Obesity and Metabolic Abnormalities in Chronic Obstructive Pulmonary Disease

Emiel F. M. Wouters

Department of Respiratory Medicine, Maastricht University Medical Center, Maastricht, the Netherlands

Abstract

Chronic obstructive pulmonary disease (COPD) and obesity are major causes of morbidity and mortality worldwide, and a relationship between COPD and obesity is increasingly recognized. The nature and underlying mechanisms of the link between obesity and COPD are still largely unknown. Obesity, and abdominal adiposity in particular, is linked to metabolic syndrome. Hypertension, hyperglycemia, and abdominal adiposity seem to be the most prevalent components of metabolic syndrome in COPD. Adipose tissues function as a source of a variety of signaling molecules in the pathobiology of respiratory diseases. Computed tomography allows measurement of various fat depots and allows better understanding of the impact of abdominal visceral fat in the pathophysiology of COPD. Innovative statistical methodology has identified obesity as a relevant and distinguishing characteristic in patients with COPD. Integrated research combining COPD and its multimorbidity network may unravel underlying endotypes to direct future interventions in this specific COPD cluster.

Keywords: metabolic syndrome; obesity; COPD

(Received in original form May 5, 2017; accepted in final form October 25, 2017)

Correspondence and requests for reprints should be addressed to Emiel F. M. Wouters, Ph.D., M.D, Maastricht University Medical Center, Department of Respiratory Medicine, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands. E-mail: e.wouters@mumc.nl.

Ann Am Thorac Soc Vol 14, Supplement 5, pp S389–S394, Nov 2017

DOI: 10.1513/AnnalsATS.201705-371AW
Internet address: www.atsjournals.org

Chronic obstructive pulmonary disease (COPD) and obesity are major causes of morbidity and mortality worldwide, and, according to current estimates, the global burden of these conditions will further increase (1). Classification of overweight and obesity are largely based on body mass index (BMI) as defined by the World Health Organization. Obesity is defined as BMI greater than or equal to 30 kg/m^2 (2). BMI is considered a reasonably good measure of general adiposity, and increased BMI is an established risk factor for several causes of death, including ischemic heart disease, stroke, and a wide variety of cancers. Analysis of data from several prospective studies demonstrated that each 5 kg/m^2 increase in BMI above the normal BMI range (22.5–25 kg/m^2) was associated with 30% higher all-cause mortality (3).

Although the association between asthma and obesity is profoundly studied, little is known about potential underlying mechanisms between obesity and COPD (4). Most studies have focused on analysis of physiological consequences of obesity. Indeed, physiologically, increasing weight gain is associated with lung volume effects in both health and disease, and this should be considered when interpreting common pulmonary function tests. As a consequence, obese patients with COPD operate at lower lung volumes, resulting in lower end-expiratory lung volume and lower respiratory mechanics loading by dynamic hyperinflation during exercise (5). This review focuses on the epidemiology of obesity and metabolic syndrome in COPD and describes our current understanding of the role of BMI and fat mass in disease mechanisms and phenotype clustering in COPD.

Prevalence of Obesity in COPD

Data on prevalence of obesity in patients with COPD are conflicting. In a cross-sectional population-based study of patients with COPD recruited from an outpatient disease management program in the Netherlands, the overall prevalence of obesity was 18%, with the highest prevalence in patients with mild to moderate COPD: 29 and 48% of these patients had mild to moderate airflow limitation according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (6, 7). On the basis of the Canadian national health survey data from 1994 to 2007, the prevalence of obesity in health professional–diagnosed self-reported COPD was significantly higher than in the population without COPD: in 2005, the prevalence of obesity was 24.6% in patients with COPD and 17.1% in control subjects without COPD ($P < 0.001$) (8). In the multicenter observational ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-Points) study, obesity was reported in 20% of

patients with COPD: median FEV_1 was 43.5% predicted in this COPD population (9). Although data suggest that obesity is more prevalent in patients with COPD than in the general population, not all studies confirm this finding. In a population-based study conducted in five Latin American cities, there were higher proportions of subjects with COPD in the underweight and normal-weight categories when compared with spirometrically confirmed patients without COPD, and a lower proportion of patients with COPD in the obese category. The prevalence of obesity in those subjects with COPD was 23%, compared with 32% in subjects without COPD (10). BMI in relation to chronic airflow limitation was also studied as part of the BOLD (Burden of Obstructive Lung Disease) initiative, a worldwide population-based study. It was found that prevalence of low and obese BMI was highly variable between sites and countries. The meta-analysis of all sites showed that, compared with subjects without chronic airflow limitation, low BMI was more frequent and obesity was less frequent in subjects with chronic airflow limitation. Obese BMI was found in 17.6% of subjects with airflow limitation versus 24.3% in those subjects without airflow limitation (11). Chronic airflow limitation in this study was defined as a post-bronchodilator FEV_1/FVC ratio below the fifth percentile of the population distribution for the FEV_1/FVC ratio (12). Although several studies have examined the prevalence of obesity in patients with COPD, no published data are available on the prevalence of COPD in obesity.

More epidemiological data about the prevalence of obesity in COPD are needed to understand the variability in prevalence around the world and the related mechanisms.

Metabolic Syndrome and COPD

BMI is strongly correlated with measured waist circumference (13). Increased waist circumference as a marker of central obesity is a characteristic finding in most widely used definitions of metabolic syndrome (MetS). Indeed, MetS is currently defined by a grouping of clinical characteristics including abdominal obesity, hyperglycemia, hypertriglyceridemia, hypertension, and low high-density lipoprotein cholesterol levels (14). High prevalence of MetS has been reported in several countries across the world, ranging from 20 to 60% (15, 16). We reported a prevalence of MetS in 38% of patients with COPD (17). A recent systematic review confirmed these findings, demonstrating that the overall mean prevalence of MetS is 34% among patients with COPD, with wide variation between geographical areas (18). In most studies, prevalence of MetS was higher than in control subjects. The most prevalent components of MetS in both patients with COPD and controls were hypertension, hyperglycemia, and abdominal obesity (16). The number of included patients, the definitions of COPD, and the characteristics of included control subjects differ widely among these studies. Despite this high prevalence of MetS in patients with COPD, the possible underlying nature remains unknown and deserves further investigation.

A recent review article reported a robust relationship between MetS and lung function impairment and particularly asthma risk (19). Baffi and colleagues formulated possible underlying mechanisms contributing to asthma risk (19). Insulin may exert a direct effect on human airways by influencing airway smooth muscle cells or airway epithelial cells. Insulin may inhibit muscarinic receptors or may induce a secondary effector inducing hypercontractility (19). Adipokines may be involved, as will be discussed in the next section, as well as fatty acid–induced inflammation. Indeed, in MetS, adipose tissue is not able to efficiently regulate fat storage, and excess triglycerides and free fatty acids remain in the circulation. These free fatty acids can activate innate immune responses via a plethora of inflammatory mechanisms, such as pattern recognition receptor activation, intracellular signaling pathways, and endoplasmic reticulum stress (19). Obese individuals often have enlarged adipocytes with a reduced buffering capacity for lipid storage, thereby exposing other tissues to an excessive influx of lipids. In addition, adipose tissue blood flow is decreased in obesity, affecting lipid handling and further contributing to excessive fat storage in nonadipose tissues (20). This adipose tissue dysfunction seems also to play a prominent role in the development and/or progression of insulin resistance. In addition, diabetes itself may negatively affect pulmonary structure and function. Diabetes is associated with an increased risk of pulmonary infections, disease exacerbations, and adverse COPD outcomes and is a strong contributing factor for the development of obstructive lung disease (18).

Further studies will be needed to assess the involvement of this variety of underlying mechanisms in understanding the interplay between MetS and COPD.

Adipose Tissue and Adipokines

Adipose tissue is largely overlooked as an important responding tissue in the human body. Fat tissue is not only an important source of a variety of signaling molecules, adipokines, but also a source of stem cells that can participate in tissue repair. Leptin and adiponectin are just two of the multiple hormones produced by adipose tissue (21). Leptin levels are increased with obesity and are secreted in direct proportion to the adipose tissue mass (22). Leptin is the product of the obese gene, primarily expressed in adipose tissue but also found in many other organs, including the lungs. It exerts pleiotropic effects by binding and activating specific leptin receptors in the hypothalamus and other organs, has direct and indirect effects in metabolically active tissues, and regulates several neuroendocrine axes (23). Leptin exerts proinflammatory effects (24). Other identified adipokines that promote inflammation include resistin, retinol-binding protein-4, lipocalin-2, IL-18, angiopoietin-like protein-2, CC-chemokine ligand-5, tumor necrosis factor, IL-6, and nicotinamide phosphoribosyltransferase (25). The functional impact of leptin on the respiratory system is less clear. Leptin and leptin receptors are present in the airways on bronchial epithelial cells (26–28). Elevated leptin levels may modulate the immune reaction in the airways by inciting a robust proinflammatory response or bias the cellular response toward a type 1 helper phenotype (29, 30). Leptin may also increase bronchial hyperreactivity (31).

Leptin seems also to be involved in neutrophil dysfunction in obesity. Obesity attenuates the inflammatory response in an inhaled lipopolysaccharide model of acute lung injury, leading to reduction in pulmonary neutrophilia and injury (32). Obesity is also associated with defects in the neutrophilic chemoattractant response,

suggesting a disruption of neutrophilic diapedesis into the lungs (33). It has also been demonstrated that induction of pulmonary leptin acts as a driver of alveolar airspace neutrophilia, possibly by direct effects of leptin on neutrophil apoptosis (34). Future studies will be required to unravel these effects of leptin and hyperleptinemia on neutrophil inflammatory changes as observed in asthma and COPD.

In contrast, adiponectin exerts significant antiinflammatory effects (21, 25). It is synthesized almost exclusively by adipocytes of lean individuals, and its expression is significantly attenuated in obese subjects (35). Adiponectin exerts its function through its receptors, AdipoR1 and AdipoR2, the former being expressed ubiquitously, particularly in skeletal muscle, whereas the latter is most abundantly expressed in the liver (36). Adiponectin has also been shown to be expressed by airway epithelial cells (37). Adipose tissue hypoxia, adipose tissue inflammation, and increased macrophage infiltration in adipose tissue may further disturb adipokine secretion and may also be involved in induction of insulin resistance (19, 25).

To link different components together, a vascularly connected network was hypothesized, with the lungs as the main external sensor, the endothelium as the internal sensor, and two key responding elements, bone marrow and adipose tissue, both producing inflammatory and repair signals (Figure 1). In this model, the lungs act as a selective and protective interface between the external and internal environments, and bronchial and alveolar cells, as well as other tissue-resident cells, are capable of sensing a variety of environmental factors and orchestrate an inflammatory response both locally and at a distance. The endothelial lining acts as the internal interface and as a sensor between circulating blood and the body cell/tissue milieu. It is hypothesized that these two main sensors communicate with the responder elements—bone marrow and adipose tissue—through a number of biological signals that circulate within the vasculature (38). According to this model, the development of COPD and associated multimorbidities depends on the manner in which the vascularly connected network responds, adapts, or fails to adapt to the inhalation of particles and gases (38). Further research will be needed to explore the potential utility and caveats of this model and to provide better insight into the pathobiology of COPD and on the role of fat tissue and adipokines in particular.

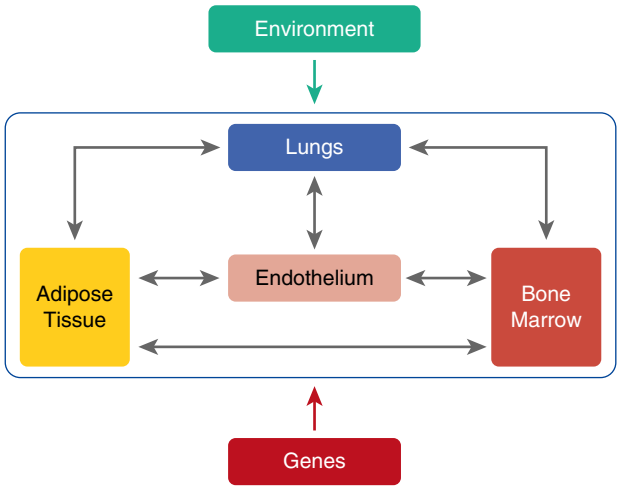

Figure 1. The lungs, bone marrow, and adipose tissue network. Chronic obstructive pulmonary disease is a condition characterized by gene–environment interactions, mediated by two sensors (lungs and endothelium), two responder organs (bone marrow and adipose tissue), and several linking biological signals. Adapted by permission from Reference 38.

Visceral Fat and COPD

Abdominal obesity is generally assessed by anthropometric measurements, such as waist circumference and waist-to-hip ratio, to estimate the amount of abdominal tissue. Computed tomography is a noninvasive, widely applied technique allowing measurements of various fat depots. It has been reported that the association between cardiovascular risk factors and visceral fat measured directly with computed tomography is stronger than the associations between these factors and anthropometric measurements (39, 40). This increased content of adipose tissue depots may include abdominal fat, abdominal visceral fat, and liver fat, and all these abdominal fat depots are associated with cardiovascular disease by potentially promoting a systemic proatherogenic and inflammatory state (41–44). It has been reported that patients with COPD have excessive visceral fat area (VFA) compared with an age-matched control group of smokers without airflow limitation (45). The prevalence of nonobese subjects with increased VFA was greater in the patients with more obstruction than in those with lesser airflow limitation according to GOLD stages (45). Although the extent of emphysema was inversely correlated with subcutaneous fat area, VFA did not decrease with the severity of emphysema (45). Others reported that patients with COPD with self-reported myocardial infarction had higher abdominal visceral fat content than those with no prior history of myocardial infarction and that higher abdominal visceral fat content was independently associated with increased odds of a history of myocardial infarction (46). Another study reported increased visceral adipose tissue and more muscle fat accumulation, measured by muscle tissue attenuation, on computed tomography images of the thorax in patients with COPD with severe airflow limitation (mean FEV_1, 40.7% predicted) compared with smoking and nonsmoking control subjects identified from the ECLIPSE cohort (47). Muscle attenuation in particular decreased as a function of severity of airflow limitation (47).

This fat tissue compartmentalization is very important to correctly interpret the reported findings of adipose tissue inflammation in fat biopsies, as subcutaneous adipose tissue has been sampled in these studies. It has been demonstrated that adipose tissue inflammation in patients with COPD increased with increasing BMI and that this adipose tissue inflammation relates to insulin resistance (48). Others reported that increased visceral fat, assessed by computed

tomography, contributes to increased plasma IL-6 and is negatively associated with adiponectin (49). More studies are needed to assess the role of visceral adipose tissue on systemic proatherogenic and inflammatory states.

To assess the metabolic activity of fat compartments as well as inflammatory changes in vessels, positron emission tomography with fludeoxyglucose F 18 has been introduced. Using this technique, increased metabolic activity in the abdominal aorta and visceral fat, but not in subcutaneous fat, has been reported in patients with COPD (50). Further research of body fat compartments combined with inflammatory, metabolic, and hormonal changes will unravel the role of visceral fat in the obese patient with COPD.

Obesity and Cluster Phenotypes in COPD

Historically, obesity is linked to the so-called blue bloater COPD phenotype (51, 52). In recent years, investigators have used innovative statistical methods to examine the hypothesis that subgroups of COPD sharing clinically relevant characteristics or phenotypes can be identified (53). In all these cluster analyses, nutritional status and overweight or obesity are identified as distinguishing characteristics. Burgel and colleagues reported four so-called COPD phenotypes, of which two were overweight (54). One overweight phenotype was characterized by mild airflow limitation in the absence of chronic heart failure or depression, and the other overweight phenotype had moderate airflow limitation with high frequency of chronic heart failure and depression (54). These findings were confirmed in another study identifying a cluster of older, male, obese patients with COPD with moderate to severe airflow limitation and with high rates of diabetic and cardiovascular comorbidities (55). Cluster analysis using baseline data of the ECLIPSE cohort identified five COPD subgroups differing in outcomes, inflammatory biomarkers, and clinical parameters, suggesting that these clusters represent clinically and biologically different subtypes of COPD (56). The cluster with the highest BMI had the least emphysema, most comorbidities, and highest levels of systemic inflammatory markers. This cluster had the worst survival, the least progression of emphysema, and a low rate of exacerbations over a 3-year follow-up period (56). Vanfleteren and colleagues reported a cluster analysis, based on validated objective measurements of 13 comorbidities and systemic inflammatory markers; they identified five comorbidity clusters (Figure 2) (12). The so-called metabolic or obese cluster included patients with COPD with less hyperinflation; a higher cardiovascular risk prediction score; a very high prevalence of diabetes, hypertension, dyslipidemia, and atherosclerosis; and slightly elevated levels of systemic inflammation (12). In a cohort of subjects hospitalized for the first time because of COPD exacerbations, Garcia-Aymerich and colleagues identified three COPD groups with different prognosis and clinical outcome (57). One group was characterized by milder airflow limitation, a high proportion of obesity, cardiovascular disorders, diabetes, and systemic inflammation. Particularly this group of patients with COPD had more admissions due to cardiovascular diseases during the 4-year follow-up period (57).

All these reported studies indicate that obesity may be relevant to identifying distinct COPD phenotypes, and more data are needed on biological associated factors related to this.

Conclusions

Obesity, metabolic syndrome, and visceral adiposity are highly prevalent conditions in patients with COPD and are associated with worse outcomes, and obesity seems relevant in distinct COPD phenotypes.

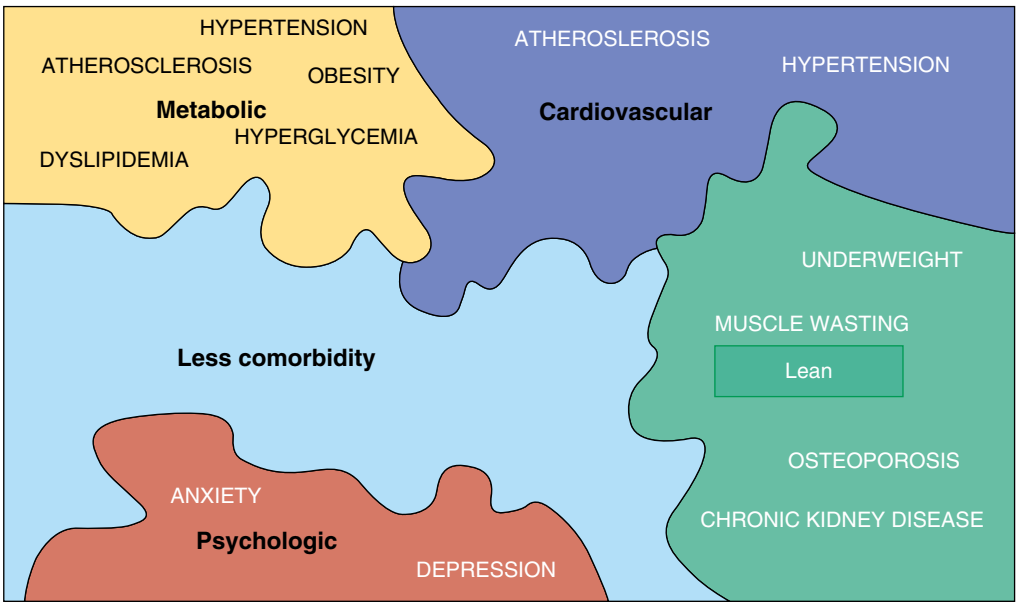

Figure 2. Clusters of comorbidities in chronic obstructive pulmonary disease.

Integrated research combining COPD and its multimorbidity disease network linked to underlying inflammatory, metabolic, and hormonal changes and lifestyle characteristics may unravel specific underlying biological mechanisms directing future research to interventions to reduce the multimorbidity profiles of COPD subgroups. Further studies are needed to unravel the role of adipose hormones on the respiratory system and to systematically evaluate the effects of insulin resistance, not only on metabolic alterations but also on the airways and skeletal muscle structure. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann H, Anderson HR, Andrews KG, Aryee M *et al*. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2224–2260.

2 Nishida C, Mucavele P; World Health Organization. Overweight and obesity: a new nutrition emergency? Monitoring the rapidly emerging public health problem of overweight and obesity: the WHO global database on body mass index. *SCN News* 2004;29:5–12.

3 Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R; Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet* 2009;373: 1083–1096.

4 Dixon AE, Rincón M. Metabolic dysfunction: mediator of the link between obesity and asthma? *Lancet Respir Med* 2016;4:533–534.

5 O'Donnell DE, Ciavaglia CE, Neder JA. When obesity and chronic obstructive pulmonary disease collide: physiological and clinical consequences. *Ann Am Thorac Soc* 2014;11:635–644.

6 Steuten LM, Creutzberg EC, Vrijhoef HJ, Wouters EF. COPD as a multicomponent disease: inventory of dyspnoea, underweight, obesity and fat free mass depletion in primary care. *Prim Care Respir J* 2006;15:84–91.

7 Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Am J Respir Crit Care Med* 2017;195:557–582.

8 Vozoris NT, O'Donnell DE. Prevalence, risk factors, activity limitation and health care utilization of an obese, population-based sample with chronic obstructive pulmonary disease. *Can Respir J* 2012;19:e18–e24.

9 Rutten EP, Calverley PM, Casaburi R, Agusti A, Bakke P, Celli B, Coxson HO, Crim C, Lomas DA, Macnee W, *et al*. Changes in body composition in patients with chronic obstructive pulmonary disease: do they influence patient-related outcomes? *Ann Nutr Metab* 2013; 63:239–247.

10 Montes de Oca M, Tálamo C, Perez-Padilla R, Jardim JR, Muiño A, Lopez MV, Valdivia G, Pertuzé J, Moreno D, Halbert RJ, *et al*.; PLATINO Team. Chronic obstructive pulmonary disease and body mass index in five Latin America cities: the PLATINO study. *Respir Med* 2008;102:642–650.

11 Vanfleteren LE, Lamprecht B, Studnicka M, Kaiser B, Gnatiuc L, Burney P, Wouters EF, Franssen FM, *et al*. Body mass index and chronic airflow limitation in a worldwide population-based study. *Chron Respir Dis* 2016;13:90–101.

12 Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Bruijnzeel PL, Rutten EP, Op 't Roodt J, Wouters EF, Franssen FM, *et al*. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;187: 728–735.

13 Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, van der Schouw YT, Spencer E, Moons KG, Tjønneland A, *et al*. General and abdominal adiposity and risk of death in Europe. *N Engl J Med* 2008;359:2105–2120.

14 Alberti KG, Zimmet P, Shaw J. Metabolic syndrome–a new world-wide definition: a Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006;23:469–480.

15 Beltrán-Sánchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999-2010. *J Am Coll Cardiol* 2013;62:697–703.

16 Cebron Lipovec N, Beijers RJ, van den Borst B, Doehner W, Lainscak M, Schols AM. The prevalence of metabolic syndrome in chronic obstructive pulmonary disease: a systematic review. *COPD* 2016;13: 399–406.

17 Breyer MK, Spruit MA, Hanson CK, Franssen FM, Vanfleteren LE, Groenen MT, Bruijnzeel PL, Wouters EF, Rutten EP, *et al*. Prevalence of metabolic syndrome in COPD patients and its consequences. *PLoS One* 2014;9:e98013.

18 Mirrakhimov AE. Chronic obstructive pulmonary disease and glucose metabolism: a bitter sweet symphony. *Cardiovasc Diabetol* 2012;11: 132.

19 Baffi CW, Wood L, Winnica D, Strollo PJ Jr, Gladwin MT, Que LG, Holguin F. Metabolic syndrome and the lung. *Chest* 2016;149: 1525–1534.

20 Goossens GH. The role of adipose tissue dysfunction in the pathogenesis of obesity-related insulin resistance. *Physiol Behav* 2008;94:206–218.

21 Guerre-Millo M. Adipose tissue hormones. *J Endocrinol Invest* 2002;25: 855–861.

22 Creutzberg EC, Wouters EF, Vanderhoven-Augustin IM, Dentener MA, Schols AM. Disturbances in leptin metabolism are related to energy imbalance during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;162: 1239–1245.

23 Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature* 1998;395:763–770.

24 Claycombe K, King LE, Fraker PJ. A role for leptin in sustaining lymphopoiesis and myelopoiesis. *Proc Natl Acad Sci USA* 2008;105: 2017–2021.

25 Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 2011;11:85–97.

26 Bruno A, Pace E, Chanez P, Gras D, Vachier I, Chiappara G, La Guardia M, Gerbino S, Profita M, Gjormarkaj M. Leptin and leptin receptor expression in asthma. *J Allergy Clin Immunol* 2009;124:230–237. e1–4.

27 Vernooy JH, Bracke KR, Drummen NE, Pauwels NS, Zabeau L, van Suylen RJ, Tavernier J, Joos GF, Wouters EF, Brusselle GG. Leptin modulates innate and adaptive immune cell recruitment after cigarette smoke exposure in mice. *J Immunol* 2010;184:7169–7177.

28 Vernooy JH, Drummen NE, van Suylen RJ, Cloots RH, Möller GM, Bracke KR, Zuyderduyn S, Dentener MA, Brusselle GG, Hiemstra PS, *et al*. Enhanced pulmonary leptin expression in patients with severe COPD and asymptomatic smokers. *Thorax* 2009;64:26–32.

29 Mancuso P, Canetti C, Gottschalk A, Tithof PK, Peters-Golden M. Leptin augments alveolar macrophage leukotriene synthesis by increasing phospholipase activity and enhancing group IVC iPLA2 (cPLA2gamma) protein expression. *Am J Physiol Lung Cell Mol Physiol* 2004;287:L497–L502.

30 Dixon AE, Johnson SE, Griffes LV, Raymond DM, Ramdeo R, Soloveichik A, Suratt BT, Cohen RI. Relationship of adipokines with immune response and lung function in obese asthmatic and non-asthmatic women. *J Asthma* 2011;48:811–817.

31 Sideleva O, Suratt BT, Black KE, Tharp WG, Pratley RE, Forgione P, Dienz O, Irvin CG, Dixon AE. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. *Am J Respir Crit Care Med* 2012;186:598–605.

32 Kordonowy LL, Burg E, Lenox CC, Gauthier LM, Petty JM, Antkowiak M, Palvinskaya T, Ubags N, Rincón M, Dixon AE, *et al*. Obesity is

associated with neutrophil dysfunction and attenuation of murine acute lung injury. *Am J Respir Cell Mol Biol* 2012;47:120–127.
33 Vernooy JH, Ubags ND, Brusselle GG, Tavernier J, Suratt BT, Joos GF, Wouters EF, Bracke KR. Leptin as regulator of pulmonary immune responses: involvement in respiratory diseases. *Pulm Pharmacol Ther* 2013;26:464–472.
34 Ubags ND, Vernooy JH, Burg E, Hayes C, Bement J, Dilli E, Zabeau L, Abraham E, Poch KR, Nick JA, *et al*. The role of leptin in the development of pulmonary neutrophilia in infection and acute lung injury. *Crit Care Med* 2014;42:e143–e151.
35 Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, Nagaretani H, Matsuda M, Komuro R, Ouchi N, *et al*. PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 2001;50: 2094–2099.
36 Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, Okada-Iwabu M, Kawamoto S, Kubota N, Kubota T, *et al*. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med* 2007;13: 332–339.
37 Miller M, Cho JY, Pham A, Ramsdell J, Broide DH. Adiponectin and functional adiponectin receptor 1 are expressed by airway epithelial cells in chronic obstructive pulmonary disease. *J Immunol* 2009;182: 684–691.
38 Agustí A, Barberà JA, Wouters EF, Peinado VI, Jeffery PK. Lungs, bone marrow, and adipose tissue. A network approach to the pathobiology of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;188:1396–1406.
39 Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, Vasan RS, Murabito JM, Meigs JB, Cupples LA, *et al*. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation* 2007;116:39–48.
40 Nicklas BJ, Penninx BW, Ryan AS, Berman DM, Lynch NA, Dennis KE. Visceral adipose tissue cutoffs associated with metabolic risk factors for coronary heart disease in women. *Diabetes Care* 2003;26: 1413–1420.
41 Canoy D, Boekholdt SM, Wareham N, Luben R, Welch A, Bingham S, Buchan I, Day N, Khaw KT. Body fat distribution and risk of coronary heart disease in men and women in the European Prospective Investigation into Cancer and Nutrition in Norfolk cohort: a population-based prospective study. *Circulation* 2007;116: 2933–2943.
42 Marques MD, Santos RD, Parga JR, Rocha-Filho JA, Quaglia LA, Miname MH, Avila LF. Relation between visceral fat and coronary artery disease evaluated by multidetector computed tomography. *Atherosclerosis* 2010;209:481–486.
43 Kim D, Choi SY, Park EH, Lee W, Kang JH, Kim W, Kim YJ, Yoon JH, Jeong SH, Lee DH, *et al*. Nonalcoholic fatty liver disease is associated with coronary artery calcification. *Hepatology* 2012;56: 605–613.
44 Choi SY, Kim D, Kim HJ, Kang JH, Chung SJ, Park MJ, Kim YS, Kim CH, Choi SH, Kim W, *et al*. The relation between non-alcoholic fatty liver disease and the risk of coronary heart disease in Koreans. *Am J Gastroenterol* 2009;104:1953–1960.
45 Furutate R, Ishii T, Wakabayashi R, Motegi T, Yamada K, Gemma A, Kida K. Excessive visceral fat accumulation in advanced chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2011;6:423–430.
46 Diaz AA, Young TP, Kurugol S, Eckbo E, Muralidhar N, Chapman JK, Kinney GL, Ross JC, San Jose Estepar R, Harmouche R, *et al*.; COPDGene investigators. Abdominal visceral adipose tissue is associated with myocardial infarction in patients with COPD. *Chronic Obstr Pulm Dis (Miami)* 2015;2:8–16.
47 Martin M, Almeras N, Després JP, Coxson HO, Washko GR, Vivodtzev I, Wouters EF, Rutten E, Williams MC, Murchison JT, *et al*. Ectopic fat accumulation in patients with COPD: an ECLIPSE substudy. *Int J Chron Obstruct Pulmon Dis* 2017;12:451–460.
48 Skyba P, Ukropec J, Pobeha P, Ukropcova B, Joppa P, Kurdiova T, Stroffekova K, Brusik M, Klimes I, Tkac I, Gasperikova D, *et al*. Metabolic phenotype and adipose tissue inflammation in patients with chronic obstructive pulmonary disease. *Mediators Inflamm* 2010;2010:173498.
49 van den Borst B, Gosker HR, Koster A, Yu B, Kritchevsky SB, Liu Y, Meibohm B, Rice TB, Shlipak M, Yende S, *et al*.; Health, Aging, and Body Composition (Health ABC) Study. The influence of abdominal visceral fat on inflammatory pathways and mortality risk in obstructive lung disease. *Am J Clin Nutr* 2012;96:516–526.
50 Vanfleteren LE, van Meerendonk AM, Franssen FM, Wouters EF, Mottaghy FM, van Kroonenburgh MJ, Bucerius J. A possible link between increased metabolic activity of fat tissue and aortic wall inflammation in subjects with COPD: a retrospective 18F-FDG-PET/ CT pilot study. *Respir Med* 2014;108:883–890.
51 Filley GF, Beckwitt HJ, Reeves JT, Mitchell RS. Chronic obstructive bronchopulmonary disease: II. Oxygen transport in two clinical types. *Am J Med* 1968;44:26–38.
52 Petty TL, Miercort R, Ryan S, Vincent T, Filley GF, Mitchell RS. The functional and bronchographic evaluation of postmortem human lungs. *Am Rev Respir Dis* 1965;92:450–458.
53 Burgel PR, Paillasseur JL, Roche N. Identification of clinical phenotypes using cluster analyses in COPD patients with multiple comorbidities. *Biomed Res Int* 2014;2014:420134.
54 Burgel PR, Paillasseur JL, Caillaud D, Tillie-Leblond I, Chanez P, Escamilla R, Court-Fortune I, Perez T, Carré P, Roche N; Initiatives BPCO Scientific Committee. Clinical COPD phenotypes: a novel approach using principal component and cluster analyses. *Eur Respir J* 2010;36:531–539.
55 Burgel PR, Paillasseur JL, Peene B, Dusser D, Roche N, Coolen J, Troosters T, Decramer M, Janssens W. Two distinct chronic obstructive pulmonary disease (COPD) phenotypes are associated with high risk of mortality. *PLoS One* 2012;7:e51048.
56 Rennard SI, Locantore N, Delafont B, Tal-Singer R, Silverman EK, Vestbo J, Miller BE, Bakke P, Celli B, Calverley PM, *et al*.; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints. Identification of five chronic obstructive pulmonary disease subgroups with different prognoses in the ECLIPSE cohort using cluster analysis. *Ann Am Thorac Soc* 2015;12:303–312.
57 Garcia-Aymerich J, Gómez FP, Benet M, Farrero E, Basagaña X, Gayete À, Paré C, Freixa X, Ferrer J, Ferrer A, *et al*.; PAC-COPD Study Group. Identification and prospective validation of clinically relevant chronic obstructive pulmonary disease (COPD) subtypes. *Thorax* 2011;66:430–437.