

Exploring the obesity–asthma link: do all types of adiposity increase the risk of asthma?

R. V. Fenger¹, A. Gonzalez-Quintela², C. Vidal², F. Gude², L. L. Husemoen¹, M. Aadahl¹, N. D. Berg¹ and A. Linneberg¹

¹Research Centre for Prevention and Health, Glostrup University Hospital, Copenhagen, Denmark and ²Department of Medicine, Complejo Hospitalario Universitario, Santiago de Compostella, Spain

Clinical & Experimental Allergy

Summary

Background Obesity and risk of asthma are linked. Different distributions of adiposity, such as visceral, subcutaneous or ectopic adiposity, may affect asthma risk differently.

Objective To explore the association of different adiposity types with self-reported asthma, bronchial inflammation and lung function, accounting for possible effect modifiers, such as atopy and gender.

Methods In a general population sample of 3471 persons aged 19–72, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) were measured by ultrasound, and fat percentage by bio-impedance. Body mass index, waist circumference, waist-to-hip ratio (WHR), bronchial inflammation as fractional expiratory nitric oxide (FeNO), lung function [FEV₁ and forced vital capacity (FVC)], and atopy (specific IgE) were measured.

Results All adiposity measures were associated with a higher risk of asthma. The risk estimates (odds ratios, OR, with 95% confidence interval, CI) of current asthma were of similar magnitude for all six adiposity measures ranging between 1.17, CI = 0.98–1.40 (SAT) and 1.51, CI = 1.17–1.95 (WHR). The adiposity–asthma associations were significantly stronger in non-atopics than in atopics. In non-atopics the risk estimates of current asthma ranged between 1.35 CI = 1.08–1.72 and 1.82 CI = 1.34–2.46 for SAT and WHR respectively. Consistent results were obtained using dichotomized adiposity measures (obese vs. non-obese). The FVC and FEV₁ decreased significantly with increasing adiposity in both atopics and non-atopics, e.g. FVC decreased between 36 mL (CI = 10, 62 mL) and 155 mL (CI = 124, 186 mL) for one unit (standard error) increase of SAT and VAT respectively. Adiposity measures were not associated with atopy and not consistently associated with FeNO levels.

Conclusions and Clinical Relevance The effect of adiposity on asthma was mainly seen in non-atopics and did not appear to depend on the distribution of adiposity as reflected by the adiposity measures used in the present study. Increasing adiposity was associated with lower lung function independent of atopic status.

Keywords asthma, atopy, epidemiology, gender, lung function, obesity

Submitted 27 June 2011; revised 23 November 2011; accepted 14 December 2011

Correspondence:

Runa Vavia Fenger, Research Centre for Prevention and Health, Glostrup University Hospital, Building 84-85, Nordre Ringvej 57, DK-2600 Glostrup (Denmark).

E-mail: Ruvafe01@regionh.dk

Cite this as: R. V. Fenger, A. Gonzalez-Quintela, C. Vidal, F. Gude, L. L. Husemoen, M. Aadahl, N. D. Berg and A. Linneberg, *Clinical & Experimental Allergy*, 2012 (42) 1237–1245.

Introduction

Epidemiological studies have consistently linked obesity to risk of asthma [1–5]. Until now, most studies on obesity and asthma have assessed obesity as body mass index (BMI), waist circumference (WC) or both [1–5]. However, different types of adiposity may influence asthma risk differently, with some adiposity phenotypes more strongly associated with asthma than others.

Obesity is considered as an inflammatory disease [6, 7], and low-grade, obesity-associated inflammation is proposed to lead to airway inflammation and asthma development [8, 9]. In support of this hypothesis, asthma prevalence is associated with metabolic syndrome in adults [10] and children [11], although not consistent with insulin resistance [12, 13]. Obesity can be classified into different types by fat distribution, such as predominantly visceral, subcutaneous on the trunk, subcutaneous on the limbs, or ectopic, and different types may

have different metabolic activities. Visceral adipose tissue (VAT) is highly metabolically active and produces a variety of hormones and cytokines, such as adiponectin and IL-6 that are believed to contribute to low-grade inflammation and insulin resistance. Ectopic skeletal muscle adiposity appears to be similar to VAT [14, 15], whereas subcutaneous adipose tissue (SAT) on the limbs seems less metabolically active [15]. In addition, increasing obesity is associated with decreasing respiratory capacity, as assessed by lung forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC) [16–18], and by static lung volumes [19].

Asthma can be divided into atopic and non-atopic types. Atopic asthma is characterized by eosinophilic inflammation of the airways that can be indirectly measured as the level of fractional expiratory nitric oxide (FeNO). However, some studies have suggested that obesity is mainly a risk factor for asthma among non-atopic individuals in both adults and children [20–23]. In support, a recent Swedish study found that obesity is associated with decreased levels of FeNO in individuals with wheezing [24]. Whether this is also the case for individuals with asthma remains to be investigated.

The present study tested the hypothesis that certain adiposity types are more strongly associated with asthma than others because different fat distributions have different inflammatory activities. We investigated the association of six different objective measures of adiposity with asthma assessed by questionnaire, lung function and levels of FeNO. We also investigated whether these associations were modified by atopic status or by gender.

Methods

Study population

The Health 2006 population-based cross-sectional study took place at the Research Centre for Prevention and Health (RCPH) between June 2006 and May 2008 [25, 26]. A random sample of men and women aged 19–72 years living in the western part of greater Copenhagen, Denmark was drawn from the Danish Civil Registration System. A total of 7931 individuals were invited and 3471 participated, for a response rate of 43.8%. All participants were Danish citizens and born in Denmark and thus mainly Caucasians. All participants gave written informed consent before taking part in the study, which was approved by the local ethics committee (KA20060011).

Questionnaire data

Information on sociodemographic variables, leisure time physical activity, smoking habits, chronic illnesses,

respiratory symptoms and medication were obtained from a questionnaire that was mailed to and filled out by the participants before their visit to RCPH.

Wheezing was defined as a confirmatory answer to 'Have you had wheezing or whistling in your chest at any time during the last 12 months?' combined with a confirmatory answer to 'If yes, have you had this wheezing or whistling when you did not have a cold?' Questions on wheezing were adopted from the ECRHS screening questionnaire [27]. Physician-diagnosed asthma was defined as a confirmatory answer to 'Has a physician ever told you that you have asthma?' Current asthma was defined as a confirmatory answer to 'Have you had asthma within the last 12 months?'. In additional analyses, we defined asthma as a confirmatory answer to 'Have you been using asthma medication within the last 12 months?'. Allergic rhinitis (AR) was defined as a confirmatory answer to one or more of the questions, 'Have you within the last 12 months had an itchy or stuffy nose or have you been sneezing: A) when near grass, trees, or flowers; B) following exposure to furry animals, e.g. horse, dog, cat, rabbit, guinea pig, or hamster; or C) following exposure to dust from cleaning or from making a bed?' Smoking habits were categorized in five levels: (1) never smoker, (2) ex-smoker, (3) current smoker < 15 g/day, (4) current smokers 15 to < 25 g/day, or (5) current smokers $\geq$ 25 g/day. One gram of tobacco corresponds to one cigarette. Educational level was categorized as: (1) less than 2 years, (2) skilled worker, (3) less than 3 years, (4) 3–4 years and (5) more than 4 years. Usual physical activity level during leisure time was categorized as: (1) mainly sedentary, (2) lightly active, (3) moderately active or (4) vigorous.

Physical measurements

Participants underwent an extensive health examination at the RCPH. At the start of the health examination, fasting blood samples were drawn.

Adiposity measures. Anthropometric measures were done with participants in light clothing and without shoes. Height was measured to the nearest cm, weight to the nearest 0.1 kg and BMI was calculated as kg/m². WC and hip circumference (HipC) were both measured to the nearest cm using a tape measure with no pressure on the body surface. WC was measured midway between the lower rib margin and the iliac crest and HipC was measured at the widest girth of the hip. The waist/hip ratio (WHR) was calculated as WC/HipC. Ultrasound measures were performed with the participants lying on their back. VAT was the distance in cm to two decimals between the posterior edge of the abdominal muscles and the front of the lumbar spine. SAT was the distance in cm to two decimals between

the front edge of the abdominal muscles and the skin. All ultrasound measures were made after a quiet expiration as described by Stolk et al. [28] with Aquila Pie Medical, Esaote Europe, Maastricht, The Netherlands. The ultrasound measures have been validated against CT/MRI [29, 30]. Fat percentage was measured using a foot-to-foot Tanita Body Composition Analyzer (TBF-300, TANITA Corporation of America, Inc., IL, USA).

Assessment of lung function and FeNO levels. FEV₁ and FVC measurements were obtained by spirometry, performed according to international standards [31] using a Spiro USB Spirometer (MicroMedical Limited, Rochester, Kent, UK). Spirometers were checked daily with a 3-L syringe, and checked every 6 months with a decompression flow simulator [32]. FeNO measurements were performed using a NIOX MINO (Aerocrine AB, Stockholm, Sweden). A dynamic flow restrictor yielded a constant flow rate of 50 mL/s, in accordance with recommendations of the American Thoracic Society and the European Respiratory Society guidelines for FeNO measurement [33]. Nitric oxide concentrations between 5 and 300 p.p.b. were measured and measurements below 5 p.p.b. were set to zero by the NIOX MINO. Values below 5 p.p.b., were assigned the value 2 p.p.b.

Biomarkers

Serum samples were analysed for specific IgE against the four most clinical important inhalant allergens in Denmark: birch, grass, cat and the house dust mite (HDM) *Dermatophagoides pteronyssinus*, using the ADVIA Centaur Specific IgE assay [34]. Atopy was defined as a positive test (≥ 0.35 kilo units/L) for specific IgE against at least one of either birch, grass, cat or HDM. Plasma glucose concentrations were analysed by a hexokinase/glucose-6-phosphate dehydrogenase assay (Roche Diagnostic, Germany), and insulin concentrations were measured by fluoroimmunoassay technique (Dako Diagnostics Ltd., Cambridgeshire, UK). High-density lipoprotein (HDL), total cholesterol and triglyceride concentrations were measured by standard enzymatic techniques (Roche Diagnostic, Germany). The homeostatic model assessment-insulin resistance (HOMA-IR) index was calculated as: fasting plasma glucose (mmol/L) $\times$ fasting serum insulin (mU/L)/22.5 and applied only to the non-diabetic. Very low-density lipoprotein (VLDL) was calculated as triglyceride $\times$ 0.45. Low-density lipoprotein (LDL) concentrations were calculated by subtracting HDL and calculated VLDL from total cholesterol.

Statistics

Statistics were performed using the R-statistical package, version 2.13.0 (<http://www.r-project.org/>). All *P*-values

were two-tailed and statistical significance was defined as *P* < 0.05. *P*-values of likelihood ratio tests were used to test for significance of all multivariate analyses. We used linear regression to model lung function and FeNO levels, and logistic regression to model wheezing, asthma or AR symptoms. We checked for non-linear associations between (A) adiposity measures and continuous variables and (B) adiposity measures and the logit of the dichotomous outcomes in different ways, for instance by using P-splines within the generalized additive model (R 'mgcv' package). Multivariate analyses were conducted without and with the interaction terms (adiposity-measure) $\times$ (atopy), and (adiposity-measure) $\times$ (gender). We also tested whether metabolic markers, (triglyceride level, LDL level, HDL level and HOMA-IR) could explain some of the association between adiposity and wheezing/asthma. We did this by repeating each analysis, with and without each metabolic marker and assessing whether the original estimates changed when the metabolic marker was included in multivariable regression models. Analyses that included lung function tests and FeNO levels were made among never-smokers only (*N* = 1435), as smoking exposure is a major determinant of decreased lung function and FeNO.

All analyses were made with the adiposity measures as dichotomous variables and as continuous variables. For dichotomous variables a cut-off level was decided for each adiposity measure, and consequently the study population was divided into obese and non-obese according to that specific measure. For BMI, WC and WHR the cut-off levels to separate obese from non-obese were chosen according to WHO recommendations [29]. For the fat percentage, VAT and SAT there were no standard cut-off levels, and we chose the 80th percentile. For fat percentage this was done for males and females separately. As for continuous variables, the adiposity measures were standardized by dividing each adiposity measure by its own distribution-specific standard deviation. This was carried out to overcome the fact that the adiposity measures are on different scales. Having the adiposity measures as standardized measures allowed for direct comparison of the magnitude of effects between different adiposity measures in our analyses. For instance, we were able to compare the effect of the increase of one standard deviation of BMI (4.7 kg/m²) with the effect of the increase of one standard deviation of WC (13.7 cm).

Results

Adiposity measures and biomarkers

Characteristics of the study population are in Table 1. All six adiposity measures (BMI, WC, WHR, VAT, SAT and fat percentage) were positively associated with

Table 1. Characteristics of the study population

Mean age (SD)	49.4 (13.0)
$N^{\S}/(\%)$	
Gender, female	1918 (55.3)
Smoking, current	886 (25.8)
Physical activity leisure time	
Mainly sedentary–lightly active	2714 (79.1)
Moderately active–vigorous	717 (20.9)
Education after mandatory first 9 years	
< 3 years	1862 (54.2)
> 3 years	1571 (45.8)
Atopy*	797 (23.2)
Wheezing	761 (22.2)
Physician-diagnosed asthma	367 (10.8)
Current asthma	118 (3.4)
Allergic rhinitis	1104 (32.3)
BMI	
< 18.5 (kg/m ²)	65 (1.9)
18.5 to < 25.0 (kg/m ²)	1571 (45.3)
25.0 to < 30.0 (kg/m ²)	1258 (36.6)
30.0 (kg/m ²)	563 (16.2)
WC	
≤ 88 cm <i>f</i> /102 cm <i>m</i>	2450 (70.7)
> 88 cm <i>f</i> /102 cm <i>m</i>	1016 (29.3)
WHR	
≤ 0.85 <i>f</i> /1 <i>m</i>	2660 (76.8)
> 0.85 <i>f</i> /1 <i>m</i>	805 (23.2)
VAT	
Lowest four quintiles	2733 (79.8)
Highest quintile	691 (20.2)
5th, 25th, 50th, 75th, 95th percentiles ^{§§} (cm)	3.4, 4.6, 5.9, 7.8, 11.4
SAT	
Lowest four quintiles	2757 (79.9)
Highest quintile	692 (20.1)
5th, 25th, 50th, 75th, 95th percentiles ^{§§} (cm)	1.2, 2.1, 2.9, 3.7, 5.3
Fat percentage (%)	
Lowest four quintiles <i>f</i> / <i>m</i>	2733 (79.8)
Highest quintile <i>f</i> / <i>m</i>	691 (20.2)
	Mean (SD)
FEV ₁ (litres)	3.12 (0.82)
FVC (litres)	3.98 (1.00)
FEV ₁ /VC	0.78 (0.07) [#]

[§]Number of participants in the specific group; (%) percentage of the study population that answered the specific question.

*Atopy, a positive test (≥ 0.35 kilo units/L) for specific IgE against at least one of either birch, grass, cat, or house dust mite.

^{§§}Percentiles of the distribution.

[#]The distribution is not symmetrical.

BMI, body mass index; WC, waist circumference; WHR, waist/hip-ratio; VAT, visceral adipose tissue; SAT subcutaneous adipose tissue; *f*, females; *m*, males; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

wheezing and with current asthma (Table 2), especially among non-atopics (Table 3). Results for physician-diagnosed asthma resembled current asthma (data not shown). However, adiposity was not associated with AR symptoms (Table 2).

Table 2. Association of adiposity measures with wheezing, current asthma and symptoms of allergic rhinitis

Adiposity measure [†]	Wheezing		Current asthma		Rhinitis [‡]	
	(n/N = 538/3434) [‡]		(n/N = 118/3426) [‡]		(n/N = 1861/3434) [‡]	
	OR [§]	CI	OR [§]	CI	OR [§]	CI
BMI	1.25	1.14, 1.37	1.23	1.04, 1.45	1.00	0.93, 1.08
WC	1.32	1.19, 1.48	1.28	1.05, 1.56	1.05	0.96, 1.14
WHR	1.48	1.29, 1.70	1.51	1.17, 1.95	1.07	0.96, 1.19
VAT	1.38	1.24, 1.54	1.21	0.97, 1.51	1.10	1.01, 1.19
SAT	1.08	0.98, 1.19	1.17	0.98, 1.40	0.99	0.92, 1.06
FAT%	1.28	1.13, 1.46	1.25	0.98, 1.61	1.05	0.95, 1.16

[†]Adiposity measure per standard deviation.

[‡]Rhinitis, symptoms of allergic rhinitis.

[‡]n, number with characteristic; N, total who answered the questionnaire question.

[§]Odds ratio (OR) estimates with 95% confidence intervals (CI) were obtained in logistic regression models adjusted for age, gender, physical activity, education, smoking, atopy [defined as a positive test (≥ 0.35 kilo units/L) for specific IgE against at least one of birch, grass, cat, or house dust mite]. OR is the increase in relative risk per standard deviation of the adiposity measure. For example, an OR of 1.23 for BMI with respect to current asthma indicates that the risk of 'current asthma' increases with approximately 23 percent for every increase in BMI of one standard deviation (4.7 kg/m²).

BMI, body mass index; WC, waist circumference; WHR, waist-hip-ratio; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; FAT%, fat percentage.

The strengths of the adiposity-wheezing associations and the adiposity-asthma associations were of similar magnitude for all six adiposity measures, although they were not identical (Tables 2 and 3). In addition to analyses with the six adiposity measures, we also investigated the association between asthma and WC/height ratio, and VAT/HipC ratio. The results for WC/height paralleled those for BMI and the results for the VAT/HipC paralleled those for WHR (data not shown).

For all adiposity measures, estimates for the adiposity-asthma association were higher for non-atopic than atopic individuals (Table 3, upper panel). Essentially the same results were obtained if a cut-off level for the adiposity measures was defined and the analyses were made for the obese vs. the non-obese population (Table 3, lower panel). In contrast, no interaction was observed between atopy and adiposity for wheezing. We found an adiposity-gender interaction with wheezing as the outcome, but only for adiposity measures related to abdominal adiposity. The *P*-values for the interaction terms were *P* = 0.07 for WC and gender, *P* = 0.03 for WHR and gender, and *P* = 0.003 for VAT and gender. In these cases, estimates of the adiposity-wheezing association were higher among women than among men. No interactions were observed between gender and adiposity for current asthma. There was no

Table 3. Risk of current asthma in the atopic and non-atopic population. Estimates are given for (A) adiposity measures per standard deviation (SD) and (B) for the obese compared with the non-obese as defined by each adiposity measure

	Atopics		Non-atopics		P-value
	OR [§]	CI	OR [§]	CI	
(A) Adiposity measures per standard deviation					
BMI/SD	0.96	0.72–1.24	1.50	1.21–1.83	0.01
WC/SD	1.02	0.76–1.33	1.60	1.25–2.03	0.01
WHR/SD	1.32	0.96–1.80	1.82	1.34–2.46	0.09
VAT/SD	1.01	0.72–1.37	1.41	1.08–1.82	0.08
SAT/SD	1.00	0.76–1.30	1.37	1.08–1.72	0.08
FAT%/SD	0.96	0.70–1.32	1.62	1.19–2.20	0.01
(B) Adiposity as defined by:					
BMI (≥ 30 kg/m ²)	0.84	0.34–1.81	2.91	1.64–5.02	0.01
WC (> 88 cm <i>f</i> /102 cm <i>m</i>)	0.79	0.38–1.53	2.45	1.44–4.16	0.01
WHR (> 0.85 <i>f</i> /1 <i>m</i>)	0.93	0.43–1.87	2.47	1.41–4.26	0.03
VAT (highest quintile)	1.33	0.60–2.70	2.07	1.05–3.87	0.51
SAT (highest quintile)	0.88	0.39–1.78	1.67	0.93–2.90	0.16
FAT% (highest quintile <i>f</i> / <i>m</i>)	0.88	0.37–1.83	1.73	0.95–3.05	0.17

[§]Odds ratio (OR) estimates with 95% confidence intervals (CI) were obtained in logistic regression models adjusted for age, gender, physical activity in leisure time, education, smoking. Atopics, individuals with atopy defined as a positive test (≥ 0.35 kilo units/L) for specific IgE against at least one of birch, grass, cat, or house dust mite; Non-atopics, individuals without atopy. P-value; test of interaction between the adiposity measure and atopy. Upper panel (A): OR is the increase in relative risk per standard deviation (SD) of the adiposity measures. For example, an OR of 1.50 for BMI in non-atopics indicates that the risk of current asthma increases with approximately 50 percent for every increase in BMI of one standard deviation (4.7 kg/m²). Lower panel (B): OR is the increase in relative risk in obese individuals compared with non-obese individuals. For example, an OR of 2.91 for BMI in non-atopics indicate that the risk of current asthma is approximately 291 percent higher in obese with a BMI ≥ 30 4.7 kg/m² compared with those with a BMI between 15 and 29.99 kg/m². BMI, body mass index; WC, waist circumference; WHR, waist-hip-ratio; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; FAT%, fat percentage; *f*, females; *m*, males.

evidence of a three-way interaction between the effects of adiposity, atopy and gender (data not shown), and the adiposity measures were not associated with atopy itself (data not shown).

The adiposity-asthma and adiposity-wheezing associations remained essentially unchanged when different metabolic biomarkers (triglyceride, LDL or HDL levels, or HOMA-IR) were added to the regression models (data not shown).

Lung function results

Forced expiratory lung volumes (FEV₁ and FVC) were significantly and inversely associated with all adiposity measures (Table 4). For instance, the FVC decreased by 82 mL for each WC increase of one standard deviation (13 cm in our population). More pronounced decreases in forced expiratory lung volumes were associated with increases in abdominal adiposity measures (WHR, VAT and WC) than with increases in weight, SAT, or fat percentage. In contrast, estimates of possible associations between adiposity measures and the FEV₁/FVC ratio were very small (Table 4). Thus, the adiposity measures did not seem to be associated with airflow obstruction as measured by decreased FEV₁/FVC ratio, although some of the estimates were significant. No significant interactions were seen between atopy and adiposity measures with respect to lung function.

As all adiposity measures were associated with lower forced expiratory lung volumes, we investigated the extent to which the associations between adiposity measures and wheezing or current asthma could be explained by decreased FVC induced by increased adiposity. We therefore reanalysed the adiposity-asthma associations with FVC included in the regression models. When FVC was included, estimates of adiposity-wheezing associations and adiposity-asthma associations decreased for all adiposity measures except SAT (Table 5, data shown only for current asthma). The

Table 4. Association of adiposity measures with lung function among never-smokers for *N* = 1435

Adiposity measure [§]	FEV ₁		FVC		FEV ₁ /FVC	
	Estimate (mL)	CI (mL)	Estimate (mL)	CI (mL)	Estimate	CI
Weight (kg)	−61	−88, −34	−89	−121, −57	0.0038	−0.0001, 0.0077
WC (cm)	−82	−108, −56	−117	−148, −86	0.0040	0.0002, 0.0078
WHR	−88	−120, −56	−116	−155, −78	0.0015	−0.0032, 0.0062
VAT (cm)	−123	−149, −97	−155	−186, −124	0.0011	−0.0028, 0.0050
SAT (cm)	−25	−47, −3	−36	−62, −10	0.0013	−0.0019, 0.0045
Fat percentage	−67	−97, −37	−103	−138, −67	0.0039	−0.0004, 0.0083

[§]Adiposity measure per standard deviation. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity. FEV₁, FVC and FEV₁/FVC ratio with 95% confidence intervals (CI) were obtained in linear regression models adjusted for age, gender, height, education, physical activity in leisure time and atopy defined as positive test (≥ 0.35 kilo units/L) for specific IgE against at least one of birch, grass, cat, or house dust mite. An estimate of −117 mL of FVC for WC indicates that if WC increases with one standard deviation (13.7 cm), the estimated FVC decreases by 117 mL.

estimate of the effect of VAT on current asthma decreased the most, indicating that the adiposity-asthma association could be partly explained by adiposity-induced lower lung volumes.

Table 5. Risk of current asthma in analyses with and without FVC

Adiposity measures	Without FVC + height (Results also presented in Table 2)		With FVC + height (Additional results)	
	§OR	CI	§OR	CI
BMI	1.23	1.04, 1.45	1.15	0.97–1.35
WC	1.28	1.05, 1.56	1.22	1.00–1.49
WHR	1.51	1.17, 1.95	1.33	1.03–1.72
VAT	1.21	0.97, 1.51	1.05	0.83–1.31
SAT	1.17	0.98, 1.40	1.18	0.99–1.41
FAT%	1.25	0.98, 1.61	1.24	0.97–1.57

§Odds ratio (OR) estimates with 95% confidence intervals (CI) were obtained in logistic regression models adjusted for age, gender, physical activity in leisure time, education, smoking and atopy [defined as a positive test (≥ 0.35 kilo units/L) for specific IgE against at least one of either birch, grass, cat, or house dust mite]. Results in the two right columns are additionally adjusted for forced vital capacity (FVC) and height. OR is the increase in relative risk per standard deviation increase of each adiposity measure. E.g. The estimates for VAT indicate that before adjustment for FVC + height the estimated risk of current asthma was 21 percent per standard deviation increase of VAT (2.5 cm), and that after adjustment for FVC + height the estimated risk of current asthma was 5 percent per standard deviation increase of VAT.

BMI, body mass index; WC, waist circumference; WHR, waist-hip-ratio; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; FAT%, fat percentage.

Table 6. Levels of fractional expiratory Nitric Oxide (p.p.b.) according to categories of obese and non-obese individuals among never smokers, $N = 1435$

	All		Atopics		Non-atopics	
	50th (25th, 75th)	P-value	50th (25th, 75th)	P-value	50th (25th, 75th)	P-value
BMI < 30 kg/m ²	17 (11, 25)	0.52	21 (14, 36)	0.42	16 (10, 23)	0.05
BMI ≥ 30 kg/m ²	17 (12, 25)		19 (12, 35)		16 (12, 25)	
WC ≤ 88 cm <i>f</i> /102 cm <i>m</i>	17 (11, 25)	0.65	20 (13, 36)	0.72	16 (11, 23)	0.42
WC > 88 cm <i>f</i> /102 cm <i>m</i>	17 (11, 25)		21 (14, 38)		16 (11, 24)	
WHR ≤ 0.85 <i>f</i> /1 <i>m</i>	17 (11, 25)	0.59	20 (13, 36)	0.69	16 (11, 23)	0.41
WHR > 0.85 <i>f</i> /1 <i>m</i>	17 (11, 26)		23 (14, 37)		16 (11, 25)	
VAT Lowest four quintiles	17 (11, 25)	0.10	20 (13, 37)	0.88	16 (10, 23)	0.02
VAT Highest quintile	19 (12, 25)		20 (14, 29)		18 (11, 23)	
SAT Lowest four quintiles	17 (12, 25)	0.01	21 (14, 37)	0.58	16 (10, 23)	0.03
SAT Highest quintile	15 (11, 23)		19 (13, 35)		15 (10, 22)	
FAT% Lowest four quintiles <i>f</i> / <i>m</i>	17 (11, 25)	0.41	21 (14, 36)	0.47	16 (10, 23)	0.03
FAT% Highest quintile <i>f</i> / <i>m</i>	18 (12, 25)		19 (12, 35)		17 (12, 25)	

Levels of fractional expiratory Nitric Oxide were directly measured and are shown unadjusted for the whole population (All) and for the population divided into Atopics and Non-atopics. Atopy was defined as a positive test (≥ 0.35 kilo units/L) for specific IgE against at least one of either birch, grass, cat, or house dust mite. 50th (25th, 75th), percentiles of the FeNO distribution; results are given in parts per billion (p.p.b.). P-values indicate tests for differences between obese and non-obese according to each adiposity measure and were obtained by Wilcoxon signed rank test. BMI, body mass index; WC, waist circumference; WHR, waist-hip-ratio; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; FAT%, fat percentage.

Results are given for never smokers only.

FeNO levels

For three of the adiposity measures (BMI, VAT Fat percentage), FeNO levels were slightly higher among obese than non-obese individuals. For SAT, FeNO levels were slightly lower among obese than non-obese individuals, and for WC and WHR there were no difference between obese and non-obese individuals. This pattern was mostly observed among non-atopic individuals (Table 6). Essentially similar results were obtained if FeNO levels were estimated in linear regression models adjusted for age, gender, obesity (obese/non-obese), atopy, education and physical activity in leisure time. All analyses of FeNO levels were made among never smokers only, because smoking induces a marked suppression of FeNO.

Physical activity and smoking

Physical activity measures were tested in all our models. Physical activity level was inversely and significantly associated with wheezing, but did not modify or explain the adiposity-wheezing association. Physical activity was not associated with current asthma. Smoking was associated with lower lung function and with increased wheezing, but not with asthma.

Discussion

This general, population-based study in adults evaluated the association of six different adiposity measures, indicating different types/distributions of adiposity,

with the presence of asthma, bronchial eosinophilic inflammation measured as FeNO, and the results of lung function tests. We found that atopy modified the adiposity-asthma association: All adiposity measures were associated with a higher prevalence of asthma, but among non-atopics only. There were no significant associations between adiposity measures and atopy (as IgE-sensitisation and AR symptoms). However, we found that abdominal adiposity measures were particularly associated with decreased forced expiratory lung volumes (FEV₁ and FVC).

We hypothesized that some types of adiposity, such as predominantly visceral adiposity, would be more strongly associated with asthma prevalence because of known strong inflammatory activity. However, estimated associations for all six adiposity measures with both wheezing and asthma were of similar magnitude. This indicated that if the adiposity-asthma association is mediated by inflammatory factors, fat in different parts of the body may not be different in the relevant inflammatory activity. Furthermore, we found that when reduced intrathoracic volume associated with adiposity (as measured by FVC) was taken into account, estimates for the VAT-asthma association decreased more than estimates for other adiposity-asthma associations (Table 5). This emphasized that VAT was not more strongly associated with asthma prevalence than the other adiposity measures. However, we assessed VAT as intraperitoneal volume, and assessing it in another way, for example as a ratio of liver and spleen sizes [35], may yield other results. Nevertheless, our findings are consistent with two recent studies. One reported that subcutaneous fat but not VAT was associated with airway hyperresponsiveness [36]. Another showed that ectopic fat storage in lean tissue (e.g. muscular tissue) was a better predictor of asthma prevalence than VAT in women [14].

Even though adiposity was consistently associated with asthma and wheezing, metabolic biomarkers (triglyceride, LDL and HDL levels, and HOMA-IR) associated with adiposity did not influence associations between adiposity and asthma, or adiposity and wheezing. Thus, the results of our cross-sectional study do not support a possible link between adiposity and asthma through insulin resistance- or dyslipidemia-related pathways. However, conflicting results on this topic have been reported [12, 13, 22], and more studies are needed to clarify the pathological pathways connecting adiposity and asthma.

Our results suggest that reduced forced expiratory lung volumes can account for part of the association between abdominal adiposity and asthma previously observed in epidemiological studies. First, we found that inverse associations of adiposity measures with FEV₁ and FVC were most pronounced for VAT, a measure that may closely reflect visceral adiposity and

reduced intra thoracic volume. Second, associations between adiposity measures and wheezing or asthma decreased when FVC were included in the regression models. This was especially true for VAT and WHR, which are measures of intra-abdominal adiposity. We observed adiposity-related decreases in lung volume in the entire population, not just among non-atopics. This may indicate that the mechanical component of the adiposity-asthma association is distinct from the possible inflammatory link between adiposity and asthma. This is supported by reviews that describe how breathing at lower lung volumes may lead to airway smooth muscles contraction and airway narrowing [23, 37]. Changes that in themselves increase the work of breathing and the feeling of dyspnoea. A recent study showed that the duration of adiposity was important for the effect of adiposity on lung volumes [38], an aspect that we have not been able to investigate.

Differential adiposity-asthma associations by atopic status have been reported in several age groups [21–23, 37, 39, 40]. At the same time adiposity seems unrelated to atopy alone [13, 41, 42]. We confirmed and extended these findings showing higher estimates of the adiposity-asthma association for six different adiposity measures, including ultrasound measurements among non-atopics. Furthermore, in our study FeNO-levels were only slightly increased in obese compared with in non-obese among non-atopic individuals for three of six adiposity measures (Table 6). Thus, we tend not to interpret it as an indicator of increased eosinophilic activity in obese compared with in non-obese. This corresponds well to findings of a recent study that suggested that airway inflammation among obese subjects (assessed by BMI) is neutrophil-driven [43], and to the finding of another study that obesity is associated with late-onset asthma, not with early predominantly atopic asthma [44].

Some studies have reported an adiposity-gender interaction for asthma severity [17, 41], but results on asthma prevalence are conflicting [4, 45–47]. A meta-analysis of the association of BMI with incident asthma including 333 102 individuals concluded no evidence of adiposity-gender interaction [5]. We found an adiposity-gender interaction for abdominal adiposity measures only with wheezing as the outcome. Thus, possible gender differential effects of adiposity on asthma may be dependent on the asthma type.

The strengths of our study include the population-based design and large sample size, the use of several different measures of adiposity including abdominal ultrasound scans, and the use of objective measures of lung function and atopy (FeNO and IgE sensitisation). The limitations include the cross-sectional design that does not allow us to make any final conclusions, and lack of tests for variability of lung function to define asthma. In this study, we used a questionnaire to define

asthma and not an evaluation by a specialist. This is likely to have caused some misclassification of asthma. However, a specialist evaluation is rarely feasible in large-scale epidemiological studies, in which questionnaires remain the most commonly used method for defining asthma. The analyses of asthma were also made with asthma defined as 'use of asthma medication within the last 12 months' and the results were essentially similar. Furthermore, a relatively low participation rate could theoretically have biased the results. However, the main focus of this article has been the adiposity-asthma association, and a biased result would only occur, if the non-participation was associated with both adiposity and asthma. Finally, a more direct or gold-standard measure of overweight/adiposity, such as one obtained by magnetic resonance imaging, could more accurately have assessed adipose tissue in different compartments for each individual. We had to use indirect, although quite different, measures of adiposity. We did not have information on nutritional status of the study population and thus unfortunately were not able to include this in our analyses.

In conclusion, we found no clear difference in the strength of the adiposity-asthma association between the different types of adiposity measures. We found that adiposity was associated with asthma only in a non-atopic population. We speculate that whatever is the mechanism linking adiposity and asthma, it is likely to be independent of atopic pathways. Reduced intrathoracic volume may account for part of the observed association between adiposity and asthma.

Acknowledgements

We are very grateful for the work of the staff at the Research Centre for Prevention and Health at Glostrup University Hospital. Funding sources: The Danish Lung Society, The Danish Board of Health, The Danish Environmental Protection Agency, The Copenhagen County Research Foundation, Aase and EinarDanielsens Foundation, The Velux Foundation, ALK-Abelló A/S, Denmark and The Danish Scientific Research Council.

Conflict of interest: No authors report any conflict of interest.

References

- Von BJ, Lipsett M, Horn-Ross PL *et al*. Obesity, waist size and prevalence of current asthma in the California Teachers Study cohort. *Thorax* 2009; **64**:889–93.
- Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol* 2005; **115**:897–909.
- Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health* 2009; **9**:88.
- McHugh MK, Symanski E, Pompeii LA, Delclos GL. Prevalence of asthma among adult females and males in the United States: results from the National Health and Nutrition Examination Survey (NHANES), 2001–2004. *J Asthma* 2009; **46**:759–66.
- Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007; **175**:661–6.
- Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. *Annu Rev Immunol* 2011; **29**:415–45.
- Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006; **444**:860–7.
- Hersoug LG, Linneberg A. The link between the epidemics of obesity and allergic diseases: does obesity induce decreased immune tolerance? *Allergy* 2007; **62**:1205–13.
- Erbay E, Cao H, Hotamisligil GS. Adipocyte/macrophage fatty acid binding proteins in metabolic syndrome. *Curr Atheroscler Rep* 2007; **9**:222–9.
- Del-Rio-Navarro BE, Castro-Rodriguez JA, Garibay NN *et al*. Higher metabolic syndrome in obese asthmatic compared to obese nonasthmatic adolescent males. *J Asthma* 2010; **47**:501–6.
- Cottrell L, Neal WA, Ice C, Perez MK, Piedimonte G. Metabolic abnormalities in children with asthma. *Am J Respir Crit Care Med* 2011; **183**:441–8.
- Husemoen LL, Glumer C, Lau C, Pisinger C, Mørch LS, Linneberg A. Association of obesity and insulin resistance with asthma and aeroallergen sensitization. *Allergy* 2008; **63**: 575–82.
- Ma J, Xiao L, Knowles SB. Obesity, insulin resistance and the prevalence of atopy and asthma in US adults. *Allergy* 2010; **65**:1455–63.
- Sood A, Qualls C, Li R *et al*. Lean mass predicts asthma better than fat mass among females. *Eur Respir J* 2011; **37**:65–71.
- Dulloo AG, Jacquet J, Solinas G, Montani JP, Schutz Y. Body composition phenotypes in pathways to obesity and the metabolic syndrome. *Int J Obes (Lond)* 2010; **34**(Suppl 2):S4–17.
- Aaron SD, Fergusson D, Dent R, Chen Y, Vandemheen KL, Dales RE. Effect of weight reduction on respiratory function and airway reactivity in obese women. *Chest* 2004; **125**:2046–52.
- Appleton SL, Wilson DH, Tucker G, Ruffin RE, Taylor AW, Adams RJ. Sex differences in asthma morbidity associated with obesity in a representative population sample. *J Allergy Clin Immunol* 2008; **121**:1285–7.
- Holguin F, Cribbs S, Fitzpatrick AM, Ingram RH Jr, Jackson AC. A deep breath bronchoconstricts obese asthmatics. *J Asthma* 2010; **47**:55–60.
- Li AM, Chan D, Wong E, Yin J, Nelson EA, Fok TF. The effects of obesity on pulmonary function. *Arch Dis Child* 2003; **88**:361–3.
- Appleton SL, Adams RJ, Wilson DH, Taylor AW, Ruffin RE. Central obesity is associated with nonatopic but not atopic asthma in a representative population sample. *J Allergy Clin Immunol* 2006; **118**:1284–91.
- Kronander UN, Falkenberg M, Zetterstrom O. Prevalence and incidence of asthma related to waist circumference and BMI in a Swedish community sample. *Respir Med* 2004; **98**: 1108–16.

- 22 Chen Y, Rennie D, Cormier Y, Dosman J. Association between obesity and atopy in adults. *Int Arch Allergy Immunol* 2010; 153:372–7.
- 23 Peroni DG, Pietrobelli A, Boner AL. Asthma and obesity in childhood: on the road ahead. *Int J Obes (Lond)* 2010; 34:599–605.
- 24 Berg CM, Thelle DS, Rosengren A, Lissner L, Toren K, Olin AC. Decreased exhaled nitric oxide (FENO) in obese with asthma symptoms: data from the population study INTERGENE/ADONIX. *Chest* 2011; 139:1109–16.
- 25 Hersoug LG, Husemoen LL, Thomsen SF, Sigsgaard T, Thuesen BH, Linneberg A. Association of indoor air pollution with rhinitis symptoms, atopy and nitric oxide levels in exhaled air. *Int Arch Allergy Immunol* 2010; 153:403–12.
- 26 Hersoug LG, Husemoen LL, Sigsgaard T, Madsen F, Linneberg A. Indoor exposure to environmental cigarette smoke, but not other inhaled particulates associates with respiratory symptoms and diminished lung function in adults. *Respirology* 2010; 15:993–1000.
- 27 Grassi M, Rezzani C, Biino G, Marinoni A. Asthma-like symptoms assessment through ECRHS screening questionnaire scoring. *J Clin Epidemiol* 2003; 56:238–47.
- 28 Stolk RP, Wink O, Zelissen PM, Meijer R, van Gils AP, Grobbee DE. Validity and reproducibility of ultrasonography for the measurement of intra-abdominal adipose tissue. *Int J Obes Relat Metab Disord* 2001; 25:1346–51.
- 29 Obesity: preventing and managing the global epidemic. Report of a WHO consultation, Geneva, World Health Organization, 2004. 2000.
- 30 Vlachos IS, Hatzioannou A, Perelas A, Perrea DN. Sonographic assessment of regional adiposity. *AJR Am J Roentgenol* 2007; 189:1545–53.
- 31 Miller MR, Hankinson J, Brusasco V *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26:319–38.
- 32 Pedersen OF, Naeraa N, Lyager S, Hilberg C, Larsen L. A device for evaluation of flow recording equipment. *Bull Eur Physiopathol Respir* 1983; 19:515–20.
- 33 American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005; 171:912–30.
- 34 Petersen AB, Gudmann P, Milvang-Gronager P *et al.* Performance evaluation of a specific IgE assay developed for the ADVIA centaur immunoassay system. *Clin Biochem* 2004; 37:882–92.
- 35 Yoshimura E, Kumahara H, Tobina T *et al.* Muscle and insulin sensitivity in Japanese individuals: a pilot study. *Diabetes Metab Syndr Obes* 2011; 4: 35–43.
- 36 Kim KM, Kim SS, Kwon JW *et al.* Association between subcutaneous abdominal fat and airway hyperresponsiveness. *Allergy Asthma Proc* 2011; 32:68–73.
- 37 Shore SA. Obesity and asthma: possible mechanisms. *J Allergy Clin Immunol* 2008; 121:1087–93.
- 38 Santamaria F, Montella S, Greco L *et al.* Obesity duration is associated to pulmonary function impairment in obese subjects. *Obesity (Silver Spring)* 2011; 19:1623–8.
- 39 Chen Y, Rennie DC, Dosman JA. Synergy of BMI and family history on diabetes: the Humboldt Study. *Public Health Nutr* 2010; 13:461–5.
- 40 Dixon AE, Pratley RE, Forgiione PM *et al.* Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol* 2011; 128:508–15.
- 41 Kattan M, Kumar R, Bloomberg GR *et al.* Asthma control, adiposity, and adipokines among inner-city adolescents. *J Allergy Clin Immunol* 2010; 125:584–92.
- 42 Leung TF, Kong AP, Chan IH *et al.* Association between obesity and atopy in Chinese schoolchildren. *Int Arch Allergy Immunol* 2009; 149:133–40.
- 43 Scott HA, Gibson PG, Garg ML, Wood LG. Airway inflammation is augmented by obesity and fatty acids in asthma. *Eur Respir J* 2011; 38:594–602.
- 44 Leone N, Courbon D, Berr C *et al.* Abdominal obesity and late-onset asthma: cross-sectional and longitudinal results: the 3C study. *Obesity (Silver Spring)* 2012; 20:628–35.
- 45 Chen Y, Rennie D, Cormier Y, Dosman J. Sex specificity of asthma associated with objectively measured body mass index and waist circumference: the Humboldt study. *Chest* 2005; 128: 3048–54.
- 46 Sood A, Qualls C, Arynchyn A *et al.* Obesity-asthma association: is it explained by systemic oxidant stress? *Chest* 2009; 136:1055–62.
- 47 Jartti T, Saarikoski L, Jartti L *et al.* Obesity, adipokines and asthma. *Allergy* 2009; 64:770–7.