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Underdiagnosis and overdiagnosis of asthma in the morbidly obese☆

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KEYWORDS
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Summary
Background: The prevalence of obesity and asthma has increased concurrently over the last decades, suggesting a link between obesity and asthma. However, asthma might not be adequately diagnosed in this population.
Aim: To investigate whether not only overdiagnosis but also underdiagnosis of asthma is present in an obese population.
Methods: Morbidly obese subjects with or without physician-diagnosed asthma were recruited from a pre-operative screening programme for bariatric surgery, and were characterized using an extensive diagnostic algorithm.
Results: 473 subjects were screened; 220 met inclusion criteria, and 86 agreed to participate. Among the 32 participating subjects who had a physician diagnosis of asthma, reversible airway obstruction and/or bronchial hyperresponsiveness could only be detected in 19 patients (59%,

Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, mini Asthma Quality of Life Questionnaire; BHR, bronchial hyperresponsiveness; BMI, body mass index; DLCO, diffusion capacity; ERV, expiratory reserve volume; ESS, Epworth Sleepiness Scale; FEF_{25-75}, Forced expiratory flow at 25% point to the 75% point of Forced Vital Capacity; FeNO, Nitric Oxide; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; GERD, Gastro oesophageal reflux disease; ICS, inhaled corticosteroid; IOS, impulse oscillometry; OSAS, obstructive sleep apnea syndrome; RV, residual volume; SPT, skin prick test; TLC, total lung capacity.

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95% CI [0.41—0.76]), whereas in 13 patients (41%, 95% CI [0.24—0.50]) the diagnosis of asthma could not be confirmed (overdiagnosis). In contrast, in the remaining 54 patients, 17 (31%, 95% CI [0.20—0.46]) were newly diagnosed with asthma (underdiagnosis).
Conclusion: Besides overdiagnosis, there is also substantial underdiagnosis of asthma in the morbidly obese. Symptoms could be incorrectly ascribed to either obesity or asthma, and therefore also in the morbidly obese the diagnosis of asthma should also be based on pulmonary function testing.

Introduction

The prevalence and incidence of asthma has increased over the recent decades.[1,2] Besides an improved awareness of the disease, there are several other explanations for the increased asthma prevalence, such as air pollution, exposure to tobacco smoke, change in diet and obesity.[2] Recently, the incidence and prevalence of obesity have increased concurrently with the incidence and prevalence of asthma, suggesting a possible link between obesity and asthma.[3,4]

International guidelines advise that asthma diagnosis should be based on both the presence of symptoms and objective measurements of variable airflow obstruction or bronchial hyperresponsiveness (BHR).[1] However, in daily practice spirometry or provocation tests are not always performed, and the diagnosis of asthma is mainly based on symptoms.[5] Since obese patients report more dyspnea and asthma-like symptoms than non-obese patients,[6,7] it might be that they unjustified get labeled as asthma (overdiagnosis) without performing adequate diagnostics. Inevitably, any misdiagnosis may lead to inappropriate treatment,[5] with increased risk of side-effects and increased costs.[8]

Many epidemiological studies concerning obesity and asthma have used physician-diagnosed asthma without confirmation by pulmonary function tests. This implies reasonable doubt as to the correctness of the diagnosis. Multiple studies report that asthma could be excluded after extensive testing in 30% of physician-diagnosed asthma,[9—11] even after stopping with asthma medication.[12] On the other hand, missing the diagnosis of asthma in this population is also an important issue. Impaired dyspnea perception is especially thought to play a role in severe asthma,[13,14] and poor perception of airflow obstruction may lead to under-treatment of asthma.[15,16] All the recent studies concerning overdiagnosis of asthma in the obese,[11,12,17] initially used selected subjects with asthma, and therefore did not take into account obese patients in which asthma was not detected. Therefore, the information about underdiagnosis of asthma in the obese is incomplete.

The hypothesis of the present study was that underdiagnosis of asthma is also present in the morbidly obese. We therefore used an extensive diagnostic algorithm to investigate whether in addition to overdiagnosis also underdiagnosis of asthma is present in a morbidly obese cohort, which was recruited from a pre-operative screening program for bariatric surgery.

Methods

Study population

The subjects included in this study were patients who underwent pre-operative screening before bariatric surgery in the Sint Franciscus Gasthuis in Rotterdam, the Netherlands from September 2009 to April 2011. Eligibility criteria for bariatric surgery were: age between 18 and 60 years old, body mass index (BMI) $\geq$ 35 kg/m^2. We excluded people who (a) were older than 50 years of age or; (b) had a history of smoking more than 10 cigarettes a day, or were currently smoking more than 10 cigarettes a day (with the aim to decrease the risk of including subjects with chronic obstructive pulmonary disease [COPD]); (c) were taking oral corticosteroid therapy; (d) had an asthma exacerbation four weeks before screening; (e) were unable to perform pulmonary function tests; or (f) had pulmonary disease other than asthma.

We aimed for 40 subjects with, and 40 subjects without asthma, as this study is a part of a longitudinal study. All subjects underwent baseline physical examinations including routine assessment of anthropometry, blood pressure and blood samples. Waist circumference was measured directly to the body surface midway between the lower rib margin and the ileac crest. Fat free mass and fat weight (in kg and % body weight) were measured using bioelectrical impedance analysis (Bodystat 1500, Bodystat Ltd, British Isles).[18]

All subjects gave written informed consent and the local ethics committee (Toetsingscommissie Wetenschappenlijk Onderzoek Rotterdam e.o.) approved the study protocol (Netherlands Trial Register 3204).

Pulmonary function tests

All subjects underwent lung function testing for the presence of reversible airflow obstruction as part of the screening protocol before bariatric surgery. Spirometry was performed with Vmax spirometer (Vmax SensorMedics Viasys, type Encore 20/22/229/62 Encore, Cardinal Health, USA) before and after 400 μg of inhaled salbutamol, according to the American Thoracic Society/European Respiratory Society guidelines.[19] All values obtained were related to height, age and gender and expressed as percentage of their predicted value (reference ERS 1993[20]). The pulmonary function results are prebronchodilator values unless otherwise specified.

All subjects who met the inclusion criteria were invited for a second visit for further lung function evaluation. Again, if applicable, subjects were asked not to use long-acting β-agonists for 48 h, short-acting β-agonists for 8 h and antihistamines or antileukotriene medication 72 h before lung function testing. Subjects who were using inhaled corticosteroids (ICS), were asked to voluntarily discontinue this. Daily symptom diary and daily peak flow rates were used to optimally screen asthma control. Subjects were permitted to use short-acting bronchodilators as rescue medication. After six weeks they returned for their second visit, during which exhaled Nitric Oxide (FeNO) (Niox mino Aerocrine, Sweden),[21] impulse oscillometry (IOS) (Masterscreen IOS system, Erich Jaeger Co., Würzburg, Germany), diffusion capacity (intrabreath method, corrected for hemoglobin and alveolar volume)[22] and methacholine provocation testing (five breath dosimeter method)[23,24] were performed. Bronchial responsiveness to methacholine was expressed as the provocative dose of methacholine inducing a 20% fall in FEV_1 (PD_{20}). A $PD_{20} < 1.8$ mg was considered as a positive provocation test. If the methacholine provocation test was negative, a second provocation test was performed six weeks later. Subjects who refused to stop the ICS, or subjects who had exacerbations of asthma symptoms during the 12 weeks of discontinuing their medication, underwent provocation testing while using ICS (Fig. 2a, supplementary files).

Definition of asthma

Asthma was defined according to GINA guidelines[1] as both the presence of symptoms and either an increase of ≥12% and 200 ml in FEV_1 after salbutamol, or a positive provocation test. Physician diagnosis of asthma was scored as a positive reaction to the following question "Did a medical doctor ever told you that you have asthma?". Patients with a physician diagnosis of asthma and fulfilling the criteria of asthma were defined as having a correct asthma diagnosis. Those without physician diagnosed asthma, but who fulfilled the criteria for asthma were defined as underdiagnosed. The subjects with physician-diagnosed asthma, but who not fulfilled the criteria of asthma after stopping inhaled corticosteroids for more than 6 weeks were defined as overdiagnosed. Patients without airway reversibility and a negative provocation test formed the control group (Fig. 2b, supplementary files).

Questionnaires

Asthma symptoms were assessed by the mini Asthma Quality of Life Questionnaire (AQLQ)[25] and the Asthma Control Questionnaire (ACQ)[26] to assess asthma complaints. The Epworth Sleepiness Scale[27] questionnaire was used to assess OSAS, and the GERD-Questionnaire for gastro-esophageal reflux disease (GERD).[28] The average of 7 days with an activity meter was used to determine the total number of steps taken a day, as a measure of activity.

Atopy

Atopic status was assessed with skin-prick tests (SPT) with a battery of common aeroallergens: house-dust mite; dog, cat, and horse dander; *Aspergillus fumigatus*; mugwort; and birch and grass pollen (Vivodiagnost; ALK Benelux BV, Groningen, The Netherlands). SPT cutaneous response was compared with a histamine-positive control and a saline solution—negative control. A positive result was defined as at least one response with a wheal diameter ≥3 mm after 15 min. Total IgE and specific plasma IgE were determined with a solid-phase two-step chemiluminescent immunoassay on the Immulite 2000 (Siemens, Los Angeles, CA). A positive inhalation screen was defined as at least one increased amount of specific IgE for fungus, house-dust mite, cat, dog, grass, birch or herbs.

Laboratory

Blood cell counts and 5-part leukocyte differentiation were determined automatically using LH750 analyzers (Beckman Coulter Miami, FL, USA). CRP was measured using LX 20 and DxC analyzers (Beckman Coulter, Miami, FL, USA). Vitamin D (was determined by RIA or chemiluminescence (LIA) on Liason analyzers (DiaSorin, Stillwater, MN, USA).

Statistical analyses

Underdiagnosis of asthma subjects were consecutively compared with correctly diagnosed asthma, overdiagnosis of asthma and controls. Unless indicated otherwise, all data are expressed as median (min—max) for scale variables or percentage for categorical variables. Unadjusted between groups comparisons were performed using Mann Withney *U* test, Chi square or Fisher exact test as appropriate. Cohen's Kappa coefficient was calculated as a measure of inter-rater agreement. IgE and FeNO were log transformed for statistical purposes. All analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, Illinois, USA). Results were evaluated at 95% confidence interval at a two-sided significance threshold of $p < 0.005$ (Bonferroni correction for multiple testing).

Results

Demographics

In total 473 patients were screened. 220 subjects met the inclusion criteria, and 86 subjects agreed to participate in the study. The most frequently reported reasons for refusing participation were "no time for additional appointments due to work" and "distance to hospital too far". The 136 subjects who declined consent did not significantly differ in demographic characteristics from the participants (BMI, weight, abdominal circumference, age or gender; data not shown) (Fig. 1).

From the 86 assessed patients, 32 patients had physician-diagnosed asthma. However, using the diagnostic algorithm, asthma could be excluded based on the absence of reversibility in FEV_1 or negative provocation test in 13 of these subjects (41%, 95% CI [0.24—0.50]) (overdiagnosis). In contrast, when analyzing the 54 patients without physician-diagnosed asthma, we found that 17 patients (31%, 95% CI [0.20—0.46]) had symptoms and a reversible airflow obstruction or airway hyperreactivity (underdiagnosis). This

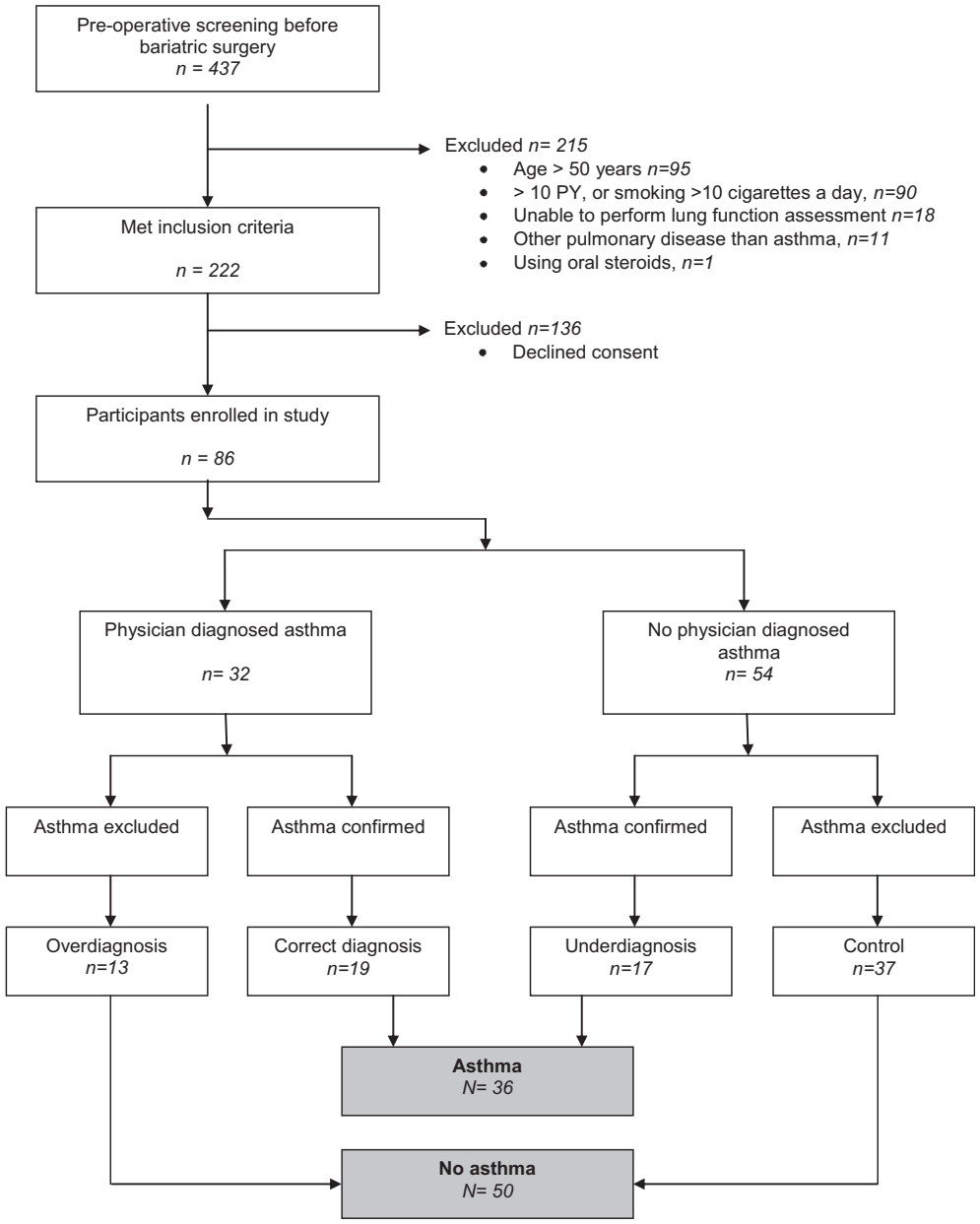

Figure 1 Selection of participants and study outcome.

way, among the 86 assessed subjects, 36 true asthma patients were diagnosed and 50 true controls. Cohen's Kappa coefficient between physician diagnosed asthma and our diagnosis of asthma was 0.251. Table 1 shows the baseline characteristics of the four groups. There were no significant differences in demographic characteristics between the groups, especially not in age, body mass index or weight. However, the subjects with underdiagnosis of asthma had a significantly larger abdominal circumference than the controls.

Symptoms and questionnaires

There were no differences in symptoms between the group with an underdiagnosis of asthma and the correctly diagnosed asthma group or the overdiagnosis asthma group (Table 2). The underdiagnosis group trended toward having more complaints of wheezing and coughing than the control group. There was also a trend that the asthma control questionnaire (ACQ) was better for the underdiagnosis group compared to the correctly diagnosed asthma group. The ACQ of the underdiagnosis group was comparable with the overdiagnosis group, and significantly better than the controls. The asthma quality of life questionnaire (AQLQ) was significant worse for the underdiagnosis group, compared with the controls, and comparable with the correctly diagnosis asthma and overdiagnosis asthma groups.

Medication use

Eleven of the patients with correctly diagnosed asthma were using ICS at the start of the study. Three refused to

Table 1 Demographics of study population.

	Underdiagnosis asthma $N = 17$	Correct asthma diagnosis $N = 19$	Overdiagnosis asthma $N = 13$	Control $N = 37$	p-Value[a]	p-Value[b]	p-Value[c]
Gender (%female)	77%	79%	92%	78%	1.000	0.355	1.000
Ethnicity (%non-Caucasian)	24%	11%	8%	14%	0.391	0.355	0.439
Age (years)	36 (19–49)	33 (24–48)	39 (19–50)	37 (18–50)	0.590	0.543	0.479
Weight (kg)	131 (111–240)	131 (101–191)	126 (99–157)	123 (94–199)	0.568	0.391	0.144
Body mass index (kg/m^2)	45.8 (38.7–74.8)	45.1 (38.4–63.8)	45.4 (37.4–53.8)	42.3 (35.6–60.0)	0.788	0.660	0.171
Abdominal circumference (cm)	137 (118–165)	129 (112–158)	130 (109–142)	125 (98–200)	0.206	0.013	0.005
Bio-impedance							
Fat free Mass	65.7 (47.8–100.5)	60.9 (50.3–94.8)	61.4 (50.9–72.6)	62.5 (47.2–83.9)	0.448	0.464	0.385
Fat weight (%)	50.9 (40.7–64.1)	52.8 (37.6–70.4)	51.6 (46.5–58.6)	50.2 (31.1–59.7)	0.499	0.568	0.578
Fat weight (kg)	68.5 (55.7–141.0)	69.1 (44.5–134.4)	64.0 (52.8–83.8)	59.2 (32.0–100.0)	0.934	0.754	0.057
Smoking status					0.865	0.932	0.236
%Never smoked	59%	53%	54%	78%			
%Stopped smoking	18%	16%	23%	14%			
%Current smoker	23%	31%	23%	8%			
Pack years	0 (0–9)	0 (0–10)	0 (0–10)	0 (0–9)	0.589	0.764	0.119

Data are presented as median (min–max).
[a] p Value for comparison between underdiagnosis asthma and correct asthma diagnosis.
[b] p Value for comparison between underdiagnosis asthma and overdiagnosis asthma.
[c] p Value for comparison between underdiagnosis asthma and control.

Table 2 Symptoms, questionnaires, and medication use.

	Underdiagnosis asthma $N = 17$	Correct asthma diagnosis $N = 19$	Overdiagnosis asthma $N = 13$	Control $N = 37$	p-Value[a]	p-Value[b]	p-Value[c]
Symptoms previous 12 months							
Dyspnea at rest	17.6%	47.4%	15.4%	5.4%	0.083	1.000	0.311
Dyspnea on exertion	94.1%	89.5%	84.6%	81.1%	1.000	0.565	0.411
Dyspnea at night	11.8%	42.1%	30.8%	5.4%	0.065	0.360	0.582
Wheezing	47.1%	84.2%	76.9%	18.9%	0.033	0.141	0.032
Coughing	52.9%	73.7%	76.9%	18.9%	0.299	0.259	0.011
Asthma control questionnaire[d]	0.9 (0.4–1.9)	1.4 (0.3–2.9)	0.8 (0–2.9)	0.3 (0–2.3)	0.021	0.563	<0.001
Asthma quality of life questionnaire (total)[e]	6.1 (5.2–6.8)	5.3 (3.7–7.0)	5.5 (3.7–6.6)	6.7 (4.9–7.0)	0.016	0.069	0.002
AQLQ symptoms	5.8 (4.6–6.6)	4.6 (3.6–7.0)	5.5 (3.4–6.8)	6.6 (3.8–7.0)	0.045	0.202	<0.001
AQLQ activities	5.8 (3.5–6.8)	5.3 (1.8–7.0)	5.4 (3.0–7.0)	7.0 (3.3–7.0)	0.641	0.505	0.001
AQLQ emotions	7.0 (5.7–7.0)	6.3 (4.3–7.0)	6.7 (5.0–7.0)	7.0 (6.3–7.0)	0.018	0.172	0.018
AQLQ environment	6.7 (4.0–7.0)	4.7 (2.0–7.0)	4.5 (3.0–7.0)	6.7 (3.0–7.0)	0.002	0.006	0.444
Medication use at inclusion study							
Short acting bronchodilator	0%	74%	77%	0%	<0.001	<0.001	1.000
Long acting bronchodilator	0%	11%	8%	0%	0487	0.433	1.000
Antileukotrienes	0%	0%	8%	0%	1.000	0.433	1.000
B_2 sympaticomimetica/ICS	0%	32%	23%	0%	0.020	0.070	1.000
Inhaled corticosteroids	0%	32%	23%	0%	0.020	0.070	1.000
Antihistamines	12%	32%	15%	11%	0.236	1.000	1.000
Nasal corticosteroids	0%	26%	15%	8%	0.047	0.179	0.544

Data are presented as median (min–max)
AQLQ = mini asthma quality of life questionnaire; ICS = inhaled corticosteroid.
[a] p Value for comparison between underdiagnosis asthma and correct asthma diagnosis.
[b] p Value for comparison between underdiagnosis asthma and overdiagnosis asthma.
[c] p Value for comparison between underdiagnosis asthma and control.
[d] Scores of the asthma control questionnaire range from 0 to 6, with lower scores indicating better asthma control.
[e] Scores of the AQLQ range from 1 to 7, with higher scores indicating better asthma-specific quality of life.

stop the ICS. Of the eight subjects who withheld their ICS, two had an increase of asthma symptoms and resumed their ICS. Also, three asthmatics without ICS before the start of the study had an increase in asthma symptoms, and started with ICS. In the overdiagnosed subjects, three were using ICS at the start of the study, and all agreed to withhold their ICS, without any change in symptoms.

Lung function parameters

A methacholine provocation test was not performed in two of the underdiagnosed subjects, because of low FEV_1 ($n = 1$) and extreme obesity (BMI 71, $n = 1$), and once in the correct diagnosis asthma group because of poor lung function technique. All three, however, had reversible airway obstruction (delta $FEV_1 \geq 12\%$). 18 correctly diagnosed asthmatics had a positive provocation test, of which 8 also had reversible airway obstruction. 11 of the underdiagnosed subjects had a positive provocation test, of which only one also had reversible airway obstruction. The diagnosis asthma was only based on reversibility, with a negative provocation test in 4 underdiagnosed asthmatics.

There was no difference in lung volumes, FeNO or diffusion capacity between the investigated groups. Among the parameters of the IOS there was a trend that R_5 and F_{res} were higher in the underdiagnosed group compared to the control group (Table 3).

Blood parameters

With regard to the laboratory parameters (Table 3), there was no difference between the investigated groups.

Allergy, activity and comorbidity

There was no difference in allergy, reflected in either a positive inhalation screen or a positive SPT, or rhinitis between the investigated groups (Table 3).

To assess the activity of the subjects, a step-counter was used, which showed no significant differences between the investigated groups. There were also no differences in comorbidities, such as obstructive sleep apnea syndrome (Epworth Sleepiness Scale) or reflux (GERD-questionnaire) (both Table 3), or the presence of the metabolic syndrome.

Discussion

We found that after discontinuation of inhaled corticosteroids and extensive lung function and provocation tests, misdiagnosis of asthma was present in our morbidly obese cohort. In addition to confirming previous reports on overdiagnosis of asthma, importantly we also found that a substantial proportion of morbidly obese asthma patients were underdiagnosed. This indicates that in the morbidly obese, the diagnosis of asthma cannot be made on asthma-like symptoms alone, and lung function testing is an essential part of the diagnosis of asthma, as confirmed with a low Cohen's kappa coefficient for physicians and our diagnosis of asthma.

This is, to our knowledge, the first study investigating both overdiagnosis and underdiagnosis of asthma in an obese cohort. Furthermore, we have used an extensive diagnostic algorithm to confirm or exclude asthma. In addition, we have also looked at co-morbidities such as reflux and OSAS, which are abundant in the obese and are known to influence asthma. Moreover, also cofactors such as immobility and allergy were taken into account.

We confirm previous reports showing that overdiagnosis of asthma is present in the morbidly obese,[11,12,17] although Aaron found that overdiagnosis of asthma was overall no more likely to occur among obese individuals than among non-obese individuals. However, in studies so far concerning overdiagnosis of asthma, assessment of underdiagnosis was not part of these studies. We also found underdiagnosis of asthma in our cohort of morbidly obese subjects, a previously overlooked problem.

In the present study symptoms turned out to be unreliable for an adequate diagnosis of asthma. Subjects with an overdiagnosis of asthma reported asthma-like symptoms, which explain the overdiagnosis. Interestingly, patients who were underdiagnosed for asthma also had symptoms. The reason why they did not receive a previous diagnosis of asthma is not clear, but may be explained by two factors. First, this discrepancy might be due to self-misperception; the patients themselves did not relate their symptoms to respiratory disease but rather to obesity and did not contact a physician for these complaints. A second possibility could be that they did contact a physician for dyspnea, but these discomforts were attributed to obesity by the physician (physician misperception). Self-misperception of respiratory symptoms is probably the most relevant factor,[29] and might be partly explained by worse perception of dyspnea. Unfortunately, no data were available on previous visits to a physician because of respiratory symptoms.

Interestingly, especially R_5 — a marker of both central and distal airways obstruction — was particularly high in the underdiagnosed subjects. The underdiagnosed subjects, in particular, had a large abdominal circumference in our study. Therefore, central obesity may lead to obstruction of the peripheral airways, which may be more related to poor perception of dyspnea than proximal airway obstruction. This suggests that it is not the amount of fat, but the location of the fat, which influences asthma perceptions, which is also supported by a study from Lessard.[30] Similar to the symptoms, the inappropriate use of inhaled medication was high in the overdiagnosis asthma group. This may result in serious side effects and, moreover, contributes to the economic burden of asthma. The symptoms could not be explained by a restriction or a low diffusion capacity. There was no difference in smoking status, furthermore as result of the exclusion criteria, the median number of pack years was nihil, so smoking is unlikely to be a contribution factor. There was no difference in co-morbidities such as allergy, GERD, OSAS or activity between asthmatics and controls, and therefore these factors do not seem to play a role in asthma in the obese.

There were few differences between the underdiagnosed and the overdiagnosed subjects. However, many of the overdiagnosed subjects had rhinitis, which can cause dyspnea perception.[31] Furthermore, the overdiagnosed scored low for the AQLQ, especially in the environment

Table 3 Pulmonary function, laboratory and co morbidity.

	Underdiagnosis asthma $N = 17$	Correct asthma diagnosis $N = 19$	Overdiagnosis asthma $N = 13$	Control $N = 37$	p-Value[c]	p-Value[d]	p-Value[e]
Spirometry							
FEV_1, pre (% predicted)	85 (62–99)	88 (66–119)	99 (84–125)	96 (73–120)	0.260	<0.001	0.001
FEV_1, post (% predicted)	92 (72–118)	96 (74–118)	102 (90–129)	99 (75–124)	0.738	0.025	0.002
FVC, pre (% predicted)	93 (74–112)	100 (75–128)	108 (91–133)	102 (77–144)	0.154	0.004	0.019
FEV_1/FVC, pre (% predicted)	77 (63–92)	75 (66–86)	81 (74–87)	82 (66–93)	0.465	0.039	0.010
RV, post (% predicted)[a]	71 (39–117)	69 (39–126)	76 (48–118)	72 (33–96)	0.595	0.596	0.764
TLC, post (% predicted)[a]	94 (83–100)	100 (80–106)	97 (85–114)	94 (75–114)	0.104	0.180	0.920
FRC, post (% predicted)[a]	61 (40–87)	56 (47–95)	64 (51–88)	63 (41–85)	0.682	0.910	0.737
RV/TLC, post (% predicted)[a]	19 (12–35)	24 (10–41)	24 (14–41)	25 (12–86)	0.289	0.176	0.146
FEF_{25-75}, pre (% predicted)	75 (33–119)	69 (38–111)	97 (64–118)	96 (49–135)	0.751	0.009	0.003
Reversibility FEV_1	10 (−6–20)	9 (−1–20)	4 (−7–9)	4 (−2–11)	1.000	0.009	0.001
FeNO (bbp)[b]	16 (5–89)	14 (8–45)	11 (3–18)	16 (5–47)	0.968	0.087	0.783
Diffusion capacity (% predicted)	97 (83–133)	95 (69–130)	97 (69–134)	95 (75–132)	0.333	0.769	0.132
IOS							
R_5 (kPa/sec)	0.69 (0.44–1.06)	0.76 (0.42–1.39)	0.59 (0.44–0.85)	0.56 (0.17–0.97)	0.738	0.139	0.008
R_{20} (kPa/sec)	0.45 (0.30–0.76)	0.40 (0.27–1.03)	0.71 (0.26–0.68)	0.42 (0.18–0.67)	0.317	0.139	0.143
X_5 (kPa/sec)	−0.24 (−0.42–-0.16)	−0.29 (−0.87–-0.11)	−0.24 (−0.40–-0.16)	−0.19 (−0.43–-0.08)	0.615	0.999	0.049
F_{res} (Hz)	22.0 (16.0–24.9)	22.8 (10.5–30.3)	18.7 (14.0–23.2)	16.3 (8.4–28.7)	0.738	0.139	0.008
Peripheral blood count							
Leukocytes (10^9/L)	8.5 (5–12)	8.9 (6–13)	7.1 (6–12)	7.4 (5–11)	0.477	0.288	0.084
Neutrophils (%)	65 (50–72)	61 (45–72)	59 (47–70)	59 (46–69)	0.555	0.166	0.099
Lymphocytes (%)	27 (15–38)	28 (17–45)	33 (20–43)	31 (23–47)	0.835	0.112	0.095
Monocytes (%)	6.61 (4.66–8.50)	6.74 (5.55–12.76)	6.45 (4.00–9.00)	6.41 (4.00–13.43)	0.795	0.945	0.840
Eosinophils (%)	2.49 (0.54–9.09)	2.35 (0.47–8.00)	2.00 (1.00–4.00)	2.04 (0.40–7.85)	0.887	0.835	0.437
Basophils (%)	0.38 (0.00–1.00)	0.52 (0.00–1.19)	0.13 (0.00–1.51)	0.50 (0.00–2.45)	0.339	0.560	0.202
IgE (kU/L)[b]	105 (7–3419)	202 (11–1838)	66.4 (10–273)	71.6 (1.5–587)	0.520	0.072	0.430
CRP (mg/L)	7(1–28)	8 (3–25)	7 (5–21)	9 (1–24)	1.000	0.724	0.858
Vitamin D (nmol/L)	27 (11–78)	37 (12–89)	39 (18–62)	41 (10–83)	0.438	0.232	0.205
Rhinitis	41%	84%	62%	30%	0.014	0.462	0.407
Positive inhalation screen	63%	73%	39%	38%	0.478	0.272	0.098
Skin prick test (% ≥1 positive wheal)	47%	74%	36%	32%	0.160	0.701	0.334
Epworth sleepiness scale	2 (0–7)	3 (0–8)	2 (0–9)	2 (0–15)	0.351	0.770	0.786
GERD-questionnaire	6 (4–10)	7 (4–12)	6 (2–10)	6.5 (3–14)	0.074	0.146	0.022
Metabolic syndrome	53%	61%	75%	40%	0.738	0.273	0.335
Steps a day	4360 (1309–10,840)	5642 (2156–12,176)	6197 (4456–10,083)	4730 (2061–11,705)	0.415	0.096	0.829

Data are presented as median (min–max).
FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; RV = residual volume; TLC = total lung capacity; FRC = functional residual capacity; ERV = expiratory reserve volume; FEF_{25-75} = Forced expiratory flow at 25% point to the 75% point of Forced Vital Capacity; FeNO = exhaled nitric oxide; Diffision capacity = kCO.

[a] Because of weight limitations (<150 kg) of bodybox different numbers; underdiagnosis asthma $n = 11$, correct asthma diagnosis $n = 10$, overdiagnosis asthma $n = 10$, control $n = 26$.

[b] Log transformed for statistical purposes.

[c] p Value for comparison between underdiagnosis asthma and correct asthma diagnosis.

[d] p Value for comparison between underdiagnosis asthma and overdiagnosis asthma.

[e] p Value for comparison between underdiagnosis asthma and control.

domain, a domain where symptoms related to external stimuli are scored. However, by definition, all overdiagnosed had a negative provocation test. This reduced QOL in morbidly obese overdiagnosed asthma subjects was also found by Scott et al.[11] These data suggest that the discrepancy between pulmonary function test and the AQLQ, might in part be explained by rhinitis.

There are several limitations to our study. Only 39% of potentially eligible subjects agreed to participate. So a volunteer bias could have influenced the study results. The large proportion of declines is most probably due to the fact that this study is a part of a longitudinal study. Another effect of this study being a part of another study, is the fact that we aimed for 40 subjects with and 40 subjects without asthma and that inclusion of the latter group went faster, so subjects were not enrolled in a consecutive order. So the prevalence of physician diagnosed asthma in our study cohort is biased, and therefore also the prevalence of under- or overdiagnosis of asthma is biased. Importantly, however, there were no differences in patient demographics between the subjects who declined consent and those who participated. Since a lean control group was not part of the study, it is not clear whether underdiagnosis is more prevalent among the obese compared to a lean cohort. The selection of subjects willing to undergo bariatric surgery could also have led to a selection bias. And finally, the small group of misdiagnosed subjects (either over- or underdiagnosis) could have given us power problems to find differences in subgroup analysis.

In summary, both overdiagnosis as well as underdiagnosis of asthma occurs in the morbidly obese. A diagnosis of asthma based on symptoms alone is unreliable in the morbidly obese, and pulmonary function testing is an essential part of the diagnosis of asthma in the morbidly obese. As a result of the most likely high prevalence, potential health risk and the high economic burden of misdiagnosis, characterization of these patients is important. Further research aiming at the effects of weight reduction on quality of life and symptoms, not only in asthmatics but also in the overdiagnosed can provide valuable further insights into this interesting problem.

Conflict of interest

GJB has received educational grants/research support for consultations and/or speaking at conferences from Novartis, GSK, AstraZeneca and MSD. All other authors state that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2013.05.007.

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