

# Effects of obesity on asthma: immunometabolic links

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## KEY WORDS

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## ABSTRACT

Asthma is a widespread chronic inflammatory disease, which has a highly heterogeneous etiopathogenesis, with predominance of either T-helper cell type 2 (Th2; type 2) or non-Th2 (non-type 2) mechanisms. Together with cardiovascular or autoimmune diseases, obesity, and others, asthma belongs to so called noncommunicable diseases, a group of disorders with immunometabolic links as underlying mechanisms. So far, obesity and asthma have been considered mostly independently, but there are clear signs of relevant interactions. First, obese patients are at increased risk of asthma or asthma-like symptoms. Second, asthma accompanied by obesity is more severe and more difficult to treat. A specific phenotype called obesity-associated asthma has been also described, which is late-onset, rather severe, non-type 2-driven disease, present mostly in women. In addition, obesity can coincide with asthma also in children, and, although obesity generally skews the Th1/Th2 balance towards Th1, it can also accompany type 2-driven asthma. However, those combinations represent less precisely defined disease entities. Despite a substantial increase in our knowledge on the mechanisms mediating the effects of obesity on the development of asthma in several recent years, still much needs to be done, especially on the molecular level.

**Introduction** In recent decades, a significant increase in asthma incidence has been observed, especially in industrialized countries.<sup>1,2</sup> Asthma is a widespread chronic inflammatory disease, which has a highly heterogeneous pathogenesis and clinical picture.<sup>3,4</sup> Asthma has been defined by the National Heart, Lung, and Blood Institute as a "common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation".<sup>5</sup> General symptoms include coughing, wheezing, or shortness of breath.<sup>5,6</sup> Asthma may be also accompanied by comorbidities, such as allergic rhinitis, atopic dermatitis, and food allergy, or nonallergic disorders like obesity and gastroesophageal reflux. Furthermore, patients with

asthma are at risk of frequent disease exacerbations resulting from exposure to allergens, pollutants, viral infections, certain drugs, or other triggers.<sup>7</sup>

There are 2 primary types of asthma: T-helper cell type 2 (Th2)-driven (or in a wider sense, type 2-driven) and non-Th2-driven (or in a broader sense, non-type 2-driven). Type 2-driven asthma is often triggered by allergens like pollens, house dust mite (HDM) or animal dander, whereas non-type 2-driven asthma may be caused by airway infections, smoking, obesity, or other irritants.<sup>7,8</sup> Several type 2-driven phenotypes have been reported by different authors, including early-onset allergic, late-onset eosinophilic, and exercise-induced asthma, which have been most consistently described. Obesity-associated

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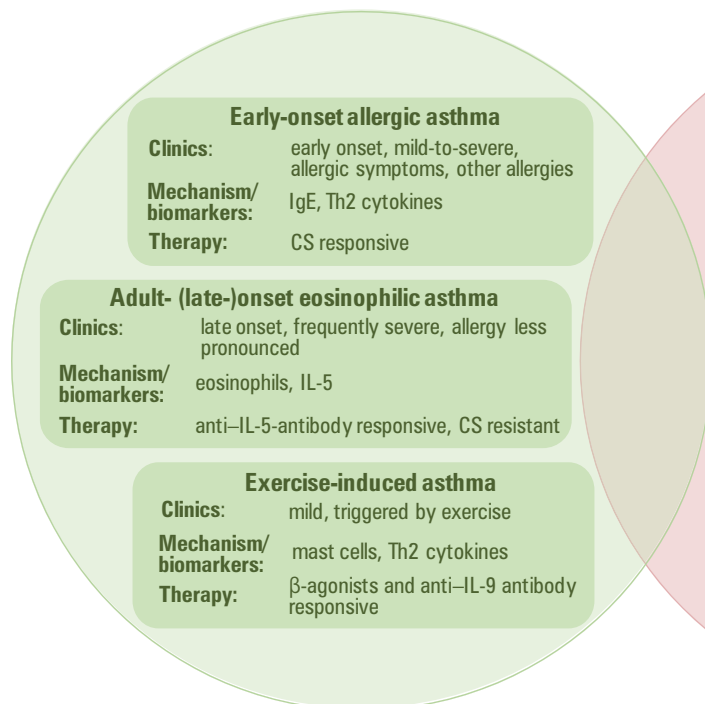
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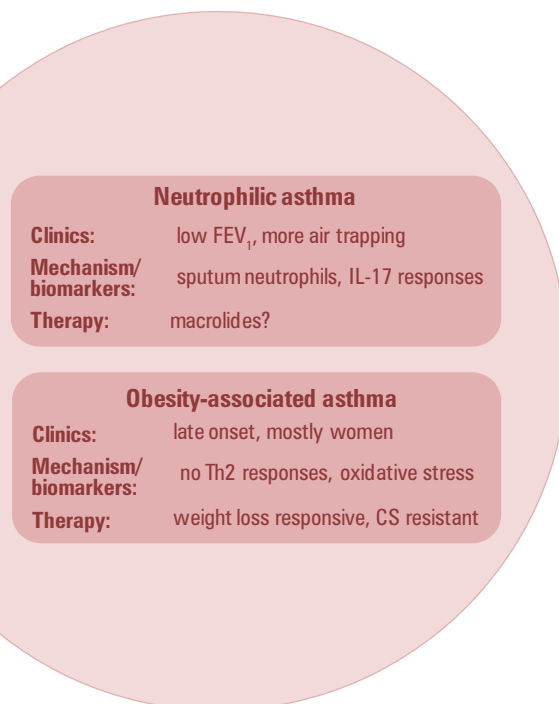
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## Type 2-driven asthma



## Non-type 2-driven asthma



**FIGURE 1** Basic characteristics of the major phenotypes of type 2-driven and non-type 2-driven asthma<sup>3,7,9,10</sup>

Abbreviations: IgE, immunoglobulin E; CS, corticosteroids; IL, interleukin; FEV<sub>1</sub>, forced expiratory volume in 1 second; Th2, T-helper 2

and neutrophilic (smoke-related) asthma are in turn the major non-type 2-driven phenotypes (FIGURE 1).<sup>3,7,9,10</sup>

**Types of asthma** **Type 2-driven asthma** Type 2-driven asthma is defined by the presence of atopic sensitization, immediate hypersensitivity type of allergic reaction, eosinophilic inflammation, and responsiveness to corticosteroids.<sup>9</sup> Th2 or innate lymphoid cells type 2 (ILC2s) and the cytokines they produce, such as interleukin (IL)-4, IL-5, and IL-13, play a crucial mechanistic role here. They stimulate allergic and eosinophilic inflammation, which further leads to changes in the epithelial and smooth muscle cells, resulting in hyperproduction of mucus, higher smooth muscle contractility, and airway hyperresponsiveness (AHR).<sup>11,12</sup> These cytokines induce differentiation from naive T-cells to Th2 cells and (especially IL-4, but also IL-13) stimulate B-cell switch towards immunoglobulin E (IgE) production, thus increasing IgE synthesis. The activation of eosinophils is in turn triggered by IL-5, whereas IL-13 induces AHR and enhanced mucus production.<sup>11-15</sup> The type 2 mechanisms underlie the disease of various levels of severity, ranging from mild through moderate to severe and showing different responses to treatment.<sup>10</sup> However, type 2 asthma is typically associated with a robust response to inhaled corticosteroids.<sup>16</sup> Several phenotypes of type 2 asthma have been described, as mentioned above (FIGURE 1).<sup>3,7,9,10</sup> Although in atopic asthma, sensitization to environmental allergens occurs and there is a clear correlation between allergen exposure and asthma symptoms,<sup>8</sup> it is rather difficult to precisely define early-onset allergic asthma, since no specific cutoff age has been determined nor an effective

test for the identification of atopic asthma at a young age is available.<sup>3</sup> Still, several of its characteristics have been rather uniformly described (FIGURE 1).<sup>3,9,10</sup> Early-onset asthma is frequently accompanied by other atopic diseases typical for childhood, such as allergic rhinitis or atopic dermatitis.<sup>9</sup> Adult-onset eosinophilic asthma, as the name suggests, is defined by an increase of eosinophils determined by sputum or blood analysis, or bronchoscopy, and it first appears in adulthood.<sup>9</sup> This phenotype is often accompanied or preceded by chronic sinusitis and nasal polyps and tends to be characterized by severe disease onset (FIGURE 1).<sup>3,9</sup> Little is known about the immunology of exercise-induced asthma. The typical symptoms occur after exercise, with patients showing mild asthma symptoms and suffering from reactive bronchoconstriction (FIGURE 1).<sup>9</sup>

**Non-type 2-driven asthma** There is still no consensus as to whether non-type 2-driven asthma ought to be considered as a single mechanistic entity or if it should be rather subdivided into several more specific endotypes (ie, disease subtypes functionally and pathologically defined by molecular mechanisms and treatment responses), possibly in close relation to the clinical characteristics or phenotypes, for example, postviral AHR or neutrophilic inflammation due to smoking.<sup>3,17,18</sup> The term “non-type 2-driven asthma” has been created somewhat in contrast to type 2-driven asthma; therefore, it partly covers so far unidentified and possibly more heterogeneous disease mechanisms sharing the feature of simply not being type 2-related. Since there is limited knowledge on the connection between clinical conditions, response to therapy, and pathology, such as the contribution of



**FIGURE 2** Schematic overview of the effects of obesity on the development of asthma

neutrophils, the distinction between such endotypes of non-type 2-driven asthma would be difficult, as it sometimes is even between type 2-driven phenotypes. Different factors, such as cigarette smoke or obesity, can lead to dysregulated innate immune responses in the airways, with no history of type 2-driven asthma during childhood.<sup>3</sup> The activation of Th17 pathways and Th1 immunity in combination with metabolic influences contribute to non-type 2-driven asthma. Interferon  $\gamma$  (IFN- $\gamma$ ), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), and IL-17, which are typical Th1 (type 1) or Th17 cytokines, promote neutrophilic inflammation.<sup>19,20</sup> There are only limited therapeutic options available in non-type 2-driven asthma because, unlike type 2-driven disease, it tends to be refractory to corticosteroid treatment.<sup>16</sup> Two non-type 2-driven phenotypes have been described most coherently (FIGURE 1).<sup>3,7,9,10</sup> The neutrophilic asthma phenotype is characterized by increased neutrophil count in peripheral blood, lungs, and sputum, and neutrophilia often develops after chronic steroid use or smoking.<sup>3</sup> This subphenotype is not characterized by AHR; rather, the signs typical of neutrophilic asthma include reduced lung function, more air trapping, and thicker airway walls (FIGURE 1).<sup>9</sup> In turn, lack of atopy, late onset, and female predominance are characteristic for the obesity-associated asthma phenotype.<sup>3</sup> The symptoms resulting from the accompanying obesity include shortness of breath, chest tightness, and a higher risk of gastroesophageal reflux (FIGURE 1).<sup>9</sup>

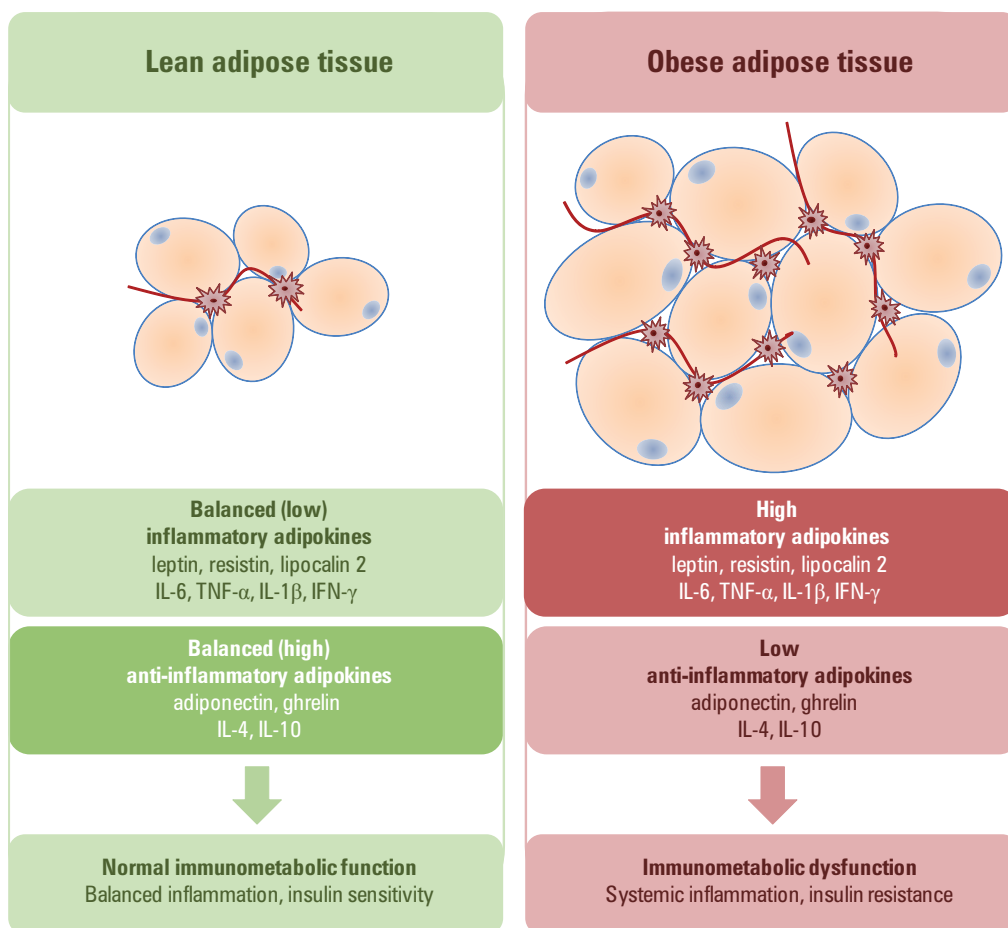
However, the spectrum of clinical coexistence of obesity and asthma is much wider and not limited to the non-type 2 disease developing in adults in the form of the “classic” phenotype of obesity-associated asthma. These complex issues are discussed in the present review. In addition, considering that our knowledge on interactions between obesity and asthma has substantially increased in the last few years, we describe some potential underlying mechanisms, with a special focus on the functional effects of obesity on asthma.

**Obesity and asthma** **General clinical picture and pathophysiology** Overweight (body mass index [BMI]  $\geq 25$  kg/m<sup>2</sup>) and obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) constitute a growing health problem in many parts of the world, and are associated with an increased risk of chronic noncommunicable diseases, such as type 2 diabetes mellitus and cardiovascular disorders.<sup>21</sup> Overweight has been reported

in almost half of the Europeans (47.6%) and obesity, in 12.8%.<sup>22</sup> The latter results in chronic low-grade systemic inflammation due to the production of inflammatory mediators in adipose tissue, described in more detail below.<sup>23</sup> This effect can add to chronic systemic inflammation observed in asthma, which presumably results in a further increase in susceptibility to airway obstruction and nonspecific AHR.<sup>23</sup> The clinical picture of asthma associated with obesity is typically characterized by poor quality of life, aggravation of daily symptoms (mostly severe), and a frequent use of rescue medications.<sup>24,25</sup> Besides the severe clinical characteristics, several comorbidities of obesity may also occur. Conditions classically accompanying obesity, such as gastroesophageal reflux disease, sleep-disordered breathing, dyslipidemia, type 2 diabetes mellitus, or hypertension, may not only increase the risk of asthma but also aggravate the disease if already present.<sup>26</sup> Some of the effects of obesity on asthma are rather mechanical, whereas some others seem to be underlying the enhancement of asthma-associated inflammation due to increased (unbalanced) production of proinflammatory mediators (adipokines) in overgrown, inflamed, and dysregulated fat tissue (FIGURES 2 and 3). This leads to further alterations in immune responses, including an increased synthesis of inflammatory cytokines: not only TNF- $\alpha$  or IL-6, at least partly derived from fat tissue and thus considered also as adipokines, but also IFN- $\gamma$  and IL-17.<sup>9,11,27</sup> However, the complete mechanism behind the contribution of obese adipose tissue to the development and clinical course of asthma has not been fully elucidated.

As indicated above, the clinical and mechanistic complexity of asthma associated with obesity seems to go far beyond the distinct obesity-associated asthma phenotype, as briefly depicted in FIGURE 1. Although this classic obesity-associated asthma is related to non-type 2 inflammatory processes, other types like type 2-driven inflammatory asthma in obese patients and asthma in obese children, have also been described.<sup>9,28</sup> Holguin et al<sup>25</sup> reported differential effects of obesity on asthma in adults depending on the age of onset. Obese patients with early age at onset had greater AHR, more severe airway obstruction, and a higher exacerbation risk compared with obese patients with late age at onset. Moreover, they were characterized by more advanced atopy with higher serum IgE levels and less severe eosinophilic inflammation. Finally, in early- but

**FIGURE 3** Effects of obesity on adipokine production and their major immunometabolic consequences. This figure is based on several previously published images, especially those by Makki et al.<sup>89</sup> and Liddle et al.<sup>90</sup> Abbreviations: IFN- $\gamma$ , interferon  $\gamma$ ; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; others, see **FIGURE 1**



not late-onset asthmatics, BMI increased with longer disease duration.<sup>25</sup> The understanding of the mechanisms and classification of the subtypes of asthma associated with obesity seems even more complex. Obesity skews CD4<sup>+</sup> cells towards Th1 polarization and can complicate the classic atopic type 2 immune response by altering eosinophilic inflammation.<sup>29</sup> This does not mean, however, that obesity never coincides with atopic asthma, because there are also patients who show airway inflammation with fewer neutrophils but more macrophages compared with obese patients with nonatopic asthma.<sup>30</sup> More human studies, preferably in combination with more mechanistic investigations in animal models, are required to better understand the complex mechanisms of the interaction between lean/obese fat tissue and allergic/nonallergic airway inflammation.

**Obesity and asthma in children** The age of onset affects the clinical picture of asthma not only in adults<sup>16,25</sup> but also in children. However, the relationship between obesity and the age of asthma onset is possibly even more complex, with a more causal role of obesity in the case of later age of onset and with obesity being more of an asthma comorbidity in the case of earlier onset.<sup>16</sup> Furthermore, to make things even more complex, although several studies demonstrated obesity to be a risk factor of pediatric asthma,<sup>31</sup> the opposite effect with childhood asthma increasing the risk of obesity has also been

reported.<sup>32</sup> Interestingly, asthma rescue medication treatment proved to reduce the risk of obesity, which was independent of physical activity or the use of other asthma medications.<sup>32</sup>

The childhood phenotype of asthma associated with obesity should possibly be differentiated from late-onset obesity-associated asthma typically observed in adult women (and concisely characterized in **FIGURE 1**).<sup>28</sup> This classic obesity-associated asthma is usually severe, whereas asthma accompanying obesity in children is difficult to treat or poorly controlled rather than severe.<sup>31</sup> Children with this phenotype are usually nonatopic, have an early-life weight gain and asthma-like symptoms, as well as impaired lung growth and altered airflow perception as putative underlying mechanisms.<sup>28</sup> On the other hand, it cannot be excluded that a substantial percentage of obese asthma patients are children who originally have type 2-driven asthma, with subsequent development of obesity due to other factors.<sup>28</sup> Interestingly, even atopic children with asthma have been described to exhibit Th1 polarization if obesity with high levels of leptin is simultaneously present.<sup>33</sup> Similarly to adults, the underlying mechanisms explaining the relationship between asthma and obesity in children are still poorly understood.

**Sex differences** The distinct non-type 2-driven phenotype of obesity-associated asthma is seen primarily in women, which is one of the major

characteristics of this phenotype.<sup>3,9</sup> Some additional sex-specific interactions between obesity and asthma have been described. For example, in a longitudinal study, obesity was found to increase the risk of asthma in Canadian women but not in men.<sup>34</sup> Furthermore, asthma severity was found to be robustly associated with BMI only in women, which was additionally affected by the hormonal status, as determined by early menarche.<sup>35</sup> Likewise, obesity was not associated with AHR in men, while such an effect was observed in women with moderate AHR.<sup>36</sup> In another study, sex had no effects on obesity-asthma association in children, but trunk predominant (central) adiposity was significantly associated with asthma only among women.<sup>37</sup> Overall, epidemiological studies suggest that the effects of obesity on asthma are greater in women, which seems to be related to the activity of estrogens.<sup>35,38</sup>

**Adipokines** Through its endocrine function reflected by the production of adipokines and possibly some other factors, adipose tissue influences the immune and metabolic responses.<sup>39</sup> Adipokines are peptide substances produced by adipose tissue; they have the properties of classic cytokines, chemokines, and hormones.<sup>40</sup>

Adiponectin is the most abundant adipokine in the adipose tissue, responsible for regulating the energy balance by, for example, stimulation of insulin secretion or increasing fatty acid oxidation.<sup>41</sup> It has anti-inflammatory effects, mediated by the stimulation of IL-10 synthesis and endogenous IL-1 receptor antagonist production, as well as by the inhibition of nuclear factor  $\kappa$ B (NF- $\kappa$ B) signaling, expansion of vascular smooth muscle cells, and expression of adhesion molecule.<sup>42</sup> In addition, adiponectin further suppresses the proinflammatory effects by inhibiting IL-6 and TNF- $\alpha$ .<sup>40</sup> The concentrations of adiponectin are higher in women than in men. This difference arises after puberty as the adiponectin synthesis is inhibited by testosterone.<sup>43</sup> In obese patients, adiponectin levels are reduced; therefore, its anti-inflammatory effects are missing, which might contribute to increased inflammation present in obesity-associated asthma.<sup>44</sup>

Another important mediator produced by adipose tissue is leptin, a hormone that regulates energy balance and appetite. Leptin is transported into the brain, where it binds to its receptor in the hypothalamus. This results in activation of the Janus kinase-signal transducer and activator of transcription protein (JAK-STAT3) signaling pathway, which further changes the production of certain peptides, thus reducing food intake.<sup>45</sup> A higher proportion of the adipose tissue in the overall body mass in obese patients leads to an increase in leptin levels. Furthermore, overweight and obese individuals may develop leptin resistance, which causes weight gain due to increased hunger.<sup>46</sup> Leptin exerts also immunomodulatory effects of the proinflammatory type, including increased IFN- $\gamma$ -mediated responses,

increased CD4<sup>+</sup> T-cell immunity and activation of mast cells, as well as activation of transcription factors such as NF- $\kappa$ B. It is not surprising that leptin may contribute to asthma development or increase its severity in obese individuals.<sup>42</sup>

Resistin is another hormone produced by adipose tissue. It interferes with insulin by modifying insulin sensitivity. Resistin levels are increased in obese patients and lead to insulin resistance (resistin was originally named for its resistance to insulin).<sup>47</sup> It further triggers the activation of NF- $\kappa$ B and production of cytokines, thereby promoting proinflammatory effects,<sup>48</sup> which in turn are thought to contribute to more severe exacerbations of asthma in obese patients.<sup>49</sup>

Ghrelin is another important appetite hormone involved in metabolism and energy balance.<sup>50</sup> It is responsible for increased food intake and decreased fat utilization.<sup>51</sup> Furthermore, ghrelin can inhibit the expression of the proinflammatory cytokines IL-1 $\beta$ , IL-6, and TNF- $\alpha$ .<sup>52</sup> However, in obese individuals, ghrelin levels are decreased, which is thought to be a physiological protective mechanism regulating energy balance.<sup>53</sup>

Adipokines exert significant effects not only on metabolism but also on the immune system, and, although detailed mechanisms of their contribution still need to be established, they seem to represent important mediators in obesity-associated asthma.

**Genetics** Although our knowledge on the genetic background of the links connecting obesity and asthma is limited among other reasons due to the polygenic character of both conditions, heredity definitely represents another aspect important for understanding the relationships between asthma and obesity.<sup>54,55</sup> The analysis of gene expression, the results of which are strongly dependent on the genetic background, is already a well-established diagnostic method in oncology and hematology. Moreover, in the near future, it might become useful also in allergology, where it could help differentiate between various asthma pheno- or endotypes on the molecular level (so called molecular phenotyping) making it possible to specifically apply an effective treatment.<sup>3,56</sup>

It has been shown that the genotype is a more stable parameter for the prediction of biological characteristics of asthma than the family history. A negative background in the family history accompanied by a high genotypic risk has been observed not only in asthma but also in obesity.<sup>57</sup> Furthermore, Hallstand et al<sup>58</sup> found that obesity shares a substantial portion of its genetic components with asthma. In addition, genetic links between blood lipid metabolism and allergic mechanisms have been reported on the molecular level.<sup>59,60</sup>

Several susceptibility loci have been identified that are shared between asthma and obesity, for example, adrenoceptor  $\beta$ 2 gene (*ADRB2*), nuclear receptor subfamily 3 group C member 1 (*NR3C1*), and TNF- $\alpha$  gene (*TNF*) (TABLE).<sup>54,61-63</sup> Adrenoceptor

**TABLE 1** Overview of susceptibility loci shared between obesity and asthma<sup>54,61-63,88</sup>

Gene	Main function
Adrenoceptor $\beta 2$ ( <i>ADRB2</i> ; chromosome 5q32)	Catecholamine receptor, expressed in various tissues (eg, respiratory tract)
Nuclear receptor subfamily 3 group C member 1 ( <i>NR3C1</i> ; chromosome 5q31.3)	Glucocorticoid receptor; regulation of transcription of glucocorticoid-responsive genes, such as those involved in metabolism or immune responses
Major histocompatibility complex ( <i>HLA-DRB1</i> , chromosome 6p21.32)	Human leukocyte antigen gene cluster; central role in the immune system
Insulin-like growth factor 1 ( <i>IGF1</i> ; chromosome 12q23.2)	Essential factor for the regulation of cell growth
Interleukin 1 $\alpha$ ( <i>IL1A</i> ; chromosome 2q14.1)	Pleiotropic cytokine involved in regulation of various immune responses
Leptin ( <i>LEP</i> ; chromosome 7q32.1)	Regulation of energy balance
Leukotriene A4 hydrolase ( <i>LTA4H</i> ; chromosome 12q23.1)	Enzyme catalyzing the final step of leukotriene B <sub>4</sub> biosynthesis
Protein kinase C $\alpha$ ( <i>PRKCA</i> ; chromosome 17q24.2)	Involved in diverse cellular signaling pathways, such as cell adhesion and transformation
Tumor necrosis factor $\alpha$ ( <i>TNF</i> ; chromosome 6p21.33)	Multifunctional proinflammatory cytokine
Vitamin D receptor gene ( <i>VDR</i> ; chromosome 12q13.11)	Transcription factor involved in metabolic pathways (eg, calcium homeostasis)
Glucosamine-6-phosphate deaminase 2 ( <i>GNPDA2</i> ; chromosome 4p12)	Enzyme participating in aminosugar metabolism
Roundabout guidance receptor 1 ( <i>ROBO1</i> ; chromosome 3p12.3)	Involved in the development of the nervous system

$\beta 2$  affects the activity of the sympathetic nervous system, which has an effect on respiration and systemic metabolism.<sup>38</sup> In turn the glucocorticoid receptor encoded by *NR3C1* modulates inflammation, a crucial component of both obesity and asthma, while TNF- $\alpha$  stimulates immunity and inflammation, which are crucial elements of the mechanisms underlying both conditions.<sup>38</sup> Several loci, including *ADRB2*, *TNF*, *LTA4H*, *GNPDA2*, and *ROBO1*, have been found to be associated with asthma and obesity in children, sometimes on the genome-wide level (TABLE 1).<sup>63,64</sup>

**Epigenetics** Both asthma and obesity are typical conditions determined by the interactions between genetic background and environmental influences, the latter mediated by epigenetic mechanisms.<sup>11,65-69</sup> Epigenetic modifications functionally alter the genome and thus gene expression without changes in the DNA nucleotide sequence. DNA methylation and histone marks, such as methylation, acetylation, phosphorylation, and others, represent classic epigenetic mechanisms. However, the extended definition of epigenetics includes also other regulatory mechanisms, for example, those mediated by microRNAs.<sup>11,65,66</sup>

Prenatal and early-life environmental exposures are known to epigenetically affect the risk of asthma and obesity.<sup>11,26,70</sup> For instance, in utero or early childhood exposure to cigarette smoke or traffic pollutants increases the risk of asthma, whereas the proper maternal diet containing fish,

legumes, or vegetables seems to decrease the risk of disease development in the offspring. Likewise, a wrong prenatal and early-life diet results in increased risk of obesity and metabolic diseases.<sup>11,26,70</sup> Nutritional status of the newborn, reflected by birthweight, has been shown to affect the risk of obesity or asthma in adulthood.<sup>26</sup>

In an epigenome-wide analysis, Rastogi et al<sup>71</sup> studied peripheral blood mononuclear cells obtained from obese children with asthma and showed a decreased promoter DNA methylation of the genes encoding molecules involved in innate immune responses or nonatopic inflammation, such as C-C motif chemokine ligand 5 (*CCL5*, chromosome 17q12), interleukin 2 receptor  $\alpha$  (*IL2RA*, chromosome 10p15.1) or T-box 21 (*TBX21*, chromosome 17q21.32). At the same time, they observed increased levels of promoter methylation of the low-affinity receptor for IgE (Fc fragment of IgE receptor II; CD23) gene (*FCER2*, chromosome 19p13.2), and transforming growth factor  $\beta 1$  gene (*TGFBI*, chromosome 19q13.2), the latter controlling T-cell immunity responses.<sup>71</sup> However, to the best of our knowledge, the study by Rastogi et al<sup>71</sup> is the one and only analyzing differential epigenetic patterns in asthma associated with obesity.<sup>11,65,66</sup>

**Insights from mouse models** Studies in animals provide research options not available in humans. In particular, in-depth investigations of the disease-underlying mechanisms are possible.

Although human diseases are only modelled in animals and not every result obtained in these settings can directly be translated into real patient situation, some of those models seem to well reflect disorders in humans, for example, mouse models of airway inflammation mimicking different mechanistic types of asthma, such as Th2, Th1-/Th17 (non-Th2), and mixed (Th2/Th1/Th17) asthma.<sup>72</sup> Mouse models mimicking human asthma are based on the application of immune response-inducing substance, such as ovalbumin (OVA) or HDM. The resulting type of immunity depends on several factors, especially the way and timing of immunogen administration.<sup>72</sup> Obesity in turn can be induced in mice using a high-fat diet (HFD) and/or through modification of the genetic background, such as leptin (*LEP*)-, leptin-receptor- (*LEPR*), or proopiomelanocortin (*POMC*)-knockout<sup>73</sup> (to simplify the genetic nomenclature, we do not distinguish between human and mice genes and the names of human counterparts are always provided). The overall genetic effect of the experimentally used strain also contributes, sometimes differentially, to the predisposition to “asthma” (eg, BALB/c mice are prone to develop Th2 responses, while C57BL/6 mice, to non-Th2 responses)<sup>74</sup> or “obesity” (eg, obesity-susceptible AKR mice).<sup>75,76</sup>

Studies in mouse models simultaneously mimicking human asthma and obesity have generated several interesting findings. It has been observed that mice with HFD-induced obesity subjected subsequently to OVA model of allergic airway inflammation showed higher levels of TNF- $\alpha$ , IL-5, and IL-10 in bronchoalveolar lavage fluid than their lean counterparts. At the same time, initially lower eosinophil levels in bronchoalveolar lavage fluid later increased due to eosinophil trafficking from the bone marrow to lung tissues.<sup>77</sup> Obesity-susceptible AKR mice fed with HFD demonstrated after OVA-induced allergic airway inflammation model an increased susceptibility to allergic sensitization as compared with animals on a low-fat diet. Serum anti-OVA IgE antibodies and airway eosinophilia correlated positively with body weight.<sup>75</sup> Another study indicated that ILC2s and ILC3s are involved in the mechanisms by which HFD-induced obesity exacerbates allergic airway inflammation triggered in mice by means of HDM application.<sup>78</sup> The results by Silva et al,<sup>79</sup> obtained in a model involving HFD-induced obesity and OVA-induced allergic airway inflammation, suggested in turn that airway inflammation is affected by obesity through mechanisms mediated by mast cells, thymic stromal lymphopoietin, and IL-25, and favoring a delayed immune response characterized by an exacerbated Th1, Th2, and Th17 profile. Interestingly, while observations in humans suggest more type 1 immunity-related mechanisms underlying obesity-associated asthma, the picture derived from animal studies seems to be, at least partly, skewed towards type 2 immunity. Therefore, comprehensive studies comparing different types of

interaction between asthma and obesity in both human cohorts and animal models are required.

The importance of some rather specific factors, potentially contributing to the interplay between obesity and asthma, has also been investigated in mouse studies. One study conducted in the HFD-OVA mouse model of obese asthma demonstrated higher AHR, airway inflammation, and proinflammatory cytokine levels. Interestingly, when compared with nonobese controls without asthma, vitamin D levels were lower in asthma-alone and obesity-alone groups and the lowest in obese mice with asthma, suggesting a link between vitamin D and inflammation in allergic airway inflammation.<sup>80</sup> Excessive dietary intake of saturated fatty acids, the nutritional factor also abundantly present in experimental HFD,<sup>81</sup> has been found to be a risk factor for obesity-related immunometabolic disorders, such as insulin resistance, type 2 diabetes mellitus, or cardiovascular diseases.<sup>82,83</sup> HFD-fed mice subsequently subjected to the HDM-based asthma model had augmented neutrophilic airway inflammation and AHR accompanied by increased levels of IL-17A and macrophage inflammatory protein 2 (MIP2).<sup>84</sup> Similar effects on airway inflammation were observed when the HDM model was combined with direct treatment with palmitic acid, the main saturated fatty acid component of HFD. Furthermore, production of proinflammatory cytokines and chemokines, such as TNF- $\alpha$  and IL-1 $\beta$ , MIP2, and/or monocyte chemoattractant protein 1 was upregulated.<sup>84</sup>

**Summary** Asthma associated with obesity represents an increasing health problem worldwide. The presence of obesity can make the clinical course of asthma more severe and more difficult to treat, while dietary weight loss interventions or bariatric surgery lead in obese asthmatics to improvements in disease control and lung function.<sup>29,85,86</sup> Obesity can also contribute to asthma development. A specific phenotype of obesity-associated asthma has been described that is characterized by the presence of severe, late-onset, non-type 2-driven asthma (mostly) in women. However, it is definitely not the only combination of asthma and obesity observed in clinical practice, although the other disease entities are not as distinct. Obesity is associated with asthma or precedes its development also in children and men. Moreover, obesity tends to skew the adaptive immune responses towards Th1, but combinations between atopic asthma and obesity also occur.

A substantial progress in our understanding of the relationships between obesity and asthma has been made in recent years. However, the mechanistic links between these conditions are still poorly understood and further research is required, especially on the basic cellular and molecular levels. The lung may be even considered as an independent metabolic organ, specifically responding to obesity and obesogenic diets.<sup>87</sup>

Certain mediators of those effects, such as adipokines, are already known, but detailed mechanisms underlying the influences of obese fat tissue on the lung remain to be identified.

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