

Increased body mass index predicts severity of asthma symptoms but not objective asthma traits in a large sample of asthmatics

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Abstract

Aim: To examine the relationship between body mass index (BMI) and different indicators of asthma severity in a large community-based sample of Danish adolescents and adults.

Methods: A total of 1,186 subjects, 14-44 years of age, who in a screening questionnaire had reported a history of airway symptoms suggestive of asthma and/or allergy, or who were taking any medication for these conditions were clinically examined. All participants were interviewed about respiratory symptoms and furthermore height and weight, skin test reactivity, lung function, and airway responsiveness were measured.

Results: A total of 516 individuals had asthma. The mean BMI was 24.9 kg/m² (SD=5.1). Asthma severity measured by GINA score increased with

increasing BMI ($p=0.009$). The result remained significant after adjusting for age, sex, medication use for asthma and smoking ($p=0.010$). Severity of individual asthma symptoms; cough ($p=0.002$) and chest tightness ($p=0.023$) was also significantly related to BMI, whereas severity of wheezing and shortness of breath was not. Airway obstruction was more pronounced in subjects with increased BMI ($p<0.001$) but the effect disappeared after adjustment for covariates ($p=0.233$). Lung function, airway responsiveness, and atopy were not significantly related to BMI as were use of medication for asthma and adherence to treatment.

Conclusions: In adults, increased body mass index predicts severity of asthma symptoms but not objective asthma traits.



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Increased body mass index predicts severity of asthma symptoms but not objective asthma traits in a large sample of asthmatics

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Abstract

Aim: To examine the relationship between body mass index (BMI) and different indicators of asthma severity in a large community-based sample of Danish adolescents and adults.

Methods: A total of 1,186 subjects, 14-44 years of age, who in a screening questionnaire had reported a history of airway symptoms suggestive of asthma and/or allergy, or who were taking any medication for these conditions were clinically examined. All participants were interviewed about respiratory symptoms and furthermore height and weight, skin test reactivity, lung function, and airway responsiveness were measured.

Results: A total of 516 individuals had asthma. The mean BMI was 24.9 kg/m² (SD=5.1). Asthma severity measured by GINA score increased with increasing BMI (p=0.009). The result remained significant after adjusting for age, sex, medication use for asthma and smoking (p=0.010). Severity of individual asthma symptoms; cough (p=0.002) and chest tightness (p=0.023) was also significantly

related to BMI, whereas severity of wheezing and shortness of breath was not. Airway obstruction was more pronounced in subjects with increased BMI ($p<0.001$) but the effect disappeared after adjustment for covariates ($p=0.233$). Lung function, airway responsiveness, and atopy were not significantly related to BMI as were use of medication for asthma and adherence to treatment.

Conclusions: In adults, increased body mass index predicts severity of asthma symptoms but not objective asthma traits.

INTRODUCTION

It has been suggested that asthma in obese individuals differs from the classical atopic asthma phenotype (1). In particular, obese subjects referred for severe asthma often seem to have poorly controlled asthma (2) and to show a reduced response to standard asthma medication (3). The association of obesity with asthma outcomes, however, remains poorly understood.

Epidemiological studies have shown a significant association between obesity and poor asthma control. In a multivariate analysis Schatz et al. (4) found that a higher body mass index (BMI) was an independent predictor of poor asthma control using The Asthma Control Questionnaire (ACQ). Using the same questionnaire Demoly et al. (5) found that 30% of those with poor asthma control vs. 22.7% with well controlled asthma had a BMI ≥ 30 kg/m². Taylor et al. (6) examined the association between BMI and asthma severity in the National Asthma Survey: a total of 3095 patients who had self-reported asthma symptoms in the past five years were included. Asthma severity measures included respiratory symptoms, healthcare utilisation, medication use, missed work days, and the Global Initiative for Asthma (GINA) severity classification. They found, even after adjusting for potential confounders that obese subjects with asthma compared to non-obese subjects with asthma were more likely to report continuous symptoms (OR=1.66), miss more work days (OR=1.35), use short acting beta-2 agonists (OR=1.36), use inhaled corticosteroids (OR=1.34) and use any controller medication (OR=1.37). Also, obese patients were less likely to be in asthma remission (OR=0.56) and were more likely to have severe persistent asthma (GINA 4) (OR=1.42). Mosen and colleagues examined the association between obesity and asthma control and severity using the Asthma Therapy Assessment Questionnaire (ATAQ), self-reported number of asthma related hospitalizations in the previous year, and the Juniper mini-Asthma Quality of Life Questionnaire (AQLQ) (7). After adjusting for demographics, smoking status, oral corticosteroid use, gastroesophageal reflux disease, and inhaled corticosteroids, BMI >30 was significantly associated with poor asthma control (OR=2.7), poor asthma-specific quality of life (OR=2.8), and history of asthma related hospitalization (OR=4.6). These findings have been supported by other studies (2, 6).

While most studies have confirmed a significant association between obesity and worsened asthma control, quality of life, and/or severity, some studies have not. Notably, Sastre et al (8) did not find a significant association between BMI and asthma control using the ACQ and Asthma Control Test (ACT) as well as physician assessment to evaluate asthma control in 607 Spanish adults. Although they did not find a significant association between BMI and asthma control, the percentage of patients with poor control was slightly greater among those with low BMI and obesity. Furthermore, Lavoie and co-workers (2) found a significant association between BMI and asthma control but they failed to show the same association with asthma severity when controlling for age and sex. Their study was based on 382 adult asthma patients who underwent demographic and medical history interviews on the day of their clinical visit. Asthma severity was classified according the GINA guidelines, ACQ, AQLQ, and spirometry.

Most of the studies reporting an association between obesity and asthma control have not included objective traits such as airway hyperresponsiveness (AHR), FEV1 and FVC, an exception being Farah et al. who examined asthma control after supervised treatment with inhaled corticosteroids and found that spirometry, airway inflammation, and AHR improved to similar extents in all BMI groups. There was still an association with ACQ scores and BMI after treatment suggesting an effect of obesity on asthma independently of airway inflammation (9).

Further studies including both objective tests as well as asthma symptoms are needed to delineate the mechanisms behind the obesity-asthma phenotype. Consequently, the aim of this study was to examine the relationship between BMI and different indicators of asthma severity using a wide range of objective tests as well as symptoms in an earlier well-described population of adolescents and adults with asthma (10).

METHODS

Subjects

The study source-population comprised 10,877 subjects from urban Copenhagen, Denmark, 14-44 years of age, randomly selected from the Danish civil registration list (11). All subjects received a short questionnaire adopted from American College of Allergy, Asthma and Immunology (ACAAI) (12) and a total of 5,849 (54%) questionnaires were returned. Among these, a total of 1,186 subjects reported at least one symptom suggesting asthma and/or allergy, or were treated for these conditions, and indicated in the return-letter that they agreed to take part in a clinical examination. The examination included an interview, and lung function, airway responsiveness, and skin test reactivity were measured. The Scientific Ethics Committee approved the study, and informed consent was obtained from all participating subjects and/or their parents.

Clinical interview

All participants were interviewed by a respiratory specialist about respiratory and allergic symptoms (in the preceding 4 weeks and at any time in the past), and about smoking habits. Height and weight were measured and BMI was calculated as $((\text{weight [kg]})/(\text{height [m]}^2))$. A respiratory specialist diagnosed and graded the severity of asthma on a scale from 1-4 (intermittent (1 point), mild (2 points), moderate (3 points), and severe persistent (4 points)) according to the GINA guidelines (13). A scale of 0-4 points was used to grade the individual asthma symptoms wheezing, shortness of breath, chest tightness, and cough according to symptomatic levels: no symptoms (0 points), intermittent symptoms (1 point), mild (2 points), moderate (3 points), and severe persistent symptoms (4 points) according to the GINA classification (13). Use of inhaler medication for asthma was recorded and self-reported adherence was noted.

Skin prick tests

Skin prick tests (SPTs) were performed using standard dilutions of 10 common aeroallergens recommended for testing in Denmark. The allergens used were birch, grass, mugwort, horse, dog, cat, house dust mite (HDM) (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), and mould (*Alternaria iridis* and *Cladosporium herbarium*) with positive and negative references being histamine, 10 mg/mL, in 50% glycerol and glycerol, 50% respectively. The concentrations of allergens were 10 HEP (Soluprick SQ system; ALK Abelló, Denmark). Reactions were read after 15 minutes. A positive result (atopy) was defined as a positive reaction to at least one of the allergens, and a reaction was considered positive if the mean wheal diameter was at least 3 mm. The participants were requested to discontinue medications that contained antihistamines at least 3 days before skin testing.

Spirometry and bronchial responsiveness tests

Pre-bronchodilator spirometry was performed using a dry wedge spirometer and the percentage of predicted normal values of FEV1 and FVC was calculated (14). We performed spirometric measurements in triplicate and accepted measurements with only 5% variation. Airway responsiveness to inhaled methacholine was measured in accordance with the method of Yan et al. (15). Each aerosol was inhaled starting with saline and followed by increasing doses of methacholine until a cumulative dose of 7.8 μ mol had been reached. The test was terminated when the maximum concentration had been reached or when a 20% decline in FEV1 had occurred before the end of the dosing regimen. For all subjects experiencing at least a 20% decline in FEV1 the concentration causing a 20% fall in FEV1 (PD₂₀) was calculated. A positive test result; AHR was defined as a PD₂₀ below 3.9 μ mol. The response-dose-ratio (RDR) of methacholine sensitivity was calculated to obtain a continuous measure of airway responsiveness. The RDR value was log-transformed in the analyses.

Statistical analysis

Data were analyzed using the statistical package SPSS 16.0 (SPSS Inc., Chicago, IL). First, individuals with asthma were grouped according to their BMI, into categories: <25 , 25-29, 30-34, and ≥ 35 kg/m². Differences between groups for descriptive variables were assessed by the chi-square test and the Kruskal-Wallis test for categorical data and by the ANOVA-test for continuous data.

Second, ordinal regression analysis was performed with GINA score as ordinal variable (categories: intermittent, mild, moderate, and severe persistent asthma) and with BMI (continuous variable), sex, age (in years), daily smoking, and use of inhaler medication for asthma as explanatory variables. Crude and adjusted p-values were reported. Also, ordinal regression was performed for the individual asthma symptoms (wheezing, shortness of breath, chest tightness and cough).

Third, to determine the relationship between objective asthma severity indicators (logRDR, FEV1 (% pred), FVC (% pred) and FEV1/FVC (%)) linear regression analysis was performed with each of the objective asthma severity indicators as dependent variable, respectively, and with BMI as explanatory variable in univariate analyses, and hereafter also including age, sex, medication use and smoking as covariates in adjusted multivariable analyses.

RESULTS

Patient characteristics

Of the 1,186 examined individuals 516 had asthma based on the symptoms reported to the respiratory specialist at the clinical interview (Table 1). The mean age of these was 29.1 years and 60.9% were women. The mean BMI for the sample was 24.9 kg/m² (SD=5.1). A total of 316 asthma patients (61.5%) had a normal BMI (<25 kg/m²); 125 (24.3%) were overweight (BMI 25-29 kg/m²); and 73 (14.2%) were obese (BMI ≥ 30 kg/m²). There was a high prevalence of rhinitis (64.7%), AHR (56.9%), and atopy (61.1%).

Symptom severity according to BMI

Correlations (Spearman's rho) between the different asthma symptoms and overall GINA score are shown in Table 2. Severity of cough was most strongly associated with overall GINA score. GINA score increased with higher category of BMI ($p=0.004$) (Table 3). Severity of individual asthma symptoms; cough ($p=0.003$) and chest tightness ($p=0.007$) also increased significantly by BMI category, whereas severity of wheezing ($p=0.540$) and shortness of breath ($p=0.071$) did not. The use of medication for asthma and adherence to treatment was not significantly related to BMI. Patients with a higher BMI were more likely to take rhinitis medication ($p=0.038$).

Ordinal regression analysis showed that BMI was a statistically significant predictor of overall GINA severity score ($p=0.009$); i.e. increasing BMI was associated with higher GINA score, also after adjustment for age, sex, medication use and smoking ($p=0.010$) (Table 4). Of the individual asthma symptoms, chest tightness ($p=0.023$) and cough ($p=0.002$) were also statistically significantly associated with BMI after adjusted for age, sex, medication use and smoking, whereas wheezing and shortness of breath were not.

Objective traits

The FEV1/FVC ratio was statistically significantly different across BMI categories ($p=0.030$), however when regressing BMI against FEV1/FVC ratio the significant relationship observed in univariate analysis ($p<0.001$) disappeared when adjusting for sex, age, smoking and medication use ($p=0.233$). BMI level was not associated with mean FEV1% predicted or FVC% predicted. Also, AHR, log RDR and atopy were not significantly related to BMI.

Sensitivity analyses

There was no differential relationship between overall GINA score and BMI in men and women ($p=0.900$), in atopic and non-atopic asthmatics ($p=0.640$), or in asthmatics who were, respectively, adherent and non-adherent to asthma medication ($p=0.882$). Furthermore, including also the objective traits; i.e. airway responsiveness, FEV1/FVC ratio and positive skin prick test in the ordinal regression analysis did not change the significant association between BMI and overall GINA score (p -value for association after also adjusting for these traits= 0.005). Adding instead an interaction term between BMI and AHR showed a positive coefficient between these variables in the prediction of asthma severity, however a formal test of interaction was statistically non-significant ($p=0.060$).

DISCUSSION

Summary of main findings

This study found that asthma severity measured by the GINA score significantly increased with higher BMI. Severity of individual asthma symptoms; cough and chest tightness, was also significantly related to BMI, whereas lung function and AHR was not. These results indicate that obesity is a determinant of asthma severity independently of airway inflammation, lung function, and AHR.

Comparison with previous reports

Our findings regarding obesity and asthma severity are in line with earlier published studies. In keeping with Mosen et al (7) and Taylor et al (6) we found that asthma severity measured by GINA score significantly increased with higher BMI. We found no differences in pulmonary function and AHR in obese compared with non-obese asthmatics as did Farrah et al. (9). Salome et al. (16) also did not find

significant differences in objective traits, i.e. no differences in methacholine responsiveness in obese and non-obese subjects. However, they did find that, with bronchoconstriction, obese subjects develop increased elastic load, which could lead to greater perception of dyspnea, indicating that asthma-like symptoms might be induced in obese subjects in the absence of any effects of obesity on AHR. Previous reports have suggested a more pronounced association between increased BMI and asthma in women compared to men, suggesting sex specific differences in the association between asthma and obesity (17). As BMI does not differentiate between lean body mass and fat mass women have a higher proportion of body fat than men for a given BMI value (18). In our study, however, the relationship between BMI and asthma severity was uniform across sexes, indicating that sex did not modify the BMI-asthma severity relationship.

Systemic inflammation

Obesity is characterized by chronic low grade systemic inflammation. Particularly, serum leptin levels are markedly increased in obesity (18, 19). Kattan et al. (18) found that markers of systemic inflammation generally increased with increasing BMI or percentage body fat, however, these markers did not correlate with asthma morbidity nor was there a correlation of adiposity and serum leptin with exhaled nitric oxide. This supports the possibility that adipokines might be related to asthma through a mechanism unrelated to inflammation. Taylor et al. (6) speculated as to how much weight must be gained to increase asthma severity. Given that the median BMI of our sample is lower than other studies failing to show a significant relationship between BMI and asthma severity (2) our results may indicate an effect of low-grade inflammation present even in mild overweight.

Strengths and limitations

Our findings are strengthened by the size of the study population. Furthermore, we sampled asthmatics from a large community-based population of adolescents and adults and therefore these results are more likely to be generalizable to the general population. However, demographic information and information on asthma symptoms was not available for non-participants, which is a limitation of the study. Still, the drop-out from the study was likely non-differential meaning that the overall association between BMI and asthma severity can be expected to be the same among responders and non-responders. In that sense the study is externally valid, although one could speculate that more individuals with asthma answered the questionnaire, thus affecting only prevalence. Nevertheless, no data were available on patients who did not agree to participate, so potential differences between them and the study group are impossible to ascertain.

Neither systemic nor specific airway inflammatory markers were measured in the current study, so we can only speculate as to the potential contribution of systemic or airway inflammation to asthma symptoms. Also we did not assess hormonal variables which may be important mediators of BMI-asthma relationships in women (20). We were not able to demonstrate causality as we were not able to differentiate between patients who gained weight because of severe asthma and those who had severe asthma because of overweight. Also, the current assumption is that patients with higher BMI have more severe asthma. However, patients with high BMI are for this reason likely to be prescribed greater quantities of asthma medication as there is a perception that heavier individuals need higher doses. Since we found an independent association between BMI and symptom severity also *after* adjusting for medication use, smoking, age and sex, we are confident that the association between BMI and symptom severity is real. However, we cannot completely rule out confounding due to different use of medication since we did not include information on doses of medication. Also, the fraction of patients treated with asthma medication was low (~40%), which questions the ability of this measure to sufficiently adjust for possible confounding between BMI and asthma severity. However, the patients recruited to this study represent individuals from a deprived urban area (11), which would tend to lower the rate of treatment. Finally, we restricted our measures of excess body weight to BMI, however, other measures such as central adiposity may also be important. Particularly, BMI does not indicate whether excess body mass is

due to excess fat mass or how the body fat is distributed. This can influence the results since especially central obesity is suspected to be associated with insulin resistance and asthma (21). The same BMI may produce different spirometric profiles in men and women. In men, presumably truncal obesity may account for a greater variability in spirometric values than in women who may have less central adiposity. Having used waist circumference or waist in relation to height would therefore possibly have revealed different associations with asthma.

This study found only a positive association between BMI and subjective asthma symptom severity, but not between objective asthma traits and BMI. However, we did note a positive interaction between AHR and BMI on the severity of asthma, meaning that in asthma patients with concomitant AHR ('true asthmatics'), having a higher BMI were more strongly associated with subjective symptom severity in comparison to asthma patients without AHR. However, this relationship was not statistically significant and therefore only indicative of an association. Future, larger studies, might sought out whether the severity of sub-types of asthma may be differentially related to BMI.

Finally, the overall aim of studying these individuals with asthma was, as described in a previous publication (11), to examine possible under-treatment and under-awareness of asthma in the general population. Because of this, the examining respiratory specialists were unaware of the current study's hypothesis about BMI and asthma severity, which, if they were, could have made them more inclined to falsely score the study subjects' asthma severity differently had they wanted to reach a desired conclusion, namely that asthma symptoms are more severe in overweight and obese patients. Therefore, the conclusion in this sense can be expected to be unbiased and valid as if the physicians were blinded to the study subjects' BMI when interviewing them about their asthma severity.

Conclusion

This study found that asthma severity measured by GINA score significantly increased with higher BMI, whereas objective traits such as pulmonary function and AHR were not significantly related to BMI. Our results indicate that obesity is a determinant of asthma severity and control independently of airway inflammation, lung function, and AHR, and therefore support that obesity could lead to a more severe asthma phenotype. Further prospective clinical trials that examine this relationship are warranted.

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Table 1. Characteristics of 516 adolescent and adult patients with asthma.

Demographics

Sex (male)	204 (39.5)
Age	29.1 (9.6)
BMI	24.9 (5.1)
Daily smoking	168 (36.8)

Asthma Severity

GINA 1	210 (40.9)
GINA 2	80 (15.6)
GINA 3	116 (22.9)
GINA 4	107 (20.9)

Associated diseases

Rhinitis	334 (64.7)
Food allergy	70 (14.0)
Eczema	153 (30.6)

Medication

Asthma medication	199 (38.6)
Adherence	360 (30.2)
Rhinitis medication	164 (31.8)

Objective traits

Positive skin prick test	299 (61.1)
AHR	261 (56.9)
LogRDR	0.61 (0.65)
FEV1 (% pred)	90.2 (0.13)
FVC (% pred)	94.8 (0.14)
FEV1/FVC (%)	81.6 (0.09)

Age, BMI (body mass index), LogRDR (response-dose-ratio, methacholine), FEV1 (forced expiratory volume in 1s), FVC (forced vital capacity) and FEV1/FVC are mean values (standard deviations); all other variables are numbers (%). GINA, Global Initiative for Asthma severity score.

JUST ACCEPTED

Table 2. Correlations between severity scores of individual asthma symptoms and overall GINA score in 516 adolescent and adult patients with asthma.

Symptom	GINA score	Wheezing	Shortness of breath	Chest tightness
GINA score				
Wheezing	0.54			
Shortness of breath	0.55	0.42		
Chest tightness	0.49	0.41	0.47	
Cough	0.78	0.34	0.27	0.27

Rank (Spearman's rho) correlations.

P-value of all correlations is <0.001.

Table 3. Association between BMI and asthma severity indicators in 516 adolescent and adult patients with asthma.

Variable	BMI <25 N=316 (61.5)	BMI 25-29 N=125 (24.3)	BMI 30-34 N=48 (9.3)	BMI ≥35 N=25 (4.9)	P-
Demographics					
Sex (male)	40.2	45.6	27.1	28.0	0.091
Age (mean)	27.3 (9.3)	31.0 (9.5)	32.2 (8.8)	37.5 (7.8)	
<0.001 Daily smoking	36.0	43.5	32.6	22.7	0.214
Asthma severity					
GINA score 246	257	273	348	0.004	
Wheezing	251	254	267	281	0.540
Shortness of breath 250	243	292	269	0.071	
Chest tightness 243	264	263	315	0.007	
Cough	245	259	272	344	0.003
Associated diseases					
Rhinitis	61.1	70.4	66.7	80.0	0.100
Food allergy	12.3	16.5	18.2	12.5	0.556
Eczema	29.1	34.7	31.8	29.2	0.723
Medication					
Asthma medication	38.3	36.0	43.8	48.0	0.608
Adherence	29.1	34.4	27.1	24.0	0.595
Rhinitis medication	28.2	35.2	47.9	28.0	0.036
Objective traits					
Atopy 60.3	62.5	66.7	56.5	0.811	
AHR	61.5	50.4	47.8	55.0	0.116
LogRDR 0.62 (0.62)	0.53 (0.63)	0.73 (0.86)	0.65 (0.44)	0.373	
FEV1 (% pred) 90.7 (13.4)	89.5 (12.0)	91.4 (14.3)	84.2 (17.4)	0.106	
FVC (% pred)	95.1 (14.8)	95.6 (12.5)	93.8 (12.7)	88.8 (12.8)	0.156

FEV1/FVC (%)	82.3 (8.54)	80.4 (8.47)	81.7 (7.37)	78.0 (10.57)	0.030
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Age, asthma severity, FEV1 (forced expiratory volume in 1s), FVC (forced vital capacity), and FEV1/FVC are mean values (standard deviations); GINA, Global Initiative for Asthma severity score is mean rank; all other variables are percentages. AHR, airway hyperresponsiveness; RDR, response-dose-ratio (methacholine).

Table 4. Results of ordinal regression analysis with GINA severity score as dependent variable in 516 adolescent and adult patients with asthma.

Variable	Asthma severity (GINA)					
	Intermittent	Mild	Moderate	Severe		
	N=210	N=80	N=116	N=107	Crude p-value	Adjusted p-value
BMI	24.4 (4.6)	23.9 (4.8)	25.4 (5.3)	25.9 (6.0)	0.009	0.010
Sex (male)	97 (46.2)	35 (43.8)	44 (37.9)	26 (24.3)	<0.001	<0.001
Age	28.6 (9.5)	27.8 (9.6)	29.9 (9.8)	30.3 (9.4)	0.109	0.865
Daily smoking	52 (28.7)	18 (23.7)	46 (44.7)	50 (53.2)	<0.001	<0.001
Asthma medication	70 (33.3)	36 (45.0)	38 (32.8)	55 (51.4)	0.014	0.002

GINA (Global Initiative for Asthma) severity score is missing for three individuals.

Crude p-values are from univariate ordinal regression; adjusted p-values are multivariably adjusted from ordinal regression.

BMI (body mass index) and age are means (standard deviations); all other variables are numbers (%).