

Obesity, insulin resistance and the prevalence of atopy and asthma in US adults

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Abstract

Background: The roles of obesity and insulin resistance in asthma and atopy are not well understood. We investigated whether there is an association of obesity and insulin resistance with asthma and atopy prevalence in US adults.

Methods: Data from the 2005–2006 National Health and Nutrition Examination Survey were analyzed by multivariate logistic regression, controlling for sex, age, ethnicity, income, and smoking status. Obesity was measured by body mass index (BMI) and waist circumference, and insulin resistance by the homeostasis model assessment. Asthma was defined by self-report of ever receiving a diagnosis and still having asthma currently, and atopy by any positive specific serum IgE responses to a panel of aeroallergens.

Results: Neither obesity measure nor insulin resistance was associated with atopy. Obesity was positively associated with asthma overall (odds ratio [OR] for obese *vs* normal BMI = 2.28, 95% CI: 1.76, 2.96; OR for obese *vs* normal waist circumference = 1.75; 95% CI: 1.22, 2.51) but insulin resistance was not (OR = 1.26; 95% CI: 0.80, 1.98). Obesity was also associated with nonatopic asthma (OR for obese *vs* normal BMI = 2.5; 95% CI: 1.2, 5.2; OR for obese *vs* normal waist circumference = 2.07, 95% CI: 1.21, 3.54), while obese BMI was also associated with atopic asthma (OR = 2.04, 95% CI: 1.37, 3.03). Obesity remained independently associated with all asthma outcomes after controlling for insulin resistance.

Conclusion: Obesity was independently associated with asthma, and atopic and nonatopic asthma, after controlling for insulin resistance and socio-demographic factors. There was no evidence that insulin resistance was associated with atopy or asthma.

The dramatic increase of aeroallergen sensitization (atopy) and asthma has been consistently shown in Western countries in studies over the last two or three decades (1–3). Atopy affected approximately 400 million people worldwide during 1996–2006 and is an important risk factor for asthma (4). As of 2004, as many as 300 million people worldwide suffered from asthma (1), with 250 000 annual deaths attributed to the disease (4). In the United States in 2008, about 16.4 million people had physician-diagnosed asthma (5). It is estimated that the worldwide number of people with asthma will grow by more than 100 million by 2025 (4). The reported prevalence of asthma and atopy and the strength of associa-

tion between asthma and atopy vary widely across countries (5, 6). Asthma is strikingly heterogeneous with respect to its etiology and clinical manifestations. While atopy undoubtedly plays an important role in the development of asthma in some individuals (5, 6), other possible etiological mechanisms and risk factors are worthy of investigation.

Over the past thirty years, the prevalence of obesity has increased concurrently with the increase in asthma. A consistent association of obesity with both asthma prevalence and incidence has been shown in an increasing number of studies (7), but the underlying mechanisms for the connection between obesity and asthma are still unclear. Obesity is a low-grade systemic inflammatory state characterized by altered levels of adipokines (e.g. adiponectin and leptin) and cytokines (e.g. tumor necrosis factor α [TNF- α], interleukin 6 [IL-6] and IL-1 β) (8). These immunological changes may result in decreased immunological tolerance to allergens and

Abbreviations

BMI, Body mass index; CI, Confidence interval; HOMA, Homeostasis model assessment; IR, Insulin resistance; NHANES, National Health and Nutrition Examination Survey; OR, Odds ratio.

cause a shift toward T helper 2 (Th2) cell immune response, thus increasing the risk of atopic disease such as asthma (9). Not all evidence supports this hypothesis, however, with some data suggesting that obesity is predominantly or exclusively associated with nonatopic asthma (10–12).

A new line of inquiry has recently emerged to identify the role of metabolic changes in the pathogenesis of asthma. Specifically, it has been proposed that insulin resistance (IR) is a common factor underlying asthma, atopy, and obesity (13). IR is strongly associated with obesity, especially in individuals with greater degrees of central adiposity (14). Obesity-associated changes in immunomodulatory factors such as adipokines and cytokines are known to be involved in the pathogenesis of IR (15), which may in turn contribute to the development of asthma. In addition, IR itself promotes systemic inflammation independent of obesity (16) and compensatory hyperinsulinemia can cause airway hyperresponsiveness and bronchoconstriction (17), linking IR with asthma. To date, only two population-based studies have been published and showed that IR was independently associated with the prevalence of atopy and atopic asthma (but not nonatopic asthma) (18) as well as incident asthma-like symptoms in Danish adults (19) and that IR mediated the relationships of obesity with atopy and asthma outcomes. However, the association of obesity with nonatopic asthma was not altered by IR (18). These findings support the hypothesized associations of obesity and IR with atopy and asthma. To our knowledge, no study has investigated these relationships in the US adult population.

The aim of this study is to examine the relative impact of obesity and IR on the prevalence of atopy and asthma (atopic and nonatopic) in a nationally representative sample of US adults.

Materials and methods

Data source

The National Health and Nutrition Examination Survey (NHANES) is a national survey involving household interviews and clinical examinations conducted by the National Center for Health Statistics. It was changed in 1999 from a periodic annual survey to a continuous annual survey, and the continuous NHANES data have been released in two-year increments for public use. The NHANES uses a stratified, multistage probability sample design and weighting methodology that allows for unbiased national estimates to be produced for the civilian, noninstitutionalized US population. NHANES sample weights adjust for unequal probabilities of selection, nonresponse, and planned oversampling (of young children, the elderly, low-income persons, and ethnic minorities). Detailed information about this survey and public use data files can be found at <http://www.cdc.gov/nchs/nhanes.htm>.

Study population

A total of 10 348 individuals of all ages were included in NHANES 2005–2006, which is the most recent data released

to date that contained the variables necessary for this study. The overall response rates were 80.5% for the household interviews and 77.3% for the examinations. In this study, we focused on the 4773 subjects aged 20 and older who had been randomly selected for allergen-specific IgE in serum tests and for medical condition interview. Respondents with missing data on the specific IgE test results ($n = 280$) were excluded. The resultant sample size for this study was 4493. Compared with study subjects, a larger percentage of persons excluded from the study had a family income $< \$20\,000$ (23% vs 17%; χ^2 test: $P = 0.04$) and were younger (mean [SD]: 42.5 [1.9] vs 46.8 [0.7]; F -test: $P = 0.02$). There were no differences by sex, ethnicity, smoking status, or BMI category.

Measurements

Atopy and asthma outcomes

In the 2005–2006 NHANES, serum samples were analyzed for total and allergen-specific IgE using the Pharmacia Diagnostics ImmunoCAP 1000 System (Kalamazoo, MI, USA). The types of allergies for which specific IgE tests were performed included: two house dust mites (*D. Farinae* and *D. Pteronyssinus*), five animal danders (cat, dog, cockroach, mouse, and rat), two fungi (alternaria and aspergillus), four grasses (ragweed, rye, thistle, and bermuda), and two trees (oak and birch). A concentration for specific IgE ≥ 0.35 kU/l was defined as a positive test result (20, 21). Atopy was defined by a positive result for any of the assays listed earlier.

Consistent with previous NHANES reports (22–24), asthma was defined based on affirmative responses to both questions ‘Has a doctor or other health professional ever told you that you have asthma?’ and ‘Do you still have asthma?’ in the medical conditions questionnaire. Atopic asthma was defined as participants having both atopy and asthma, whereas nonatopic asthma was defined as having asthma but no atopy.

Insulin resistance

A homeostasis model assessment (HOMA) was used to quantify IR. The HOMA index is defined as [fasting serum insulin (Mu/l) $\times$ fasting plasma glucose (mmol/l)]/22.5 (25). Plasma fasting glucose and insulin measurements were taken by the Fairview Medical Center Laboratory at the University of Minnesota using hexokinase and ELISA methods, respectively. IR was defined as HOMA index in the upper 25% quartile (≥ 3.29 μ U/ml) of the nondiabetic population in the study, based on World Health Organization criteria (26). Diabetic patients were classified into a separate category.

Body mass index

Height and weight were measured by trained technicians using standardized protocols and calibrated equipment. BMI was calculated and rounded to the nearest 0.1 kg/m². BMI categories were defined using widely accepted cut points, i.e., BMI < 18.5 kg/m² for underweight, BMI 18.5–24.9 kg/m² for normal weight, 25.0–29.9 kg/m² for overweight, and BMI ≥ 30.0 kg/m² for obesity (27). The obese

category was further subdivided into obese class I (BMI 30.0–34.9 kg/m²), obese class II (35.0–39.9 kg/m²), and obese class III (≥ 40.0 kg/m²) (27).

Waist circumference

Waist circumference, an accepted clinical indicator of abdominal obesity, was measured in a horizontal plane around the abdomen at the level of the uppermost lateral border of the right ilium. Measurements were recorded to the nearest 0.1 cm. Waist circumference categories were sex-specific: normal (<94 cm for men, <80 cm for women), overweight (94–102 cm for men, 80–88 cm for women), and obese (≥ 102 cm for men, ≥ 88 cm for women) (28).

Demographic, socioeconomic and smoking status

Age was classified into three categories: 20–44 years, 45–64 years, and ≥ 65 years, and race/ethnicity into four categories: non-Hispanic white, non-Hispanic black, Hispanic, and other. This latter category included participants reporting multiple racial/ethnic identities. We also categorized participants by annual family income (<\$20 000, \$20 000–\$45 000, \$45 000–<\$75 000, or $\geq$ \$75 000), and smoking status (nonsmoker, current smoker, or former smoker).

Statistical analysis

Characteristics of the study population were examined by frequency tables and descriptive statistics. Prevalence estimates were age-adjusted using the 2000 US Census (27). In addition to being examined as categories, both BMI and waist circumference (standardized as [raw value–mean]/standard deviation) met the assumption of linearity in the logit and were therefore also evaluated as continuous measures; odds ratios for both categorizations are presented for completeness.

Each of the four outcome variables (atopy, asthma, atopic asthma, and nonatopic asthma) was tested against BMI, waist circumference, and IR separately, controlling for age, sex, ethnicity, income, and smoking status (as categorized earlier). Additional multivariate models, again controlling for the socio-demographic variables, examined separately the relationship between each obesity measure and the outcomes, while controlling for IR and, conversely, examined the relationship between IR and the outcomes, while controlling for BMI. Additional multivariate regression models tested interactions for BMI $\times$ IR and waist circumference $\times$ IR, separately. Finally, sex was examined as an effect modifier by adding the interaction terms of sex with BMI, sex with waist circumference, or sex with IR in the models.

All analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC, USA) and accounted for the complex sample design and sample weights of the NHANES. All *P*-values reported are two-tailed, and statistical significance was defined as *P* < 0.05.

Results

The study sample included 2337 women and 2156 men, representative of 103 million women and 95 million men in the

general US population. Based on BMI, the study population was 2% underweight, 31% normal weight, 33% overweight, and 34% obese (19% in obese class I, 9% in obese class II, and 6% in obese class III); 54% had abdominal obesity based on waist circumference (Table 1). Thirty-seven percent of the study population was either diabetic or insulin resistant. Both BMI and waist circumference were positively associated with HOMA values (both *r* = 0.4, *P* > 0.001) in nondiabetics (data not shown). The overall prevalence of atopy and asthma was 41% and 8% (5% atopic and 3% nonatopic), respectively. Compared to men, women had a lower prevalence of atopy (36% vs 47%, *P* < 0.001) and a higher prevalence of asthma (10% vs 6%, *P* < 0.001) and nonatopic asthma (5% vs 2%, *P* < 0.001). Significant sex differences were also detected for BMI and waist circumference distributions, IR prevalence, and socio-demographic variables.

Atopy

The prevalence of atopy was 40.9% in the obese, defined by BMI or waist circumference, 43.3% in insulin-resistant individuals, and 51.3% in diabetics (Table 2). Neither obesity nor IR was associated with atopy, nor were they associated with atopy when both BMI (or waist circumference) and IR were present in the same model.

Asthma Overall

Obesity

As shown in Table 3, the prevalence of asthma was significantly higher in the obese compared with normal-weight individuals (BMI: 11.9% vs 6.1%, *P* = 0.0002; and waist circumference: 9.9% vs 6.0%, *P* = 0.004). The odds of asthma increased approximately 1% per standard deviation (SD) increase in BMI and waist circumference, regardless of IR status, a modest but significant association. Among obesity subgroups defined by BMI, the odds of asthma increased from 2.09 (95% confidence interval [CI]: 1.54, 2.85) for obesity class I to 3.24 (95% CI: 2.01, 5.23) for obesity class III compared to normal-weight individuals. The association persisted, and appeared to strengthen, when IR status was added to the model, with prevalence ORs ranging from 2.37 (95% CI: 1.34, 4.19) to 4.12 (95% CI: 2.04, 8.32) when comparing obesity subgroups with normal-weight individuals. A similar association was observed for asthma when comparing abdominal obesity, as measured by waist circumference, to abdominal nonobesity (OR = 1.75, 95% CI: 1.22, 2.51) and persisted after controlling for IR status (OR = 2.23, 95% CI: 1.30, 3.85).

Insulin resistance

Among nondiabetics, there was no difference in the prevalence of asthma between insulin-resistant and insulin-sensitive individuals (9.0% vs 7.9%, *P* = 0.54). IR was not significantly associated with asthma prevalence (OR = 1.26, 95% CI: 0.80, 1.98), nor was the association significant after controlling for BMI (OR = 0.72, 95% CI: 0.43, 1.20).

Table 1 Characteristics of the study population by sex

Characteristic	Estimated population, No. in millions	Survey participants, No. (%)	Men, No. (%)*	Women, No. (%)*	P-value
Socio-demographic factors					
Sex					
Female	103	2337 (52)	N/A	N/A	
Male	95	2156 (48)	N/A	N/A	
Age, year (mean, SD)	199	46.8 ± 0.7	46.1 ± 0.8	47.4 ± 0.8	0.030
Age					
18–44 years	95	2098 (48)	931 (48)	1167 (47)	0.010
45–64	70	1331 (35)	661 (36)	670 (34)	
≥65	34	1064 (17)	564 (16)	500 (19)	
Ethnicity					
Hispanic	22	1050 (11)	495 (12)	555 (11)	0.023
Non-Hispanic white	144	2270 (73)	1114 (73)	1156 (72)	
Non-Hispanic black	22	1000 (11)	481 (10)	519 (12)	
Other Race	10	173 (5)	66 (5)	107 (6)	
Income					
<\$20 000	33	1061 (17)	480 (15)	581 (19)	<0.001
\$20 000–<\$45 000	57	1419 (29)	697 (30)	722 (29)	
\$45 000–<\$75 000	46	896 (24)	423 (24)	473 (24)	
≥\$75,000	57	940 (30)	469 (31)	471 (28)	
Smoking					
Never smoker	102	2360 (51)	911 (43)	1449 (58)	<0.001
Current smoker	48	989 (24)	572 (28)	417 (21)	
Former smoker	50	1141 (25)	673 (29)	468 (21)	
Anthropometrics					
BMI continuous, kg/m ²	196	28.6 ± 0.2	28.6 ± 0.3	28.6 ± 0.3	0.888
BMI category					
Underweight: <18.5	3	73 (2)	28 (1)	45 (2)	<0.001
Normal: 18.5–<25	61	1263 (31)	546 (25)	717 (36)	
Overweight: 25–<30	65	1519 (33)	873 (41)	646 (26)	
Obese: ≥30	68	1566 (34)	2119 (33)	2302 (36)	
Obese I: 30–<35	38	904 (19)	440 (21)	464 (18)	
Obese II: 35–<40	18	398 (9)	146 (8)	252 (11)	
Obese III: 40+	12	264 (6)	86 (4)	178 (7)	
Waist circumference, cm	193	97.8 ± 0.7	101.4 ± 0.7	94.4 ± 0.7	<0.001
Waist circumference category					
Normal: <94 cm for men, <80 for women	51	1046 (26)	678 (33)	368 (21)	<0.001
Overweight: 94–102 for men, 80–88 for women	38	834 (20)	460 (22)	374 (18)	
Obese: ≥102 for men, ≥88 for women	103	2432 (54)	924 (46)	1508 (61)	
Insulin resistance					
HOMA insulin resistance index	94	3.12 ± 0.09	3.32 ± 0.13	2.92 ± 0.17	0.134
Insulin resistance (HOMA-IR ≥3.29)	23	541 (22)	279 (26)	262 (19)	0.002
Diabetes	16	457 (15)	224 (14)	233 (17)	0.195
Atopy	82	1896 (41)	1013 (47)	883 (36)	<0.001
Asthma	16	351 (8)	138 (6)	213 (10)	<0.001
Atopic asthma	10	210 (5)	93 (5)	117 (5)	0.950
Nonatopic asthma	6	141 (3)	45 (2)	96 (5)	<0.001

SD, Standard deviation; BMI, body mass index; HOMA, homeostasis model assessment.

*Column percentages for categorical variables.

Table 2 Prevalence of atopy associated with obesity measures and insulin resistance

Risk factors	Age-standardized prevalence of atopy, % (SD)	Odds ratio (95% CI)	
		Adjusted for confounders*	Adjusting for confounders + insulin resistance status†
BMI, kg/m ²			
Underweight: <18.5	42.2 ± 5.5	0.88 (0.6, 1.29)	1.18 (0.56, 2.49)
Normal: 18.5–<25	41.4 ± 1.5	1	1
Overweight: 25–<30	43.4 ± 1.5	0.94 (0.81, 1.09)	1.18 (0.87, 1.60)
Obesity: ≥30	40.9 ± 1.6	0.89 (0.67, 1.19)	0.88 (0.66, 1.17)
Obese I: 30–<35	41.8 ± 1.7	0.88 (0.76, 1.02)	0.86 (0.63, 1.19)
Obese II: 35–<40	38.7 ± 2.4	0.78 (0.63, 0.97)	0.82 (0.59, 1.14)
Obese III: 40+	41.4 ± 4.1	0.95 (0.68, 1.35)	1.08 (0.72, 1.62)
Waist circumference (cm)			
Normal: <94 for men, <80 for women	42.2 ± 1.6	1	1
Overweight: 94–102 for men, 80–88 for women	44.1 ± 1.7	1.14 (0.96, 1.35)	1.20 (0.84, 1.71)
Obese: ≥102 for men, ≥88 for women	41.1 ± 1.5	1.01 (0.86, 1.19)	1.13 (0.86, 1.47)
		Odds ratio (95% CI)	
		Adjusted for confounders*	Adjusted for confounders + BMI‡
Insulin resistance category			
Insulin sensitive	40.3 ± 1.8	1	1
Insulin resistant: HOMA ≥ 3.29 μU/ml	43.3 ± 2.3	1.05 (0.82, 1.35)	1.13 (0.84, 1.52)
Diabetic	51.3 ± 3.5	1.16 (0.86, 1.56)	1.22 (0.92, 1.63)

SD, Standard Deviation; CI, Confidence Intervals; BMI, body mass index; HOMA, homeostasis model assessment.

*Adjusted for age (20–44, 45–64, ≥65 years), sex (male, female), ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), smoking status (nonsmoker, current smoker, former smoker), and annual income (<\$20 000, \$20 000–\$45 000, \$45 000–<\$75 000, ≥\$75 000).

†Adjusted for age, sex, ethnicity, smoking status, and income (as categorized above), and insulin resistance status.

‡Adjusted for age, sex, ethnicity, smoking status, and income (as categorized above), and BMI.

The association between diabetes and asthma prevalence was not statistically significant either.

Atopic and NonAtopic Asthma

Obesity

Similar to asthma overall, the odds of having atopic and nonatopic asthma increased approximately 1% per SD increase in BMI and waist circumference (Table 4). Compared with normal-weight individuals, the odds of having atopic and nonatopic asthma were significantly greater in obese individuals based on BMI (OR for atopic asthma = 2.04, 95% CI: 1.37, 3.03; OR for nonatopic asthma = 2.50, 95% CI: 1.20, 5.20), particularly individuals in obesity class III (OR for atopic asthma = 3.06, 95% CI: 2.05, 4.59; OR for nonatopic asthma = 3.01, 95% CI: 1.05, 8.64).

The positive associations of atopic asthma with obesity did not change when IR status was added to the multivariate model (OR for BMI ≥30 = 2.63, 95% CI: 1.64, 4.2; OR for obesity class III = 4.66, 95% CI: 2.38, 9.15). For nonatopic asthma, the addition of IR status to the model did not change the association for obese individuals (OR for BMI ≥30 = 3.24, 95% CI: 1.33, 7.89) but it diminished the association for those in obesity class III (OR for BMI ≥ 40 = 2.30, 95% CI: 0.76, 7.0).

A similar pattern, albeit weaker, for both atopic and nonatopic asthma was also observed for participants with abdominal obesity, and the associations persisted after controlling for IR status.

Insulin resistance

Insulin-resistant individuals did not have increased odds of either atopic or nonatopic asthma whether or not BMI was included in the multivariate model (Table 4). Further, there was also no association between diabetes and either atopic or nonatopic asthma.

Effect modification

None of the interaction terms between either obesity measure and IR was significant. Similarly, there was no evidence that sex modified the relationships between either obesity measure, IR, and the four outcomes.

Discussion

This analysis found that neither obesity, measured by BMI and waist circumference, nor IR was associated with atopy. Both obesity measures were significantly associated with asthma, and atopic and nonatopic asthma, after adjusting for

Table 3 Prevalence of asthma associated with obesity measures and insulin resistance

Risk factors	Age-standardized prevalence of asthma, % (SD)	Odds ratios (95% CI)	
		Adjusted for confounders*	Adjusted for confounders + insulin resistance status†
BMI, kg/m ²			
Continuous, standardized‡		1.01 (1.006, 1.014)	1.011 (1.003, 1.019)
Underweight: <18.5	8.9 ± 4.3	0.91 (0.27, 3.05)	0.3 (0.06, 1.59)
Normal: 18.5–<25	6.1 ± 0.7	1	1
Overweight: 25–<30	6.4 ± 1.1	1.28 (0.82, 2.01)	1.83 (0.93, 3.61)
Obese: ≥30	11.9 ± 1.2	2.28 (1.76, 2.96)	3.04 (1.90, 4.87)
Obese I: 30–<35	10.7 ± 1.5	2.09 (1.54, 2.85)	2.37 (1.34, 4.19)
Obese II: 35–<40	11.2 ± 1.8	2.06 (1.41, 3.00)	4.05 (2.29, 7.17)
Obese III: 40+	16.3 ± 3.2	3.24 (2.01, 5.23)	4.12 (2.04, 8.32)
Waist circumference (cm)			
Continuous, standardized‡		1.012 (1.007, 1.018)	1.014 (1.007, 1.022)
Normal: <94 for men, <80 for women	6.0 ± 0.8	1	1
Overweight: 94–102 for men, 80–88 for women	7.0 ± 1.2	1.26 (0.81, 1.97)	1.39 (0.83, 2.34)
Obese: ≥102 for men, ≥88 for women	9.9 ± 0.8	1.75 (1.22, 2.51)	2.23 (1.30, 3.85)
		Odds ratio (95% CI)	
		Adjusted for confounders*	Adjusted for confounders + BMI§
Insulin resistance category			
Insulin sensitive	7.9 ± 0.8	1	1
Insulin resistant: HOMA ≥ 3.29 μU/ml	9.0 ± 1.6	1.26 (0.80, 1.98)	0.72 (0.43, 1.20)
Diabetic	11.9 ± 2.9	1.27 (0.81, 2.00)	0.82 (0.54, 1.25)

SD, Standard Deviation; CI, Confidence Intervals; BMI, body mass index; HOMA, homeostasis model assessment.

*Adjusted for age (20–44, 45–64, ≥65 yrs), sex (male, female), ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), smoking status (nonsmoker, current smoker, former smoker), and annual income (<\$20 000, \$20 000–\$45 000, \$45 000–<\$75 000, ≥\$75,000).

†Adjusted for age, sex, ethnicity, smoking status, and income (as categorized above), and insulin resistance status.

‡Standardized as (raw value–mean)/standard deviation and examined as a continuous variable in the logistic regression model.

§Adjusted for age, sex, ethnicity, smoking status, and income (as categorized above), and BMI.

socio-demographic factors and smoking status. Further, the strength of the association persisted with adjustment of IR status, providing evidence that, in this representative sample of US adults, obesity had an independent, possibly dose–response effect on asthma (atopic and nonatopic), and IR does not appear to be a mediator of this relationship. In contrast, there was no observed association between IR and any asthma outcome.

This is the first known analysis of the association between obesity, IR, and atopy and asthma in a population-based US sample. Findings from this analysis are somewhat consistent with a similar recent cross-sectional analysis of approximately 3600 men and women in Denmark, a subsample in a population-based survey (18). Like this analysis, that study reported a positive association between obesity measures (BMI and waist circumference) and both atopic and nonatopic asthma after controlling for similar individual factors. However, after adding IR to the multivariate model that included BMI, the positive association with both

asthma outcomes persisted in the NHANES sample while the association disappeared for atopic asthma in the Danish sample.

Other important differences between the studies' findings also exist. For example, a positive association was also observed in the Danish sample between both obesity and IR and atopy, findings that were not observed in this analysis. The Danish study also reported a positive association between IR and atopic asthma, a finding that persisted after controlling for BMI, whereas this study observed no association at all.

In a more recent prospective cohort study drawn from the same Danish study population as the previous study, Thuesen et al. (19) reported a positive association between multiple obesity measures and IR, independently, and the incidence of asthma-like symptoms after controlling for similar socio-demographic factors. However, the prospective study did not include atopy, nor atopic and nonatopic asthma, as outcomes.

Table 4 Prevalence of atopic and nonatopic asthma associated with obesity measures and insulin resistance

Risk factors	Atopic asthma, OR (95% CI)		Nonatopic asthma, OR (95% CI)	
	Adjusted for confounders*	Adjusted for confounders + insulin resistance status†	Adjusted for confounders*	Adjusted for confounders + insulin resistance status†
BMI, kg/m ²				
Continuous, standardized‡	1.008 (1.003, 1.014)	1.011 (1.002, 1.019)	1.011 (1.005, 1.017)	1.007 (1.001, 1.014)
Underweight: <18.5	1.4 (0.3, 6.45)	N/A	0.33 (0.07, 1.6)	0.87 (0.16, 4.61)
Normal: 18.5–<25				1
Overweight: 25–<30	1.03 (0.57, 1.87)	1.28 (0.67, 2.43)	1.75 (0.78, 3.94)	2.83 (0.9, 8.88)
Obese: ≥30	2.04 (1.37, 3.03)	2.63 (1.64, 4.2)	2.5 (1.2, 5.2)	3.24 (1.33, 7.89)
Obese I: 30–<35	1.96 (1.14, 3.39)	2.1 (1.08, 4.08)	2.11 (1.07, 4.17)	2.51 (0.95, 6.63)
Obese II: 35–<40	1.53 (0.88, 2.64)	2.97 (1.54, 5.76)	2.9 (1.36, 6.17)	5.1 (1.99, 13.11)
Obese III: 40+	3.06 (2.05, 4.59)	4.66 (2.38, 9.15)	3.01 (1.05, 8.64)	2.3 (0.76, 7.0)
Waist circumference (cm)				
Continuous, standardized‡	1.011 (1.004, 1.018)	1.016 (1.007, 1.025)	1.013 (1.004, 1.021)	1.009 (1.001, 1.017)
Normal: <94 for men, <80 for women	1	1	1	1
Overweight: 94–102 for men, 80–88 for women	1.2 (0.73, 1.98)	1.07 (0.55, 2.07)	1.39 (0.79, 2.44)	1.97 (0.92, 4.24)
Obese: ≥102 for men, ≥88 for women	1.55 (0.98, 2.46)	1.95 (1.13, 3.36)	2.07 (1.21, 3.54)	2.49 (1.09, 5.7)
Insulin resistance category	Atopic asthma, OR (95% CI)		Nonatopic asthma, OR (95% CI)	
	Adjusted for confounders*	Adjusted for confounders + BMIs	Adjusted for confounders*	Adjusted for confounders + BMIs
Insulin sensitive	1	1	1	1
Insulin resistant: HOMA ≥ 3.29 µU/ml	1.15 (0.66, 2.01)	0.61 (0.33, 1.14)	1.36 (0.8, 2.31)	0.93 (0.54, 1.62)
Diabetic	1.6 (0.89, 2.85)	0.95 (0.59, 1.54)	0.91 (0.49, 1.71)	0.68 (0.35, 1.32)

SD, Standard Deviation; OR, Odds Ratio; CI, Confidence Intervals; BMI, body mass index; HOMA, homeostasis model assessment; N/A, estimate not available because of no atopic asthma in the underweight category after adjusting for IR status.

*Adjusted for age (20–44, 45–64, ≥65 years), sex (male, female), ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), smoking status (nonsmoker, current smoker, former smoker), and annual income (<\$20 000, \$20 000–\$45 000, \$45 000–\$75 000, ≥\$75 000).

†Adjusted for age, sex, ethnicity, smoking status, and income (as categorized above), and insulin resistance status.

‡Standardized as (raw value–mean)/standard deviation and examined as a continuous variable in the logistic regression model.

§Adjusted for age, sex, ethnicity, smoking status, and income (as categorized above), and BMI.

The incongruent findings between the NHANES and Danish studies may be at least partially explained by differences in the study populations. For example, the NHANES sample had a higher prevalence of obesity than the Danish samples – 34% vs 15–18% of participants having BMI ≥ 30 kg/m². Further, 54% of the NHANES sample was obese based on their waist circumference compared to 20–21% of the Danish samples. The NHANES sample also had a higher prevalence of atopy (41% vs 26%), although the prevalence of asthma was similar in the studies (~8%).

The findings of this study regarding obesity and asthma and nonatopic asthma are supported in the rest of the literature (7). However, data on the relationship between obesity and atopic asthma are mixed, with some reporting a positive association as did this study and others reporting null findings (10, 11). It is clear that additional research is needed to clarify the association.

Contrary to recent research inquiries regarding the role of metabolic changes in asthma pathophysiology, this study did not provide support for the hypothesis that IR mediates the relationship between obesity and asthma. Indeed, the lack of association between IR and any of the asthma outcomes, with or without controlling for BMI, suggests no relationship between IR and prevalent asthma, but such a conclusion needs further investigation through prospective cohort or experimental studies.

The contribution of these results should be interpreted in the context of the study limitations. Cross-sectional data such as NHANES are inherently limited when trying to clarify disease mechanisms, such as the direction and causality of the relationship between obesity and IR and atopy and asthma. Moreover, because prevalence is a function of both incidence of disease and survival with disease, the associations observed in this analysis can reflect factors associated with living with asthma as well as causes/mechanisms of asthma. Consequently, these results alone cannot clarify whether obesity is related to asthma incidence or prevalence, although past studies have shown that obesity is related to both (29–31). Although the interpretations of cross-sectional data are limited, such data can be useful in identifying factors associated with disease prevalence and in generating potential hypotheses for longitudinal studies. As such, the use of prevalence data such as NHANES is a necessary step toward developing hypotheses to be investigated in prospective cohort and/or

intervention studies to further elucidate the relationship between obesity, insulin resistance, and asthma.

Another limitation of NHANES is the definition of asthma based on self-report, which is subject to recall bias and misclassification. However, it is not feasible for large epidemiological studies such as NHANES to validate all self-reported medical histories. The 2-part definition of asthma used in this analysis (ever diagnosed plus still have asthma) is consistent with other NHANES asthma reports (22–24). To gauge the risk of bias and misclassification, we performed sensitivity analyses using more stringent asthma case definitions – ever diagnosed by a doctor and still have asthma *plus* chest wheezing/whistling in the past year *plus* asthma medication use in the past month. With each added criterion, the prevalence decreased (from 8% to 3%) but with relatively little change in the direction and magnitude of the observed association with obesity and IR measures.

Likewise, it is not practical to use the 'gold standard' euglycemic-hyperinsulinemic clamp method to quantify insulin resistance in the NHANES sample because of its complexity and high cost. The HOMA model has been validated and is in widespread use in epidemiological and clinical studies (32). Despite these limitations, the NHANES provides a large national sample that is generally considered representative of US population, with minimum selection bias.

In conclusion, neither obesity nor IR was associated with atopy in a representative sample of US adults. Obesity was, however, positively associated with asthma overall, as well as atopic and nonatopic asthma, while IR was associated with none of them. Further, the association between obesity and asthma persisted after controlling for IR, which implies that the obesity–asthma relationship is not explained by metabolic changes associated with IR. The findings need to be confirmed in prospective cohort and experimental studies to provide further information about the mutual roles of both obesity and IR in the pathophysiology of atopy and asthma. More research is also needed to unravel the mechanisms underlying the obesity and asthma relationship.

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