

Obesity and pulmonary host defense

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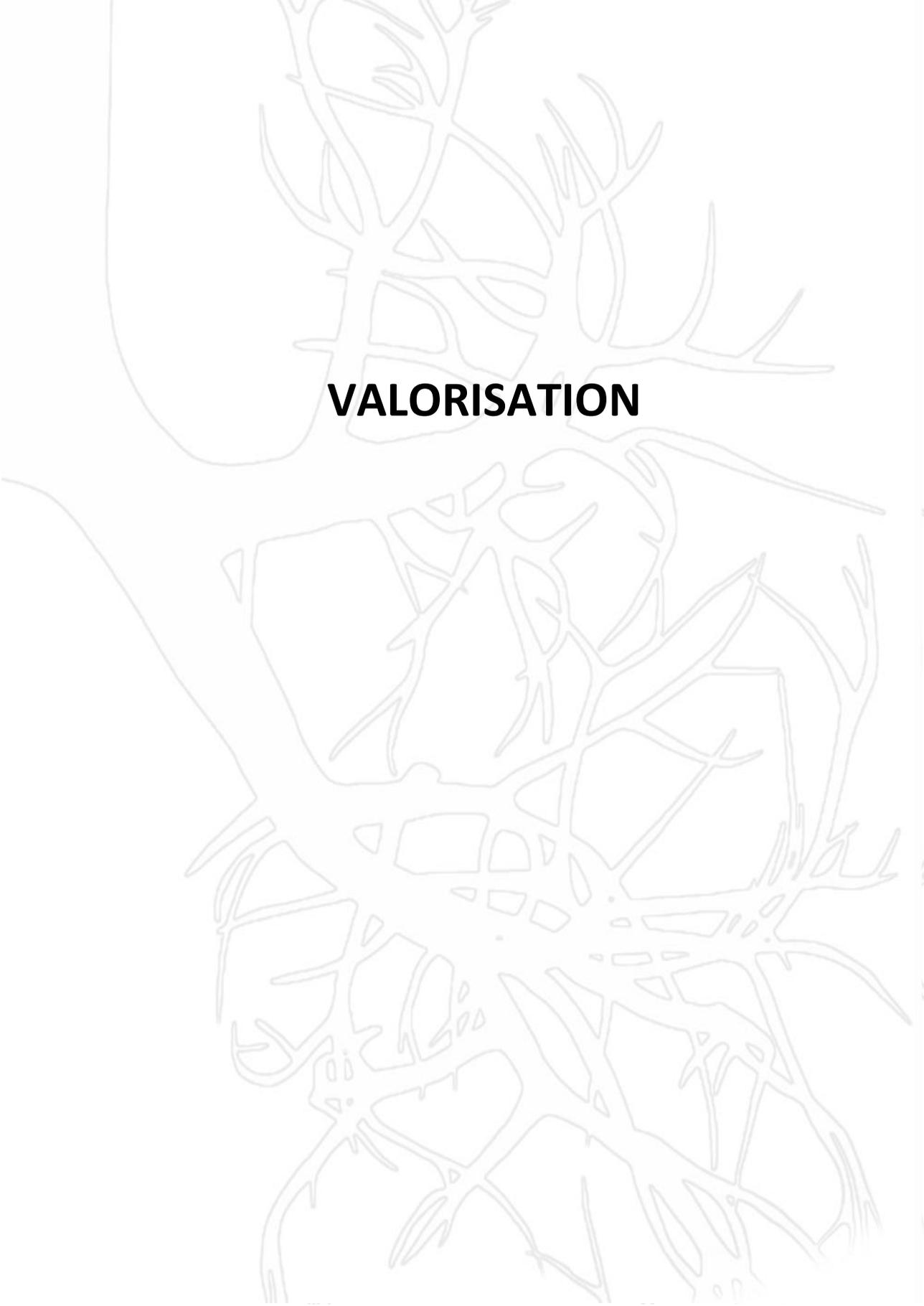
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VALORISATION

Socioeconomic relevance

Obesity is a rapidly expanding global epidemic – “globesity” – leading to a markedly increased number of overweight and obese adults (27.5%) and for children (47.1%) in the past 30 years (1). Recent reports from the World Health Organization (WHO) indicate that in 2014 more than 1.9 billion adults (18 years and older) were overweight (BMI>25), and of this overweight population, over 600 million people were obese (BMI>30). The increased prevalence of overweight and obesity has been accompanied by a substantial increase in the direct medical costs of these conditions. Obesity alone accounts for 0.7% - 2.8% of total health care expenditures worldwide (2, 3) and when costs associated with being overweight are also included, this figure increases to 9.1% (4, 5). As indicated, obesity is a growing problem, not only from a public-health perspective, but also in relation to many communicable and non-communicable respiratory diseases. Pneumonia and respiratory infections are, according to the WHO, ranked among the leading causes of death worldwide. Therefore, the research described in this thesis is highly relevant looking from both the perspective of obesity, as well as from pneumonia and respiratory infections. Obesity has been associated with an increased susceptibility to and severity of both bacterial and viral respiratory infections (6), however the underlying mechanisms are poorly understood. The importance of investigating the impact of obesity on respiratory diseases is not limited to respiratory infections, but can also include other lung diseases including: obesity and asthma and obesity and primary pulmonary hypertension. The current thesis significantly adds to the understanding of obesity-associated defects in pulmonary host defense, which are accompanied by dysregulation of neutrophil and macrophage function. In addition, critical evidence was provided that the adipokine leptin is an important mediator of pulmonary host defense. Further understanding of the mechanisms underlying the impairment of pulmonary host defense in this at risk population (obese subjects), which is as mentioned before a large part of the general population, is of critical importance. Obese subjects are usually not mentioned separately when one makes a statement about the “general population”, but the findings in this dissertation add to the view that these subjects have a different profile when it comes to health risks, especially when looking at infections and more specifically in the respiratory tract. Furthermore, obese subjects are not only at risk for developing respiratory infections, but recent studies also suggested that prophylactic measures such as flu-vaccinations are less effective in this population (7). Therefore, the obese population appears to be at higher risk for developing respiratory infections, even in the setting of appropriate prophylaxis.

Target groups

Health care providers and obese patients

The present thesis provides important insights for health care providers. The prevalence of obesity is still increasing; in addition the incidence of respiratory infections in the obese population is high and likely underestimated. An increased awareness of the respiratory health risks associated with obesity is warranted, and healthy behavior and weight loss, until a healthy weight is reached, should be encouraged.

Several organizations can benefit from the work described in this thesis, including the European Lung Foundation (ELF). The ELF aims to bring together patients and the public with respiratory professionals to positively influence lung health within Europe. In some areas, such as Germany, obesity incidence is much higher compared to the incidence in the Netherlands, and with the help of the ELF the outcomes of the studies performed in this thesis can be communicated to the European public. Furthermore, the patient organizations of the Dutch Lung Foundation as well as the obesity society can also benefit from these studies. The Dutch Lung Foundation does have a “Longpunt” in the Limburg area (Maastricht, Sittard and Weert) where I will present and discuss my research to and with patients suffering of a lung diseases to inform them about the study outcomes, but also to receive their input for further research studies and grant applications. Furthermore, the study outcomes will also be communicated towards obese subjects and their relatives which are involved in the “Obesitas Vereniging”. Furthermore, “Zwaartepunt”, an organization aimed at competence-based training of health care providers (physicians, nurses, dieticians) related to obesity, organizes conferences, symposia and hands-on training courses related to the care and management of obese patients. The studies described in this dissertation have led to an increased understanding of the impact of body weight and nutritional status on pulmonary host defense, and will be communicated towards healthcare providers with the help of “Zwaartepunt”.

Science

Future research questions

This thesis contributes to research in the field, as the results elucidate possible mechanisms which underlie the impaired pulmonary host defense in obesity. Although valuable new insights have emerged from the work presented in this dissertation, a number of issues remain unresolved and new questions arise. Foci of additional research should include examining the effects of obesity-associated metabolic abnormalities (dyslipidemia, hyperglycemia and adipokine dysregulation) on pulmonary host defense, which may lead to identification of subjects at elevated risk for developing respiratory infections and ARDS. In addition, further understanding of host defense and the specific

mechanisms underlying its impairment in hyperleptinemic conditions, including not only obesity, but also pregnancy, renal failure and diabetes, is critical to further develop improved identification and treatment of populations at risk for pneumonia.

The importance of pulmonary host defense is not limited to protection against respiratory infections. Episodic airway infections can lead to a worsening of existing chronic lung diseases, such as Chronic Obstructive Pulmonary Disease (COPD). Such exacerbations of the disease have been shown to be more prevalent in underweight COPD patients, whereas obese subjects have a lower risk for exacerbations. Knowledge transfer through collaborations between a variety of respiratory professionals is needed to implement the findings of this dissertation in other respiratory diseases.

Relevant mouse model to study obesity

Several animal models of obesity have been used in literature to investigate the effects of obesity and associated comorbidities on the pulmonary immune response related to diverse acute and chronic lung diseases. However, important caveats may exist when studying the available murine models of obesity and these should be taken into account when interpreting the generated data, as well as extrapolating this to the own study set. In addition, with these caveats in mind, one should also be cautious when extrapolating studies performed in murine obesity models to human obesity. In Chapter 4 we investigated the pulmonary immune response and host defense, in particular neutrophil function, following an acute inflammatory insult in four models of murine obesity. In addition, several metabolic parameters were characterized. Until now, very few studies were performed which compare pulmonary host defense and immune function in obesity. Our work greatly enhances the understanding of how results obtained in the different models should be interpreted and to which extent the metabolic parameters vary between different models of obesity. The diet-induced model of obesity is the best model thus far to study pulmonary infection in the context of human obesity, however, caution should be used when extrapolating data from this model to the human situation as mice in this model may manifest features of a more 'metabolic healthy obese phenotype'.

Personal development

The outcomes of the studies described in this thesis have resulted in multiple scientific abstracts on national and international conferences. The abstract containing the results of Chapter 7 and Chapter 8 were awarded with an ERS Lung Science Conference Bursary in 2013 and an ATS abstract scholarship at the annual ATS conference in Denver, CO, USA in 2015, respectively. Furthermore, the results and insights gathered from the studies performed have served as the foundation for several grant applications of which one was shown to be successful already.

The studies described in Chapter 3, Chapter 6 and Chapter 7 have been published in peer reviewed scientific journals in the fields of critical care medicine as well as respiratory medicine. The results of Chapter 7 were accompanied by an editorial describing the march of leptin from satiety hormone to an important immune modulator. The results of Chapter 8 are currently in revision. The study results of Chapter 4 are submitted and Chapter 5 will be submitted when additional experiments are performed.

The work described in this thesis was performed within the structural collaboration between the Department of Respiratory Medicine, Maastricht University Medical Center, Maastricht, The Netherlands and the Vermont Lung Center, University of Vermont College of Medicine, Burlington, VT, USA, thereby strengthening this collaboration. Furthermore, several national and international collaborations between the authors and other research groups including: the Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium, the Cytokine Receptor Lab (CRL), VIB Department of Medical Protein Research, Ghent, Belgium and the Department of Pediatrics, National Jewish Health, Denver, CO, USA.

Schedule and implementation

The studies described in this thesis are already published in or submitted to international peer-reviewed scientific journals, and discussed during various national and international conferences, thereby facilitating scientific progress and contribution to the scientific community.

The studies presented in this thesis indicate that obese and/or hyperleptinemic subjects should be considered as high risk patients for severe pneumonia. Furthermore, the results of the studies described in this thesis contributed to the awareness and importance of this topic. The new research questions that arose from this thesis regarding the mechanisms underlying the impaired pulmonary host defense in obesity and how this can be integrated into clinical practice can consequently contribute to new therapeutic strategies and better care for the obese patients. In addition, the comparison of the four most commonly used mouse models of obesity provided by this work, shed light on the importance of understanding which metabolic factors are affected before extrapolating data from one model to another.

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