

## GENDER DIFFERENCES IN RELATIONSHIP BETWEEN BODY MASS INDEX AND ASTHMA

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### SUMMARY

**Background:** Asthma is one of the most common chronic diseases in the world. Obesity is the most common comorbidity of asthma and is connected to incidence and course of the disease. Obesity is associated with non-allergic asthma phenotype, but this relation could be influenced by gender. The aim of our study was to determine the relationship between BMI and asthma and to explore possible gender differences.

**Subjects and methods:** Study included 149 patients with asthma (examined group) and 153 healthy blood donors (control group). Data from the medical records of patients with asthma were used, and all included subjects had their BMI calculated using standard formula. Data were analyzed using descriptive statistics methods. Data with non-parametric distribution were analysed with Mann-Whitney U test and showed through medians with corresponding interquartile ranges. Statistical significance of BMI differences between non-allergic asthma, allergic asthma and control groups were analyzed by one-way analysis of variance - ANOVA. The results were interpreted at a significance level of  $P < 0.05$ .

**Results:** The comparison between median BMI values of two groups shows that examined group of patients with asthma has significantly higher median BMI value in comparison with control group ( $P = 0.035$ ). Correlation was stronger for women than men ( $P = 0.002$  vs  $P = 0.898$ ). Increased BMI of the examined group of patients with asthma was not associated with non-allergic asthma ( $P = 0.085$ ). However, when stratified according to gender, there was a strong association of increased BMI with non-allergic asthma in women ( $P < 0.001$ ).

**Conclusion:** Patients with asthma in our study have higher BMI in comparison to healthy individuals, which contributes to hypothesis that BMI is a risk factor for development of asthma. We found that possible effect that BMI has on asthma is stronger in women, since there was a strong association between increased BMI and non-allergic asthma only in women.

**Key words:** asthma - body mass index - gender

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### INTRODUCTION

Asthma is one of the most common chronic diseases that affects all age groups and is subject of numerous clinical and public health interventions. Morbidity and mortality of asthma are both significant, but it also has major effect on the quality of life and is often compared to the effect that diabetes mellitus, cyrosis or schizophrenia have on it (Bousquet et al. 2005). Prevalence of asthma is quite heterogeneous throughout the world. Studies about risk factors for development of asthma were mostly based on investigation of exogenous factors such as home allergens, mold and polluted aerosol, especially the one connected to traffic, whereas new studies have recognised the importance of metabolic and nutritive factors (Sears 2014). Asthma is a heterogeneous clinical syndrome, which primarily affects lower airways and is characterised with episodes or persistent symptoms of wheezing, dyspnea and cough.

Diagnosis is based on presence of the mentioned symptoms and on spirometry values that show reverse airway obstruction (MsCracken et al. 2017). Main pathophysiological process in asthma is chronic airway inflammation with elevated levels of eosinophils, mastocytes and activated helper T-lymphocytes. Inflammatory cells release mediators (cytokines, chemokines, growth factors, lipid mediators, immunoglobulins, histamin) that are responsible for the beginning of bronchoconstriction, mucous secretion and airway remodeling. Inflammation in asthma is mostly guided by Th2 cytokines that can, through positive feedback, enhance the production of more inflammatory mediators, which leads to stronger inflammatory process (Hamid 2012). Development of allergic asthma, as a major asthma phenotype, can be viewed upon as a process that has two phases. First phase involves development of allergen specific immunological memory against inhaled antigen. This phase takes place during the childhood and leads

immunological response towards Th2 phenotype, which makes an individual susceptible for development of allergic inflammation. The second phase involves consolidation and maintenance of polarised Th2 response, which results in chronic inflammation that is responsible for tissue remodeling and airway hyperreactivity, both being important features of asthma (Babu & Arshad 2003). The definition of nonallergic asthma includes that subset of subjects with asthma and with whom allergic sensitization cannot be demonstrated. These individuals should have negative skin prick test or in vitro specific-IgE test to a panel of seasonal and perennial allergens. Nonallergic asthma occurs in 10% to 33% of individuals with asthma and has a later onset than allergic asthma, with a female predominance. Non-allergic asthma appears to be more severe than allergic asthma in many cases and may be less responsive to standard therapy (Peters 2014).

Hence, asthma is a chronic disease that can be successfully controlled and its exacerbations minimized, by using the most appropriate therapy protocols. Therapy for persistent asthma requires minimization of exposure or avoiding the environmental factor that represents a trigger of asthma for particular patient, use of short-acting  $\beta_2$ -agonists for a quick symptom relief and daily use of inhaled corticosteroids. In therapy of moderate and severe asthma long acting bronchodilators and biologic drugs can be used (McCracken et al. 2017). However, besides classification of patients according to the severity of asthma, it is rather clinically important to determine response to the therapy and according to this criterion asthma can be controlled, partially controlled and uncontrolled chronic asthma (Dennis et al. 2011). There are clinical proves about association of obesity with poor asthma control (Barros et al. 2011, Stream & Sutherland 2012), which means that obesity affects control of the disease, one of the most important aspect of any chronic disease.

According to the World Health Organization (WHO) overweight and obesity are “abnormal or excessive fat accumulation that presents a risk to health“, and its measure is body mass index (BMI) (WHO 2018). Obesity is associated with increased morbidity and mortality. Most known complications of severe obesity are increased risks of developing diabetes, hypertension and hyperlipidemia. It also increases mortality from number of cancers (esophagus, colon, rectum, liver, gallbladder, pancreas, kidney, non-Hodgkin's lymphoma and multiple myeloma). It is important to emphasize that severe obesity has been associated with an increased rate of death from all cause and decreased life expectancy regardless of age, smoking, educational achievement, geographic region, and physical activity levels (Jarolimova et al. 2013, WHO 2018). Obesity with overweight affects more than third of the world's population and projections estimate that by 2030 about 38% of the world's adult population will be overweight and another 20%

will be obese (Hruby & Hu 2015). Obesity is the most common comorbidity of asthma and is connected to both, incidence and course of the disease. Obesity is associated with non-allergic asthma phenotype, but some studies shows that this relation is influenced by gender (Çelebi Sözen et al. 2016, Papaioannou et al. 2016, Scott et al. 2016). The aim of our study was to determine the relationship between BMI and asthma and to investigate possible gender differences.

## SUBJECTS AND METHODS

Study included 149 patients of examined group that had diagnosis of asthma and 153 healthy blood donors that made control group.

After collecting patients' consent and having approval of Ethical committee of University Hospital Centre Zagreb, we obtained 149 blood samples (subjects of examined group) in Clinic of Lung Diseases Jordanovac, University Hospital Centre Zagreb. Examined group consisted of 92 women and 52 men, aged from 18 to 88. We obtained detailed medical history that included age, lifestyle, positive family medical history, respiratory problems during the childhood, triggers of asthmatic attacks, information about the allergen that affects the course of disease, need for urgent interventions and number of hospitalizations because of exacerbations of disease during the previous year, comorbidities (hypertension, diabetes mellitus, GERD, cerebrovascular diseases) and smoking. We determined asthma phenotype for each patient. Patients were examined (physical status) and lung function test were performed to determine the grade of ventilation dysfunction, Ventolin-test was performed, FeNO and IgE were measured and BMI was calculated (body mass divided by the square of the body height). Control group consisted of 82 women and 71 men, aged 23 to 73 (comparable with the examined group according to age). After collecting subjects' consent and having the approval of Ethical Committee of Croatian Institute of Transfusion Medicine, we obtained 153 blood samples, taken from healthy and non-related blood donors, who did not have ventilatory lung disorders, not in their or their family medical history. BMI of subjects of control group was calculated using identical formula. All blood samples (8.5 mL of peripheral blood) of both group were drawn in syringe (Vacutainer® Plastic PPT) with anticoagulant polymer gel with dry K2EDTA (Ethylenediaminetetraacetic acid).

Collected data were analyzed using descriptive statistics methods. Kolmogorov-Smirnov test was used to analyse data distribution. Data with non-parametric distribution were analysed with Mann-Whitney U test and showed through medians with corresponding interquartile ranges. Statistical significance of BMI differences between non-allergic asthma, allergic asthma and control groups were analyzed by one-way analysis of

**Table 1.** Data on sex and age of examined group and the control group

	Group		P $\chi^2$ test
	Experimental - n=149	Control - n=153	
Males: n (%)	57 (38.3%)	71 (46.4%)	0.152
Females: n (%)	92 (61.7%)	82 (53.6%)	
Age (years): median (interquartile range)	60.0 (40.0-70.0)	43.0 (34.5-53.0)	<0.001

**Table 2.** Differences in the levels of body mass index between the experimental and control groups

Group		N	Min	Max	Percentile			P
					25.	Median	75.	
BMI (kg/m <sup>2</sup> )	Experimental	147	16.9	47.1	23.30	26.6	30.1	0.004
	Control	153	18.3	36.7	22.45	25.1	27.9	

**Table 3.** Differences in mean body mass index between genders

Gender		N	Mean	SD	Std. Error Mean	95% Confidence Interval for Mean		Min	Max	P
						Lower Bound	Upper Bound			
Males	Non-allergic asthma	68	27.89	5.16	0.63	26.64	29.14	16.90	47.10	0.085
	Allergic asthma	82	26.28	4.44	0.49	25.30	27.25	18.40	38.60	
	Control group	71	27.36	3.93	0.47	26.43	28.29	18.16	38.20	
Females	Non-allergic asthma	47	28.12	5.65	0.82	26.46	29.78	16.90	47.10	<0.001
	Allergic asthma	46	25.55	4.16	0.61	24.32	26.78	18.40	33.00	
	Control group	82	24.80	3.32	0.37	24.07	25.53	19.18	33.00	

variance - ANOVA. The results were interpreted at a significance level of  $P < 0.05$ . Statistical data processing was performed using IBM Statistical Package for the Social Sciences (SPSS) v. 25.

## RESULTS

In our study there were more women than men in both groups – in examined group (61.17% vs 38.3%) and control group (54.4% vs 45.6%) (Table 1).

The lowest BMI in examined group was 16.9 kg/m<sup>2</sup>, the highest was 47.1 kg/m<sup>2</sup> and median was 26.6 kg/m<sup>2</sup>. The lowest BMI in control group was 18.3 kg/m<sup>2</sup>, the highest was 36.7 kg/m<sup>2</sup> and median was 25.1 kg/m<sup>2</sup> (Table 2).

The comparison between median BMI values of these two groups showed that examined group of patients with asthma has significantly higher median BMI value in comparison with control group ( $P = 0.035$ ). When stratified according to gender, results showed that increased BMI was associated with asthma only in women ( $P = 0.002$ ), while this was not observed in men ( $P = 0.898$ ). Patients with BMI  $< 25$  kg/m<sup>2</sup> make up 63.5% of patients with allergic asthma phenotype and only 36.5% of patients with nonallergic asthma phenotype. Obese patients with BMI  $> 30$  kg/m<sup>2</sup> make up 43.2% of patients with allergic asthma phenotype and 56.8% of patients with nonallergic asthma phenotype. However, statistical analysis did not show significant correlation between BMI and non-allergic asthma phenotype ( $P = 0.085$ ). After stratification according to

sex there was a significant correlation ( $P < 0.001$ ) between BMI and non-allergic asthma in women. Women diagnosed with non-allergic asthma had mean BMI of 28.12 kg/m<sup>2</sup>, in comparison with women who had allergic asthma, whose mean BMI was 25.55 kg/m<sup>2</sup> (Table 3).

## DISCUSSION

Obesity is the most common comorbidity of asthma and is associated with higher risk of exacerbation, symptoms aggravation and poor asthma control (Baffi et al. 2015). Asthma in obese patients could be considered a unique phenotype of this disease, since in these patient disease is more difficult and shows poor response to conventional therapy. Etiological factors that could participate in asthma pathogenesis in obese patients are mechanical ones (impaired lung ventilation), altered inflammatory and immunological response that are characteristic for obesity (Dixon et al. 2010).

In obese patients presence of fat tissue around thorax, abdomen and in abdominal cavity burdens thoracic wall and reduces functional residual capacity (FRC) and this leads to a higher risk for expiration flow limitation and airway closure. Expiratory reserve volume (ERV) reductions can lead to abnormalities in ventilation distribution, with airways closure in dependent zones and ventilation/perfusion mismatch. There is a view that obesity alone has a negative effect on lung function, even in the absence of specific respiratory disease, but may also exaggerate the effects

of existing airway disease, such as asthma (Salome et al. 2010). In obese patients with asthma there is an absence of bronchodilative and bronchoprotective effect of deep breath. In these patients after deep breath, there is an increase in airway resistance, whereas this phenomenon is not noticed in asthmatics with similar severity of asthma that are not obese (Holguin et al. 2010). Because of the previously mentioned, it could be concluded that high BMI has a negative impact on respiratory function in patients with asthma. Sutherland et al. investigated this relationship by conducting study that included 361 non-smoking, non-asthmatic participants from a population-based birth cohort. Changes in adiposity between ages 32 and 38 years were inversely associated with changes in lung volumes. These associations were generally stronger in men than women, but an association between increasing adiposity and lower airway function (forced expiratory volume in 1 s/forced vital capacity) was only found in women (Sutherland et al. 2016).

Obesity is a systemic disease and, in fact, a chronic systemic inflammatory disorder (Monteiro & Azevedo 2010) and that way it could have an effect on chronic inflammation that takes place in airways in asthma. However, contrary to the expected, despite high levels of inflammatory markers in serum and fat tissue in obese patients with asthma, airway inflammation in these patients was reduced. Because of this, there is a suggestion that obesity, as an etiological factor in asthma, probably does not affect asthma through inflammation enhancement in airways, but directly via leptin and other adipokines, whose levels are increased in obese patient (Sideleva et al. 2012). This could explain discrepancy between finding of reduced inflammation in airways of obese patients with asthma and simultaneously more severe grade of asthma, in comparison to the patients with asthma that are not obese. Besides, it is known that obese patients are more likely to have non-allergic asthma phenotype and some studies point that this phenotype is direct consequence of obesity (Al-Alwan et al. 2014). Ex vivo studies have shown that alveolar macrophages of overweight and obese patients with asthma are somehow different than macrophages of other patients with asthma, especially because they are very sensitive to leptin. This macrophage phenotype, in the light of high levels of leptin in obese patients, could contribute to pathogenesis of airway disease that are connected to obesity (Lugogo et al. 2012). Despite very justified suspicion that obesity is a risk factor for development of asthma, there is a great heterogeneity in published studies about its role in incidence of asthma, especially when it comes to male population. One meta-analysis included seven studies with altogether 333,102 participants and authors concluded that overweight and obesity are associated with a dose-dependent increase in the odd of incident asthma in men and women, suggesting asthma incidence could be reduced by interven-

tions targeting overweight and obesity (Beuther & Sutherland 2007). This meta-analysis is accordant with our findings, since the study we conducted showed that patients with asthma have statistically higher median BMI in comparison with control group. Results of our study are in concordance with studies that suggested BMI as a risk factor for development of asthma. One of these studies found that, compared with individuals who had a BMI <25 kg/m<sup>2</sup>, the hazard of adult-onset asthma progressively increased with increasing BMI, from a 12% increase among persons with a BMI of 25.0-29.9 kg/m<sup>2</sup> to an almost 250% increase among persons with a BMI ≥50 kg/m<sup>2</sup> (Koebnick et al. 2016). However, over time studies showed that the connection between asthma and obesity is affected by factors such as race, age and sex. This connection is stronger in women (in comparison with man) and weaker in black race (in comparison to non-hispanic white race) (Koebnick et al. 2016). We found similar results in our study, since after stratification according to sex, it was obvious that the connection was significant for women only, with P=0.002. Since this connection was not statistically significant in men (P=0.898) the main reason why the results showed significant correlation between BMI and asthma in the whole group of patients with asthma was because of this strong correlation in women. One prospective cohort study tested whether asthma diagnosis is associated with weight gain and physical activity in 4,547 18 to 30-yr-old African American and white men and women, followed prospectively for up to 10 years. Based on results, study concluded that gain in BMI predisposes to new asthma diagnosis in female young adults, but decreased physical activity does not explain the association of weight gain with asthma. This correlation was not observed in males (Beckett et al. 2001). Furthermore, obesity is associated with non-allergic asthma phenotype, but our results showed that BMI significantly correlates with non-allergic asthma only in women (P<0.001), while this cannot be observed in men (P=0.085). This gender differences in frequency of non-allergic asthma were investigated in a study that included 9091 men and women randomly selected from the general population and followed up after 8-10 years as a part of the European Community Respiratory Health Survey. Results were following: asthma was 20% more frequent in women than in men over the age of 35 years and the follow-up of subjects without asthma at baseline showed a higher incidence of asthma in women than in men (HR 1.94; 95% CI 1.40 to 2.68), which was not explained by differences in smoking, obesity or lung function. More than 60% of women and 30% of men with new-onset asthma were non-atopic. The incidence of non-allergic asthma was higher in women than in men throughout all the reproductive years (HR 3.51; 95% CI 2.21 to 5.58), whereas no gender difference was observed for the incidence of allergic asthma (Leynaert et al. 2012). The results of

this large population- based cohort study confirmed what our results discovered – female sex is an independent risk factor for non-allergic asthma. Gender differences in asthma incidence, prevalence and severity have been reported worldwide. A role for sex hormones is frequently suggested, especially because of 'gender-switch' around puberty, when asthma becomes more prevalent and severe in women, in comparison with men (Zein & Erzurum 2015). One of these theories suggests that estrogen and other sex hormones may play an important role through modulation of Th2 cytokine production. Furthermore, estrogen may influence on airway responsiveness, immune or inflammatory processes. Some answers could be found in comparable increase in overall muscles in males, in comparison with females and different fat distribution – gynoid vs androgenic (Alipour et al. 2015). In the previously mentioned cohort-study the incidence of asthma remained significantly higher in women than in men after adjustment for smoking, occupational exposure and lung function. The fact that the gender differences in asthma prevalence were consistent during the two survey periods and across countries with different levels of exposure to environmental factors suggests an effect of genetic and biological factors rather than socio-cultural and environmental factors (Leyneart et al. 2012). One of these factors could easily be an increased BMI. Women could be more susceptible to an effect that BMI has on asthma. Apart from sex hormones, some regulatory molecules secreted by the adipose tissues (such as leptin) could explain gender differences in non-allergic asthma (Melgert et al. 2007).

We have to emphasise that it is rather important to define the correlation between obesity and asthma – not only because obesity is associated with higher incidence of asthma, but also because it affects severity of the disease and response to the therapy. Studies showed that compared with non-overweight subjects, obese subjects with asthma were more likely to report continuous symptoms, miss more workday, use short acting beta, use inhaled corticosteroids and use any controller medication according to GINA guidelines. In addition, obese respondents were less likely to be in asthma remission, and were more likely to have severe persistent asthma (Taylor et al. 2008). Studies also found connection between obesity and asthma control and results have shown that increased body mass and absence of atopy worsen control of asthma (Çelebi Sözen et al. 2016). This could mean that losing weight could improve the course of the disease. However, this needs to be investigated furtherly. Different factors are associated with asthma control for different subpopulations of patients. Adherence to standard therapy did not improve obese (BMI > 30) patients' ability to achieve asthma control. Female patients were less likely to obtain well-controlled asthma per unit increase of BMI (Scott et al. 2016). Some studies have found that, besides low FEV1

levels in stability and the need for permanent treatment with oral corticosteroids, one of the predictors of asthma exacerbations is high BMI (Papaioannou et al. 2016). After all, this connection between obesity and asthma is of great importance because of the high frequency of asthma phenotype that is related to obesity, since this phenotype shows growing incidence, which is not surprising if one is familiar with high prevalence of obesity on a global scale (Çelebi Sözen et al. 2016).

## CONCLUSION

Results of our study are similar to the results of other studies from different areas of the world and they mosaicly contribute to the knowledge about connection between asthma and obesity. Since this connection is affected by factors such as age, race and surrounding, it is important to conduct further studies about this topic in order to determine for which populations BMI represents the biggest risk factor. That way we could decrease prevalence of asthma and achieve better control of disease, since it is one of the most common and widespread chronic diseases in the world.

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### **Contribution of individual authors:**

Marina Lampalo & Marjeta Majer had substantial contribution to the conception and design of the study.

Marina Lampalo, Marjeta Majer, Nikola Ferara, Milan Milošević, Marija Barišić Kutija & Irena Jukić had substantial contribution to the literature searches and analyses.

Marina Lampalo, Marjeta Majer & Milan Milošević had substantial contribution to the statistical analyses and interpretation of data.

Marina Lampalo, Marjeta Majer, Nikola Ferara, Milan Milošević, Marija Barišić Kutija & Irena Jukić drafted the manuscript and revised it critically for important intellectual content, and approved the final version to be published.

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