

Original article

Association of obesity and insulin resistance with asthma and aeroallergen sensitization

Background: It has been hypothesized that obesity and insulin resistance may play a role in the development of asthma and allergy. The aim of the study was to examine the association of obesity and insulin resistance with asthma and aeroallergen sensitization.

Methods: Cross-sectional population-based study of 3609 Danish men and women aged 30–60 years. Aeroallergen sensitization was defined as positive levels of specific IgE against a panel of inhalant allergens. Asthma was defined as self-reported physician diagnosed asthma. Allergic asthma was defined as the presence of both asthma and aeroallergen sensitization. The homeostasis model assessment of insulin resistance was used to estimate the degree of insulin resistance. Body mass index, waist-to-hip ratio, and waist circumference were used as measures of obesity. Data were analyzed by multiple logistic regression analyses.

Results: Obesity was associated with increased risk of aeroallergen sensitization as well as allergic and nonallergic asthma. Insulin resistance was associated with aeroallergen sensitization and allergic asthma, but not nonallergic asthma. The associations of obesity with aeroallergen sensitization and allergic asthma became nonsignificant after adjustment for insulin resistance, whereas the association of obesity with nonallergic asthma was unaffected. No sex-differences were observed.

Conclusion: Obesity may be related to an increased risk of aeroallergen sensitization and allergic asthma through mechanisms also involved in the development of insulin resistance.

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The prevalence of aeroallergen sensitization (atopy) and asthma has increased in adults during recent decades (1–3). The specific factors responsible for this increase are unknown. Changes towards a westernized, urban, and affluent lifestyle appear to be followed by an increasing prevalence of aeroallergen sensitization and atopic diseases such as asthma (4–7). Research on the causes of this epidemic has to a large extent been focusing on environmental factors, such as exposure to allergens, microorganisms, and air pollution. However, in most countries the increase in aeroallergen sensitization and asthma has been accompanied by a marked increase in overweight and obesity. Furthermore, an increasing number of epidemiological studies support that obesity is associated with increased risk of developing asthma (8–11), but the underlying biological mechanisms are not known. The epidemiological association of obesity with IgE sensitization is less clear (8). Insulin resistance is considered to be a major contributing factor to the close relationship between obesity and the development of type 2 diabetes. Recently, it has been hypothesized that insulin resistance may play a role in the causation of asthma and allergy

(12–14). The possible links between insulin resistance and allergic diseases may be that they share some common inflammatory pathways or mediators of immune responses e.g. adipokines and cytokines secreted from adipose tissue (15–17). As yet, there are no epidemiological population-based studies on the relationship of insulin resistance to asthma and allergy.

The aim of this study was to examine the association of obesity measures and insulin resistance with aeroallergen sensitization and asthma in a population-based sample of 3609 Danish men and women aged 30–60 years.

Methods

Study population

The subjects were participants in the Inter99 study, a population-based randomized controlled trial, investigating the effect of nonpharmacological intervention on cardiovascular disease and diabetes. The Inter99 study has been approved by the ethics committee, and informed consent has been obtained from all participants. The Inter99 study has been described in detail elsewhere (18).

Briefly, an age- and sex-stratified random sample of 13 016 persons born in 1939–1940, 1944–1945, 1949–1950, 1954–1955, 1959–1960, 1964–1965, 1969–1970 and living in 11 municipalities in the southwestern part of the Copenhagen County was drawn from the Civil Registration System and invited to a health examination from March 1999 through January 2001. A total of 12 934 persons were eligible for invitation of which 6784 (52.5%) participated. The health examination included a self-administered questionnaire, a physical examination, a 2-h oral glucose tolerance test, and various blood tests. A sub-sample of 3609 participating individuals (those born in 1939–1940, 1949–1950, 1959–1960, and 1969–1970) were selected for assessment of aeroallergen sensitization status and included in the current study.

Assessment of aeroallergen sensitization

Measurement of aeroallergen sensitization was performed by using the ADVIA Centaur® Allergy Screen (AS) assay (Bayer HealthCare Diagnostics division, Tarrytown, NY, USA) (19). The AS assay is a multi-allergen assay for the qualitative detection of IgE antibodies specific to common inhalant allergens in serum. The test encompasses a mixture of the 19 most commonly encountered inhalant allergens: two house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*), three animal danders (horse, cat, and dog), two grasses (*Phleum pratense* and *Cynodon dactylon*), three molds (*Cladosporium herbarium*, *Aspergillus fumigatus*, and *Alternaria alternata*), four trees (*Betula verucosa*, *Quercus alba*, *Olea europae*, and *Cryptomeria japonica*), four weeds (*Ambrosia artemisifolia*, *Artemisia vulgaris*, *Plantago lanceolata*, and *Parietaria officinalis*), and finally one insect (*Blattella germanica*). Aeroallergen sensitization was defined as a positive result of the dichotomized AS assay test output. The AS assay has previously been validated and proved to be a valid measure of allergic respiratory disease and skin prick test reactivity (19).

Assessment of asthma

Information on asthma was obtained from a self-administered questionnaire. Asthma was defined as a positive answer to the question: 'has a physician ever told you that you have asthma?' Allergic asthma was defined as having asthma as well as aeroallergen sensitization. Nonallergic asthma was defined as having asthma without aeroallergen sensitization.

Assessment of insulin resistance

The homeostasis model assessment of insulin resistance (HOMA-IR) was used to estimate the degree of insulin resistance. The HOMA-IR index was estimated from fasting plasma glucose and fasting serum insulin concentrations using the following formula: $\text{HOMA-IR index} = [\text{fasting plasma glucose (mmol/l)} \times \text{fasting serum insulin (mU/l)}] / 22.5$ (20, 21). Insulin was measured by a fluoroimmunoassay technique (Dako Diagnostics Ltd, Ely, UK). Glucose concentrations were analyzed by hexokinase/glucose-6-phosphate dehydrogenase assay (Boehringer Mannheim, Germany). Insulin resistance was defined as HOMA-IR index in the upper 25% quartile (≥ 1.77) of the nondiabetic population (22). Individuals with diabetes ($n = 203$) were categorized in a separate category.

Assessment of obesity

Height and weight were measured wearing light clothes and no shoes. Body mass index (BMI) was calculated as weight divided by

height squared. Waist circumference (WC) was measured without clothes midway between the lower rib margin and iliac crest. Hip circumference was measured over light clothing at the widest girth of the hip, using an un-stretched tape meter, without any pressure to the body surface. Waist-to-hip ratio (WHR) was calculated as WC divided by hip circumference. Degrees of obesity based on BMI, WHR, and WC were defined and categorized according to the following criteria. Body mass index criteria: underweight ($< 18.50 \text{ kg/m}^2$), normal range ($\geq 18.50\text{--}25.00 \text{ kg/m}^2$), overweight ($\geq 25\text{--}30 \text{ kg/m}^2$), and obese ($\geq 30 \text{ kg/m}^2$). Waist-to-hip ratio criteria: normal (≤ 1.00 for men and ≤ 0.85 for women), and obese (> 1.00 for men and > 0.85 for women). Waist circumference criteria: normal ($< 94 \text{ cm}$ for men and $< 80 \text{ cm}$ for women), overweight ($\geq 94\text{--}102 \text{ cm}$ for men and $\geq 80\text{--}88 \text{ cm}$ for women), and obese ($\geq 102 \text{ cm}$ for men and $\geq 88 \text{ cm}$ for women) (23).

Confounders

The self-administered questionnaire provided information on the potential confounders adjusted for in the regression analyses. Socioeconomic status was defined on the basis of questions regarding employment status and number of years of vocational training and categorized into four social classes: 1 (unemployed, no vocational training), 2 (unemployed, ≥ 1 year of vocational training), 3 (employed, no vocational training), and 4 (employed, ≥ 1 year of vocational training). In addition missing values ($n = 315$) were categorized in a separate category. Smoking status was defined in four categories: never smokers, ex-smokers, occasional smokers ($< 1 \text{ g}$ of tobacco/cigarettes/day), and daily smokers ($\geq 1 \text{ g/day}$).

Statistical analyses

Statistics were computed using SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA). Risk (odds ratio) of aeroallergen sensitization, asthma, allergic asthma, and nonallergic asthma associated with obesity measures and insulin resistance were estimated in multiple logistic regression models adjusted for sex, age, smoking status, and socioeconomic status. Effect modifications by sex were examined by including the relevant interaction terms in the various models i.e. sex $\times$ BMI, sex $\times$ WHR, sex $\times$ WC, and sex $\times$ HOMA-IR. Continuous variables were tested for nonlinear associations by including the squared term of the variables in the models. Linear trends (dose-response relationship) across ordered categories were tested by scoring the categories and modeling the variables as continuous variables in the models. Persons with missing values were excluded where relevant. P -values of likelihood ratio tests were used to test for statistical significance ($P < 0.05$) in all logistic regression analyses.

Results

Characteristics of the study population are shown in Table 1. The overall prevalence of aeroallergen sensitization and self-reported asthma was 25.8% and 8.3%, respectively. The prevalence of aeroallergen sensitization and insulin resistance was higher among men than among women, whereas the prevalence of asthma was higher among women than among men. The prevalence of obesity ranged from 7.2% to 23.4% depending on sex and the anthropometric measure used.

Table 1. Characteristics of the study population by sex¶

Characteristics	All participants ($N_{\text{total}} = 3609$)†	Men ($N_{\text{total}} = 1743$)†	Women ($N_{\text{total}} = 1866$)†
Demographics			
Men	48.3 (1743)‡	—	—
Younger age (30 + 40 years)	46.3 (1669)‡	43.9 (765)‡	48.5 (904)‡***
Confounders			
Low socioeconomic status (social class 1 + 2)	12.4 (409)‡	10.7 (172)‡	14.0 (137)‡***
Daily smoker	34.9 (1250)‡	35.8 (619)‡	34.1 (631)‡
Anthropometrics			
Body mass index (kg/m ²)	25.6 (19.4–37.5)§	26.3 (20.5–36.1)§	24.7 (18.8–39.3)§***
Waist-to-hip ratio	0.85 (0.70–1.02)§	0.91 (0.80–1.05)§	0.79 (0.69–0.94)§***
Waist circumference (cm)	85 (64–114)§	92 (75–116)§	78 (62–109)§***
Obesity _{BMI} (BMI ≥ 30 kg/m ²)	17.6 (634)‡	17.8 (310)‡	17.4 (324)‡
Obesity _{WHR} (♂: WHR >1.00, ♀: WHR >0.85)	12.4 (448)‡	7.2 (125)‡	17.4 (323)‡***
Obesity _{WC} (♂: WC ≥102 cm, ♀: WC ≥88 cm)	21.1 (760)‡	18.7 (325)‡	23.4 (435)‡***
Insulin resistance			
HOMA insulin resistance index	1.15 (0.37–4.09)§	1.28 (0.38–4.44)§	1.08 (0.36–3.90)§***
Diabetes or insulin resistance (HOMA-IR ≥ 1.77)	29.7 (978)‡	36.0 (572)‡	23.8 (406)‡***
Asthma and aeroallergen sensitization			
Aeroallergen sensitization	25.8 (865)‡	28.0 (468)‡	23.6 (397)‡***
Asthma	8.3 (290)‡	6.8 (114)‡	9.8 (176)‡***
Allergic asthma	4.5 (146)‡	4.5 (72)‡	4.6 (74)‡
Nonallergic asthma	3.7 (121)‡	2.1 (34)‡	5.3 (87)‡***

BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; HOMA-IR, HOMA insulin resistance index.

† N_{total} may vary on account of missing information on some of the covariates.

‡% (n).

§Median (2.5–97.5 percentiles).

¶The differences between men and women were tested by Wilcoxon two-sample test and chi-square analyses: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Tables 2 and 3 shows that the prevalence of aeroallergen sensitization and asthma was higher in the obese and in the insulin resistant participants compared to the nonobese and noninsulin resistant participants, respectively. Additionally, obesity (BMI, WHR, and WC) and insulin resistance were associated with a significantly higher risk of aeroallergen sensitization as well as asthma when examined by multiple regression analyses (Tables 2 and 3). Adjustment for age, sex, smoking, and socioeconomic status did not change these associations substantially.

However, in analyses with aeroallergen sensitization as outcome, the effects of obesity measures were attenuated towards the null value and became nonsignificant (except for WHR) after adjusting for insulin resistance (Table 2). In contrast, the association between insulin resistance and aeroallergen sensitization was neither affected by adjustment for BMI (Table 2) nor WHR or WC (data not shown).

In analyses with asthma as outcome, mutually adjustment for insulin resistance and obesity did not seem to affect the associations to a great extent, except for the association between insulin resistance and asthma became statistically nonsignificant (Table 3).

Table 4 shows the results of the regression analyses using allergic and nonallergic asthma as outcomes, respectively. The obesity measures were associated with increased risk of allergic asthma as well as nonallergic asthma. However, only the associations with nonallergic

asthma remained statistically significant, while the associations with allergic asthma attenuated toward the null value after adjustment for insulin resistance (Table 4). In contrast, insulin resistance was associated with a higher risk of allergic asthma, but not with nonallergic asthma (Table 4). The association with allergic asthma remained statistically significant after adjustment for BMI (Table 4). Similar results were obtained when including WHR or WC instead of BMI in the model (data not shown).

Finally, we tested whether any of the associations of obesity measures and insulin resistance with aeroallergen sensitization and asthma outcomes were modified by sex. No statistically significant interactions were observed (results not shown).

Discussion

All obesity measures (BMI, WHR, and WC) examined in this study were associated with increased risk of aeroallergen sensitization and asthma including allergic and nonallergic asthma. Insulin resistance was associated with aeroallergen sensitization and allergic asthma, but not with nonallergic asthma.

The association between obesity and allergic disease has been examined in several epidemiological studies. In agreement with our results, a positive association between BMI and asthma has relatively consistently been demon-

Table 2. Risk of aeroallergen sensitization associated with obesity measures and insulin resistance

Risk factors	Prevalence of aeroallergen sensitization % (n/n_{total})	Risk of aeroallergen sensitization OR (95% CI)	
Obesity measures	Crude	+Confounders	+Confounders + HOMA-IR
Body mass index			
Underweight (<18.5 kg/m ²)	18.9 (7/37)	0.90 (0.39–2.11)*	0.92 (0.39–2.15)†
Normal (≥18.5–25 kg/m ²)	23.4 (309/1318)	1.00	1.00
Overweight (≥25–30 kg/m ²)	27.0 (317/1176)	1.18 (0.98–1.42)*	1.13 (0.93–1.36)†
Obese (≥30 kg/m ²)	28.7 (154/537)	1.33 (1.05–1.68)*	1.11 (0.86–1.44)†
	$N = 3068¶$	$P_{\text{trend}} = 0.01$	$P_{\text{trend}} = 0.28$
BMI continuous (per 5 kg/m ²)		1.10 (1.00–1.20)*	1.01 (0.91–1.12)†
		$P = 0.04$	$P = 0.90$
Waist-to-hip ratio			
Normal	25.1 (674/2687)	1.00	1.00
Obese (♂ ≥1.00, ♀ ≥0.85)	29.8 (111/373)	1.55 (1.20–1.98)*	1.38 (1.07–1.80)†
	$N = 3060¶$	$P = 0.00$	$P = 0.02$
WHR continuous (per 0.1)		1.31 (1.15–1.51)*	1.22 (1.06–1.41)†
		$P = 0.00$	$P = 0.01$
Waist circumference			
Normal	24.7 (427/1731)	1.00	1.00
Overweight (♂: ≥94–102 cm, ♀: ≥80–88 cm)	26.6 (183/689)	1.15 (0.93–1.41)*	1.09 (0.88–1.34)†
Obese (♂: ≥102 cm, ♀: ≥88 cm)	27.3 (175/642)	1.25 (1.01–1.55)*	1.06 (0.84–1.34)†
	$N = 3062¶$	$P_{\text{trend}} = 0.03$	$P_{\text{trend}} = 0.94$
WC continuous (per 5 cm)		1.05 (1.01–1.09)*	1.02 (0.98–1.06)†
		$P = 0.01$	$P = 0.45$
Insulin resistance	Crude	+Confounders	+Confounders + BMI
HOMA insulin resistance index			
Noninsulin resistant	23.6 (510/2165)	1.00	1.00
Insulin resistant (HOMA-IR ≥ 1.77 µU/ml)	30.9 (222/718)	1.37 (1.13–1.66)*	1.32 (1.07–1.63)‡
Diabetic§	29.7 (55/185)	1.59 (1.13–2.25)*	1.55 (1.08–2.21)‡
	$N = 3068¶$	$P_{\text{trend}} = 0.00$	$P_{\text{trend}} = 0.00$
HOMA-IR continuous (per 1.0)		1.15 (1.06–1.24)*	1.15 (1.05–1.25)‡
		$P = 0.00$	$P = 0.00$

BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; HOMA-IR, HOMA insulin resistance index; OR, odds ratio; CI, confidence interval.

*Adjusted for age, sex, smoking status, and socioeconomic status.

†Adjusted for age, sex, smoking status, socioeconomic status, and insulin resistance.

‡Adjusted for age, sex, smoking status, socioeconomic status, and body mass index.

§Diabetics were categorized in a separate category.

¶Number of observations with complete data used in the regression analyses.

strated in both cross-sectional and longitudinal studies (8, 9). However, most studies on the relation between obesity and allergic disease have considered only BMI and not alternative obesity measures, such as WHR and WC as examined in this study. Although the prevalence of obesity was lower using the WHR criteria compared to the BMI or WC criteria the associations with aeroallergen sensitization and asthma generally seemed to be in the same order of magnitude suggesting that all measures can be used. However, WHR and WC are probably better measures of visceral obesity, which is hypothesized to be of importance regarding insulin resistance. Future studies may consider other measures of obesity, such as body fatness (bio-impedance) and visceral fatness as assessed by ultrasound.

Some studies have reported a stronger relation between BMI and asthma among women than among men. We did not observe any effect modification by sex for any of the obesity measures examined.

Studies examining the relationship of obesity with allergic and nonallergic asthma have been inconsistent. In agreement with our observations, some studies have found an association between obesity and both allergic and nonallergic asthma (24). In contrast, other studies have observed an association between obesity and non-allergic asthma but not allergic asthma (25, 26).

The relation between BMI and aeroallergen sensitization (atopy) has been examined in a few studies, and in contrast with our results, no association or an association only among females was found (8).

To our knowledge this is the first epidemiological population-based study on the relationship of insulin resistance with asthma and aeroallergen sensitization. However, our results are supported by a recent study in morbidly obese children also reporting an association between insulin resistance and asthma (14).

We also reported that the associations of obesity measures with aeroallergen sensitization and allergic

Table 3. Risk of asthma associated with obesity measures and insulin resistance

Risk factors	Prevalence of asthma % (n/n _{total})	Risk of asthma OR (95% CI)	
Obesity measures	Crude	+Confounders	+Confounders + HOMA-IR
Body mass index			
Underweight (<18.5 kg/m ²)	11.1 (4/36)	1.31 (0.45–3.82)*	1.33 (0.46–3.88)†
Normal (≥18.5–25 kg/m ²)	8.0 (109/1364)	1.00	1.00
Overweight (≥25–30 kg/m ²)	6.9 (83/1207)	0.92 (0.68–1.25)*	0.87 (0.64–1.19)†
Obese (≥30 kg/m ²)	12.3 (69/561)	1.61 (1.16–2.23)*	1.38 (0.95–2.00)†
	N = 3168¶	P _{trend} = 0.02	P _{trend} = 0.25
BMI continuous (per 5 kg/m ²)		1.24 (1.10–1.40)	1.20 (1.04–1.38)
		P = 0.00	P = 0.01
Waist-to-hip ratio			
Normal	7.6 (211/2769)	1.00	1.00
Obese (♂ ≥1.00, ♀ ≥0.85)	13.6 (53/391)	1.68 (1.20–2.35)*	1.51 (1.06–2.15)†
	N = 3160¶	P = 0.00	P = 0.02
WHR continuous (per 0.1)		1.26 (1.03–1.54)	1.18 (0.96–1.47)
		P = 0.03	P = 0.12
Waist circumference			
Normal	6.8 (120/1778)	1.00	1.00
Overweight (♂: ≥94–102 cm, ♀: ≥80–88 cm)	8.6 (61/711)	1.32 (0.95–1.83)*	1.28 (0.92–1.78)†
Obese (♂: ≥102 cm, ♀: ≥88 cm)	12.3 (83/673)	1.85 (1.37–2.50)*	1.69 (1.20–2.38)†
	N = 3162¶	P _{trend} = 0.00	P _{trend} = 0.00
WC continuous (per 5 cm)		1.10 (1.105–1.16)	1.09 (1.03–1.16)
		P = 0.00	P = 0.00
Insulin resistance			
HOMA insulin resistance index			
Noninsulin resistant	7.4 (166/2232)	1.00	1.00
Insulin resistant (HOMA-IR ≥1.77 μU/ml)	10.6 (79/745)	1.52 (1.14–2.03)*	1.35 (0.98–1.87)‡
Diabetic§	10.5 (20/191)	1.39 (0.83–2.30)*	1.20 (0.71–2.05)‡
	N = 3168¶	P _{trend} = 0.01	p _{trend} = 0.17
HOMA-IR continuous (per 1.0)		1.14 (1.02–1.27)	1.07 (0.94–1.21)
		P = 0.02	P = 0.32

BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; HOMA-IR, HOMA insulin resistance index; OR, odds ratio; CI, confidence interval.

*Adjusted for age, sex, smoking status, and socioeconomic status.

†Adjusted for age, sex, smoking status, socioeconomic status, and insulin resistance.

‡Adjusted for age, sex, smoking status, socioeconomic status, and body mass index.

§Diabetics were categorized in a separate category.

¶Number of observations with complete data used in the regression analyses.

asthma (except for WHR and aeroallergen sensitization) were weakened and became nonsignificant after adjusting for insulin resistance, suggesting that obesity is related to aeroallergen sensitization and allergic asthma through mechanisms that may also be involved in the development of insulin resistance.

Obesity and Insulin resistance are causal factors of major importance to the incidence of type 2 diabetes and cardiovascular disease. Cardiovascular disease has been associated with self-reported asthma along with several surrogate measures of allergic disorders, such as total IgE levels, eosinophilia, positive skin prick test results, daily pollen burden, and measurements of lung function (27–31). This supports that asthma, allergy, and cardiovascular disease may share central effector pathways and some common risk factors. At present, cardiovascular disease and type 2 diabetes are considered as low-grade inflammatory diseases (32, 33). Accordingly, asthma and allergy have been associated not only with local, but also

with systemic inflammatory markers e.g. C-reactive protein and fibrinogen, and should probably also be considered as systemic inflammatory diseases (15, 16). The possible links between asthma, allergy, cardiovascular disease, and diabetes may be that they share some common inflammatory pathways or mediators of immune responses. Interestingly, it has been proposed that the relationship of obesity to asthma and allergy may be on account of decreased immunological tolerance to allergens as a consequence of immunological changes induced by adipokines, immunological mediators secreted by adipose tissue (17).

Because of the cross-sectional study design, cause, and effect cannot be determined, as the presence of obesity/insulin resistance and asthma/aeroallergen sensitization were determined simultaneously. Thus, reverse causation cannot be excluded. For example, it is possible that subjects with asthma have adopted a more sedentary lifestyle and thus have gained more weight. Additionally,

Table 4. Risk of allergic and nonallergic asthma associated with obesity measures and insulin resistance

Risk factors	Risk of allergic asthma OR (95% CI)		Risk of nonallergic asthma OR (95% CI)	
	+Confounders	+Confounders + HOMA-IR	+Confounders	+Confounders + HOMA-IR
Obesity measures				
Body mass index ($n = 2974^{\P}$)				
Underweight ($<18.5 \text{ kg/m}^2$)	1.78 (0.41–7.76)*	1.84 (0.42–8.05)†	1.03 (0.24–4.48)*	1.02 (0.23–4.44)†
Normal ($18.5\text{--}25 \text{ kg/m}^2$)	1.00	1.00	1.00	1.00
Overweight ($\geq 25\text{--}30 \text{ kg/m}^2$)	1.03 (0.67–1.56)*	0.94 (0.61–1.45)†	0.89 (0.56–1.40)*	0.89 (0.56–1.40)†
Obese ($\geq 30 \text{ kg/m}^2$)	1.73 (1.10–2.72)* $P_{\text{trend}} = 0.05$	1.31 (0.78–2.18)† $P_{\text{trend}} = 0.50$	1.35 (0.83–2.21)* $P_{\text{trend}} = 0.36$	1.38 (0.79–2.42)† $P_{\text{trend}} = 0.44$
BMI continuous (per 5 kg/m^2)	1.23 (1.04–1.46) $P = 0.02$	1.11 (0.91–1.35) $P = 0.30$	1.21 (1.02–1.45) $P = 0.04$	1.27 (1.03–1.57) $P = 0.03$
Waist-to-hip ratio ($n = 2966^{\P}$)				
Normal	1.00	1.00	1.00	1.00
Obese ($\text{♂} \geq 1.00$, $\text{♀} \geq 0.85$)	1.82 (1.14–2.91)* $P = 0.02$	1.51 (0.92–2.47)† $P = 0.11$	1.59 (0.99–2.55)* $P = 0.06$	1.63 (0.99–2.68)† $P = 0.06$
WHR continuous (per 0.1)	1.29 (0.97–1.70) $P = 0.08$	1.13 (0.84–1.52) $P = 0.43$	1.24 (0.92–1.67) $P = 0.16$	1.27 (0.92–1.74) $P = 0.15$
Waist circumference ($n = 2968^{\P}$)				
Normal	1.00	1.00	1.00	1.00
Overweight ($\text{♂}: \geq 94\text{--}102 \text{ cm}$, $\text{♀}: \geq 80\text{--}88 \text{ cm}$)	1.38 (0.89–2.14)*	1.28 (0.81–2.00)†	1.27 (0.78–2.06)*	1.29 (0.79–2.10)†
Obese ($\text{♂}: \geq 102 \text{ cm}$, $\text{♀}: \geq 88 \text{ cm}$)	1.78 (1.16–2.71)* $P_{\text{trend}} = 0.01$	1.42 (0.88–2.29)† $P_{\text{trend}} = 0.14$	1.69 (1.08–2.65)* $P_{\text{trend}} = 0.02$	1.85 (1.11–3.08)† $P_{\text{trend}} = 0.02$
WC continuous (per 5 cm)	1.10 (1.02–1.18) $P = 0.01$	1.06 (0.98–1.14) $P = 0.18$	1.10 (1.03–1.18) $P = 0.01$	1.13 (1.04–1.23) $P = 0.01$
Insulin resistance				
HOMA insulin resistance index ($n = 2974^{\P}$)				
Noninsulin resistant	1.00	1.00	1.00	1.00
Insulin resistant ($\geq 1.77 \text{ } \mu\text{U/ml}$)	1.73 (1.17–2.54)*	1.58 (1.03–2.43)‡	1.26 (0.80–1.96)*	1.10 (0.66–1.82)‡
Diabetic§	2.01 (1.05–3.86)* $P_{\text{trend}} = 0.00$	1.79 (0.90–3.56)‡ $P_{\text{trend}} = 0.03$	0.67 (0.26–1.69)* $P_{\text{trend}} = 0.96$	0.57 (0.21–1.50)‡ $P_{\text{trend}} = 0.49$
HOMA-IR continuous (per 1.0)	1.22 (1.06–1.40) $P = 0.01$	1.18 (1.01–1.38) $P = 0.05$	1.10 (0.92–1.31) $P = 0.31$	0.98 (0.79–1.23) $P = 0.88$

BMI, body mass index; WHR, waist-to-hip ratio; WC, waist circumference; HOMA-IR, HOMA insulin resistance index; OR, odds ratio; CI, confidence interval.

*Adjusted for age, sex, smoking status, and socioeconomic status.

†Adjusted for age, sex, smoking status, socioeconomic status, and insulin resistance.

‡Adjusted for age, sex, smoking status, socioeconomic status, and body mass index.

§Diabetics were categorized in a separate category.

$\P$ Number of observations with complete data used in the regression analyses.

certain medical treatments for asthma e.g. steroids may induce metabolic changes. Unfortunately, we did not have data on asthma medications in the present study. However, in Denmark steroids for asthma are mainly administered by the inhalant route, possibly resulting in only minor systemic effects.

The definition of asthma was based on self-reported asthma, having been diagnosed by a physician anytime earlier. This may have led to some misclassification of asthma. For example, childhood asthma without current asthma may be a specific phenotype with an etiology different from asthma in adulthood. Additionally, other diseases such as chronic obstructive pulmonary disease may have been misclassified as asthma. Unfortunately, specific information on current asthma symptoms was not available in the present study. This is clearly a limitation in the interpretation of the results and future studies should address the role of the asthma phenotype in more detail. However, this type of misclassification is

likely to be nondifferential, and thus would tend to attenuate the observed associations toward the null value. Moreover, in the analyses with allergic and nonallergic asthma as outcomes, an association between insulin resistance and asthma was only observed for allergic asthma, and not for nonallergic asthma, indicating that obesity and insulin resistance are in fact related to the allergic phenotype. This finding may also suggest that the effect of insulin resistance on asthma risk is mainly driven by an effect on atopy. However, obesity measures were also strongly associated with nonallergic asthma, which is consistent with misclassification of asthma in the nonallergic asthma group, as respiratory symptoms, such as cough and breathlessness occur more frequently among obese persons than others (34, 35). On the other hand, obesity may be causally related to nonallergic asthma by mechanisms not related to insulin resistance. It has been suggested that the effects of obesity on asthma may be mediated through alterations in airway mechanics,

immune responses, hormonal influences, and genetic factors (8).

In conclusion, in this cross-sectional population-based study, obesity, and insulin resistance were associated with an increased risk of aeroallergen sensitization and asthma. These findings raise the hypothesis that obesity is related to aeroallergen sensitization and allergic asthma through mechanisms that may also be involved in the development of insulin resistance. Prospective studies preferably using a more strict asthma diagnosis are necessary to confirm the results. Also studies that include other metabolic biomarkers e.g. adiponectin, leptin, IL-6 are important to further

examine the individual contributions of these markers and insulin resistance to the possible increased risk of allergy and asthma.

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