonary functions tests could indeed serve as a guide in patient selection and optimization of the preoperative medical condition of patients undergoing bariatric surgery, which could lead to additional improvement in the outcomes after bariatric surgery.

The current guidelines of the American Society of Metabolic and Bariatric Surgery state that spirometry as a preoperative test is indicated only in the presence of risk factors previously identified by other tests\textsuperscript{31}. A recent study by Clavellina et al in 602 patients, which investigated the relationship between spirometry results and the frequency of postoperative complications\textsuperscript{32}, supports our study results. They also found that using multivariate logistic regression analysis, an abnormal spirometry was a significant predictor of post-operative pulmonary complications in patients with respiratory symptoms and/ or obstructive sleep apnea syndrome (OSAS). However, they state that there was a significant number of asymptomatic patients that in spite of an abnormal spirometry, did not develop respiratory complications\textsuperscript{32}, and therefore argue that spirometry should not be performed regularly before bariatric surgery. A large study of 158405 patients in the USA, which focused on pulmonary complications of bariatric surgery, found that not only the metabolic syndrome, but also asthma is a risk factor for postoperative pulmonary complications\textsuperscript{33}. However, as discussed previously, the major pitfall of this article was that the asthma diagnosis was based on physician assessment and no spirometry was performed. As the metabolic syndrome is seen as a state of systemic inflammation, it is logical to speculate that subjects with (more) systemic inflammation have a higher change of complications of bariatric surgery. The abovementioned US study found that the metabolic syndrome is associated with complications of bariatric surgery, we although did not find such an association.

Interestingly, our study has shown that spirometry is not only useful in predicting pulmonary complications, but it might predict all complications of bariatric surgery. This it is in line with previous findings that FEV\textsubscript{1} is associated with mortality\textsuperscript{34}. FEV\textsubscript{1} could possibly be a marker of general health or fitness. So abnormal spirometry does not only indicate obstructive pulmonary disease, but might also indicate poor general health. In this cohort we had no data on systemic or bronchial inflammation. It is purely speculative to say that the group with abnormal spirometry also had more systemic inflammation.

Only a randomized controlled intervention study which investigates whether therapy in subjects with abnormal spirometry could prevent complications of bariatric surgery, could answer whether spirometry should be standard in all bariatric subjects. Such a study has not yet been performed to our knowledge.
After showing in chapter 5 that bronchial inflammation is absent in the morbidly obese, in contrast to systemic inflammation, we further explored the effects of weight loss by bariatric surgery. In chapter 7 we extensively looked at both clinical, physiological, systemic and bronchial musical inflammatory parameters before and after bariatric surgery in morbidly obese asthma subjects and morbidly obese control subjects. Although we found no improvement in our primary endpoint FEV$_1$/FVC, we did find improvement in asthma control, quality of life, medication use and PD$_{20}$ methacholine. The significant improvement of R$_5$-R$_{20}$ (peripheral airway function) after bariatric surgery, which was associated with BMI, ACQ and PD$_{20}$, suggests that peripheral airways play a major role in the relationship between obesity and asthma. Finally, bariatric surgery also decreased markers of systemic inflammation, and mast cell counts in bronchial submucosa of obese asthma subjects.

The fact that we did not find clear evidence that also bronchial inflammation is decreased concordantly with the systemic inflammation, is in contrast to the results of Arismendi et al. They showed not only that in a group of healthy obese subjects, systemic inflammation is not modified by sex, smoking status or metabolic syndrome, but also that pulmonary inflammation, as measured by exhaled IL-8, IL-10 and 8-isoprostane, is increased in obese healthy subjects as compared to lean healthy subjects, and furthermore that this pulmonary inflammation is decreased after bariatric surgery. However, they did not include subjects with asthma. And as stated previously, the question remains whether there are cellular differences with regard to inflammation between the submucosa and the epithelium.

Obesity is associated with increased oxidative stress. Exhaled 8-isoprostane, derived from free radical-catalyzed peroxidation of arachidonic acid, is a marker of oxidative stress. Oxidative stress is characterized by the presence of increased reactive oxygen species (ROS). ROS production contributes to increased mucus production and increased airway reactivity. Increased plasma 8-isoprostane levels have been noted in asthma, but were not present after adjusting for obesity. This suggests that the elevated plasma levels are a consequence of obesity rather than asthma.

Recently there is more recognition that bioenergetic failure is a common pathway rather than an outcome of disease, in obesity, metabolic syndrome and asthma. Mitochondrial dysfunction seems to be related to the metabolic syndrome. Surplus nutrient supply overloads mitochondria, leading to overproduction of (ROS) and accumulation of incompletely oxidized substrates. The damage of these ROS causes reduction in mitochondrial integrity, and triggers stress pathways that reduce insulin sensitivity. Together with the sedentary lifestyle, this appears to be the foundation of insulin resistance. As fatty acid oxidation for energy can only happen in mitochondria, fats are not adequately metabolized, leading to intracellular accumulation and increased circulating lipids. This is the trias of obesity, hyperglycaemia and dyslipidemia, also known as the...
metabolic syndrome. As hypersinsulinemia seems to be an independent risk factor for asthma\(^{(15)}\), mitochondrial mechanisms important in the metabolic syndrome can also contribute to asthma. Although in mice models of allergic airway inflammation, mitochondrial dysfunction has been demonstrated\(^{(41)}\), there is limited evidence for a causal role of mitochondrial dysfunction in human asthma. The exact role of oxidative stress in the relationship between asthma and obesity has yet to be elucidated, and should be focus of further research.

As previously discussed, we take the view that morbidly obese asthmatics are a distinct phenotype on its own, in contrast to obese asthmatics. It is also speculated that the obese asthma phenotype could be further divided into Th2-high (high serum IgE) obese asthmatics having pre-existing allergic asthma that is complicated by obesity, whereas Th2-low (low serum IgE) obese asthmatics develop asthma symptoms as a consequence of obesity. This subphenotyping is confirmed by the fact that airway hyperresponsiveness in Th2-low obese asthmatics improves after weight loss following bariatric surgery, in contrast to Th2-high obese asthmatics\(^{(42)}\).

Traditionally asthma research has focused on the large airways. However, small airways are also an important site of airway inflammation and remodeling in asthma\(^{(43)}\). There are only a few studies on small airways in (lean) asthma\(^{(44, 45)}\), the list of small airway studies in subjects with obesity is even smaller\(^{(46)}\). With impulse oscillometry (IOS) the resistance and reactance of the airways can be measured easily. Resistance at 20Hz is considered to reflect the large airways (\(R_{20}\)) and resistance at 5Hz the total airways (\(R_5\)). Small airway resistance can be calculated with the difference \(R_5-R_{20}\). Reactance of the system at 5Hz (\(X_5\)) is also assumed to reflect small airway function\(^{(47)}\). Asthma symptoms correlate poorly with FEV\(_1\), and in a recent study by Van der Wiel et al\(^{(44)}\), which also included some obese subjects, it was shown that also small airway dysfunction poorly associated with asthma symptoms. However, they showed that small airway dysfunction is associated with more severe bronchial hyperresponsiveness to methacholine.

As small airways are now subject of current research in obese asthmatics, Chapman et al. investigated the effect of bariatric surgery on small airways and the two phenotypes of obese asthma, and found that weight loss does not alter small airway responsiveness in Th2-high obese asthmatics, in contrast to Th2-low obese asthmatics where weight loss is associated with a reduction in small airway responsiveness\(^{(46)}\). However, the patient numbers in this study are small (Th2-low, n=8; Th2-high, n=5). As our numbers are larger, this could explain why we did not find differences in subjects with either high or low IgE.

Treatment of (morbidly) obese asthmatics has proven to be difficult, as they respond poorly to conventional asthma therapies such as inhaled corticosteroids (ICS)\(^{(48)}\). As the conventional asthma therapies do not work, other researchers have investigated alternative options such as the effect of dietary weight loss\(^{(49-52)}\). The study by Stenius et
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Al. showed that a 14-week weight reduction program using a low calorie diet leads to sustained improvement in lung function and health status. The role of exercise as intervention has not been studied extensively, although exercise or pulmonary rehabilitation could be of use especially in the morbidly obese asthma patient. However, it is difficult to obtain sustained weight loss in the morbidly obese with calorie restriction and behavioral interventions. Bariatric surgery causes a larger and prolonged effect on weight loss. Previous studies have also shown that bariatric surgery improves asthma control and airway hyperresponsiveness. Some, however, state that the surgical technique is of influence on asthma related outcomes. A study of 257 patients with asthma showed after 1-year an overall reduction in asthma medication in all patients. Those who underwent a laparoscopic gastric banding procedure were 37% more likely to show improvement in self-reported asthma severity compared to those operated with the Roux-and-Y procedure. Gastric banding is however a procedure that has become less common, due to complications, and is not performed in the Sint Franciscus Gasthuis. As far as we know there are no studies comparing the effects on medication use between gastric sleeve resection and gastric Roux-and-Y bypass. In addition, bariatric surgery does not only influence asthma, it also improves asthma comorbidities such as gastroesophageal reflux disease (GERD) and obstructive sleep apnea.

Other treatment options discussed in literature of obese asthma patients could be the use of either metformin or statins. Metformin restores insulin sensitivity and promotes mitochondrial metabolism. In mice with diet-induced obesity, metformin attenuated allergen-induced eosinophilic inflammation. The beneficial effects of metformin were not found in a genetically obese mice model with intrinsic airway hyperresponsiveness. There is little data on the effect of metformin in human (obese) subjects with asthma. Further research is needed.

Statins which are classically prescribed for hyperlipidemia, have also found to have anti-inflammatory effect, and improve lung function. In a retrospective study of 165 adult asthmatics it was found that patients on statins had significantly increased ACT scores as compared to those without statins. However, medication related interventions were not part of our study.

All these findings together are underlining the importance of substantial weight reduction, in particular by bariatric surgery, which should be a cornerstone in the treatment of morbidly obese asthma patients. Furthermore, I would like to advocate that asthma should also be considered as one of the comorbidities – just like diabetes and OSAS – that makes patients eligible for bariatric surgery from a BMI level of 35 kg/m². Perhaps in future, morbidly obese asthmatic subjects will be sent more often to the surgeon, in addition to being sent to the pulmonologist, as “the surgeon can cure asthma in the morbidly obese”.
**FINAL REMARKS**

The studies performed in this thesis illustrate the complicated interplay between obesity and asthma. With the results of our studies and recent findings reported in literature, figure 2 from the introduction could be altered into:

![Diagram](image)

*Figure 1* Hypothesis explaining the obesity-asthma association

The studies from this thesis show the complexity of relation and interaction between obesity and asthma. The observed epidemiological relationship between obesity and asthma does not prove causality, and cannot be completely explained by overdiagnosis of asthma, especially because also underdiagnosis of asthma exists within the obese population. The fact that in this population of morbidly obese we found an association between airway obstruction and eosinophils in the peripheral blood, particularly in those patients with the metabolic syndrome, indicates a possible causal relationship between obesity and asthma. However, this was contradicted by the fact that we found no difference in bronchial inflammation, including eosinophils between morbid obese patients with and without asthma. Despite evidence for more systemic inflammation, analysis of bronchial biopsies did not provide further clues for a pathophysiological basis of the interaction between obesity and asthma. Besides the clear need for a rigorous diagnosis of asthma in the morbidly obese, the question arises whether asthma in the *morbidly* obese is a distinct phenotype characterized by the absence of eosinophilic or neutrophilic inflammation. However, despite the absence of bronchial inflammation, substantial weight loss induced by bariatric surgery does improve lung function, quality of life and systemic inflammation in as both morbidly obese asthma patients as morbidly obese controls. This indicates that weight loss is the cornerstone for treatment of
the morbidly obese asthma phenotype, and that this observation may provide further clues for understanding the relationship between obesity and asthma.

Further research is necessary to show whether the abovementioned effects of bariatric surgery are also present after long term follow-up. Also research regarding the role of small airways in the morbidly obese asthma subject is necessary. Finally, the effect of pulmonary rehabilitation before bariatric surgery is an interesting topic for further research, and might reveal whether it decreases complications of bariatric surgery, and whether pulmonary rehabilitation on its own has any effect in the (morbidly) obese asthma patient.

Taken together, despite the fact that further research, especially directed at the role of the small airways, is necessary, I take the view that there is a causal relationship between obesity and asthma.
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