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Title: Obesity-related risk factors for impaired lung function
Issue Date: 2018-03-07
CHAPTER 1

General introduction
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**GENERAL INTRODUCTION**

Asthma and COPD are chronic respiratory diseases, which are a major public health problem in many countries. The global prevalence of asthma ranges from 1 to 18% of the population in different countries \(^1\) and in a worldwide study the prevalence of COPD stage II or higher was 10% \(^2\).

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by a 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 \(^3\). In 2013, the World Health Organization (WHO) estimated that every year 25 billion disability-adjusted life years are lost because of asthma \(^4\). Asthma is often accompanied with allergic airways disease and this increases susceptibility for infections \(^5;6\). The main risk factors associated with childhood-onset asthma are genetic predisposition, a family history of allergy and asthma, infections, allergic sensitization, and tobacco exposure \(^7\). Risk factors for adult onset asthma are irritant exposure in the work place, environmental pollutants, upper airway disease, infections, obesity \(^8\) and the metabolic syndrome \(^9\).

Chronic obstructive pulmonary disease (COPD) is another chronic respiratory disease and it is typically associated with tobacco smoking, is usually present in persons older than forty years of age, and is characterized by progressive and irreversible airway obstruction \(^10\). COPD is the sixth leading cause of death since 2000 \(^11\). Although COPD is mainly a smoking-related disorder there are other risk factors for this disease. External risk factors are second hand smoking, occupational exposure, indoor air pollution from the burning of biomass fuels and outdoor air pollution; intrinsic risk factors are genetic predisposition, damaged airways due to prenatal maternal smoke exposure or childhood infection \(^12\). In addition, the metabolic syndrome and type 2 diabetes have been associated with COPD \(^13\).

Obesity contributes to the overall burden of disease worldwide \(^14;15\), and its prevalence remains increasing due to the abundant availability of energy-dense (fast) food and a sedentary lifestyle. Body mass index (BMI) is widely used to classify obesity and is expressed as body weight in kilograms divided by height in meters squared. According to the WHO classification overweight is defined as a BMI of 25 kg/m\(^2\) or higher, obesity as a BMI of 30 kg/m\(^2\) or higher and a BMI of 40 kg/m\(^2\) or higher is considered morbid obesity \(^16\). In the Netherlands, 60 percent of adult men and 44 percent of adult women have a BMI ≥ 25 kg/m\(^2\) and 13 percent of the men and 14 percent of the women have a BMI ≥ 30 kg/m\(^2\) \(^17\).

It is increasingly recognized that there is a relationship between obesity and asthma, although the cause of this association remains largely unknown \(^9;18;19\). In a meta-analysis of prospective epidemiological studies the risk of incident asthma in obese persons was 2-fold increased, compared with persons with a normal weight \(^19\). Obesity also appeared to worsen asthma control \(^20;21\) and in several studies obesity was associated with the severity of asthma \(^22\), whereas weight loss after bariatric surgery in obese asthmatic patients decreased the severity of asthma \(^23;24\). Although severe COPD is often accompanied by weight loss, in mild to moderate COPD patients obesity is more prevalent than in the normal population \(^25;26\).
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Historically, the loss of lung function associated with obesity is ascribed to altered mechanics, however more recently it is recognised that systemic effects of obesity and the metabolic syndrome may play a role. It is established that obesity is associated with a modest reduction in total lung capacity and a larger reduction in functional residual capacity and that it increases the work of breathing. Several studies have directly measured the impact of BMI on respiratory mechanics and demonstrated a reduced respiratory system compliance. This reduction in respiratory compliance may be due to a reduction in chest wall compliance, a reduction in lung compliance or a combination of both and might vary depending on body fat distribution.

Although most studies use BMI to define obesity, it is not an ideal measure to define obesity, because it does not distinguish body fat from fat free mass. Moreover, BMI provides no information on the distribution of body fat, which is an important contributing factor to morbidity and mortality. Abdominal obesity appeared even more important than overall obesity in relation to diabetes and cardiovascular disease and is an important component of the metabolic syndrome.

The metabolic syndrome and lung function

The metabolic syndrome is defined as a cluster of symptoms that occur together and increase the risk of obesity-related diseases. Several definitions exist, and according to the International Diabetes Federation the metabolic syndrome is defined by abdominal obesity based on a high waist circumference plus any two of the following four parameters: hyperglycemia, hypertriglyceridemia, low high-density lipoprotein cholesterol concentrations, and hypertension. More than one-fifth of the adult population and roughly 60% of obese individuals in the United States is affected by the metabolic syndrome.

In a prospective cohort study, the metabolic syndrome and in particular high waist circumference and hyperglycemia or diabetes were associated with an increased risk of asthma. All features of the metabolic syndrome may influence lung function. In various studies type 2 diabetes mellitus was related to impaired lung function. In patients with diabetes, glycosylation of extracellular matrix proteins in the chest wall and bronchial tree by high circulating glucose might explain in part this association. Glycosylation leads to irreversible collagen cross-linking, which causes collagen to be stiffer and less susceptible to proteolysis, resulting in accumulation of collagen in lung connective tissue.

Before patients develop overt diabetes, insulin resistance may already be present. Insulin plays a central role in glucose uptake and intracellular glucose metabolism, and high insulin concentrations - as observed in patients with insulin resistance - may also impair lung function.

Elevations in insulin promote net muscle protein accumulation primarily by inhibiting protein breakdown, rather than by stimulating protein synthesis and insulin resistance is associated with poor muscle strength. This may link insulin resistance to lung function impairment, because a decrease in skeletal muscle strength is associated with decreases in spirometric pulmonary function. Furthermore patients who inhale insulin have more dyspnea, cough and a reduced lung function. This could be explained by an increased...
calcium response to insulin by airway smooth muscle cells, and increased insulin-induced collagen release in these cells. These mechanisms could explain the increased contractility and remodeling of airway smooth muscle cells that was observed in an in vitro study 52. Hyperlipidemia is also associated with lung function impairment 53. In patients with the metabolic syndrome, often an excess of triglycerides and free fatty acids is observed in the circulation. Plasma saturated fatty acids are positively associated with sputum neutrophil percentage 54. In addition, sputum neutrophil percentage increased after a high fat meal in asthmatics 55. This could be due to the activation of innate immune responses via several inflammatory mechanisms by free fatty acids 56.

Adipose tissue stores energy in the form of lipids, acts as an insulating layer, and it provides mechanical protection and support for some major organs. Nowadays it is recognized that adipose tissue is also an endocrine organ. It secretes several pro-inflammatory cytokines and hormones that may result in a low grade systemic inflammatory state that could contribute to several obesity-related diseases 57;58. Visceral adipose tissue has a high secretion rate of pro-inflammatory cytokines 59 and other markers of inflammation 60, and it is hypothesized that the excess cardiometabolic risk associated with abdominal obesity is due to increased amounts of visceral adipose tissue 61-63. In large population-based studies the positive relationships between features of the metabolic syndrome and lung function were predominantly attributed to abdominal obesity as measured by waist circumference 53;64;65. Leptin and adiponectin are two of the multiple hormones produced by adipose tissue that may exert metabolic effects on the lung. Leptin is not only secreted by adipocytes but also by bronchial epithelial cells 66;67. A study in patients with heart failure showed that circulating leptin was associated with lung function impairment also after adjusting for percentage of body fat 68. This may be due to a leptin-induced pro-inflammatory response 69. In contrast to leptin, adiponectin concentrations decrease with increasing BMI and adiponectin has predominantly anti-inflammatory effects. A lower leptin/adiponectin ratio was associated with lung function decline in patients with COPD 70. Furthermore, low adiponectin is associated with a future risk of asthma 71. In a study in which obese patients with asthma were compared with an obese control group without asthma, assessment of several inflammation parameters in bronchial biopsies revealed no difference between these groups, but a subgroup analysis showed lower adiponectin concentrations in uncontrolled asthmatics 72. After bariatric surgery in this study group, systemic inflammation decreased in all patients (asthmatic and non-asthmatics) and mast cells decreased in bronchial biopsies of the patients with asthma 23. In the same study group morbidly obese patients with the metabolic syndrome had a higher proportion of blood monocytes and eosinophils, and their lung function was slightly more obstructed than that of obese patients without the metabolic syndrome 73. Therefore, these components of systemic inflammation might contribute to the lung function impairment in obese asthmatics.

Vitamin D, lung function and infections
Several studies have suggested that vitamin D, lung function and (respiratory) infections are interconnected. First, obesity is associated with lower vitamin D concentrations 74;75;76. The mechanism underlying this inverse association has not yet been fully elucidated. One possible explanation for the observed relation is that plasma vitamin D is reduced in obesity due to an increased uptake in subcutaneous adipose tissue 77;78 Precursors of vitamin D
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synthesized in the skin under the influence of sunlight, might not easily reach the circulation because of subcutaneous fat 79. Furthermore, there is a positive association between vitamin D status and lung function in the general population 80-84. This association may be explained in part by the impact of (respiratory) infections or airway inflammation on lung function, because of the regulatory role of vitamin D in immunity and infection 85,86.

Several observational studies showed that serum vitamin D status is inversely associated with the number of respiratory tract infections 87-90. Especially in asthmatics and COPD patients, respiratory tract infections play an important role as they are associated with exacerbations 91-93, which are the main cause of disease progression, decreased lung function and mortality in these patients 94-96. Vitamin D treatment in patients with vitamin D deficiency reduced exacerbations in those COPD patients with severe vitamin D deficiency 97,98. A recent meta-analyses of placebo controlled trials in asthmatic patients showed that vitamin D treatment reduces the number of exacerbations 99. If high vitamin D concentrations prevent respiratory infections one of the explanations could be that vitamin D increases production of antimicrobial peptides in lung tissue 100, and thereby decreasing the number of exacerbations in asthma and COPD patients. In that case vitamin D suppletion may be an attractive preventive strategy for progressive lung function impairment in these patient groups.

Asthma is often characterized by allergic airways disease and this is accompanied by increased susceptibility to infections 5,6. Allergic inflammation and especially the T helper 2 (Th2) cytokines produced during allergic inflammation could decrease local host defense against infections by reducing the expression of antimicrobial peptides and proteins 101,102. Furthermore, this Th2 cytokine-mediated inflammation has also been shown to impair epithelial anti-viral defenses 103 and epithelial cells from asthmatics have decreased antirhinovirus activity 104. Antimicrobial peptides and proteins form an essential element of innate immunity and eliminate a wide range of bacteria, fungi, and viruses 105. Various studies revealed deficiencies of selected antimicrobial peptides and proteins in airway secretions of patients with allergic rhinitis, sinusitis and asthma 101,106,107. Vitamin D is an important regulator of the production of antimicrobial peptides and proteins 108-110, and vitamin D administration has been shown to increase antimicrobial peptide expression in neonates and patients with atopic dermatitis 111,112. These data suggest that allergic inflammation contributes to impaired host defense against infections, and that vitamin D could improve this by stimulating antimicrobial peptide production. Therefore, it is important to establish the effect of vitamin D on antimicrobial peptides in allergic asthma patients by appropriately designed studies.

Outline and aims of the thesis

The aim of the research presented in this thesis was to unravel effects of obesity-related risk factors on lung function. Historically it is thought that lung function impairment is a consequence of abdominal obesity on lung mechanics. As described above metabolic effects of visceral fat on systemic inflammation and insulin resistance could cause airway inflammation and therefore also influence lung function. Furthermore obesity and especially subcutaneous fat is associated with low serum vitamin D concentration. Low vitamin D may influence lung function and the susceptibility to airway infections. A possible mechanism explaining a protective effect of vitamin D against respiratory tract infections is not yet elucidated.
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If vitamin D increases the production and expression of antimicrobial peptides this could influence airway inflammation and protect against respiratory infections. This thesis consists of two parts. First, we investigated to what extent components of the metabolic syndrome are associated with lung function. This is described in the first part of the thesis. In chapter 2 we explored the association of components of the metabolic syndrome and measurement of visceral fat with lung function as assessed with forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC) and exhaled nitric oxide in men with the metabolic syndrome. In chapter 3 we investigated the association between insulin resistance and lung function (FEV₁, FVC) in a population-based cohort. In chapter 4 the reproducibility of exhaled nitric oxide measurements in overweight and obese participants was established, and based on these findings we used a single exhaled nitric oxide measurement for the studies described in chapter 5 and 6. To examine whether exhaled nitric oxide could be used as a marker of adipose tissue-associated pulmonary inflammation, we investigated the association between visceral fat and exhaled nitric oxide in a population-based cohort study in chapter 5. In the second part of this thesis we aimed to investigate associations between vitamin D, lung function, exhaled nitric oxide and symptoms of the common cold. Therefore in chapter 6 we examined the associations of vitamin D status with lung function (FEV₁, FVC), exhaled nitric oxide, and symptoms of the common cold in a population-based cohort. Furthermore, we hypothesized that antimicrobial peptide levels in nasal secretions are lower in allergic asthmatic patients and that vitamin D could increase these levels. Therefore, in chapter 7 we first examined the expression of antimicrobial peptide levels in nasal secretions from patients with allergic asthma and in healthy controls in a case-control design. Secondly, we assessed if vitamin D administration increased antimicrobial levels in both asthma patients and healthy controls in a placebo-controlled cross-over study. And finally, in chapter 8 we summarize the results of this thesis and discuss its strengths, limitations and implications.

Study designs and data used in this thesis

The Rubens study

For the research question in chapter 2 we used the data from the “Rosiglitazone versus placebo on the prevention of progression of atherosclerosis” (RUBENS) trial. This is a double-blind placebo controlled randomized trial, testing the hypothesis that Rosiglitazone prevents progression of atherosclerosis in 110 participants aged between 50–70 years with the metabolic syndrome. All participants had a waist circumference > 94 cm and at least two other metabolic syndrome criteria: high triglycerides (TG) ≥ 1.7 mmol/L, high density lipoprotein (HDL) < 1.03 mmol/l, blood pressure ≥ 130 / ≥ 85 mm Hg. Exclusion criteria were presence of type 2 diabetes, overt cardiovascular disease, use of statins or fibrates, and BMI> 40 kg/m². In chapter 2 we used the data from the 98 participants who underwent lung function testing after the conclusion of this trial.

The NEO study

To answer the research questions in chapters 3 to 6, we used the baseline measurements of the “Netherlands Epidemiology of Obesity” (NEO) study. The NEO study is a population-based prospective cohort study in 6,671 individuals aged between 45 and 65 years, with an oversampling of persons with a BMI of 27 kg/m² or higher, who were recruited in the greater area of Leiden between September 2008 and October 2012. All participants underwent an
extensive physical examination including anthropometric measurements, blood sampling and lung function tests. In a random subset of 2,580 participants without contraindications for undergoing Magnetic Resonance Imaging (MRI), abdominal subcutaneous and visceral adipose tissue was assessed by MRI. Detailed information about the study design and data collection has been described previously.\textsuperscript{114}

The AVID study
To answer the research question in chapter 7 we performed the “Asthma and vitamin D” (AVID) study. We designed this study to measure levels of antimicrobial peptides in nasal secretions in asthmatics and healthy controls and to establish the effect of vitamin D treatment on these levels. In this trial, all participants were treated with active vitamin D (2 microgram 1,25(OH)\textsubscript{2}D3 or placebo once daily during seven days\textsuperscript{115;116}) in a double-blind, placebo-controlled cross-over design that was identical in asthmatics and healthy controls. This study included 19 patients with mild-to-moderate asthma and 23 healthy controls aged between 18 and 45 years recruited by advertisement in the Leiden area of the Netherlands. All participants underwent vacuum aided suction for collection of nasal secretions and blood sampling at several visits.
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