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Risk of Misdiagnosis, Health-Related Quality of Life, and BMI in Patients Who Are Overweight With Doctor-Diagnosed Asthma

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Background: Obesity and asthma both cause breathlessness, and there is a risk of misdiagnosis of asthma in patients who are obese. Impaired health-related quality of life (HRQoL) and increased BMI increase physician attendance rates, increasing this risk. We explored the possibility of misdiagnosis and the relationship between BMI, HRQoL, and other traditional measures of asthma severity in subjects who were obese with a doctor's diagnosis of asthma.

Methods: Data were obtained from subjects who were overweight with physician-diagnosed asthma screened as part of another study, including bronchial provocative concentration of methacholine to produce a 20% fall in FEV₁ (PC₂₀) or reversibility to bronchodilators, HRQoL measured using generic (Short Form-36 [SF-36]) and disease-specific (St. George Respiratory Questionnaire and Impact of Weight on Quality of Life-Lite) questionnaires. The fraction of exhaled nitric oxide (FENO), height, weight, and atopic status were also recorded.

Results: Of 91 subjects (mean BMI, 38 kg/m²; mean FEV₁%, 85.8%; mean FEV₁/FVC, 70.0%; mean FENO, 25.1 parts per billion taking a mean chlorofluorocarbon-beclomethasone-equivalent dose of 1,273.5 µg/d), 36.3% had no bronchial hyperresponsiveness (possible misclassification of asthma diagnosis.) The BMI and HRQoL were significantly related: The St. George Respiratory Questionnaire total ($r = 0.33$, $P < .001$), SF-36 physical health subtotal ($r = -0.42$, $P < .001$), SF-36 mental health subtotal ($r = -0.39$, $P < .001$), and Impact of Weight on Quality of Life-Lite total ($r = 0.51$, $P < .001$) showed no relationship to airways inflammation and bronchial reactivity. There was no significant difference in quality-of-life scores in subjects with or without bronchial hyperreactivity.

Conclusions: We found evidence of misdiagnosis of asthma in subjects who were obese. The BMI in subjects who were obese and had asthma negatively correlates with the HRQoL, which may relate to the diagnostic uncertainty and requires further exploration.

Trial registry: ISRCTN Register; No.: 54432221; URL: www.controlled-trials.com/isrctn

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Abbreviations: ATS = American Thoracic Society; FENO = fraction of exhaled nitric oxide; HRQoL = health-related quality of life; IQR = interquartile range; IWQoL-Lite = Impact of Weight on Quality of Life-Lite; PC₂₀ = provocative concentration of methacholine to produce a 20% fall in FEV₁; SF-36 = Short Form-36; SGRQ = St. George Respiratory Questionnaire

Asthma is characterized by variable airflow limitation together with bronchial hyperresponsiveness to stimuli, resulting in airway narrowing and symptoms of wheeze and breathlessness.^{1,2} The prevalence of physician-diagnosed asthma is increasing, in part because of a link between asthma and obesity.³ Several mechanisms lead to asthma-like symptoms in patients who are obese,^{4,5} including the mechanical effects of increased BMI on lung volumes, increased work of breathing, and increased release of adipokines

from adipose tissue, although whether these mechanisms are associated with objectively demonstrated bronchial hyperresponsiveness is less certain.⁶ As breathlessness is a common symptom of both asthma and obesity, there is a risk of diagnostic misclassification of asthma, a view supported by a Canadian study that found one-third of subjects with a prior physician diagnosis of asthma had no evidence of asthma as judged by symptoms, lung function, and bronchial challenge testing.⁷

Obesity, like asthma, affects health-related quality of life (HRQoL),^{8,9} and increased BMI has been related to increased general practitioner attendance rates.¹⁰ Since HRQoL and asthma control are related,¹¹ it is easy to see how health impairments arising from obesity could be attributed to asthma, further increasing the likelihood of a misdiagnosis.

We hypothesized that patients who are obese with physician-diagnosed asthma are at risk for misdiagnosis of asthma and would have a significantly impaired HRQoL. Also, BMI may correlate more strongly with HRQoL than traditional markers of asthma severity. To test this hypothesis, we used data from an interventional study investigating weight loss in patients with asthma who were obese (ISRCTN 54432221), in which we recruited subjects with a diagnosis of asthma receiving respiratory therapy with a BMI ≥ 30 . At the screening visit, we collected data about bronchial hyperresponsiveness and health status, both generic and disease-specific, to establish which aspects of their baseline condition related best to their health problems. Additionally, the relationship of exhaled nitric oxide (a marker of airways inflammation in asthma¹²) and bronchial responsiveness to HRQoL were secondary outcome measures.

MATERIALS AND METHODS

Patient Selection

Subjects were recruited from clinics at University Hospital Aintree or by poster advertisement, with a self-reported BMI ≥ 30 kg/m², aged 18 to 65 years, either nonsmokers or ex-smokers of > 2 years, and taking asthma medication. Individuals receiving long-term oral corticosteroid therapy, those with other significant comorbidities, or those reporting an exacerbation within the previous 2 weeks were excluded. Four subjects had a BMI < 30 kg/m². In these, the BMI was ≥ 28 kg/m² and inclusion did not significantly affect the outcome, so they were included in the intention to recruit analysis. The study was approved by the Sefton Local Ethics Committee Institutional Review Board (04/Q1508/51), and all subjects gave written informed consent.

Before their visit, subjects withheld medication as per American Thoracic Society (ATS) guidelines for challenge testing.¹³ Demographic data, including medication history and physical examination, were recorded. Weight and height were measured using calibrated scales and a stadiometer, respectively, and BMI (kg/m²) was calculated. Venous blood was drawn to exclude significant

anemia, hypothyroidism, hyperthyroidism, diabetes, or other biochemical abnormalities that might adversely affect health status.

Questionnaires

Participants completed the St. George Respiratory Questionnaire (SGRQ),¹⁴ Short Form-36 (SF-36),¹⁵ and Impact of Weight on Quality of Life-Lite (IWQoL-Lite)¹⁶ questionnaires. These questionnaires are validated to assess the effect of respiratory disease, generic factors, and weight, respectively, on quality of life.

Atopy

Atopic status was determined using skin prick testing with a battery of common aeroallergens. A positive result was defined as at least one response with a wheal diameter ≥ 3 mm or larger than a control response after 15 min.

Exhaled Markers of Inflammation

Participants abstained from caffeinated drinks and food for 12 h before testing. The fraction of exhaled nitric oxide (FENO), measured in parts per billion, was measured using a chemiluminescence analyzer (NIOX; Aerocrine) at a flow rate of 50 mL/s, as per European Respiratory Society and ATS guidelines.¹⁷

Bronchial Responsiveness

Methacholine inhalation testing was performed using the five-breath dosimeter method, as per ATS guidelines.¹³ Airways responsiveness to methacholine was expressed as the provocative concentration of methacholine to produce a 20% fall in FEV₁ (PC₂₀). Subjects unable to undergo methacholine testing due to an FEV₁ $\leq 50\%$ predicted underwent spirometry with bronchodilator response to nebulized salbutamol. Bronchial hyperresponsiveness was defined by a $\geq 20\%$ drop in FEV₁ with ≤ 8 mg/mL methacholine or an increase $\geq 15\%$ and 200 mL in FEV₁ from baseline following nebulized salbutamol.

Statistical Methods

This was an observational study with the sample size determined by the number of subjects recruited for an interventional trial powered for subjects who were obese and had asthma with bronchial hyperresponsiveness. Categorical variables are expressed as percentages of total subjects and compared using a χ^2 test. Continuous variables are expressed using mean $\pm$ SD and compared using the Student unpaired *t* test if normally distributed. Nonnormal distributions determined by Shapiro-Wilk testing are expressed using median and interquartile range (IQR). Correlations were performed between normally distributed variables using Pearson correlations two-tailed tests, and between nonnormally distributed variables using Spearman tests. PC₂₀ and FENO were log transformed to provide normal distributions before correlations were calculated using Pearson tests. A weak correlation was defined as $r = 0.2$ - 0.4 , a moderate correlation as $r = 0.4$ - 0.7 , and a strong correlation as $r = 0.7$ - 1.0 . The SPSS software, version 16 for Windows (SPSS Inc) was used for calculation.

Significance was determined if $P < .05$. Significance of comparisons of multiple variables was adjusted using the Bonferroni correction.

RESULTS

Subject Recruitment

In total, 397 subjects underwent telephone screening, as outlined in Figure 1. Of these, 91 subjects were retained in the analysis.

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Subject Characteristics: All Subjects

Data on the demographic characteristics, pulmonary function, and FENO of the study participants are summarized in Table 1. Subjects were obese with relatively well-preserved lung function. Five subjects were taking inhaled steroid medication but did not know their inhaled dose, while four were not using inhaled steroid. Short-acting β agonists were prescribed for all. Fifty-five subjects (60.4%) used long-acting β agonists. One subject refused skin-prick testing.

The dose of inhaled steroid (chlorofluorocarbon-beclomethasone-equivalent) weakly related to FEV₁ % predicted ($r = -0.29$, $P = .007$) and FEV₁/FVC ($r = -0.26$, $P = .017$), but not PC₂₀. There was no significant difference in PC₂₀ ($P = .630$), presence of bronchial hyperresponsiveness ($P = .673$), FEV₁ % predicted ($P = .055$), or FEV₁/FVC ($P = .179$) between those taking and those not taking long-acting β agonists. The BMI weakly correlated with the PC₂₀ ($r = 0.29$, $P = .033$) and FENO ($r = -0.32$, $P = .025$).

Questionnaires

SF-36 data were not available in one subject due to a completion error. Questionnaire scores for the whole group are shown in Table 2. The mean (SD)

Table 1—Demographics, Medical Characteristics, Pulmonary Function, and Bronchial Responsiveness to Methacholine and FENO for All Subjects

Variables	Data
Age, y	49.2 (9.6)
Female sex	60/91 (65.9)
Ex-smokers	32/91 (35.2)
Pack-year (ex-smokers)	17.2 (19.3)
BMI, kg/m ²	38 (7)
Weight, kg	105.6 (22.6)
Subjects with atopy	61/90 (67.8%)
Dose of inhaled steroids, μ g/d	1,273.5 (937.1)
FEV ₁ , % predicted	85.8 (19.8)
FVC, % predicted	103.1 (17.2)
FEV ₁ /FVC, %	70 (10.6)
PC ₂₀ , mg/mL	5.087 (6.71)
FENO, ppb	25.1 (21.5)

Numbers expressed as mean (SD) or No. cases/No. in group (%). FENO = fraction of exhaled nitric oxide; PC₂₀ = provocative concentration of methacholine to produce a 20% fall in FEV₁; ppb = parts per billion.

total scores were: SGRQ, 44.4 (17.0); SF-36 (mental health subtotal), 56.9 (21.2); SF-36 (physical health subtotal), 52.0 (22.9); and IWQoL-Lite, 39.1 (21.6), with good correlations between them ($P < .001$) (Fig. 2).

HRQoL, Pulmonary Function, Bronchial Responsiveness, BMI, and Airways Inflammation

The influence of pulmonary function, airways responsiveness, BMI, and airways inflammation on HRQoL are shown in Table 3.

Airways Inflammation and HRQoL

There were no significant correlations with FENO and SGRQ domains or SF-36 domains following Bonferroni correction. There were statistically significant weak correlations found with FENO and IWQoL-Lite physical functioning ($r = -0.30$, $P = .004$), public distress ($r = -0.28$, $P = .008$), and total ($r = -0.31$, $P = .003$) domains.

BMI and HRQoL

St. George Respiratory Questionnaire: The BMI correlated moderately with the Activity domain of the SGRQ ($r = 0.42$, $P < .001$) and weakly with the SGRQ total domain ($r = 0.33$, $P < .001$), but not symptoms.

Short Form-36: There were moderate negative correlations between the BMI, physical function ($r = -0.43$, $P < .001$), and physical health subtotals ($r = -0.42$, $P < .001$), and weak negative correlations with the body pain ($r = -0.34$, $P < .001$), general health ($r = -0.30$, $P = .005$), role emotional ($r = -0.30$, $P = .004$), mental health ($r = -0.22$, $P = .033$), and mental health subtotals ($r = -0.35$, $P < .001$). (Note

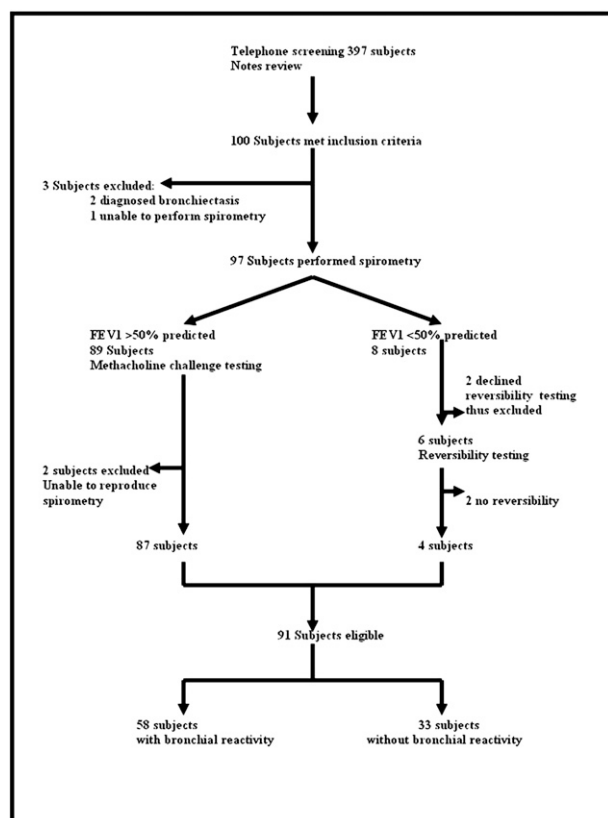


FIGURE 1. Consort diagram shows study organization.

Table 2—Questionnaire Scores for All Subjects for SGRQ, SF-36, and IWQoL-Lite

Domain	Score, Mean (SD)
SGRQ domain	
Symptoms	61.1 (18.4)
Activity	54.7 (22.2)
Impacts	33.2 (17.6)
Total	44.4 (17.0)
SF-36 domain	
Role, physical	53.3 (43.3)
Body pain	62.5 (25.8)
General health	50.0 (22.3)
Vitality	43.5 (23.3)
Social functioning	65.3 (26.2)
Role, emotional	61.1 (42.6)
Mental health	64.4 (19.3)
Mental health, total	56.9 (21.2)
Physical health, total	52.0 (22.9)
IWQoL-Lite domain	
Physical function	42.8 (25.5)
Self-esteem	50.6 (28.0)
Sexual life ^a	31.3 (56.2)
Public distress ^a	25.0 (30.0)
Work ^a	18.8 (37.5)
Total	39.1 (21.6)

IWQoL-Lite = Impact of Weight on Quality of Life-Lite; SF-36 = Short Form-36; SGRQ = St. George Respiratory Questionnaire.

^aDistribution nonnormal.

that a lower score indicates a worse HRQoL for SF-36).

Impact of Weight on Quality of Life-Lite: There were moderate correlations between the BMI, physical function ($r = 0.56$, $P < .001$), public distress ($r = 0.62$, $P < .001$), and total domains ($r = 0.51$, $P < .001$), with a weak correlation between the BMI and work domains ($r = 0.39$, $P < .001$).

FEV₁ % Predicted, FVC % Predicted, and HRQoL

There were no significant correlations between any measures of quality of life and FEV₁ % predicted or FVC % predicted.

Bronchial Hyperresponsiveness as an Explanatory Variable

Subjects with bronchial hyperresponsiveness ($n = 58$, 63.7%) were compared with those without ($n = 33$, 36.3%), and subject characteristics for each group are summarized in Table 4.

Those with bronchial hyperresponsiveness (median PC₂₀, 1.64 [IQR 3.48] mg/mL) were younger (47.6 [9.7] years vs 52.0 [9.0] years, $P < .05$), had lower FEV₁ % predicted (81.3% [21.3%] vs 93.7% [13.7%], $P < .05$), and lower FEV₁/FVC (67% [11.3%] vs 75% [6.3%], $P < .05$). There was no significant difference in FVC % predicted. The FENO (median [IQR]) was significantly greater (19.1 [22.8] ppb vs 15

[16.2] ppb, $P \leq .05$), and the percentage with atopy was greater in the bronchial hyperresponsive group (78.9% vs 48.5%, $P < .05$), as were ex-smokers (43.1% vs 21.2%, $P \leq .05$).

Between groups there was no significant difference in female sex, BMI, dose of inhaled steroids, or those taking β agonists. There were no significant differences in any domain or total scores for the SGRQ, SF-36 subtotals, or IWQoL-Lite (Table 5) between those with and without bronchial hyperresponsiveness. There were no significant correlations between PC₂₀ and any HRQoL domains.

DISCUSSION

In a group of subjects who were obese (mean BMI 38.0 kg/m²) with a prior diagnosis of asthma using inhaled medication, 36.3% did not demonstrate bronchial hyperresponsiveness. Although this does not exclude asthma, it has a high negative predictive value¹³ and suggests a misclassification of diagnosis supported by lower FENO,¹² higher FEV₁/FVC percentage, and less atopy in the unresponsive patients.

These patients had significant health impairment despite relatively well-preserved lung function, the disease and weight-specific quality of life being worse than in previous published healthy populations.¹⁸⁻²¹ There was good correlation between the total scores of all questionnaires, suggesting they were measuring similar outcomes. The variable that correlated strongest with the degree of health impairment was BMI rather than other traditional markers of asthma severity,¹ that is, airways responsiveness (PC₂₀), lung function (FEV₁ % predicted and FVC % predicted), or airways inflammation (FENO). There was no significant difference in HRQoL between those with and without bronchial hyperresponsiveness, again suggesting less influence than BMI.

Our study supports the results of Aaron et al,⁷ who showed that one-third of subjects with a prior physician diagnosis of asthma had no evidence of asthma as judged by symptoms, lung function, and bronchial challenge testing, and it also extends the observations from a more rigidly prespecified population, where it might be expected that the incidence of hyperresponsiveness in patients who are obese would be higher.²²

We have shown a consistent negative correlation of increasing BMI with HRQoL as measured by both generic and disease-specific instruments. This effect was much greater than any associations with the degree of airways inflammation as assessed by FENO, which might have been expected to track asthma severity.^{12,23} The presence of bronchial hyperresponsiveness itself was not a good discriminator of impaired health status, while medication use, specifically long-acting bronchodilators in addition to inhaled corticosteroids, was

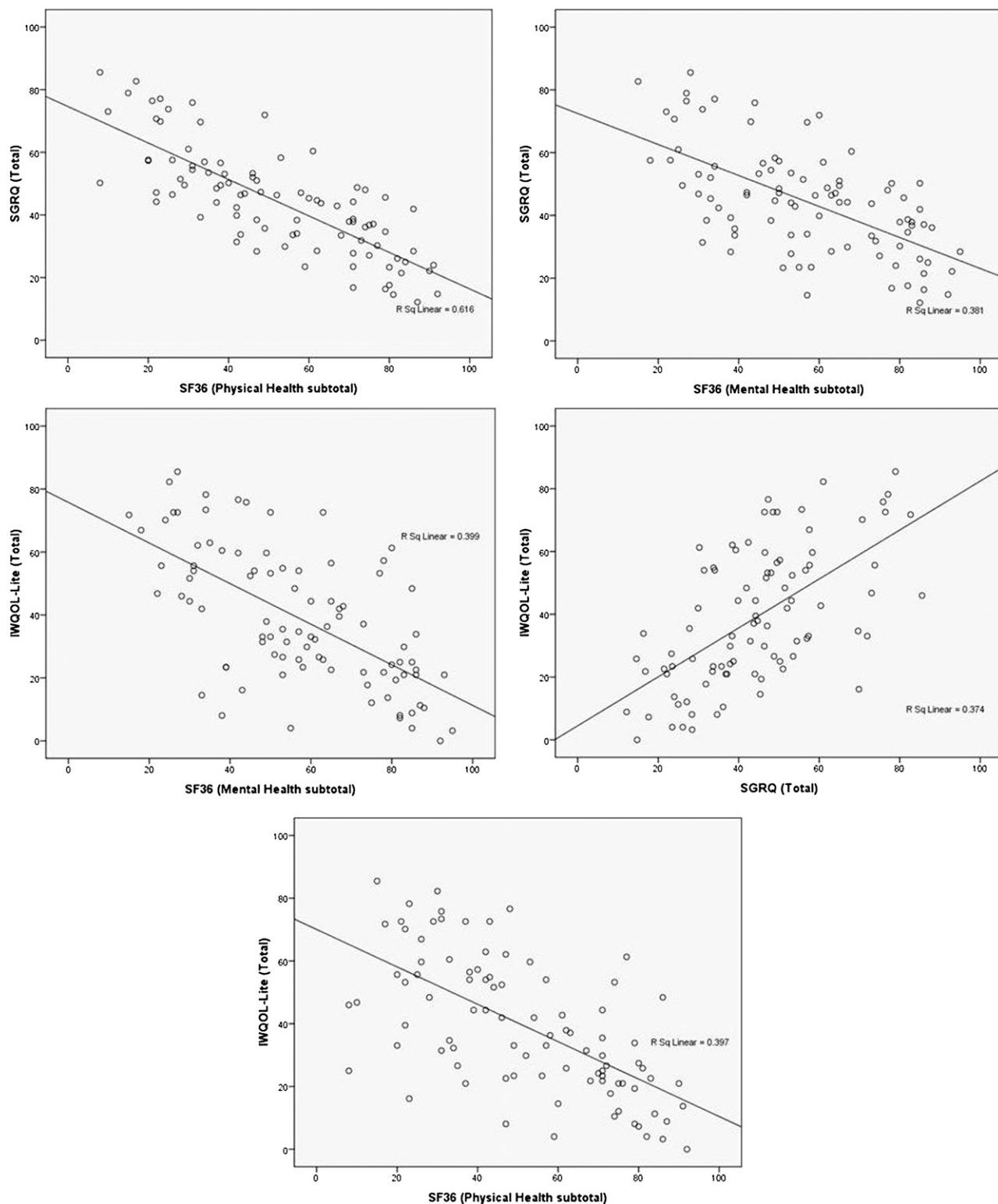


FIGURE 2. Scatterplots show the correlation of total scores for the SGRQ and IWQoL-Lite questionnaires and subtotals for mental health and physical health scores for the SF-36 questionnaire. IWQoL-Lite = Impact of Weight on Quality of Life-Lite; SF-36 = Short Form-36; SGRQ = St. George Respiratory Questionnaire.

neither different in the reactive and nonreactive groups nor predictive of differences in health status. As might be expected, reactive individuals tended to have marginally worse lung function, more obstruc-

tion, and more atopy, but none of these factors would be a reliable discriminator.

A reduced quality of life associated with obesity is related to increased attendance rates to primary

Table 3—Correlations (r Values Shown) Between Measures of Pulmonary Function, Airway Responsiveness, BMI, and Airway Inflammation

Domain	FEV ₁ , % predicted	FVC % predicted	Log10 PC ₂₀	BMI	Log10 FENO
SGRQ domain					
Symptoms	−0.14	−0.07	−0.10	0.09	0.20
Activity	−0.06	−0.24	−0.20	0.42 ^a	−0.15
Impacts	−0.17	−0.09	−0.12	0.24	−0.04
Total	−0.14	−0.16	−0.00	0.33 ^a	−0.05
SF-36 domain					
Physical function	0.01	0.23	−0.10	−0.43 ^a	0.07
Role, physical	−0.13	−0.00	−0.08	−0.26 ^a	0.28 ^a
Body pain	−0.26 ^a	0.27	−0.00	−0.34 ^a	0.19
General health	0.19	0.02	0.06	−0.29 ^a	0.21
Vitality	0.03	−0.05	−0.11	−0.29 ^a	0.06
Social functioning	0.01	−0.06	−0.01	−0.26 ^a	0.13
Role, emotional	0.01	0.01	0.04	−0.30 ^a	0.15
Mental health	−0.06	0.03	−0.07	−0.22 ^a	0.22 ^a
Physical health, subtotal	0.01	0.13	−0.11	−0.42 ^a	0.25 ^a
Mental health, subtotal	0.04	−0.02	−0.07	−0.35 ^a	0.19
IWQoL-Lite domain					
Physical function	−0.05	−0.14	0.23	0.56 ^a	−0.30 ^a
Self-esteem	−0.07	−0.15	−0.02	0.22 ^a	−0.14
Sexual life	−0.02	−0.14	−0.15	0.19 ^a	−0.19
Public distress	−0.12	0.00	−0.18	0.62 ^a	−0.28 ^a
Work	−0.02	−0.7	−0.01	0.39 ^a	−0.26
Total	−0.07	−0.14	0.11	0.51 ^a	−0.31 ^a

See Table 1 and Table 2 legends for expansion of the abbreviations.

^a*P* < .05 Bonferroni adjusted.

care,¹⁰ where patients have the opportunity to report respiratory symptoms^{24–26} and each visit can potentially lead to misclassification of asthma diagnosis. Increased physician interaction may explain some of the association of asthma with obesity, and care must be taken when interpreting studies of asthma and obesity based on self-reporting of asthma diagnosis.

It is likely that the negative correlation of body mass with HRQoL is due to a generic effect,⁹ as there were correlations across all questionnaires and we did not find a significant correlation between BMI and the symptoms domain of the SGRQ, which includes questions on the frequency of cough, sputum, breathlessness, wheeze, and exacerbations.

Table 4—Demographics, Medical Characteristics, Pulmonary Function, Bronchial Responsiveness to Methacholine, and FENO between Subjects With Bronchial Hyperresponsiveness, Defined as PC₂₀ Methacholine ≤ 8 mg/mL, and Those Without

Variables	Subjects With Bronchial Hyperresponsiveness (n = 58)	Subjects Without Bronchial Hyperresponsiveness (n = 33)	P Value
Age, y	47.7 (9.7)	52.0 (9.0)	< .05
Female sex	38/58 (65.5)	22/33 (66.7)	.911
Ex-smokers	25/58 (43.1)	7/33 (21.2)	< .05
Pack-year (ex-smokers)	17.4 (20.7)	16.1 (14.1)	.882
BMI, kg/m ²	37.6 (6.5)	38.5 (7.9)	.560
Weight, kg	105.4 (21.6)	106.0 (22.1)	.895
Subjects with atopy	45/57 (78.9)	16/33 (48.5)	< .05
Dose of inhaled steroids (chlorofluorocarbon-beclomethasone-equivalent), µg/d	1,370.9 (1033.5)	1,082.1 (688.0)	.186
FEV ₁ , % predicted	81.3 (21.3)	93.7 (13.7)	< .05
FVC, % predicted	102.2 (19)	104.8 (13.5)	.498
FEV ₁ /FVC, %	67 (11.3)	75.3 (6.3)	< .05
FENO, ^a ppb	19.1 (22.8)	15.0 (16.2)	< .05
Taking SABA, %	57/58 (98.3)	32/33 (97)	.683
Taking LABA, %	36/58 (62.1)	19/33 (57.6)	.673

Numbers expressed as mean (SD) or No. cases/No. in group (%). LABA = long-acting β agonist; SABA = short-acting β agonist. See Table 1 legend for expansion of other abbreviations.

^aDistribution nonnormal, therefore median/IQR quoted.

Table 5—Comparison of Questionnaire Scores for SGRQ, SF-36, and IWQoL-Lite Between Subjects With and Without Bronchial Hyperresponsiveness

Domain	Subjects With Bronchial Hyperresponsiveness (n = 58)	Subjects Without Bronchial Hyperresponsiveness (n = 33)	P Value
SGRQ domain			
Symptoms	63.0 (19.5)	57.7 (16.0)	.194
Activity	53.0 (21.4)	57.7 (23.7)	.332
Impacts	32.7 (15.8)	34.2 (26.6)	.710
Total	43.9 (15.7)	45.2 (19.3)	.721
SF-36 domain			
Physical functioning	51.5 (25.8)	57.2 (23.5)	.297
Role, physical	41.7 (42.7)	59.9 (42.7)	.054
Body pain	55.4 (28.2)	66.5 (23.6)	.060
General health	50.5 (24.1)	49.7 (21.3)	.870
Vitality	45.6 (23.1)	42.3 (23.5)	.521
Social functioning	60.5 (27.3)	68.1 (25.4)	.194
Role, emotional	56.5 (42.1)	63.8 (43.0)	.435
Mental health	63.2 (21.5)	65.0 (18.1)	.673
Physical health, subtotal	48.9 (24.0)	53.7 (22.2)	.349
Mental health, subtotal	55.2 (22.8)	57.8 (20.4)	.585
IWQoL-Lite domain			
Physical function	47.3 (27.9)	40.2 (23.8)	.223
Self-esteem	51.8 (29.5)	49.9 (27.3)	.773
Sexual life ^a	37.5 (65.6)	21.9 (50.0)	.080
Public distress ^a	25.0 (42.5)	22.5 (30.0)	.304
Work ^a	25.0 (46.9)	15.6 (37.5)	.123
Total	43.3 (23.8)	36.7 (20.1)	.182

Numbers expressed as mean (SD).

^aDistribution nonnormal, therefore median/IQR quoted. Mann Whitney *U* test as test of significance.

Our study has some limitations due to its observational nature and use of data from screening subjects for an interventional study. Subject numbers were not equally matched between groups, but groups were well matched for age, weight, and BMI. Although there were more ex-smokers in the bronchial hyperresponsiveness group, excluding ex-smokers from analysis did not alter outcomes. Our study entry criteria precluded the inclusion of patients with normal BMI, and so our data are confined to patients who were obese.

There is no universally accepted definition of asthma,¹ and patients can have asthma without demonstrable bronchial hyperresponsiveness. Many studies require the presence of bronchial responsiveness defined as a PC₂₀ calculated by linear interpolation of the log concentration to methacholine to cause a 20% fall in FEV₁ of < 8 mg/mL or reversibility of FEV₁ to inhaled bronchodilators of 15%.¹³ We, therefore, used these criteria toward making our diagnosis of asthma, which is supported by the evidence of less airway inflammation, less airway obstruction, and less atopy in those who did not show bronchial hyperresponsiveness.

It is possible that the use of inhaled steroids resulted in improvement in bronchial responsiveness.¹¹ However, there was no difference in the mean dose of inhaled steroid between those with and without increased bronchial responsiveness.

The screening protocol was not designed to measure static lung volumes, and therefore we are unable to show a relationship between HRQoL and functional residual capacity or expiratory reserve volume, which are reduced in obesity^{27,28} and possibly linked to bronchial hyperresponsiveness.²² We did however measure FVC, which can give an idea of lung volume, and there was no difference in FVC between those with and without bronchial hyperresponsiveness and no correlation between FVC and PC₂₀ or HRQoL.

The SGRQ is not specific for asthma but is validated as a tool for asthma research,²⁹ with a similar ability to discriminate among groups of patients based on asthma severity and control compared with the asthma quality-of-life questionnaire.³⁰ Obesity increases the risk of other comorbidities, which may influence HRQoL.³¹ We excluded these through screening.

Previous studies of the impact of asthma on HRQoL exist,³² and the effect is multifactorial, including disease severity, pulmonary function, symptoms, and other measures, although little is known about the impact of weight on this complex relationship.⁸ There are similar relationships between the effect of BMI on HRQoL,⁹ and further work is required to explore these complex relationships.

We found a significant number of patients with a potential misclassification of a diagnosis of asthma in a population that is obese. The strongest correlations with either generic or disease-specific HRQoL were

found with BMI. This has some clinical implications. Much of modern asthma treatment is focused on symptom reduction, either by increasing the intensity of maintenance treatment (Gaining Optimal Asthma Control [GOAL]³³) or adjusting the daily treatment regimen (Single Inhaler for Maintenance and Reliever Therapy [SMART]³⁴). Applying such approaches to patients who remain as symptomatic as our patients, who were nonreactive and obese, might be harmful. The reactive and nonreactive groups reported similar degrees of symptom intensity and used similar amounts of asthma treatment. Future studies should consider whether therapy can be withdrawn effectively in these patients who are obese and receiving more therapy. Certainly a more robust initial diagnostic approach might save time and money over the long term by identifying patients whose asthma corresponds to more conventional diagnostic criteria. These data emphasize the complex problems of identifying respiratory disease accurately in subjects who are obese. Future work is needed to study the impact of weight loss in this patient group and its impact on HRQoL.

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Author contributions: Dr Scott is the guarantor and takes responsibility for the integrity of the work.

Dr Scott: collected and analyzed the data, undertook the statistical analysis, and wrote the initial and final drafts of the manuscript.

Ms Currie: helped to collect the data and reviewed the manuscript.

Dr Albert: helped to collect the data and reviewed the manuscript.

Dr Calverley: helped to conceive of the study and assisted with writing the manuscript and the revision.

Dr Wilding: conceived of the study and assisted with writing the manuscript and the revision.

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REFERENCES

1. British Thoracic Society Standards of Care Committee. BTS statement on criteria for specialist referral, admission, discharge and follow-up for adults with respiratory disease. *Thorax*. 2008;63(suppl 1):i1-i16.

2. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;31(1):143-178.
3. 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(2):282-288.
4. Shore SA. Obesity and asthma: cause for concern. *Curr Opin Pharmacol*. 2006;6(3):230-236.
5. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. *Am J Respir Crit Care Med*. 2006;174(2):112-119.
6. Schachter LM, Salome CM, Peat JK, Woolcock AJ. Obesity is a risk for asthma and wheeze but not airway hyperresponsiveness. *Thorax*. 2001;56(1):4-8.
7. Aaron SD, Vandemheen KL, Boulet LP, et al; Canadian Respiratory Clinical Research Consortium. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ*. 2008;179(11):1121-1131.
8. Schmier JK, Chan KS, Leidy NK. The impact of asthma on health-related quality of life. *J Asthma*. 1998;35(7):585-597.
9. Kolotkin RL, Meter K, Williams GR. Quality of life and obesity. *Obes Rev*. 2001;2(4):219-229.
10. van Steenkiste B, Knevel MF, van den Akker M, Metsemakers JF. Increased attendance rate: BMI matters, lifestyles don't. Results from the Dutch SMILE study. *Fam Pract*. 2010;27(6):632-637.
11. Juniper EF, Kline PA, Vanzielegheem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis*. 1990;142(4):832-836.
12. Kharitonov SA, Yates D, Robbins RA, Logan-Sinclair R, Shinebourne EA, Barnes PJ. Increased nitric oxide in exhaled air of asthmatic patients. *Lancet*. 1994;343(8890):133-135.
13. Popa V. ATS guidelines for methacholine and exercise challenge testing. *Am J Respir Crit Care Med*. 2001;163(1):292-293.
14. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis*. 1992;145(6):1321-1327.
15. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.
16. Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. *Obes Res*. 2001;9(2):102-111.
17. American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. 2005;171(8):912-930.
18. Ferrer M, Villasante C, Alonso J, et al. Interpretation of quality of life scores from the St George's Respiratory Questionnaire. *Eur Respir J*. 2002;19(3):405-413.
19. Ware JE Jr, Kosinski M. *SF-36 Physical and Mental Health Summary Scales: A Manual For Users of Version 1*. 2nd ed. Lincoln, RI: QualityMetric Incorporated; 2001.
20. Ware JE Jr, Snow KM, Gandek B. *SF-36 Health Survey Manual and Interpretation Guide*. Lincoln, RI: QualityMetric Incorporated; 2005.
21. Crosby RD, Kolotkin RL, Williams GR. An integrated method to determine meaningful changes in health-related quality of life. *J Clin Epidemiol*. 2004;57(11):1153-1160.
22. Ding DJ, Martin JG, Macklem PT. Effects of lung volume on maximal methacholine-induced bronchoconstriction in normal humans. *J Appl Physiol*. 1987;62(3):1324-1330.

23. Delgado-Corcoran C, Kissoon N, Murphy SP, Duckworth LJ. Exhaled nitric oxide reflects asthma severity and asthma control. *Pediatr Crit Care Med* 2004;5(1):48-52.
24. Babb TG, Ranasinghe KG, Comeau LA, Semon TL, Schwartz B. Dyspnea on exertion in obese women: Association with an increased oxygen cost of breathing. *Am J Respir Crit Care Med*. 2008;178(2):116-123.
25. Ofir D, Laveneziana P, Webb KA, O'Donnell DE. Ventilatory and perceptual responses to cycle exercise in obese women. *J Appl Physiol*. 2007;102(6):2217-2226.
26. Deesomchok A, Fisher T, Webb KA, et al. Effects of obesity on perceptual and mechanical responses to bronchoconstriction in asthma. *Am J Respir Crit Care Med*. 2010;181(2):125-133.
27. Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest*. 2006;130(3):827-833.
28. King GG, Brown NJ, Diba C, et al. The effects of body weight on airway calibre. *Eur Respir J*. 2005;25(5):896-901.
29. Apfelbacher CJ, Hankins M, Stenner P, Frew AJ, Smith HE. Measuring asthma-specific quality of life: structured review. *Allergy*. 2011;66(4):439-457.
30. Sanjuás C, Alonso J, Prieto L, Ferrer M, Broquetas JM, Antó JM. Health-related quality of life in asthma: a comparison between the St George's Respiratory Questionnaire and the Asthma Quality of Life Questionnaire. *Qual Life Res*. 2002;11(8):729-738.
31. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA*. 1999;282(16):1523-1529.
32. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med*. 2006;100(4):648-657.
33. Bateman ED, Boushey HA, Bousquet J, et al; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med*. 2004;170(8):836-844.
34. Rabe KF, Pizzichini E, Ställberg B, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. *Chest*. 2006;129(2):246-256.

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