ORIGINAL ARTICLE

Relation of bronchial responsiveness to body mass index in the ECRHS

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Background: There is substantial evidence for an association between symptoms of asthma and overweight or obesity. However, a study that reported no association between bronchial responsiveness (BHR) and body mass index (BMI) suggested that the relation of symptoms to obesity was due to increased diagnosis of asthma. The relation of BHR to BMI was therefore investigated in a large multicentre study.
Methods: Data were obtained for 11 277 participants in stage II of the European Community Respiratory Health Survey (ECRHS). BHR to methacholine was analysed in relation to BMI adjusted for a number of factors known to be associated with BHR, including baseline lung function and allergen sensitisation, and combined across 34 centres using random effects meta-analysis.
Results: BHR increased with increasing BMI in men (ECRHS slope changed by –0.027 for each unit increase in BMI, 95% confidence interval –0.044 to –0.010, p=0.002), but the relation in women was weak (–0.014, 95% CI –0.033 to 0.005, p=0.14). There was no evidence for an interaction of sex with BMI (p=0.41).
Conclusions: BHR is related to BMI in the ECRHS. This suggests that the association is not due to greater diagnosis or perception of symptoms in obese people compared with those of normal weight. The data do not support the finding by some studies of a relation between asthma and obesity in women but not in men.

The body of evidence for an association between symptoms of asthma and obesity is now substantial, both in adults[1–6] and children.[7–12] Tantisira and Weiss reviewed the possible mechanisms that could explain the association, and concluded that "it is unlikely that the noted relationship is due to any one single factor".[13] Others, however, have been sceptical that symptoms found to be associated with obesity are due to asthma. Schachter *et al*[14] found associations between obesity and reported symptoms, but not with airway responsiveness, and concluded that the increased symptoms were not caused by asthma.

The European Community Respiratory Health Survey (ECRHS) was one of the studies that reported an association between symptoms of asthma, but not hayfever or serological markers of atopy, and body mass index (BMI), in a large population survey of adults aged 20–44 years.[6] Bronchial responsiveness (BHR) to methacholine was measured in the majority of participants.[15] We therefore used this sample to ascertain whether there is an association between BHR and BMI.

METHODS

Study participants

The protocol for the ECRHS has been described in detail elsewhere.[16 17] Briefly, participating centres selected an area defined by pre-existing administrative boundaries with a population of at least 150 000. Where possible an up to date sampling frame was used to select randomly at least 1500 men and 1500 women aged 20–44 years.

Study design

In stage I subjects were sent a questionnaire enquiring about respiratory symptoms and attacks of asthma in the last 12 months, current use of asthma medication, and nasal allergies including hayfever. A random sample of subjects was selected to take part in stage II. Those who had already responded to stage I were invited to answer a more detailed administered questionnaire and to take part in blood tests, assessment of lung function by spirometry, and airway challenge with methacholine. BHR was summarised using ECRHS slope as described below. Height and weight were measured before spirometry. Other independent variables were those included in the analysis of BHR in relation to sensitisation to individual allergens.[18] The questionnaire collected information on symptoms, use of medication, current smoking, and smoking history.

Methacholine challenge

As far as possible, clinic appointments were made so that participants who were taking medication were seen at least 4 hours after inhaled medication and at least 8 hours after oral medication. Appointments were made at a time of day convenient to participants, and it was not possible to standardise testing by time of day in the young adult population. Season of testing varied, but was controlled for in the analysis. The details of the challenge have been described elsewhere.[15 19] Bronchial responsiveness to methacholine was measured in eligible subjects using one of two dosing schedules, one delivering methacholine to a maximum dose of 1 mg and the other to a maximum of 2 mg. Methacholine was delivered via a Mefar dosimeter (Mefar, Bovezzo, Italy), forced expiratory volume in 1 second (FEV_1) was recorded 2 minutes after each inhalation, and the test was stopped when either a 20% fall in FEV_1 was achieved or the final dose had been given. Only data from the doses common to the two schedules, 0.0078–1 mg cumulative dose, were used in multicentre analyses.[15]

The measure of the dose-response slope adopted for between centre analyses in the ECRHS is used as the measure of BHR.[15] The term "slope" is used for transformed log slope as

Table 1 Number (%) of participants in each country with data on bronchial responsiveness in each category of body mass index, ordered by the percentage of obese men

	Men				Women			
Country	<20	20–<25	25–<30	30+	<20	20–<25	25–<30	30+
Belgium	32 (10.5)	183 (60.0)	84 (27.5)	6 (2.0)	77 (25.8)	167 (56.0)	45 (15.1)	9 (3.0)
France	69 (7.8)	602 (67.7)	200 (22.5)	18 (2.0)	265 (31.3)	472 (55.8)	79 (9.3)	30 (3.5)
Sweden	43 (5.7)	465 (61.6)	222 (29.4)	25 (3.3)	117 (16.2)	484 (67.1)	99 (13.7)	21 (2.9)
Switzerland	24 (7.0)	206 (60.4)	97 (28.4)	14 (4.1)	84 (26.7)	184 (58.4)	32 (10.2)	15 (4.8)
Netherlands	21 (3.8)	304 (54.9)	199 (35.9)	30 (5.4)	65 (12.1)	330 (61.6)	125 (23.3)	16 (3.0)
UK	27 (6.7)	227 (56.0)	129 (31.9)	22 (5.4)	57 (12.7)	260 (58.0)	96 (21.4)	35 (7.8)
Norway	13 (4.4)	176 (59.5)	90 (30.4)	14 (5.7)	30 (11.2)	162 (60.4)	58 (21.6)	18 (6.7)
Iceland	4 (1.7)	135 (56.3)	87 (36.3)	14 (5.8)	38 (16.2)	148 (63.2)	36 (15.4)	12 (5.1)
Italy	21 (5.6)	207 (54.9)	127 (33.7)	22 (5.8)	87 (24.9)	198 (56.7)	44 (12.6)	20 (5.7)
Germany	60 (6.9)	466 (53.9)	286 (33.1)	52 (6.0)	144 (19.0)	441 (58.3)	132 (17.4)	40 (5.3)
Spain	15 (2.1)	300 (42.9)	309 (44.2)	75 (10.7)	64 (10.3)	361 (57.9)	155 (24.8)	44 (7.1)
Ireland	4 (2.6)	81 (52.3)	53 (34.2)	17 (11.0)	12 (9.5)	70 (55.6)	3 (26.2)	11 (8.7)
Australia	3 (1.1)	114 (42.1)	122 (45.0)	32 (11.8)	14 (5.6)	151 (60.9)	56 (22.6)	27 (10.9)
New Zealand	12 (3.0)	153 (37.7)	191 (47.0)	50 (12.3)	21 (5.9)	173 (49.0)	105 (29.7)	54 (15.3)
USA	2 (1.3)	68 (42.8)	63 (39.6)	26 (16.4)	18 (10.1)	68 (38.2)	50 (28.1)	42 (23.6)
Total	350 (5.2)	3687 (54.9)	2259 (33.6)	420 (6.3)	1093 (17.3)	3669 (58.2)	1145 (18.2)	39 (6.3)

used in the ECRHS,[15 18 19] with a low "slope" indicative of high BHR. This measure was developed to provide a symmetrically distributed continuous measure of BHR that was robust to variation in nebuliser output.[20] Only a few individuals in a population survey have a measurable dose producing a 20% fall in forced expiratory volume (PD_{20}). Analysis of a continuous measure has greater power than that of PD_{20} dichotomised into "reactive" and "non-reactive". However, some results were converted to approximate PD_{20} units.[20]

Weight for height and obesity

BMI was calculated as weight in kilograms divided by the square of the height in metres. It was analysed as a continuous variable and also as a categorical variable divided into underweight (<20), normal weight (20–<25), overweight (25–<30), and obese (30+).

Total and specific IgE

Serum total IgE and specific IgE to cat, house dust mite (*D pteronyssinus*), *Cladosporium*, and timothy grass were measured using the Pharmacia CAP System (Pharmacia Diagnostics AB, Uppsala, Sweden). The measurement range for total IgE was 2–2000 kU/l, and 0.35–100 kU_A/l for specific IgE. Specific IgE results were regarded as positive if >0.35 kU_A/l. Total IgE was logarithmically transformed.

Statistical analysis

"Slope" was analysed for each centre using multiple linear regression, regression coefficients on BMI being combined across centres in a random effects meta-analysis.[21] Analyses were stratified by sex as a number of studies have found a relation between asthma and BMI only in women or girls.[1 9 11] Additional independent variables were those included in a previous analysis of risk factors for BHR.[18] These were age, smoking (current, ex or never) and an age/smoking interaction, height, baseline FEV_1 expressed as a standardised difference from an internally derived predicted value and as a percentage of forced vital capacity (FVC), season of testing, total IgE, and sensitisation to all four allergens including titres as measures of degree of sensitisation. Internally predicted FEV_1 was used because the published standards[22] were found to underestimate FEV_1 on average for almost all centres.[23] The BMI/sex interaction was tested in an analysis of data for both men and women, adjusting also for age/sex interaction, as participation rates varied by age and sex across centres.

Because height is used to standardise FEV_1 and is a component of BMI, there is potential for the relation of BHR to BMI to vary with the method of standardisation. A similar problem is found with FEV_1 itself.[24] The sensitivity of the results to alternative standardisation of FEV_1 and weight was examined by including FEV_1/height^2 in place of standardised difference of FEV_1 from the predicted value, and also by replacing standardised FEV_1 and BMI by FEV_1, weight, height, and height^2 in the multiple regression.

The relation of lung function, both standardised FEV_1 and FEV_1/FVC, to BMI was analysed with and without adjustment

Table 2 Relation of ECRHS "slope" to body mass index or weight, with three methods of adjustment for baseline FEV_1, estimated by random effects meta-analysis of regression coefficients across 34 centres. All analyses adjusted for independent variables as described in text

	Men (n=5899)				Women (n=5354)				
Adjustment for baseline FEV_1	Meta-analysis regression coefficient	95% CI	p value for regression coefficient	p value for heterogeneity	Meta-analysis regression coefficient	95% CI	p value for regression coefficient	p value for heterogeneity	p value for interaction of sex and BMI
Standardised difference*	–0.027	–0044 to –0.010	0.002	0.10	–0.014	–0.033 to 0.005	0.14	0.011	0.41
FEV_1/height^2	–0.027	–0044 to –0.010	0.002	0.10	–0.005	–0.033 to 0.004	0.13	0.011	0.46
Regression method†	–0.009	–0.014 to –0.003	0.003	0.09	–0.002	–0.013 to 0.002	0.13	0.005	0.60

*Internally standardised difference between FEV_1 and value predicted for sex, age and height, divided by residual standard deviation.
†Regression coefficient on weight with adjustment for FEV_1, height, and height^2.

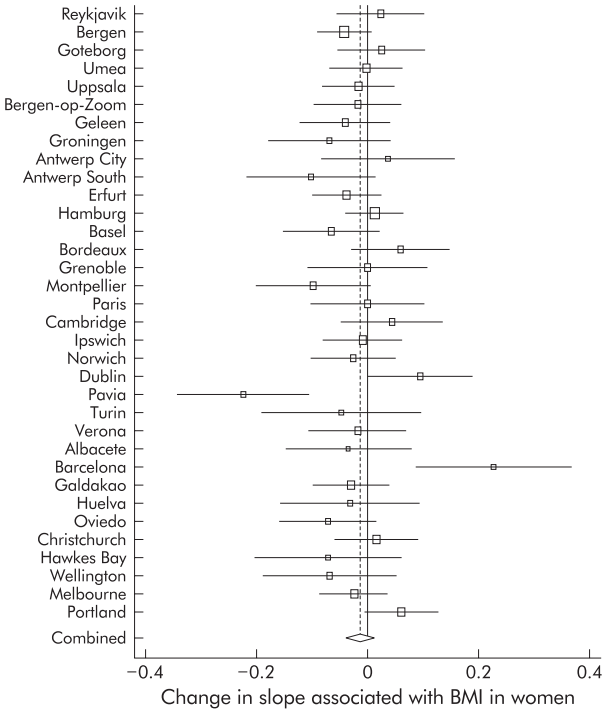

Figure 1 Increase in slope associated with an increase in 1 kg/m^2 in body mass index (BMI) by centre in women. The area of each square is proportional to the reciprocal of the variance of the estimate for the centre. The combined random effects estimate is shown by the dashed line, the diamond having the width of its 95% confidence interval.

for BHR. In these analyses adjustment was also made for all other independent variables in the analysis of BHR.

RESULTS

Study population

Details of the response to BHR testing[15] and blood sampling[18] are given elsewhere. Of the 36 centres in 16 countries included in the ECRHS analysis of symptoms and BMI,[6] one centre did not carry out methacholine challenge and one had technical problems with the Mefar dosimeter that precluded inclusion of their data in the analysis. Table 1 gives the numbers of subjects with BHR data in each of the remaining 15 countries by category of BMI and sex. Underweight and obesity were more common in women than in men in almost all countries. Of 13 108 participants who had at least one dose of methacholine administered, 1861 (14.2%) had a measurable PD_{20} or a fall in FEV_1 of 20% or more at the first dose, and 13 059 (99.6%) had a value for "slope"—that is, at least two doses of methacholine.

Relation of BHR to BMI

There were 11 277 participants with data for BHR, BMI, and all independent variables. There was no evidence of non-linearity in the relation of "slope" to BMI, so the main results are presented with BMI analysed as a continuous variable (table 2). "Slope" declined with increasing BMI in men—that is, BHR increased. The statistical significance of the result was similar (p=0.002 or 0.003) for the three methods used to adjust for baseline FEV_1, and the regression coefficient the same for the first two methods. The third method estimated change in "slope" with weight in kg, adjusted for height, rather than with change in BMI in kg/m^2. There was only weak evidence for heterogeneity in the estimates across the centres (p~0.1) in men. In women the estimates were lower and not statistically significant (p=0.14 or 0.13) and, again, they were consistent over the three methods. However, the interaction with sex was far from statistically significant (p>0.4), and the combined estimate for men and women corresponding to the first analysis was –0.021 (95% confidence interval (CI) –0.032 to –0.010, p<0.001), with no evidence for heterogeneity. There was strong evidence for heterogeneity between centres in women (p~0.01), due largely to a strongly negative association in Pavia and a strongly positive one in Barcelona (fig 1); excluding these two centres, the heterogeneity was not statistically significant.

Effects of confounding variables

To assess the effect of the various adjusting factors, the analysis was carried out with no adjustment and with separate adjustment for baseline lung function as in the first analysis (line 1, table 2) for all IgE variables and for the remaining variables (table 3). The unadjusted analysis showed a negative relation of "slope" to BMI in both men and women, which was considerably reduced on adjustment for lung function. However, adjustment for total IgE and specific IgE strengthened the negative relation. There was little effect of adjustment for the other variables, which slightly strengthened the relation in men and reduced it in women. In men the net effect of the adjustments gave a fully adjusted estimate close to that for the unadjusted, whereas in women the adjusted estimate was reduced and no longer statistically significant.

Table 3 Relation of ECRHS "slope" to body mass index, estimated by random effects meta-analysis of regression coefficients across 34 centres, with adjustment for variables as specified

	Men (n=5870)				Women (n=5407)			
Adjustment	Meta-analysis regression coefficient	95% CI	p value for regression coefficient	p value for heterogeneity	Meta-analysis regression coefficient	95% CI	p value for regression coefficient	p value for heterogeneity
None	–0.026	–0.044 to –0.009	0.003	0.10	–0.022	–0.040 to –0.003	0.02	0.019
Lung function variables	–0.010	–0.026 to 0.007	0.26	0.10	–0.010	–0.028 to 0.007	0.24	0.031
All IgE variables	–0.035	–0.052 to –0.018	<0.001	0.10	–0.029	–0.047 to –0.011	0.002	0.016
Height, age, season of testing, smoking and smoking–age interaction	–0.031	–0.049 to –0.012	0.001	0.09	–0.017	–0.037 to 0.002	0.09	0.01

Table 4 Relation of BHR, in approximate doubling dose units of PD_{20}, to body mass index, estimated by random effects meta-analysis of regression coefficients across 34 centres. All analyses adjusted for independent variables as described in text

	Men		Women	
Body mass index in model	Estimate	95% CI	Estimate	95% CI
As continuous variable	–0.031	–0.050 to –0.011	–0.016	–0.037 to 0.005
As categorical variable				
Underweight <20	0.016	–0.232 to 0.264	0.165	–0.008 to 0.338
Normal weight 20–<25 (reference group)	0		0	
Overweight 25–<30	–0.081	–0.213 to 0.051	–0.170	–0.363 to 0.023
Obese 30+	–0.327	–0.591 to –0.063	0.044	–0.255 to 0.344

Results converted to PD_{20} units

To facilitate understanding of the results by readers more familiar with PD_{20}, results from the first analysis (line 1, table 2) have been converted to approximate change in PD_{20} in doubling dose units (table 4). From this it can be seen that the change in PD_{20} with each extra kg/m^2 of BMI was small. Also shown in table 4 are the results, again in approximate doubling dose units, when BMI was analysed in categories. The trend across the categories in men is clear, and the decrease in PD_{20} in obese men compared with men of normal weight was statistically significant (p=0.015). In women the trend is less clear; there was weak evidence for a decrease in overweight women (p=0.085), but no evidence for a difference between obese women and those of normal weight (p=0.77).

Relation of lung function to BMI

Table 5 shows the relation of FEV_1—expressed as a standardised difference from the predicted value and FEV_1/FVC—to BMI, with adjustment for all other independent factors in the analysis of BHR. Results are shown for men and women with BHR data so that the effect of adjustment for BHR could be assessed. The first two lines are without adjustment for BHR, showing a negative relation of lung function with increasing BMI which was statistically significant for both FEV_1 (p=0.001, p=0.025, men and women respectively) and FEV_1/FVC (p=0.011, p=0.017). On adjustment for BHR, in addition to other factors, estimates were still negative, but smaller in magnitude. Only FEV_1 in men (p=0.018) reached the conventional level of significance; FEV_1/FVC in women (p=0.063) was weakly related to BMI.

As standardised FEV_1 and FEV_1/FVC are highly correlated, the analysis was repeated, each adjusted for the other. Although all estimates were still negative, most were not statistically significant (data not shown). There was evidence for an independent relation of FEV_1 to BMI in men without adjustment for BHR (p=0.013), and weak evidence for the BHR adjusted relation (p=0.045) and for the relation of FEV_1/FVC in women (p=0.062) without adjustment for BHR.

DISCUSSION

Our results show clear evidence for a relation of BHR to BMI. Although not statistically significant in women after adjustment, there was no evidence for a difference in the association between men and women, as shown by the test for interaction. We found an association of BHR with BMI that was independent of baseline lung function, while the relations of FEV_1 and FEV_1/FVC to BMI were largely explained by BHR.

We did not divide obese subjects into obese and severely obese, as the obese group was already small and less than 1.5% of the sample was severely obese (BMI ⩾35 kg/m^2). We also used BMI <20 kg/m^2 as the definition of underweight, chosen a priori in line with our previous paper,[6] rather than the cut off of 18.5 kg/m^2. Only about 5% of men were underweight using the cut off of 20 kg/m^2. Around 2.5% of the total sample had a BMI <18.5 kg/m^2, most of whom were women. Although the cut off of 18.5 kg/m^2 may be clinically desirable, it is less useful in an epidemiological study. The results are presented in table 4 by BMI category only to aid interpretation. As no non-linearity was detected, we were able to analyse BMI as a continuous variable which has greater power.

Table 5 Relation of lung function to body mass index or weight, with and without adjustment for BHR, estimated by random effects meta-analysis of regression coefficients across 34 centres. All analyses adjusted for independent variables as described in text

		Men (n=5899)				Women (n=5354)			
Lung function parameter	Adjustment for BHR	Meta-analysis regression coefficient	95% CI	p value for regression coefficient	p value for heterogeneity	Meta-analysis regression coefficient	95% CI	p value for regression coefficient	p value for heterogeneity
FEV_1, standardised difference*	No	–0.015	–0.025 to –0.006	0.001	0.149	–0.008	–0.014 to 0.001	0.025	0.84
FEV_1/FVC%	No	–0.067	–0.120 to –0.015	0.012	0.39	–0.072	–0.132 to –0.013	0.017	0.002
FEV_1, standardised difference*	Yes	–0.011	–0.020 to –0.002	0.018	0.15	–0.005	–0.011 to 0.002	0.15	0.58
FEV_1/FVC%	Yes	–0.030	–0.079 to 0.019	0.22	0.50	–0.051	–0.105 to 0.003	0.063	0.011

*Internally standardised difference between FEV_1 and value predicted for sex, age and height, divided by residual standard deviation.

The percentage of obese subjects in the sample was lower than in our previous paper.[6] To obtain BHR data, participants had to agree to lung function measurement and have an FEV_1 that was more than 70% predicted[22] and more than 1.5 l. Obese subjects were under-represented in those with BHR data compared with those who had baseline lung function measured. Subjects who were not tested due to low FEV_1 had slightly greater BMI than those who declined methacholine challenge following baseline lung function, but this was partly explained by a greater proportion of men with low lung function. Few subjects without baseline lung function had height and weight measured. Symptoms of wheeze with breathlessness or wheeze without a cold were more common in subjects who were found ineligible for methacholine challenge, when baseline lung function was measured, than in those with BHR data or those who did not have baseline lung function measured. It therefore seems likely that the association between BHR and BMI has been underestimated in our study. It is unclear in the paper by Schachter *et al*[14] whether the symptom results are confined to participants with BHR data. If not, selection bias could explain the difference in their findings between symptoms and BHR with BMI.

This was a community based study; only 4% of doctor-diagnosed asthmatics had taken oral steroids in the previous 12 months. Omission of data for these participants had no effect on the results.

Although there was potential for selection bias in our study, the findings presented for lung function without adjustment for BHR, which were in participants with BHR data, were almost the same as those in the larger group including those without BHR data.

The results are in line with those for symptoms in the ECRHS[6] and do not support a stronger association in women than in men, as had been reported elsewhere.[1 3 9 11]

It is well established that BHR is strongly related to atopy, and the main results presented here are adjusted for sensitisation and degree of sensitisation to four common allergens. However, there is no evidence that atopy is associated with BMI in adults. It is not known why asthma is associated with obesity. The possibility that asthmatic individuals become obese through less exercise is unlikely as other studies have shown obesity to precede the onset of symptoms.[2 9] The inconsistency in the sex difference and associations of symptoms and weight-for-height in prepubertal children[10 11] make it unlikely that hormonal influences explain much of the association.

The association between asthma and obesity seems to have arisen recently. One study of adults carried out in 1981 showed a relation between BMI calculated from self-reported height and weight and a report of long standing asthma or bronchitis in women but not in men,[25] but most other studies are much more recent.[1–12] Furthermore, in the National Study of Health and Growth[26] which collected data from 1972 to 1994, the association was stronger in the latest data and none of the upward trend in asthma prevalence could be explained by increases in obesity. The relative lack of reports of an association before the 1990s is unlikely to be due to failure to analyse the relation between symptoms and BMI or weight-for-height, especially in children, as there was concern in the 1970s and 1980s that asthmatic children were shorter and lighter than children without symptoms.[27 28]

Of the possible mechanisms discussed by Tantisira and Weiss, that of diet or diet–gene interaction, coupled with the fact that obese individuals tend to consume a poor diet,[13] has the potential to explain the above findings. Diets change over time, and if they have changed more in the obese this could explain the recent emergence of the association. This could also explain heterogeneity between studies carried out in different countries. A randomised trial which showed a decrease in symptoms and improvement in lung function achieved weight reduction with a low energy diet preparation but allowed the control group to eat normally.[4] It is likely to prove very difficult to disentangle the effects of change in weight from change in diet.

A robust biological explanation for the association between symptoms and obesity is elusive. It is unlikely to be due to greater diagnosis of asthma or increased perception of symptoms in the obese, as we have shown that obesity is associated with objective markers of asthma and lung function. Longitudinal studies that collect information on a variety of factors, ideally including diet, are required.

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