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General introduction and outline of the thesis
GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

General introduction
Obesity is currently a major health problem and is developing into a global epidemic. Obesity is classified by the Body Mass Index (BMI) (table 1) and is defined as abnormal or excessive fat accumulation which can cause health problems. The World Health Organisation’s (WHO) latest projections indicate that, globally in 2005, approximately 1.6 billion adults (age 15+) were overweight, and at least 400 million adults were obese. The WHO further predicts that - by 2015- approximately 2.3 billion adults will be overweight and more than 700 million will be obese. High body mass index has overtaken tobacco smoking as the most costly and detrimental preventable cause of deadly diseases in the United States (1).

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Classification</th>
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<tbody>
<tr>
<td>&lt;18.5</td>
<td>Underweight</td>
</tr>
<tr>
<td>18.5-25</td>
<td>Normal weight</td>
</tr>
<tr>
<td>25-30</td>
<td>Overweight</td>
</tr>
<tr>
<td>30-40</td>
<td>Obesity</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Morbid Obesity</td>
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</table>

The prevalence and incidence of asthma has increased over the recent decades (2, 3). Besides an improved awareness of the disease, there are several other explanations for the increased asthma prevalence, such as decreased exposure to microbial products, changes in microbiota, increased exposure to air pollution and tobacco smoke, a change in diet and obesity (3). As the incidence and prevalence of obesity have increased concurrently with the incidence and prevalence of asthma (as shown in Figure 1 for the Netherlands), this is suggestive for a possible link between obesity and asthma (4, 5). The observation that asthma symptoms decrease after weight loss with either bariatric surgery or low caloric diet supports a causal relationship between obesity and asthma (5). Moreover, obese patients with persistent asthma have significantly worse asthma-related quality of life (6), less asthma control (7, 8), more severe disease (9-12), and more asthma-related hospital admissions than asthma patients with a normal BMI. As asthma is a heterogeneous disease, with different underlying disease processes, recognizable clusters of demographic, clinical and/or pathophysiological characteristics are called asthma phenotypes (13). Asthma with obesity is one of these recognized phenotypes.
**Figure 1** Temporal trends of obesity and asthma in the Netherlands

Temporal trends in the prevalence of obesity in adults and asthma in the Netherlands. The dotted line represents the prevalence of asthma, while the solid line represents the prevalence of obesity. Asthma year prevalence is standardized to population of the Netherlands in 2010 and is index-linked to 1992 (source CMR-Nijmegen). Obesity data are standardized to age- and gender distribution of 1981 (source CBS stat-line, 2013).

**Diagnosis of asthma in the morbidly obese**

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\(^\text{(13)}\).

GINA guidelines advise that asthma diagnosis should be based on both the presence of symptoms and objective measurements of variable expiratory airflow limitation\(^\text{(13)}\). However, in daily practice the diagnosis of asthma is mainly based on symptoms, and spirometry or provocation tests are not always performed\(^\text{(14)}\). Since obese subjects report more dyspnea than non-obese subjects\(^\text{(15, 16)}\), it might be that they get mislabelled as asthma (overdiagnosis). Inevitably, any overdiagnosis may lead to inappropriate treatment\(^\text{(14)}\), with increased risk of side-effects and increased costs\(^\text{(17)}\).

Many epidemiological studies concerning obesity and asthma have used physician-diagnosed asthma without confirmation by pulmonary function tests. This implies, as discussed earlier, reasonable doubt as to the accuracy of the diagnosis of asthma. Several studies report that the diagnosis of asthma could be revisited after extensive testing in 30% of physician-diagnosed asthma\(^\text{(18-20)}\), even after stopping with asthma medication\(^\text{(21)}\). On the other hand, missing the diagnosis of asthma in the obese population is also an important aspect. Impaired perception of dyspnea is thought to play a role especially in severe asthma\(^\text{(22, 23)}\), and poor perception of airflow obstruction may lead
to under-treatment of asthma\(^{(24,25)}\). All the recent studies investigating overdiagnosis of asthma in the obese\(^{(20,21,26)}\) initially used selected subjects with asthma, and therefore did not take into account obese patients with so far undetected asthma. Therefore, only limited information is available about the underdiagnosis of asthma in the obese.

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

*Obesity and asthma relationship*

The mechanisms underlying the relationship between asthma and obesity are unclear. In previous reviews concerning the relationship between obesity and asthma, five hypotheses were suggested (figure 2)\(^{(27)}\).

![Diagram](image)

**Figure 2** Explaining the obesity-asthma association

First, the diet of obese people consists of food with less nutritional value, fewer vitamins and more fat. A high amount of fat intake is associated with asthma\(^{(28)}\). Mineral deficiencies such as zinc- and magnesium deficiencies are associated with asthma and bronchial hyperreactivity (BHR)\(^{(29)}\). Second, asthma and obesity may share the same genetic risk factors. In a large-scale study among 1384 twins, a strong association between asthma and BMI was found\(^{(30)}\). The third hypothesis is that shared co-morbidities link these diseases. Obesity is a risk factor for gastro-oesophageal reflux disease (GERD) which, in turn, is a risk factor for asthma\(^{(31)}\). Another example is Obstructive Sleep Apnoea Syndrome (OSAS); the prevalence of OSAS is higher in severe asthma patients as well as in obese patients\(^{(32)}\). Fourth, obesity may influence lung function parameters. Typically, obesity causes a modest reduction in total lung capacity (TLC), and a larger reduction in functional residual capacity (FRC) (figure 3)\(^{(33)}\).
Figure 3. Altered lung function in obesity

Obesity leads to alternations of lung volumes. ERV: expiratory reserve volume; FRC: functional residual capacity; RV: residual volume; TLC: total lung capacity

The fifth hypothesis suggests that systemic inflammation may lead to asthma by means of fat-tissue derived adipokines. Obesity is considered to be a state of chronic low-grade systemic inflammation, characterized by an imbalance of pro- and anti-inflammatory proteins derived from adipocytes. Fat tissue was traditionally seen as an organ for storage of energy, however, it is now considered to act as an endocrine organ. The fat tissue is a source of bioactive peptides and proteins, which are called adipokines. Examples of adipokines are leptin, adiponectin and resistin. Also interleukin (IL)-6 and TNF-α, produced by macrophages in the fat tissue, play a role.

Leptin (Greek leptos, thin) is secreted by fat tissue and causes the feeling of satiation and increases the metabolism. Moreover, leptin influences the T-cell response and stimulates the proliferation of T-helper cells, which causes increased production of pro-inflammatory cytokines. Adiponectin is an insulin-regulating hormone. It also has anti-inflammatory effects: it decreases the production of pro-inflammatory cytokines and it increases the production of IL-10 and IL-1β. The assumption is that inflammatory mediators from the fat tissue enter the systemic circulation, and find their way to the lung tissue, where they may cause or intensify airway inflammation.

Systemic inflammation in the morbidly obese
The increasing prevalence of obesity may result in development of the metabolic syndrome. Metabolic syndrome is defined by a cluster of cardiometabolic risk factors characterized by abdominal obesity, insulin resistance and chronic systemic inflammation.

For components of the metabolic syndrome, such as hypertension, type 2 diabetes mellitus, low-density lipoprotein cholesterol and overall obesity positive as-
Associations with lung function impairment have been reported. In recent large cohort studies it has been shown that there is also a relationship between metabolic syndrome and lung function impairment\(^{(43-45)}\). Data on the association between lung function impairment and the metabolic syndrome in the morbidly obese are limited.

The mechanisms underlying the relationship between the metabolic syndrome and impaired lung function are unclear. The relationship might be explained by the chronic low-grade systemic inflammation that is associated with obesity. One hypothesis is that this low-grade systemic inflammation causes inflammation in the lungs, and hence lung function impairment (figure 4).

**Figure 4** Inflammatory mechanism linking obesity and asthma
Inflammatory mechanisms linking obesity to asthma (adapted from Lugogo\(^{(46)}\))

**Bronchial inflammation in the morbidly obese**
As stated previously, asthma is a chronic inflammatory disorder of the airways. The systemic inflammation, known to be present in the morbidly obese, may spill over into the lungs, and cause local inflammation in the airways, and thereby asthma. Indeed, asthma in the obese has been described as a specific phenotype, with a high symptom expression and late onset of symptoms\(^{(47, 48)}\). Typical allergic asthma is characterized by airway sputum eosinophilia and increased exhaled nitric oxide. Several studies in obese patients with asthma have shown an inverse relationship between BMI and exhaled nitric oxide and sputum eosinophilia\(^{(49-51)}\). Airway neutrophilia has been reported in obese asthmatic women as compared to obese controls and lean asthmatics\(^{(52)}\). There is however, some discrepancy in the literature concerning the nature of bronchial inflammation in obese asthmatics. While some research groups show increased sputum neutrophil counts\(^{(52, 53)}\), others report no relationship between obesity and neutrophilic airway inflammation\(^{(50, 51, 54)}\). All aforementioned studies in obese asthmatics investigated induced sputum or bronchial alveolar lavage cell counts, which may not fully reflect tissue inflammation.
Bariatric surgery
Bariatric surgery procedures affect weight loss through two mechanisms: malabsorption and restriction. In the Sint Franciscus Gasthuis\(^{(55)}\) two different bariatric surgery procedures are performed: the gastric sleeve resection and the (Roux-and Y) gastric bypass surgery. Sleeve gastrectomy is a partial gastrectomy, in which the majority of the greater curvature of the stomach is removed\(^{(56)}\), and is thereby a restrictive method. During the gastric bypass surgery a small proximal gastric pouch is divided and separated from the distal stomach and anastomosed to a Roux limb of small bowel 75 to 150 cm in length\(^{(56)}\) (figure 5). This is a combination of a restrictive and malabsorptive procedure.

![Figure 5: Gastric sleeve resection and gastric bypass surgery](image)

Complications of bariatric surgery
In line with the epidemic of obesity, the number of bariatric surgery procedures being performed is increasing every year, with a 22-fold increase between 1996 and 2008\(^{(57)}\). The postoperative morbidity rate after bariatric surgery is about 5%. In a large cohort study it was shown that postoperative pneumonia and respiratory failure, despite being infrequent complications of bariatric surgery, account for one fifth of the morbidity. Moreover, these complications are also associated with increased mortality\(^{(58)}\) and represent the largest attributable costs of all complications\(^{(59)}\). Since the surgery is elective and complications are difficult to treat in this group of morbidly obese patients, the prevention of complications of bariatric surgery is of great importance. Obesity is found to be a risk factor for the development of postoperative pulmonary complications after
abdominal surgery\(^{60}\). Obesity-related co-morbidities – such as asthma\(^{61}\) – may predispose obese patients to postoperative complications.

Current guidelines do not indicate pulmonary function testing in patients without evidence of pre-existing lung disease who are evaluated for non-thoracic surgical procedures. However, whether this is also true for morbidly obese is unclear. Spirometry could identify patients who are at risk for complications, although this is not the current consensus\(^{62}\). The guidelines state that spirometry is only mandatory in patients who are heavy smokers, or have complaints of dyspnea or cough\(^{63}\). However, there is a poor correlation between the presence of symptoms and lung function measurements\(^{64}\) in the general population, but also among the morbidly obese.

**Bariatric surgery in the management of asthma**

A recent position paper on weight loss interventions in asthma\(^{65}\) concluded that the evidence of benefits from weight reduction on asthma outcomes is weak. They included studies with dietary interventions, including the only randomized controlled trial by Stenius\(^{66}\). Besides effect on asthma outcomes, weight loss from dietary interventions also have been associated with reduction in markers of systemic inflammation\(^{67, 68}\). However, in the morbidly obese is has been shown that bariatric surgery leads to more and persistent weight loss in contrast to dietary weight loss\(^{69}\). So it is to be expected that weight loss by bariatric surgery has a greater and prolonged effect on asthma.

To our knowledge only six prospective studies have been published in which the effects of bariatric surgery on obese asthmatic patients have been evaluated\(^{70-75}\). These six studies conclude that airway responsiveness, lung volumes and asthma control do markedly improve with weight loss following bariatric surgery in severely obese asthmatic patients. However, the numbers of included subjects were small in all six studies. Furthermore, they either lacked (follow-up of) a non-asthmatic control group of subjects with bariatric surgery\(^{70, 71, 73, 75}\), or they lacked a non-intervention control group\(^{71, 72, 74, 75}\).

**Outline / aim of the thesis**

The aim of the thesis is threefold. First, we investigated whether not only overdiagnosis but also underdiagnosis of asthma is present in an obese population. Secondly, we studied the following research questions:

- Is bronchial inflammation present in obese asthmatics?
- Is there a relationship between bronchial inflammation in obese asthmatics and obesity-associated low-grade systemic inflammation?

Finally, we studied the effect of bariatric surgery on asthma symptoms, lung function and bronchial and systemic inflammation.
This thesis consists of three parts. Part A describes in chapter 2 the complex diagnosis of asthma in the morbidly obese, and especially focuses on underdiagnosis and overdiagnosis of asthma in this patient group. Part B investigates bronchial and systemic inflammation. It starts in chapter 3 with a review on the association between obesity and asthma, where the metabolic syndrome – as state of systemic inflammation – is mentioned as possible explanation for the association between obesity and asthma. In chapter 4 systemic inflammation and the metabolic syndrome and impaired lung function in morbidly obese subjects are discussed. This is followed by chapter 5, in which the presence and possible relationship between bronchial and systemic inflammation in morbidly obese asthma subjects are discussed. Part C focuses on bariatric surgery, first pulmonary function testing and complications of bariatric surgery are discussed in chapter 6. In chapter 7 the effect of bariatric surgery on asthma is described. And finally, in chapter 8, a summary and general discussion of these studies is presented.
REFERENCES


