Insulin resistance modifies the association between obesity and current asthma in adults

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Abstract

Insulin resistance potentiates the association between obesity and childhood asthma, but this relationship appears inconsistent in relatively small studies of adults. We investigated effect modification in adults using the National Health and Nutrition Examination Survey 2003–2012, a large, nationally representative database.

Insulin resistance and a history of physician-diagnosed current asthma were obtained from 12 421 adults, ages 18–85 years. We used logistic regression to determine associations between obesity and current asthma, adjusting for age, sex, race/ethnicity, poverty income ratio and smoking status. An interaction term evaluated effect modification by insulin resistance of the obesity–asthma association.

As expected, obesity was positively associated with current asthma. Insulin resistance modified this association, with obesity measured as body mass index, waist circumference or waist-to-height ratio. The relationship between obesity and current asthma was stronger with increasing insulin resistance tertiles (OR 2.05, 95% CI 2.76–3.00; p-value for interaction 0.03). This association was robust to adjustments for other components of the metabolic syndrome (hypertriglyceridaemia, hypertension, hyperglycaemia and systemic inflammation). None of these components were themselves effect modifiers of the obesity–asthma association.

In this large, nationally representative sample, insulin resistance modified the association between obesity and current asthma in adults. Targeting insulin resistance may represent a novel therapeutic strategy for obese patients with asthma.

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Introduction

Obesity and asthma are common chronic diseases of public health importance [1–3]. Cluster analyses of asthma patients have revealed "obese asthma" as a relatively distinct subtype characterised by increased severity, resistance to usual therapy, late onset and female predominance [4–11]. Although the mechanisms underlying obese asthma are incompletely understood, systemic inflammation, adipokine alterations, and mechanical stress may each have a role in its pathobiology and blunted response to usual therapy [12–15]. Obesity as a clinical entity is heterogeneous [16] and may be associated with the metabolic syndrome, which is marked by dyslipidaemia, hypertension, hyperglycaemia and insulin resistance, central obesity, and a systemic inflammatory state [17].

As with the metabolic syndrome, asthma is also characterised by dysregulated inflammation. This has sparked interest in whether the metabolic syndrome constitutes a subtype of obesity that most associates with asthma. Several studies have suggested that each of the individual components of the metabolic syndrome are indeed associated with asthma, independently of obesity [18–20]. However, the relative contribution of each component of the metabolic syndrome to a more severe asthma phenotype has not been established, as recently reviewed by Baffi *et al.* [21]. Whether components of the metabolic syndrome are also effect modifiers of the association between obesity and asthma is unclear. Effect modification is distinct from confounding, and indicates that the magnitude of the association between obesity and asthma varies by the levels of a third variable, the effect modifier. That is, the effect modifier potentiates the association between obesity and asthma. To our knowledge, insulin resistance is the only component of the metabolic syndrome that has been reported to modify the effect of obesity on asthma, and this relationship has been shown only in children and adolescents [20], not in adults [22, 23].

Effect modification may not have been demonstrated in adults due to small sample sizes and because few study cohorts include data on insulin resistance. We hypothesised that insulin resistance is an effect modifier of the association between obesity and asthma in adults: that obese adults with the highest levels of insulin resistance are at greater odds of having asthma than obese adults with the lowest levels of insulin resistance. Using a large, nationally representative dataset, we show that obese adults have greater odds of current asthma with increasing levels of insulin resistance and not with increasing levels of other components of the metabolic syndrome.

Methods

Study design and population

Data were obtained from the 2003–2012 National Health and Nutrition Examination Survey (NHANES), a survey designed to sample the non-institutionalised US population. Participation in the survey is voluntary and informed consent was obtained from all participants. NHANES was approved by the Institutional Review Board of the National Center for Health Statistics of the US Centers for Disease Control and Prevention [24].

Data on sociodemographic factors, respiratory disease, medical conditions and household smoke exposure were obtained by questionnaire. Body measurements, spirometry and blood samples were acquired at a subsequent visit to a mobile NHANES clinical station. Height, weight and waist circumference were obtained on all subjects by trained health technicians using procedures described in the NHANES Anthropomorphic Procedures Manual [25]. Body mass index (BMI) was defined as weight in kilograms divided by the squared height in metres and was divided into traditional categories: <25 (lean), ≥25 and <30 (overweight), and ≥30 kg·m^{-2} (obese). Obesity was also measured in terms of waist circumference and waist-to-height ratio.

Blood samples were processed to determine serum insulin, fasting total triglycerides, haemoglobin A1C (HbA1C) and C-reactive protein (CRP) levels in the morning after a 9-h fast. Spirometry was only available for survey years 2007–2012. Subjects were excluded from the spirometry portion of the exam if they reported current chest pain or a physical problem with forceful expiration; taking supplemental oxygen; recent surgery of the eye, chest or the abdomen; a recent heart attack or stroke; tuberculosis exposure; or recently coughing up blood. Adults with a personal history of detached retina or a collapsed lung and children with painful ear infections were also excluded. Spirometry was performed according to the American Thoracic Society guidelines using Ohio 822/827 dry-rolling spirometers (Ohio Medical, Gurnee, IL, USA). Forced expiratory volume 1 s (FEV$_1$) % predicted values were determined using NHANES III equations [26, 27].

A participant was considered to have "current asthma" if he or she responded affirmatively to the question, "Has a doctor or other health professional ever told you that you have asthma?", and to the question, "In the past 12 months have you had wheezing or whistling in your chest?". Race/ethnicity was self-reported and dichotomised into "Caucasian" and "non-Caucasian". The poverty income ratio (PIR), which is the ratio of family income to the poverty threshold, was used as a measure of socioeconomic status. Based on prior studies, insulin resistance was defined using the homeostatic model assessment of insulin resistance (HOMA-IR): insulin in milliunits per litre multiplied by fasting blood glucose in millimoles per litre divided by 22.5 [20, 28].

Statistical analyses

Statistical analyses were performed with STATA 12.0 software (StataCorp, College Station, TX, USA). Primary sampling units and strata variables provided in the NHANES dataset were used in the analysis to account for the complexity of the survey design. Sampling weights corresponding to each NHANES survey year were used to generate estimates representative of the US noninstitutionalised population.

The Chi-squared test was used to determine whether demographic characteristics were different between asthmatic and non-asthmatic adults for whom data on insulin resistance and covariates were available. This test was also used to compare demographic characteristics for those on whom data on insulin resistance were and were not available. Logistic regression was used to determine associations between the predictors "BMI categories" and "tertiles of insulin resistance", and the outcome "current asthma". All analyses were adjusted for age, sex, race/ethnicity, PIR and smoking status. Interaction terms

were developed to test effect modification by insulin resistance (tertiles) on the association between current asthma and obesity (BMI, waist circumference, and waist-to-height ratio). The effect of insulin resistance on the association between obesity and current asthma was quantified by stratification by insulin resistance tertiles. Additional models were constructed with adjustments by other components of the metabolic syndrome (triglyceride levels, hypertension, HbA1C and CRP). Furthermore, interaction terms were developed to test effect modification by these components of the metabolic syndrome and obesity on the outcome of current asthma. Linear regression was used to compare lung function parameters (FEV_1 % predicted) between BMI categories, adjusting for age, sex, race/ethnicity, PIR, current asthma status and height. Again, the interaction term for "BMI $\times$ insulin resistance" was introduced to test whether significant spirometric differences exist between obese individuals with the highest *versus* lowest levels of insulin resistance.

Results

Data on current asthma and insulin resistance were available for 12421 participants from NHANES 2003–2012 (table 1). Of these, 6% reported currently experiencing symptoms of asthma. As compared to adults without asthma, asthmatic adults were slightly younger, more likely to be female and less likely to be Caucasian; they had slightly lower PIRs and were more likely to be current smokers. Asthmatic adults were more likely to be obese (51 *versus* 33%, p<0.001) and they had the highest levels of insulin resistance (42% *versus* 32%, p<0.001).

As expected, BMI was positively associated with current asthma (table 2). Relative to lean individuals, the odds of current asthma were 2.25 (95% CI 1.63–3.10) times greater for obese participants, adjusting for age, sex, race/ethnicity, PIR, smoking status and insulin resistance level. Insulin resistance was not statistically significantly associated with current asthma (p=0.28) but the point estimate for current asthma was 7% (95% CI –5–21%) greater for the highest tertiles of insulin resistance relative to the lowest tertile.

Having corroborated the association between BMI and asthma in our model, we then investigated our hypothesis of whether or not insulin resistance is an effect modifier of this association by introducing an interaction term. We found that insulin resistance is indeed an effect modifier of the relaptionship between obesity and asthma (p-value for interaction 0.03) (table 2). Since obesity can be defined in ways other than BMI, such as waist circumference and waist-to-height ratio, we addressed the possibility that the significance of the interaction term between BMI and insulin resistance is due to assumptions inherent in the definition of "BMI". We therefore conducted similar analyses using interaction terms between insulin resistance and "waist circumference", and "waist-to-height ratio", respectively. The magnitude and significance of the effect estimates for the interaction terms for obesity defined as either waist circumference or waist-to-height ratio were similar to those for obesity defined as BMI (table 2).

Having identified insulin resistance as a statistically significant effect modifier, we then quantified the magnitude of this interaction by constructing a logistic regression model for current asthma and BMI, stratifying by tertiles of insulin resistance using the same prior

adjustments. In this analysis, the odds ratio of current asthma for obese individuals relative to lean individuals increased with increasing tertiles of insulin resistance (OR 2.05, 2.76 and 3.00 for the three tertiles) (figure 1). This suggests that obese adults with the highest levels of insulin resistance have higher odds of being currently asthmatic than obese adults with the lowest levels of insulin resistance.

Insulin resistance is one of several other characteristics of the metabolic syndrome. We therefore considered the possibility that the significance of the above findings was due to confounding by one or more of the other components of the metabolic syndrome. To test this possibility, we first added each of the other components of the metabolic syndrome individually (serum triglyceride levels, hypertension, HbA1C and CRP) to the original adjusted model in four additional models. None of these adjustments substantially changed the point estimates for the interaction term for BMI and insulin resistance, and the interaction term lost statistical significance only when adjusting by hypertension (p-value for interaction 0.06) (table 3). Second, we created interaction terms between BMI and each of the other components of the metabolic syndrome (triglyceride levels, hypertension, HbA1C and CRP) for the outcome of current asthma. We found that none of these interactions were statistically significant (table 4). This suggests that other components of the metabolic syndrome are neither confounders to the modifying effect of insulin resistance on the association between BMI and current asthma, nor effect modifiers themselves of that association.

We then proceeded to investigate whether insulin resistance modifies the effect of obesity on objective metrics of airflow obstruction characteristic of asthma (spirometry). As expected, relative to lean individuals, obese individuals were found to have lower % predicted FEV_1 (1.18% (95% CI 0.1–2.27%) lower, p=0.03) adjusting for the same covariates as previously and for current asthma status. When we added insulin resistance to the model, we found that individuals with the highest levels of insulin resistance had lower % predicted FEV_1 than those with the lowest levels (4.71% (95% CI 3.27–6.15%) lower, p<0.001). Having detected an association between both obesity and insulin resistance with the % predicted FEV_1, we then tested whether insulin resistance modifies the effect of obesity on spirometry. The interaction term for obesity and insulin resistance was statistically significant (p-value for interaction 0.01). Relative to obese asthmatic adults with the lowest levels of insulin resistance, obese asthmatic adults with the highest levels of insulin resistance had a statistically significantly lower % predicted FEV_1 (1.15% (95% CI 0.35–1.95%) lower). These analyses suggest that although insulin resistance modifies the effect of obesity on the prevalence of current asthma symptoms, the magnitude of its effect on airway obstruction is small.

Obese asthmatic adults with the highest levels of insulin resistance are clinically similar to those with lower levels of insulin resistance in terms of race/ethnicity, PIR and smoking status (online supplementary table S1). Although both groups were more likely to be female, obese asthmatic adults with the highest levels of insulin resistance were less represented by women than those with lower levels (57% *versus* 78%, p<0.001). They were also slightly older (mean age 50 *versus* 47 years, p=0.03).

Discussion

Using a large, nationally representative cohort, we have found that obesity is associated with asthma in adults, and that insulin resistance potentiates this association. Obese individuals with the highest levels of insulin resistance have greater odds of currently having asthma than obese individuals with the lowest levels of insulin resistance. Furthermore, we have found that effect modification is specific to insulin resistance and not to other components of the metabolic syndrome (hypertriglyceridaemia, hypertension, hyperglycaemia and systemic inflammation).

Our results are consistent with those of Forno *et al.* [20], who documented insulin resistance as an effect modifier of obesity–asthma among children. Our findings expand on theirs in two ways: 1) by analysing the adult population and 2) by understanding effect modification by insulin resistance in the context of the other components of the metabolic syndrome. As a clinical entity, we expected extensive collinearity between other components of the metabolic syndrome and insulin resistance, which should bias results to the null. Conversely, our results on the modifying effect of insulin resistance were robust to adjustments by hypertriglyceridaemia, hypertension, hyperglycaemia and elevated levels of CRP. We did not detect effect modification of the obesity–asthma association with any of these other components of the metabolic syndrome. This suggests that insulin resistance, and not other components, is the feature of the metabolic syndrome that interacts with obesity to promote an asthmatic phenotype.

Although the mechanism by which insulin resistance potentiates the pro-asthmatic effects of obesity are unknown, we suspect that compensatory hyperinsulinaemia in the lung is responsible for the deleterious effects of insulin resistance. Insulin resistance occurs differentially in a signalling pathway- and cell type-specific manner [29–31]. The insulin receptor may become resistant to insulin agonism in some tissues (mainly the liver, adipocytes and skeletal muscle), more so than in the lung, which may leave pulmonary cells vulnerable to the effects of compensatory hyperinsulinaemia [32]. There are several pathways by which hyperinsulinaemia may impair pulmonary function, such as causing hypercontractility in airway smooth muscle cells [29, 30], reducing bioavailability of the endogenous bronchodilator nitric oxide [31], promoting mast cell survival [33] or fibroblast proliferation [34].

Our results suggest that the impact of insulin resistance as an effect modifier of the association between obesity and lung function is statistically significant but small (the % predicted FEV_1 of obese asthmatic adults with the highest levels of insulin resistance is only 1.15% lower than that of obese asthmatic adults with the lowest levels of insulin resistance). This may imply that the airway smooth muscle hypercontractility mechanism may predominate: insulin resistance may thus make asthmatic individuals more prone to be symptomatic with bronchoconstrictive stimuli yet not have more severe airflow limitation. Indeed, insulin therapy has been found to increase airway hyperresponsiveness in diabetic individuals [35]. The mechanism by which insulin resistance and hyperinsulinaemia potentiate the pulmonary effects of obesity needs to be investigated in *in vitro* and *in vivo* models.

This study has several limitations. First, data on insulin resistance were available for a subset of participants of NHANES 2003–2012. Missing data could result in overrepresentation of patient characteristics and bias our results. However, the subset for which insulin resistance data were available was not significantly different from the subset in which they was unavailable, in terms of sex, age, PIR, history of asthma, wheezing in the past year and smoking status (table S2). There were slightly more Caucasian participants in the subset on which insulin data was available (70% *versus* 66%) but, as previously shown, obese asthmatic adults with the highest insulin resistance levels were similar in their racial/ethnic composition as those with the lowest levels (table S1). This suggests that missing data probably do not contribute to our results. Second, spirometric data were only available on a subset of patients, but with this smaller subset, one would expect limitations in power and a bias towards the null, assuming that missingness is random. Despite this limitation, we did observe a statistically significant (albeit small) effect mediation by insulin resistance on the effect of obesity on pulmonary function. Third, we found that insulin resistance, and not other components of the metabolic syndrome, is an effect modifier of the obesity–asthma association. These negative results for other metabolic syndrome components could be due to limited power. However, the number of participants for which data on all other components of the metabolic syndrome was essentially the same as the number of participants for which we had data on insulin resistance. Although larger sample sizes could perhaps overcome this limitation, the effect size would also likely be small and of questionable clinical significance.

In summary, we have found, in a nationally representative cross-sectional study, that insulin resistance differentiates itself from other components of the metabolic syndrome in that it is the only component that potentiates the obesity–asthma association. This study suggests that insulin resistance distinguishes a distinct group of obese asthmatic adults. Therapies targeting insulin resistance to improve asthma control may benefit obese asthmatic adults with insulin resistance. Traditional insulin sensitisers [36], such as biguanides (like metformin) and thiazolidinediones (like pioglitazone), or emerging ones (such as free fatty acid receptor 1 agonists [37] or BGP-15 [38]), could be preferentially used in obese, insulin-resistant, asthmatic adults allowing a precision medicine approach. Additionally, it is possible that some of these drugs, metformin for example, which is now used for weight loss in nondiabetics with obesity, may have some benefit in obese asthmatics without diabetes. Both basic and prospective clinical research studies are needed to clarify whether organ-specific compensatory hyperinsulinaemia is the pathophysiological mechanism by which insulin resistance potentiates the association between obesity and asthma, and whether drugs that target insulin resistance can reduce asthma morbidity in obese patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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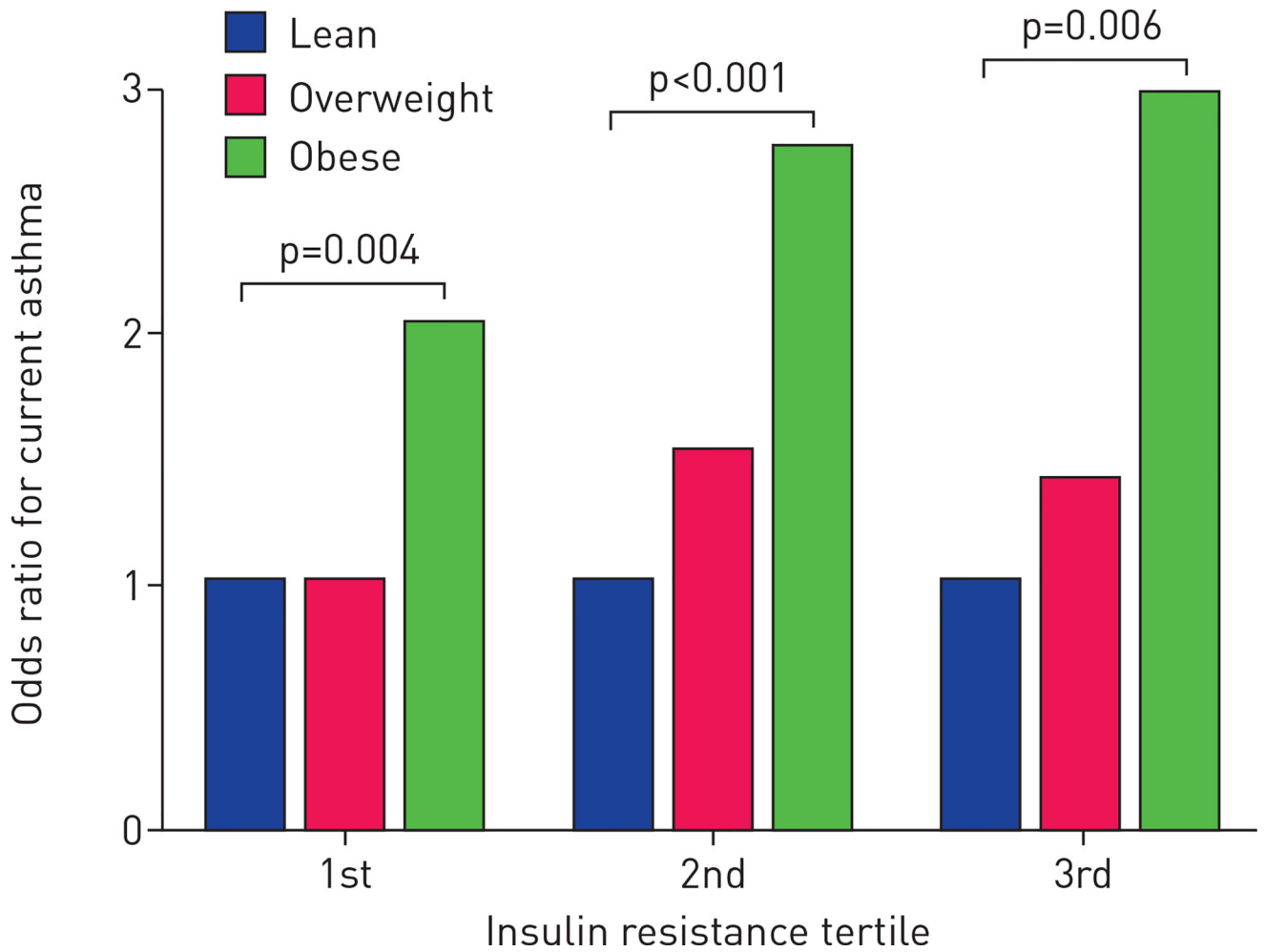
FIGURE 1.
Relationship between between body mass index (BMI) and current asthma stratified by tertiles of insulin resistance. The BMI categories were lean (<25 kg·m^{-2}), overweight (25 and <30 kg·m^{-2}) and obese (30 kg·m^{-2}). p-value for interaction 0.03.

TABLE 1

Prevalence of current asthma by subject characteristics

Characteristic	Current asthma		p-value
	Yes	**No**	
Subjects n	752	11669	
Age years mean (SD)	47 (29–65)	49 (30–67)	0.01
Females	60	51	<0.001
Caucasians	49	43	0.001
Insulin resistance			<0.001
Lowest tertile	28	34	
Middle tertile	30	34	
Highest tertile	42	32	
Body mass index kg·m^{-2}			<0.001
<25	23	33	
25–29.9	25	34	
30	51	33	
Poverty index ratio 1	79	89	<0.001
Physician-diagnosed asthma	100	8	<0.001
Self-reported recent wheezing	100	9	<0.001
Smoking status			<0.001
Never	42	54	
Former	26	25	
Current	32	21	

Data are presented as % unless otherwise stated.

TABLE 2

Interaction between body weight and insulin resistance, and current asthma

Measure of obesity	Current asthma	
	Crude OR (95% CI)	Adjusted OR (95% CI)
Model 1: BMI categories		
Lean	1.0 (ref.)	1.0 (ref.)
Overweight	1.01 (0.73–1.38)	1.11 (0.80–1.55)
Obese	**2.20 (1.63–2.97)**	**2.25 (1.63–3.10)**
Test for trend p-value	<0.001	<0.001
p-value for interaction between BMI and insulin resistance	0.10	0.03
Model 2: waist circumference tertiles		
1st	1.0 (ref.)	1.0 (ref.)
2nd	1.19 (0.72–1.95)	1.38 (0.84–2.29)
3rd	**2.17 (1.35–3.47)**	**2.68 (1.66–4.33)**
Test for trend p-value	<0.001	<0.001
p-value for interaction between waist circumference and insulin resistance	0.03	0.01
Model 3: waist-to-height ratio tertiles		
1st	1.0 (ref.)	1.0 (ref.)
2nd	0.97 (0.65–1.44)	1.10 (0.74–1.64)
3rd	**2.08 (1.46–2.97)**	**2.29 (1.56–3.35)**
Test for trend (p-value)	<0.001	<0.001
p-value for interaction between waist-to-height ratio and insulin resistance	0.11	0.02

All models adjust for age, sex, race/ethnicity, poverty income ratio and smoking status.

BMI: body mass index.

Bold odds ratios are statistically significant.

TABLE 3

The interaction between current asthma, body mass index (BMI) and insulin resistance is not substantially altered by adjustments with other components of the metabolic syndrome

Models with current asthma as outcome, with interaction term for "BMI × insulin resistance"	p-value for interaction term	Point estimate for interaction term (95% CI)
Model 1: original model	0.03	**1.23 (1.02–1.49)**
Model 2: model 1 plus adjustment by triglyceride levels	0.03	**1.23 (1.02–1.49)**
Model 3: model 1 plus adjustment by hypertension	0.06	1.20 (0.99–1.44)
Model 4: model 1 plus adjustment by HbA1C levels	0.02	**1.24 (1.03–1.49)**
Model 5: model 1 plus adjustment by CRP levels	0.02	**1.31 (1.05–1.63)**

All models adjust for age, sex, race/ethnicity, poverty income ratio and smoking status.

HbA1C: glycohaemoglobin; CRP: C-reactive protein.

Bold point estimates are statistically significant.

TABLE 4

Tests for interaction are negative between current asthma, obesity and components of the metabolic syndrome other than insulin resistance[#]

BMI categories	Current asthma	
	Crude OR (95% CI)	Adjusted OR (95% CI)
Model 1: triglyceride tertile		
Lean	1.0 (ref.)	1.0 (ref.)
Overweight	0.98 (0.78–1.22)	1.12 (0.89–1.42)
Obese	**1.92 (1.59–2.31)**	**2.13 (1.75–2.60)**
Test for trend p-value	<0.001	<0.001
p-value for interaction between BMI and triglyceride levels	0.60	0.54
Model 2: hypertension		
Lean	1.0 (ref.)	1.0 (ref.)
Overweight	0.97 (0.78–1.22)	1.07 (0.85–1.35)
Obese	**1.95 (1.60–2.36)**	**1.94 (1.58–2.38)**
Test for trend p-value	<0.001	<0.001
p-value for interaction between BMI and hypertension	0.53	0.73
Model 3: HbA1C level		
Lean	1.0 (ref.)	1.0 (ref.)
Overweight	0.99 (0.79–1.23)	1.12 (0.89–1.41)
Obese	**1.95 (1.62–2.35)**	**2.09 (1.73–2.54)**
Test for trend p-value	<0.001	<0.001
p-value for interaction between BMI and HbA1C levels	0.91	0.19
Model 4: CRP level		
Lean	1.0 (ref.)	1.0 (ref.)
Overweight	1.04 (0.80–1.34)	1.11 (0.85–1.44)
Obese	**2.05 (1.71–2.46)**	**1.96 (1.59–2.41)**
Test for trend p-value	<0.001	<0.001
p-value for interaction between BMI and CRP levels	**0.02**	0.43

All models adjust for age, sex, race/ethnicity, poverty income ratio smoking status.

BMI: body mass index; CRP: C-reactive protein; HbA1C: glycohaemoglobin.

[#]: hypertriglyceridaemia, hypertension, diabetes and systemic inflammation (serum CRP levels).

Bold odds ratios are statistically significant.