

Obesity – A Promoter of Allergy?

Susanne Baumann Axel Lorentz

Department of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany

Key Words

Allergy · Obesity · Asthma · Inflammation

Abstract

The prevalence of both obesity and allergy has been increasing throughout the world, leading to the hypothesis that the two are linked to one another. This overview summarizes the results of 34 studies from 2002 to 2012 that investigated a possible contributing effect of increasing body mass on the development and prevalence of various atopic diseases. Obesity was found to clearly affect bronchial asthma. However, the correlation was stronger in the nonatopic asthma phenotype. Obesity was found to be associated with the development of atopic dermatitis in children only. No clear association was found between obesity and the prevalence of allergic rhinitis or allergic conjunctivitis or increased sensitization to food allergens. This review sums up our study results and discusses a possible role of obesity in the promotion of allergy and asthma.

Copyright © 2013 S. Karger AG, Basel

number of overweight adults rose to more than 1.4 billion, about 500 million of whom were obese [4]. According to the results of studies to date, it is supposed that obesity is linked to the increased prevalence of bronchial asthma (BA). Currently, about 235 million people in the world suffer from asthma [5]. The rising number of obese subjects along with the increase in asthma prevalence supports the hypothesis that the two conditions may be linked to one another [6]. Various studies are currently giving attention to a possible effect of obesity on other allergic diseases like allergic rhinitis (AR), allergic conjunctivitis (AC), atopic dermatitis (AD) or food allergy. An imbalance in the immune cell responses may support or facilitate a hypersensitive reaction of the immune system or even decrease the body's immunological tolerance, ultimately leading to allergic diseases [7]. This overview summarizes the results of 34 studies concerning the contributing effects of obesity on the development and prevalence of various atopic diseases.

Methods

Thirty-four epidemiological studies published between 2002 and 2012 were collected through an electronic search of the MEDLINE database. Selected keywords for the search were 'obesity' in relation to 'asthma', 'atopic asthma', 'atopy', 'allergic rhinitis', 'atopic dermatitis', 'allergic conjunctivitis', 'sensitization' and 'allergic diseases'. Most of the studies were case-control studies retrospectively comparing subjects suffering from a disease to

Introduction

Obesity is a growing health problem throughout the world [1–3]. In the past few decades, the number of obese and overweight people has reached extremely high levels. The World Health Organization states that in 2008, the

KARGER

E-Mail karger@karger.com
www.karger.com/iaa

© 2013 S. Karger AG, Basel
1018–2438/13/1623–0205\$38.00/0

Correspondence to: PD Dr. Axel Lorentz
Department of Nutritional Medicine, University of Hohenheim
Fruwirthstr. 12
DE-70593 Stuttgart (Germany)
E-Mail Lorentz@uni-hohenheim.de

those not suffering from the disease. Prospective studies were also included, providing measurements of a variety of variables in the selected population over a certain period of time to observe the development of allergic disease [8].

Results were grouped by the individual type of body composition (normal-weight, overweight or obese) and the risk of developing allergy. To compare and categorize the data, studies were selected that used standardized ranges of the body mass index (BMI). Normal weight, overweight or obesity in adults was defined as a BMI of 18.5–24.9, 25.0–29.9 or ≥ 30 , respectively [9]. Normal weight in children was defined as a BMI ≤ 84 th percentile (age- and sex-specific) of a reference group. Overweight or obesity was defined as a BMI between the 85th and 94th percentile or ≥ 95 th percentile, respectively [10]. Only statistically significant results were considered ($p < 0.05$) and only studies using the odds ratios (OR) as statistical values were included. The OR describes the degree of association between two variables, in this case between the type of allergy and the body weight. An OR of 1 is equivalent to no association while an OR > 1 shows an increased risk [11].

Results

Obesity and its Relation to Wheezing and BA

The study results to date support the view that obesity is linked to the increased prevalence of BA (table 1). Studies investigating overweight and obese children found that obesity increases the prevalence of wheezing and respiratory symptoms in subjects with a higher BMI compared to normal-weight subjects [12–16]. One study showed that, up to the age of eight, the risk for wheezing rises steadily with increasing BMI [12]. Especially in infants, obesity increases the risk for late-onset and persistent wheezing, particularly in girls [12].

Concerning its link to obesity, in children as well as adults, BA was consistently found to be strongly associated to being overweight and obese. An increased BMI even has a dose-response effect on the risk of developing BA (table 1) [12–27]. Other obesity parameters, such as waist circumference, body fat percentage (%BF) or the waist-to-hip ratio, were also associated with an increased prevalence of BA [20, 27–29]. For example, a waist circumference > 102 cm for men and > 88 cm for women almost doubled the risk for BA [20]. The study results also show a gender difference in BA prevalence, with being overweight a much stronger risk factor for BA in girls than in boys [12, 30, 31]. However, in yet another study, no gender differences in children at the age of 12 were found [14]. Results for adults indicate that women who are overweight had a significantly higher prevalence for BA than men (table 1) [19, 20, 28, 32, 33].

Some studies not only focused on the impact of obesity on BA in general, but differentiated between the atop-

ic and the nonatopic phenotype. For both phenotypes, an association between greater weight and the prevalence of BA was observed, but this association was even stronger for the nonatopic phenotype, especially in girls and women (table 2) [16, 20, 21, 29, 31, 33, 34].

To further differentiate between the two phenotypes, some studies included investigations of interleukin (IL)-4, immunoglobulin E (IgE) and C-reactive protein (CRP) as markers for inflammation and allergic sensitization, and therefore characterized the atopic asthma phenotype. Although levels of IL-4, CRP and IgE were elevated in overweight and obese children, no positive correlation to an increased risk for BA was found [35]. In addition, analyses of skin prick tests (SPTs) or IgE serum levels support that the association between obesity and asthma is independent from the subject's atopic status [26].

Greater BMI as well as other adiposity parameters impacted on lung function in children and adults in a negative way, leading to a decline in lung function parameters such as the functional residual capacity and the residual volume [14, 17, 29, 36–38]. The forced expiratory volumes (FVC and FEV₁) investigated via lung function measurements were significantly decreased compared with BMI and other adiposity measures [29, 38]. The FEV₁ was reported to be inversely correlated to BA [36]. These observations were independent of the subject's atopic status [29]. The decline in lung function indicates a worsening of asthmatic symptoms because breathing becomes more and more difficult [14]. For children, the study results show an impairment of asthmatic symptoms with increasing body weight [14, 36]. In addition, overweight and obese asthmatic children showed a significantly less positive response to steroid treatment than normal-weight asthmatics, and lung function parameters improved only slightly [39].

Obesity and Its Relation to Other Allergic Diseases

As obesity does not amplify the risk for the atopic asthma phenotype (compared to the nonatopic type) it seems it is not linked to allergic mechanisms in BA. We went on to examine studies investigating the effect of obesity on allergic diseases other than BA.

Increasing weight was found to have a positive influence on the risk of developing AD in childhood, meaning that children with an increased body weight have an increased prevalence for AD [12, 40, 41]. In addition, the earlier a child becomes obese and the longer this state persists, the more the risk increases. However, this observation was only seen in the early childhood and disappeared around the age of 5 years [40]. An association of

Table 1. Relationship between overweight or obesity with wheezing and BA

Type of allergy	Study design	Subjects n	Age years	Overweight OR (95% CI)	Obese OR (95% CI)	Reference	Year
Current wheeze	cc	457	12	1.7 (1.0–2.5)	1.9 (1.0–3.6)	[14]	2003
	cc	74	infants	2.6 (0.5–12.1)	–	[35]	2004
	cc	8,334	13–14	–	1.38 (1.07–1.80)	[13]	2010
	pc	731	3	1.26 (1.04–1.53)	–	[12]	2011
			5	1.33 (1.06–1.67)	–		
			8	1.27 (1.0–1.62)	–		
			8	1.09 (0.79–1.51) (m)	–		
				1.52 (1.01–2.28) (f)	–		
	pc	1,879	1 1/2	1.62 (1.13–2.32)	–	[15]	2012
BA	pc	9,149	20–64	1.1 (0.3–3.6) (m)	–	[32]	2002
				1.9 (1.1–3.4) (f)	–		
	cc	18,393	20+	0.96 (0.68–1.35)	1.43 (1.07–1.92)	[22]	2002
	pc	10,597	25–52	1.07 (0.62–1.85) (m)	3.47 (1.56–7.72) (m)	[23]	2002
				1.60 (0.91–2.80) (f)	2.30 (0.87–6.08) (f)		
	pc	9,456	25–74	0.95 (0.68–1.33)	1.28 (0.83–1.96)*	[24]	2003
					1.87 (1.12–3.13)**		
	pc	16,191	20–44	1.14 (0.93–1.41)	1.67 (1.24–2.25)	[25]	2004
	pc	74	infants	5.8 (1.2–27)	–	[35]	2004
	pc	135,405	14–60	1.27 (1.13–1.43) (m)	1.78 (1.35–2.34) (m)	[19]	2004
				1.30 (1.17–1.45) (f)	1.99 (1.67–2.37) (f)		
	cc	618	20–60	1.7 (1.2–2.5)	2.3 (1.4–3.9)	[26]	2005
				2.6 (1.2–5.5) (m)	3.3 (1.2–9.3) (m)		
				1.8 (1.1–3.2) (f)	3.0 (1.4–6.1) (f)		
	cc	86,144	20–64	–	1.21 (1.05–1.40) (m)	[33]	2006
				–	1.85 (1.65–2.07) (f)		
	cc	50,086	7–15	1.08 (0.96–1.22)	1.18 (0.98–1.44)	[30]	2008
				–	1.01 (0.78–1.32) (m)		
				–	1.46 (1.10–1.93) (f)		
	cc	88,304	18+	1.40 (1.31–1.49)	1.89 (1.73–2.05)*	[27]	2009
				1.45 (1.36–1.56)	1.97 (1.79–2.16)*		
	cc	4,493	20+	1.28 (0.82–2.01)	2.28 (1.76–2.96)	[20]	2010
	pc	754	18+	1.09 (0.61–1.94) (m)	1.31 (0.42–4.04) (m)	[28]	2011
				1.95 (1.22–3.12) (f)	13.83 (3.15–60.7) (f)		
	pc	1,815	3	–	2.3 (1.5–3.3)	[18]	2011
	cc	13,970	20+	–	1.67 (1.44–1.94)	[16]	2012
				–	1.43 (1.13–1.82) (m)		
				–	1.83 (1.54–2.18) (f)		
	cc	681,122	6–19	1.22 (1.20–1.24)	1.37 (1.34–1.40)	[17]	2012
	pc	396	7	1.87 (1.23–2.84)	–	[41]	2012

cc = Case-control study; f = female; m = male; pc = prospective cohort study.

* Relates to obese subjects with a BMI 30–34.9. ** Relates to obese subjects with a BMI ≥ 35 .

increased body weight and AD was not encountered for children older than 7 years of age [13, 30]. Several studies also showed that the severity of AD symptoms increased with an increase in body weight [30, 40]. Murray et al. [12] observed a slight gender difference between girls and boys at the age of 3, 5 and 8 years. Particularly at the age of 5 years, girls had a significantly higher risk for AD

than boys (boys: OR 1.04, 95% CI 0.82–1.32 and girls: OR 1.55, 95% CI 1.18–2.03; table 3) [12]. As AD is encountered more in childhood, no significant results were reported for the effect of obesity on AD in adults. It should also be noted that these studies did not differentiate between the IgE-mediated and non-IgE-mediated type of AD.

Table 2. Relationship between overweight or obesity and BA, differentiated into the atopic and nonatopic form

Type of allergy	Study design	Subjects n	Age years	Overweight OR (95% CI)	Obese OR (95% CI)	Reference	Year
Atopic BA	pc	1,289	0–12	1.24 (0.76–2.04)	1.92 (0.99–3.71)	[21]	2005
	cc	86,144	20–64	–	1.18 (0.98–1.53) (m)	[33]	2006
				–	1.57 (1.36–1.82) (f)		
	cc	17,145	6–7	–	1.09 (0.57–2.07) (m)	[31]	2008
				–	1.78 (0.88–3.62) (f)		
	cc	4,493	20+	1.03 (0.57–1.87)	2.04 (1.37–3.03)	[20]	2010
	cc	13,970	20+	–	1.95 (1.29–2.95)	[16]	2012
	cc	3,471	19–72	0.84 (0.34–1.81)	–	[29]	2012
Nonatopic BA	pc	1,289	0–12	1.24 (0.73–2.12)	1.89 (1.00–3.60)	[21]	2005
	cc	86,144	20–64	–	1.30 (1.05–1.62) (m)	[33]	2006
				–	2.53 (2.11–3.04) (f)		
	cc	17,145	6–7	–	1.92 (1.13–3.25) (m)	[31]	2008
				–	2.99 (1.68–5.32) (f)		
	cc	4,493	20+	1.75 (0.78–3.94)	2.5 (1.2–5.2)	[20]	2010
	cc	13,970	20+	–	1.66 (0.97–2.83)	[16]	2012
	cc	3,471	19–72	2.91 (1.64–5.02)	–	[29]	2012

cc = Case-control study; f = female; m = male; pc = prospective cohort study.

Table 3. Relationship between overweight or obesity and specific types of allergy

Type of allergy	Study design	Subjects n	Age years	Overweight OR (95% CI)	Obese OR (95% CI)	Reference	Year
AD*	cc	50,086	7–15	1.08 (0.97–1.21)	1.11 (0.93–1.32)	[30]	2008
	cc	1,242	1–21	0.77 (0.53–1.12)	1.97 (1.21–3.21)	[40]	2011
	pc	731	0–8	1.79 (1.03–3.13)	–	[12]	2011
AD* and wheeze	cc	457	12	2.20 (1.0–4.6)	–	[14]	2003
AC/ rhinoconjunctivitis**	cc	283,077	17–20	1.01 (0.99–1.04)	1.01 (0.97–1.06)	[34]	2005
	cc	50,086	7–15	0.87 (0.81–0.94)	0.85 (0.75–0.96)	[30]	2008
AR**	cc	50,086	7–15	1.00 (0.94–1.07)	0.94 (0.84–1.05)	[30]	2008

cc = Case-control study; pc = prospective cohort study.

* There was no differentiation between the extrinsic and intrinsic types of AD.

** There was no differentiation between the extrinsic and intrinsic types of AC/rhinoconjunctivitis and AR.

The results of studies analyzing the relationship between obesity and AR, AC and rhinoconjunctivitis are inconclusive. One study did not find a significant correlation [34], and in another, a negative correlation with AR and with AC, especially in boys up to the age of 15, was even reported (table 3) [30].

In 2 studies, overweight subjects were found to be significantly more prone to sensitization to food allergens

than normal-weight subjects [42–44]. IgE levels in blood serum were elevated as well as the levels of CRP, showing that obesity might indeed be linked to increased sensitization [43, 44]. Especially in the age group of 2- to 5-year-olds, the risk for food sensitization was particularly strong. Interestingly, obesity was more strongly associated with sensitization to food allergens in males than in females [43, 44]. There were other studies that did not

Table 4. Relationship between overweight or obesity and atopy or IgE levels

	Study design	Subjects n	Age years	Overweight OR (95% CI)	Obese OR (95% CI)	Reference	Year
Atopy/sensitization*	cc	1,576	3–14	1.10 (0.8–1.5)	0.8 (0.5–1.3)	[45]	2009
	cc	4,269	2–19	0.68 (0.23–1.99)	1.37 (0.71–2.62)	[43]	2009
	cc	1,187	18–39	1.67 (1.00–2.80) (m)	1.57 (0.86–2.83) (m)	[44]	2009
				0.90 (0.53–1.52) (f)	1.56 (0.76–3.21) (f)		
	cc	4,493	20+	0.94 (0.81–1.09)	0.89 (0.67–1.19)	[20]	2010
	cc	2,090	18–79	1.12 (0.87–1.45)	1.51 (1.17–1.95)	[42]	2010
				0.87 (0.58–1.32) (m)	1.27 (0.73–1.93) (m)		
				1.30 (0.98–1.82) (f)	1.63 (1.18–2.26) (f)		
Specific IgE							
Total IgE	cc	4,269	2–19	1.16 (0.93–1.45)	1.26 (1.03–1.55)	[43]	2009
Food IgE				1.25 (1.02–1.54)	1.31 (1.10–1.57)		
Inhalant IgE				1.27 (0.98–1.65)	1.59 (1.28–1.98)		
				1.08 (0.83–1.42)	1.17 (0.91–1.50)		

cc = Case-control study; f = female; m = male. * Atopy or allergic sensitization was defined as being positive to at least one allergen tested in SPTs [43–45] or as having elevated serum levels for at least one specific IgE [20].

report increased sensitization in overweight and obese adults (table 4) [20, 45], and in complete contrast, 1 study found that the risk of sensitization for underweight children was doubled compared to that for normal-weight children [45].

Discussion

The study results summarized in this review support the view that, in general, obesity is not a promoter of allergy. It may, however, affect atopic diseases depending on the age and gender of the individual as well as on the type of disease. It has been shown that it increases the prevalence of BA in children and adults. However, with regard to the different phenotypes of asthma, there was a stronger impact of obesity on the nonatopic than on the atopic asthma phenotype (table 1, 2). Thus, it is likely that the link between obesity and BA is not mediated through allergic mechanisms. Although some studies showed an increased concentration in T-helper (Th)2 cell cytokines (e.g. IL-4 and IL-13) in obese asthmatics [37], these may only play a small role in the interaction between obesity and BA. Results for IL-4 levels and sensitization in SPTs in obese asthmatic children are contradictory [46, 47]. In addition, the total mast cell burden in obese compared to nonobese children was not increased [48], suggesting that

Th2 immune responses are not augmented. Likewise, obesity was not associated with elevated IgE levels in adults, while the results for children are inconsistent [16, 43, 49]. The observed relationship concerning the atopic phenotype may be due to the overall association between obesity and BA, and may be independent from allergic sensitization and an increased Th2 cell response [50].

Obesity was also investigated in its relation to other allergic diseases. In children, obesity and AD seem to be linked to one another [12, 14, 30, 40]. The earlier a child becomes obese, the more the risk for AD rises [40]. This may be explained through the fact that from birth on, the child's immune system has to evolve steadily to be able to defend itself against all the different incoming molecules. During this time the immune system is prone to launching hypersensitive reactions due to development not being complete [51, 52]. If the child also becomes obese, this supposedly leads to a greater imbalance of the immune system and results in extreme reactivity to innocuous molecules.

The results reported in the studies concerning the effect of obesity on AD prevalence were varied [12, 14, 30, 40]. This might be due to the different ages of the children in the different studies (table 3). AD usually starts in infancy and the obesity-AD relationship loses its significance already by the age of 5 years [40], which might explain why there was no association seen in children

who were older than 7 years [14, 30]. However, Silverberg et al. [40], Murray et al. [12] and Kusunoki et al. [30] did not differentiate between the two forms of AD. The extrinsic type is characteristic for its elevated serum IgE levels and increased Th2 cell activity and affects about 70–85% of AD patients. The intrinsic type of AD is also called the nonallergic type; it lacks an increased Th2 response and affects about 15–30% of AD patients [53]. It was not clear to which type of AD the study results referred. Murray et al. [12] included SPTs and showed that greater BMI in children is not related to an increased sensitization in SPTs. Another study also found no positive relationship between increased BMI and increased sensitivity in SPTs [14]. Subjects with the extrinsic, IgE-mediated type of AD often have positive reactions in SPTs for both aeroallergens and food allergens [53]. The increased OR of 1.79 in the study of Murray et al. [12] may relate to the intrinsic, non-IgE-mediated type of AD. We should not exclude the possibility that the proposed relationship of the prevalence of AD in children and being overweight is not due to an enhancement of an allergic mechanism, but rather to other mechanisms, as yet unknown.

Study results concerning the effect of obesity on the development of AR and AC did not support a rise in the prevalence of either in children who were obese [30, 34]. Another study investigated the effect of other obesity parameters such as waist circumference and waist/height on AR or AC prevalence, but no correlation was established [36]. Obesity leads to an increase of various cytokines in the human body, especially those derived from Th1 cells, e.g. tumor necrosis factor alpha (TNF- α), interferon gamma (IFN- γ), IL-6 and IL-2 [54, 55]. Because the concentrations of these cytokines increase through the effects of leptin [55–57], various studies have proposed that the high concentrations of leptin in obese subjects modulate the Th1/Th2 balance towards a Th1 phenotype [30, 58, 59]. AR and AC, being primarily diseases related to the Th2 cell-mediated response [30] involving Th2 cells, mast cells and IgE, are not significantly affected by the metabolic changes that occur with obesity. Thus, it is proposed that obesity does not contribute to the pathogenesis of AR or AC. Contrary to AR, Th2 and Th1 responses are found to be involved in the pathogenesis of AD [60]. However, none of the studies used SPTs or examined serum IgE levels in the investigated subjects, and therefore did not distinguish between IgE-mediated and non-IgE-mediated AR. Such investigations were not made for AC either. To be able to further clarify a possible contribution of obesity to the development of AR or AC, it would be

necessary to make this differentiation between the two types.

Obesity may increase sensitization to allergens, especially food allergens. The sensitization of obese subjects to food allergens is even stronger than to aeroallergens and was particularly strong in 2- to 5-year-olds [43]. This may be due to an immune system that is not yet completely developed, as it has been observed that allergies often disappear as the child grows older [48, 60]. However, it has also been reported that increased sensitization to food allergens is often seen in people who are underweight [45, 61]. The exact correlation between an altered body weight and its effects on food sensitization is not yet well understood. A weakness of many of the studies that investigated the relationship between obesity and allergy is that SPTs often included only one specific food allergen or even none. Additionally, very few studies focused on the evaluation of specific food IgE in the blood serum [14, 45]. For the examination of sensitivities to food allergens, IgE testing is imperative to obtain more precise results about the obesity-allergy relationship.

The strong link observed between obesity and BA may be due to other factors arising from obesity. The results of the studies indicate that changes in the properties of the lungs in the obese may account for the effect of obesity on BA. This is supported by the observation that obesity leads to a decline in lung function parameters, independently of the subject's atopic status [29, 36–38]. The enlarging adipose tissue accumulates in the visceral tissue around the lungs and reduces the space in the thorax, thereby impeding lung expansion and the movement of the diaphragm, and as a consequence, it is not possible to breathe easily. To counteract the imbalance created in breathing and gas exchange, the airway smooth muscles launch a greater contractile response, which ultimately leads to shortness of breath [62].

The increased risk for BA might also be due to an aggravation of inflammation in the human body resulting from an increased cytokine production and altered levels of adiponectin and leptin. Obesity is thought to lead to a state of low-grade systemic inflammation, with elevated levels of CRP and circulating leptin [16, 21, 35, 37, 42, 46, 63–66]. Leptin levels are elevated in obese subjects and reach the highest levels in obese asthmatics (e.g. normal-weight individuals: 2.8 ng/ml, obese individuals: 14.3 ng/ml and obese asthmatics: 30.8 ng/ml) [35, 46, 66]. Leptin possibly leads to a downregulation of regulatory T cells [46]. Consequently, the balance between Th1/Th2 cells will be lost and a shift to an increased Th1 cell activity may

occur. Furthermore, some studies showed that leptin activates macrophages and increases their production of macrophage-derived cytokines, switching the balance to a proinflammatory state in obese people [67]. This would explain the increased concentration of TNF- α , IFN- γ , IL-6 and IL-2 in obese and asthmatic subjects [68]. In vitro experiments showed an increased production of Th2 cytokines and reduced apoptosis of basophils and eosinophils following treatment with leptin [69–71]. However, high doses of leptin were used in these in vitro experiments compared to the concentrations in human blood serum (50–100 μ g/ml [70] vs. 7.5 ng/ml in normal-weight and 31.3 ng/ml in obese adults [72]). At present, the exact influence of leptin on immune responses remains unclear [55].

CRP as an inflammatory marker is released by the liver after stimulation with IL-6 in the event of acute infection or tissue damage. In addition, hypoxia in the adipose tissue leads to apoptosis of adipocytes, and thereby increases CRP levels. CRP may maintain and enhance inflammation, but it may also inhibit the production of IFN- γ and induce production of anti-inflammatory mediators. So far, the role of CRP as a possible contributor in the pathogenesis of atopic diseases is not entirely understood.

Gender differences are consistently reported for the prevalence of BA in both children and adults. Differences in body composition may be one reason for this observation. Women have greater intramuscular fat infiltration in their lean mass compared to men, which results in high systemic leptin and low systemic adiponectin levels as well as in an increased expression of TNF- α [73, 74]. In addition, differences in %BF between genders are likely to influence the association of obesity with asthma. In both genders, BMI is not linearly correlated to body fat. At any given age, women have a higher %BF than men, while men have a greater muscle mass [75]. The differences in BA prevalence between genders might therefore arise because of differences in %BF [37]. Differences in estrogen levels between genders may also explain the stronger association in women who are obese compared to men. Estrogen is also produced by the adipose tissue and so, in obese subjects, its levels are elevated. Estrogen leads to eosinophilic degranulation and to a significant enhancement of eosinophilic adhesion to human mucosal cells. It may also inhibit oxidative burst in leukocytes, thereby enhancing their survival, which may contribute to an increased inflammatory state and to chronic inflammation in obese subjects [50, 76–79].

Other studies investigated if the systemic inflammation caused by obesity may also enhance airway inflammation and therefore lead to BA. In animal models, obesity seems to correlate with increasing airway inflammation, e.g. accumulation of eosinophils, neutrophils, monocytes and macrophages in lung tissue due to low levels of adiponectin or increased levels of IL-6 [80, 81]. In asthmatics, more sputum eosinophils were found [82]. However, there was no correlation between BMI and number of sputum eosinophils in humans, nor was there any significant difference in the percentage of eosinophilic and neutrophilic cells between genders and BMI subgroups. In addition, adults without BA did not show any elevation or difference in total or specific sputum cell counts. In other words, BMI was not associated with these counts and thus may not be responsible per se for increased airway inflammation [82].

Finally, the question remains: Does obesity promote the development of asthma or do asthma and reduced lung function result in reduced physical activity and therefore the subjects gain weight? Many prospective studies show that the state of overweight or obesity existed before the patients received their asthma diagnosis [19, 23, 24, 28, 32, 35, 41]. A study by Beckett et al. [83] suggests that the data of many studies do not support the hypothesis that asthma results in less activity and therefore leads to obesity. As it could be shown that obesity can increase the severity of asthma symptoms, it is proposed that obesity does indeed promote asthma [14, 17, 36, 46, 66].

Conclusion

Obesity affects different atopic diseases, but the extent of its influence varies, i.e. depending on the age and gender of the individual as well as on the specific disease. Obesity modulates children's developing adaptive immune system, which results in a shift of the balanced responses of immune cells. It is associated with AD in children. In obese children as well as in adults, there is a strong correlation for the risk of developing BA, especially concerning the nonatopic asthma phenotype, with a much stronger link in females than in males. The general association of obesity with BA might result mainly from mechanical and anatomical changes in the obese human body. It is likely that obesity does not enhance the Th2-mediated responses of the immune system in adults, with allergic disease as a result, but it may not be called a promoter of allergy as such.

References

- ▶ 1 Bergeron C, Boulet LP, Hamid Q: Obesity, allergy and immunology. *J Allergy Clin Immunol* 2005;115:1102–1104.
- ▶ 2 Wyatt SB, Winters KP, Dubbert PM: Overweight and obesity: prevalence, consequences, and causes of a growing public health problem. *Am J Med Sci* 2006;331:116–174.
- ▶ 3 World Health Organization: Obesity: preventing and managing the global epidemic: report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000;894:1–253.
- 4 World Health Organization: Obesity and overweight, 2012. Fact Sheet No. 133. <http://www.who.int/mediacentre/factsheets/fs311/en/index.html>.
- 5 World Health Organization: Asthma, 2012. Fact Sheet No. 307. <http://www.who.int/mediacentre/factsheets/fs307/en/index.html>.
- 6 Rance K, O'Laughlen M: Obesity and asthma: a dangerous link in children. *JNP* 2011;7:287–292.
- ▶ 7 Hersoug LG, Linneberg A: The link between the epidemics of obesity and allergic diseases: does obesity induce decreased immune tolerance? *Allergy* 2007;62:1205–1213.
- ▶ 8 Mann C: Observational research methods – research design II: cohort, cross-sectional, and case-control studies. *Emerg Med J* 2003;20:54–60.
- 9 World Health Organization: 10 facts on obesity – BMI classification. <http://www.who.int/features/factfiles/obesity/facts/en/index.html> (accessed 15 September 2012).
- ▶ 10 Barlow SE: Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 2007;120:S164–S192.
- ▶ 11 Szumilas M: Explaining odds ratios. *J Can Acad Child Adolesc Psychiatry* 2010;19:227–229.
- ▶ 12 Murray CS, Canoy D, Buchan I, Woodcock A, Simpson A, Custovic A: Body mass index in young children and allergic disease: gender differences in a longitudinal study. *Clin Exp Allergy* 2011;41:78–85.
- ▶ 13 Wang H-Y, Pizzichini MMM, Becker AB, Duncan JM, Ferguson AC, Greene JM, Rennie DC, Senthilselvan A, Taylor BW, Sears MR: Disparate geographic prevalences of asthma, allergic rhinoconjunctivitis and atopic eczema among adolescents in five Canadian cities. *Pediatr Allergy Immunol* 2010;21:867–877.
- ▶ 14 Mai XM, Nilsson L, Axelsson O, Brabäck L, Sandin A, Kjellman NIM, Björkstén B: High body mass index, asthma and allergy in Swedish schoolchildren participating in the International Study of Asthma and Allergies in Childhood: Phase II. *Acta Paediatr* 2003;92:1144–1148.
- ▶ 15 Herr M, Just J, Nikasinovic L, Foucault C, Le Marec AM, Giordanela JP, Momas JJ: Influence of host and environmental factors on wheezing severity in infants: findings from the PARIS birth cohort. *Clin Exp Allergy* 2012;42:275–283.
- 16 Visness CM, London SJ, Gergen PJ, Mitchell HE, Zeldin DC: Obesity is associated with asthma among atopic as well as non-atopic adults. *J Allergy Clin Immunol* 2012;125:AB191.
- ▶ 17 Black MH, Smith N, Porter AH, Jacobsen SJ, Koebnick C: Higher prevalence of obesity among children with asthma. *Obesity (Silver Spring)* 2012;20:1041–1047.
- ▶ 18 Suglia SF, Chambers E, Rosario A, Duarte CS: Asthma and obesity among 3-year-old urban children: the role of sex and the home environment. *J Pediatr* 2011;159:14–20.e1.
- ▶ 19 Nystad W, Meyer HE, Nafstad P, Tverdal A, Engeland A: Body mass index in relation to adult asthma among 135,000 Norwegian men and women. *Am J Epidemiol* 2004;160:969–976.
- ▶ 20 Ma J, Xiao L, Knowles SB: Obesity, insulin resistance and the prevalence of atopy and asthma in US adults. *Allergy* 2010;65:1455–1463.
- ▶ 21 Olafsdottir IS, Gislason T, Thjodleifsson B, Olafsson I, Gislason D, Jögi R, Janson C: C reactive protein levels are increased in non-allergic but not allergic asthma: a multicentre epidemiological study. *Thorax* 2005;60:451–454.
- ▶ 22 Arif AA, Deldos GL, Lee ES, Tortolero SR, Whitehead LW: Prevalence and risk factors of asthma and wheezing among US adults: an analysis of the NHANES III data. *Eur Respir J* 2003;21:827–833.
- ▶ 23 Huovinen E, Kaprio J, Koskenvuo M: Factors associated to lifestyle and risk of adult onset asthma. *Respir Med* 2003;97:273–280.
- ▶ 24 Ford ES, Mannino DM, Redd SC, Mokdad AH, Mott JA: Body mass index and asthma incidence among USA adults. *Eur Respir J* 2004;24:740–744.
- ▶ 25 Gunnbjörnsdóttir MI, Omenaas E, Gislason T, Norrman E, Olin A-C, Jögi R, Jensen EJ, Lindberg E, Björnsson E, Franklin K, Janson C: Obesity and nocturnal gastro-oesophageal reflux are related to onset of asthma and respiratory symptoms. *Eur Respir J* 2004;24:116–121.
- ▶ 26 Rönmark E, Andersson C, Nyström L, Forsberg B, Järholm B, Lundbäck B: Obesity increases the risk of incident asthma among adults. *Eur Respir J* 2005;25:282–288.
- ▶ 27 Von Behren J, Lipsett M, Horn-Ross PL, Delfino RJ, McConnell R, Bernstein L, Clarke CA, Reynolds P: Obesity, waist size, and prevalence of current asthma in the California Teachers Study cohort. *Thorax* 2009;64:1–11.
- ▶ 28 Wang TN, Lin MC, Wu CC, Huang MS, Leung SY, Huang CC, Ho PS, Ko YC: Role of gender disparity of circulating high-sensitivity C-reactive protein concentrations and obesity on asthma in Taiwan. *Clin Exp Allergy* 2011;41:72–77.
- ▶ 29 Fenger RV, Gonzalez-Quintela A, Vidal C, Gude F, Husemoen LL, Aadahl M, Berg ND, Linneberg A: Exploring the obesity–asthma link: do all types of adiposity increase the risk of asthma? *Clin Exp Allergy* 2012;42:1237–1245.
- ▶ 30 Kusunoki T, Morimoto T, Nishikomori R, Heike T, Ito M, Hosoi S, Nakahata T: Obesity and the prevalence of allergic diseases in schoolchildren. *Pediatr Allergy Immunol* 2008;19:527–534.
- ▶ 31 Garcia-Marcos L, Arnedo Pena A, Busquets-Monge R, Morales Suárez-Varela M, García de Andoin N, Batlles-Garrido J, Blanco-Quirós A, Lopez-Silvarrey Varela A, Garcia-Hernandez G, Aguinaga-Ontoso I, Gonzalez-Diaz C, Garcia-Merino A: How the presence of rhinoconjunctivitis and the severity of asthma modify the relationship between obesity and asthma in children 6–7 years old. *Clin Exp Allergy* 2008;38:1174–1178.
- ▶ 32 Chen Y, Dales R, Tand M, Krewski D: Obesity may increase the incidence of asthma in women but not in men: longitudinal observations from the Canadian National Population Health Surveys. *Am J Epidemiol* 2002;155:191–197.
- ▶ 33 Chen Y, Dales R, Jiang Y: The association between obesity and asthma is stronger in non-allergic than allergic adults. *Chest* 2006;130:890–895.
- ▶ 34 Bråbäck L, Hjern A, Rasmussen F: Body mass index, asthma and allergic rhinoconjunctivitis in Swedish conscripts – a national cohort study over three decades. *Respir Med* 2005;99:1010–1014.
- ▶ 35 Mai XM, Böttcher MF, Leijon I: Leptin and asthma in overweight children at 12 years of age. *Pediatr Allergy Immunol* 2004;15:523–530.
- ▶ 36 Musaad SMA, Patterson T, Ericksen M, Lindsey M, Dietrich K, Succop P, Hershey GK: Comparison of anthropometric measures of obesity in childhood allergic asthma: central obesity is most relevant. *J Allergy Clin Immunol* 2009;123:1321–1327.
- ▶ 37 Sutherland TJJ, Cowan JO, Young S, Goulding A, Grant AM, Williamson A, Brassett K, Herbison GP, Taylor DR: The association between obesity and asthma: interactions between systemic and airway inflammation. *Am J Respir Crit Care Med* 2008;178:469–475.
- ▶ 38 Browatzki A, Ulrik CS, Lange P: Prevalence and severity of self-reported asthma in young adults, 1976–2004. *Eur Respir J* 2009;34:1046–1051.
- ▶ 39 Forno E, Lescher R, Strunk R, Weiss S, Fuhlbrigge A, Celedón JC: Decreased response to inhaled steroids in overweight and obese asthmatic children. *J Allergy Clin Immunol* 2011;127:741–749.
- ▶ 40 Silverberg JI, Kleiman E, Lev-Tov H, Silverberg NB, Durkin HG, Joks R, Smith-Norowitz TA: Association between obesity and atopic dermatitis in childhood: a case-control study. *J Allergy Clin Immunol* 2011;127:1180–1186.
- ▶ 41 Sevelsted A, Bisgaard H: Neonatal size in term children is associated with asthma at age 7, but not with atopic dermatitis or allergic sensitization. *Allergy* 2012;67:670–675.

- ▶ 42 Chen Y, Rennie D, Cormier Y, Dosman J: Association between obesity and atopy in adults. *Int Arch Allergy Immunol* 2010;153:372–377.
- ▶ 43 Visness CM, London SJ, Daniels JL, Kaufman JS, Yeatts KB, Siega-Riz AM, Liu AH, Calatroni A, Zeldin DC: Association of obesity with IgE levels and allergy symptoms in children and adolescents: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol* 2009;123:1163–1169.
- ▶ 44 Ouyang F, Kumar R, Pongracic J, Story RE, Liu X, Wang B, Xing H, Liu X, Li Z, Zhang W, Fang Y, Zhang S, Xu X, Wang X: Adiposity, serum lipid levels, and allergic sensitization in Chinese men and women. *J Allergy Clin Immunol* 2009;123:940–948.e10.
- ▶ 45 Van Gysel D, Govaere E, Verhamme K, Doli E, De Baets F: Body mass index in Belgian schoolchildren and its relationship with sensitization and allergic symptoms. *Pediatr Allergy Immunol* 2009;20:246–253.
- ▶ 46 Yuksel H, Sogut A, Yilmaz O, Onur E, Dinc G: Role of adipokines and hormones of obesity in childhood asthma. *Allergy Asthma Immunol Res* 2012;4:98–103.
- ▶ 47 Arshi M, Cardinal J, Hill RJ, Davies PSW, Wainwright C: Asthma and insulin resistance in children. *Respirology* 2010;15:779–784.
- ▶ 48 Ward BR, Arslanian SA, Andreatta E, Schwartz LB: Obesity is not linked to increased whole-body mast cell burden in children. *J Allergy Clin Immunol* 2012;129:1164–1166.
- ▶ 49 Visness CM, London SJ, Daniels JL, Kaufman JS, Yeatts KB, Siega-Riz AM, Liu AH, Calatroni A, Zeldin DC: Association of obesity with IgE levels and allergy symptoms in children and adolescents: results from the National Health and Nutrition Examination Survey 2005–2006. *J Allergy Clin Immunol* 2009;123:1163–1169.
- ▶ 50 Van den Berge M, Heijink HI, van Oosterhout AJM, Postma DS: The role of female sex hormones in the development and severity of allergic and non-allergic asthma. *Clin Exp Allergy* 2009;39:1477–1481.
- ▶ 51 Holt PG, Jones CA: The development of the immune system during pregnancy and early life. *Allergy* 2000;55:688–697.
- 52 Chirico G: Development of the immune system in neonates. *J Arab Neonatal Forum* 2005;2:5–11.
- ▶ 53 Bardana EJ Jr: Immunoglobulin E- (IgE) and non-IgE-mediated reactions in the pathogenesis of atopic eczema/dermatitis syndrome (AEDS). *Allergy* 2004;59:25–29.
- ▶ 54 Hajer GR, van Haeften TW, Visseren FLJ: Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur Heart J* 2008;29:2959–2971.
- ▶ 55 Tilg H, Moschen AR: Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006;6:772–783.
- ▶ 56 Lam QLK, Lu L: Role of leptin in immunity. *Cell Mol Immunol* 2007;4:1–13.
- ▶ 57 Ali Assad N, Sood A: Leptin, adiponectin and pulmonary diseases. *Biochimie* 2012;94:2180–2189.
- ▶ 58 Pacifico L, Renzo LD, Anania C, Osborn JF, Ippoliti F, Schiavo E, Chiesa C: Increased T-helper interferon- γ -secreting cells in obese children. *Eur J Endocrinol* 2006;154:691–697.
- ▶ 59 Fantuzzi G: Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 2005;115:911–919.
- ▶ 60 Sampson HA: Atopic dermatitis: immunological mechanisms in relation to phenotype. *Pediatr Allergy Immunol* 2000;12:62–68.
- ▶ 61 Christie L, Hine J, Parker JG, Burks W: Food allergies in children affect nutrient intake and growth. *J Am Diet Assoc* 2002;102:1648–1651.
- ▶ 62 Von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST: Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. *Thorax* 2001;56:835–838.
- ▶ 63 Wisse BE: The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol* 2004;15:2792–2800.
- ▶ 64 Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2011;306:327–334.
- ▶ 65 Wilders-Truschnig M, Mangge H, Lieners C, Gruber HJ, Mayer C, März W: IgG antibodies against food antigens are correlated with inflammation and intima media thickness in obese juveniles. *Exp Clin Endocrinol Diabetes* 2008;116:241–245.
- ▶ 66 Kilic H, Oguzulgen IK, Bakir F, Turktaş H: Asthma in obese women: outcomes and factors involved. *J Investig Allergol Clin Immunol* 2011;21:290–296.
- ▶ 67 Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, Klein AS, Bulkley GB, Bao C, Noble PW, Lane MD, Diehl AM: Leptin regulates proinflammatory immune responses. *FASEB J* 1998;12:57–65.
- ▶ 68 Kryštofová J, Jeseňák M, Bánovčin P: Bronchial asthma and obesity in childhood. *Acta Medica* 2011;54:102–106.
- ▶ 69 Suzukawa M, Nagase H, Ogahara I, Han K, Tashimo H, Shibui A, Koketsu R, Nagase H, Ogahara I, Han K, Nakae S, Yamaguchi M, Ohta K: Leptin enhances survival and induces migration, degranulation, and cytokine synthesis of human basophils. *J Immunol* 2011;186:5254–5260.
- ▶ 70 Wong CK, Cheung PF, Lam CW: Leptin-mediated cytokine release and migration of eosinophils: implications for immunopathophysiology of allergic inflammation. *Eur J Immunol* 2007;37:2337–2348.
- ▶ 71 Conus S, Bruno A, Simon HU: Leptin is an eosinophil survival factor. *J Allergy Clin Immunol* 2005;116:1228–1234.
- ▶ 72 Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohanesian JP, Marco CC, McKee LJ, Bauer TL, Caro J: Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996;334:292–295.
- ▶ 73 Sood A, Qualls C, Li R, Schuyler M, Beckett WS, Smith LJ, Thyagarajan B, Lewis CE, Jacobs DR Jr: Lean mass predicts asthma better than fat mass among females. *Eur Respir J* 2011;37:65–71.
- ▶ 74 Sutherland TJJ, Goulding A, Grant AM, Cowan JO, Williamson A, Williams SM, Skinner MA, Taylor DR: The effect of adiposity measured by dual-energy X-ray absorptiometry on lung function. *Eur Respir J* 2008;32:85–91.
- ▶ 75 McLachlan CR, Poulton R, Car G, Cowan J, Filsell S, Greene JM, Taylor DR, Welch D, Williamson A, Sears MR, Hancox RJ: Adiposity, asthma, and airway inflammation. *J Allergy Clin Immunol* 2007;119:634–639.
- ▶ 76 Simpson ER: Sources of estrogen and their importance. *J Steroid Biochem Mol Biol* 2003;86:225–230.
- ▶ 77 Nelson LR, Bulun SE: Estrogen production and action. *J Am Acad Dermatol* 2001;45:S116–S124.
- ▶ 78 Kirschner MA, Schneider G, Ertel NH, Worton E: Obesity, androgens, estrogens, and cancer risk. *Cancer Res* 1982;42:3281s–3285s.
- ▶ 79 Kirschner MA, Samojlik E, Drejka M, Szmalec E, Schneider G, Ertel N: Androgen-estrogen metabolism in women with upper body versus lower body obesity. *J Clin Endocrinol Metab* 1990;70:473–479.
- ▶ 80 Medoff BD, Okamoto Y, Leyton P, Weng M, Sandall BP, Raher MJ, Kihara S, Bloch KD, Libby P, Luster AD: Adiponectin deficiency increases allergic airway inflammation and pulmonary vascular remodeling. *Am J Respir Cell Mol Biol* 2009;41:397–406.
- ▶ 81 Lang JE, Williams ES, Mizgerd JP, Shore SA: Effect of obesity on pulmonary inflammation induced by acute ozone exposure: role of interleukin-6. *Am J Physiol Lung Cell Mol Physiol* 2008;294:L1013–L1020.
- ▶ 82 Todd DC, Armstrong S, D'Silva L, Allen CJ, Hargreave FE, Parameswaran K: Effect of obesity on airway inflammation: a cross-sectional analysis of body mass index and sputum cell counts. *Clin Exp Allergy* 2007;37:1049–1054.
- ▶ 83 Beckett WS, Jacobs DR Jr, Yu X, Iribarren C, Williams OD: Asthma is associated with weight gain in females but not males, independent of physical activity. *Am J Respir Crit Care Med* 2001;164:2045–2050.