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ORIGINAL RESEARCH

The relation between visceral fat and lung function in the general population is in part mediated by CRP and leptin

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ABSTRACT

Background: Abdominal obesity is associated with reduced lung function. It remains unclear whether this results from mechanical pressure or whether visceral fat also plays a role via inflammation. Our aim was to examine the association between visceral fat and lung function, and the role of inflammation.

Methods: In this cross-sectional analysis, visceral fat was measured by magnetic resonance imaging and lung function by spirometry. We examined the association between visceral fat and lung function, and mediation by CRP, GlycA, Fe_{NO}, leptin, and adiponectin.

Results: We included 2,266 participants, mean age 56 (6) years and 90 (56) cm^2 visceral fat. After adjusting for confounding factors including total body fat and waist circumference, per SD of visceral fat, FEV_1 was 3.6% lower (95% CI: −4.9,-2.4), and FVC was 3.6% (−4.6,-2.6) lower. No mediation was observed by GlycA, Fe_{NO} and adiponectin. CRP and leptin together mediated 22% of the association with FEV_1 and 19% with FVC.

Conclusion: In a middle-aged general population with a normal lung function, visceral fat was associated with reduced lung function. This association was for 20% mediated by CRP and leptin. Future research should explore the remaining mechanisms underlying the association between visceral fat and lung function.

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KEYWORDS
Abdominal obesity; CRP; inflammation; leptin; lung function; visceral fat

1. Introduction

Obesity is increasingly prevalent in the world and a strong risk factor for not only metabolic and cardiovascular disease, but also for pulmonary diseases such as asthma [1–3]. It is well established that obesity, and in particular abdominal obesity, is associated with reduced lung function, but the underlying mechanisms remain unknown [4].

One of the potential mechanisms underlying reduced lung function in people with abdominal obesity is mechanical pressure: the presence of abdominal fat restricts lung volume by impacting the ventilation mechanics [5] including limitation of diaphragmatic mobility [6]. Another suggested but not fully investigated mechanism for the impact of obesity on lung function is inflammation [7].

It is well known that in particular intra-abdominal visceral adipose tissue is metabolically active and secretes pro-inflammatory cytokines, primarily interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) and hormones such as leptin and adiponectin. Furthermore, visceral fat is associated with increased circulation of fatty acids, which may contribute to an inflammatory state [8]. Whereas C-reactive protein (CRP) and Glycoprotein acetylation (GlycA) are considered potential markers of low-grade systemic inflammation [9,10], fractional exhaled nitric oxide (Fe_{NO}) is nitric oxide in exhaled air which is produced by the airway epithelium and is considered a marker of airway inflammation [11]. It is yet unknown whether excess visceral fat has an impact on airway inflammation. Leptin plasma concentrations are increased in overweight and obesity and associated with reduced Forced Expiratory Volume in 1 s (FEV_1) [12]. Adiponectin plasma concentrations are reduced in overweight and obesity, but not much been known about the association between adiponectin levels and lung function [13].

Only few studies have investigated the relation between visceral fat and lung function in the general population. A recent study observed that women aged ≥65 years with a visceral fat area below 100 cm^2, measured with the bioelectrical impedance analysis method, had a higher Forced Vital

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Capacity (FVC) than women with visceral fat ≥100 cm^2, whereas no difference was observed in FVC between those with high and low visceral fat in women aged below 65 years and in men [14]. An earlier study reported that visceral fat was negatively associated with lung function in both men and women, also after adjustment for other measures of adiposity [15]. In line with the aforementioned studies in Asian populations, a study in 98 Caucasian men found that an additional 200 cm^2 of visceral fat was associated with a 4.6% decrease in Forced Expiratory Volume in 1 s (FEV_1) predicted [16]. However, this study was in men with the metabolic syndrome and the analysis was not adjusted for total body fat, which is important because visceral fat is strongly related to total body fat [17]. Therefore, it remains unclear to what extent excess visceral fat is specifically associated with reduced lung function.

Based on these considerations, here we aimed to investigate the specific association between visceral fat and lung function and to examine the mediating role of inflammation measured via CRP, GlycA, Fe_{NO}, leptin, and adiponectin in the pathway of excess visceral fat to reduced lung function. The hypothesized underlying model of this study is visualized in Figure 1.

2. Methods

2.1. Study design and population

The present study is a cross-sectional analysis of baseline measurements of the Netherlands Epidemiology of Obesity (NEO) study, a population-based, prospective cohort study. Between September 2008 and September 2012, 6,671 men and women aged between 45 and 65 years were included. The study design and population are described in detail elsewhere [18].

In short, men and women with a self-reported BMI ≥27 kg/m^2 living in the greater area of Leiden (in the West of the Netherlands) were eligible to participate in the NEO study. In addition, in one municipality (Leiderdorp), all inhabitants aged 45–65 years were invited irrespective of their BMI, allowing for a reference distribution of BMI. Participants completed a general questionnaire at home and underwent an extensive physical examination at the study center, including blood sampling and spirometry. Research nurses recorded names and dosages of current medication used during the month preceding the study visit. At the study center, the participants completed a screening form, asking about anything that might create a health risk or interfere with MRI (most notably metallic devices, claustrophobia, or a body circumference of more than 1.70 m). Of the participants who were eligible for MRI, approximately 35% were randomly selected to undergo direct assessment of abdominal subcutaneous adipose tissue and visceral adipose tissue. For the present study, we included participants with an assessment of visceral fat by MRI. Participants with missing data on confounding factors, mediating, or outcome variables were excluded. The study was approved by the medical ethics committee of the LUMC and all participants gave written informed consent.

2.2. Data collection

Participants reported their medical history of asthma, chronic obstructive pulmonary disease (COPD), diabetes and cardiovascular disease (including myocardial infarction, angina, congestive heart failure, stroke or peripheral vascular disease) on the questionnaire. The participant reported their ethnicity which was grouped into white and other. The highest completed level of education was reported and grouped into low education (no education, primary education or lower vocational education) and high education (other). Smoking behavior was reported, and participants were divided into three groups: never, former, and current smoker. In addition, the number of pack-years was calculated. The participants reported the frequency and duration of their physical activity during leisure time using the SQUASH questionnaire [19], which we expressed as the Metabolic Equivalent of Task-hours (MET-hours) per week [20]. In women, menopausal

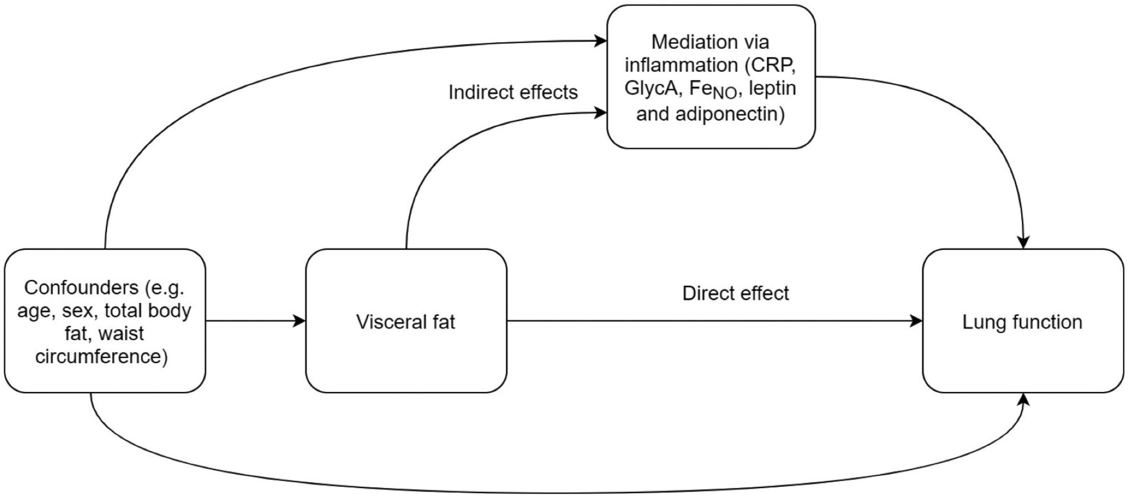

Figure 1. Overview of the proposed underlying model and role of confounders. Figure presents the hypothesized pathways from effect of visceral fat to lung function, with a direct effect and an indirect effect via mediation of inflammation. Also the influence of potential confounding factors is depicted. No confounding between the mediators and the outcome is assumed.

status was categorized in pre- and postmenopausal state according to information on oophorectomy, hysterectomy, and self-reported state of menopause in the questionnaire.

Blood was drawn after an overnight fast. Plasma glucose, glycosylated hemoglobin-type A1C (HbA1c), serum triglycerides and serum high-density lipoprotein-cholesterol (HDL-c) were analyzed at the central clinical chemistry laboratory of the LUMC using standard assays. LDL-c concentrations were calculated using the Friedewald equation [21]. Serum concentrations of CRP were determined using a high-sensitivity CRP assay (hs-CRP, TINA-Quant CRP HS system, Roche, Germany and Modular P800, Roche, Germany). GlycA concentrations were measured in plasma that had undergone one previous freeze–thaw cycle, using a high-throughput proton nuclear magnetic resonance (NMR) spectroscopy (Nightingale Health Ltd., Helsinki, Finland). GlycA is a composite measure of changes in N-glycan side chains that are attached to acute-phase proteins [22]. Serum leptin was measured by a human leptin competitive RadioImmunoAssay (Cat Nr HL-81HK, Merck Millipore, Darmstadt, Germany) using a gamma counter (Wizard 2 3470, PerkinElmer, StatLia software). Serum total adiponectin was measured using a latex particle-enhanced turbidimetric immunoassay (Cat Nr A0299, Randox Laboratories Limited) on an automated analyzer (Roche Modular P800).

During the study visit, blood pressure was measured on the right arm, while seated, with a validated automatic oscillometric device (OMRON, Model M10-IT; Omron Health Care Inc, IL, U.S.A.). The Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III as the presence of at least three out of the five following criteria: (1) increased waist circumference (>102 cm for men, >88 cm for women); (2) raised serum triglyceride levels (1.7 mmol/L) or on drug treatment to reduce triglyceride concentrations; (3) reduced serum HDL-cholesterol levels (1.03 mmol/L for men, 1.3 mmol/L for women) or on drug treatment to elevate HDL-cholesterol; (4) raised blood pressure (≥130 mmHg systolic/≥85 mmHg diastolic) or on antihypertensive drug treatment; (5) raised fasting plasma glucose (5.56 mmol/L) or on drug treatment to lower glucose concentrations [23].

2.3. Body fat and visceral fat

At the study site, body height, weight and waist circumference were measured with precision of 0.1 cm or kg. BMI was calculated by dividing the weight in kilograms by the height in squared meters. Waist circumference was measured between the border of the lower costal margin and the iliac crest. Total body fat was estimated by bio-electrical impedance analysis (BIA) with the Tanita foot-to-foot BIA system TBF-300A Body Composition Analyzer (Tanita Corporation of America, Inc., Arlington Heights, IL, USA).

Abdominal subcutaneous and visceral adipose tissue were directly assessed by MRI (1.5 T MR imaging, Philips Medical Systems, Best, the Netherlands) using a turbo spin echo imaging protocol. At the level of the fifth lumbar vertebra, three 10 mm transverse images were obtained during a breath hold. The visceral and subcutaneous fat areas were quantified by converting the number of pixels to cm^2 for all three slices, of which the average was used in the analyses, using in-house-developed software (MASS, Medis, Leiden, the Netherlands).

2.4. Lung function tests

Lung function of participants was measured by spirometry at the Pulmonology department of the LUMC. The Forced Expiratory Volume in 1 s (FEV_1) and Forced Vital Capacity (FVC) were obtained and expressed as percentage of predicted taking age, height, sex and race into account [24]. The FEV_1 /FVC ratio was calculated as well. The National Health and Nutrition Examination Survey (NHANES) III reference equations were used [25]. Participants were required to perform at least three reproducible pulmonary function measurements, with a maximum difference of 5% or 150 mL between the highest and lowest measurement. Of these, three spirometry tests, the one with the highest value of FEV_1 (% predicted) and FVC (% predicted) together was recorded for the analyses in this study [26].

Fe_{NO} was measured with a portable analyzer, the NIOX MINO (Aerocrine AB, Solna, Sweden). Participants performed a 10-s slow steady exhalation in which exhaled NO was expressed in parts per billion (ppb) [27].

2.5. Statistical analysis

Data were analyzed using STATA version 16.1 (StataCorp LP, College Station, TX, USA). Participants with a BMI 27 kg/m^2 were oversampled in the NEO study. To correct for this oversampling, all analyses were weighted toward the BMI distribution of the NEO participants from Leiderdorp [28], whose BMI distribution was similar to the general Dutch population [29,30]. Consequently, the results apply to a population-based study without oversampling of individuals with a BMI >27 kg/m^2.

Baseline characteristics were expressed as mean (standard deviation, SD) or percentage, and stratified by sex. We compared participants with an assessment of visceral fat by MRI with participants without an MRI for demographic characteristics, mediators and lung function. Scatterplots were constructed to visualize the crude association between visceral fat and lung function for men and women. We derived regression coefficients with 95% confidence intervals using linear regression analyses to examine the associations between adiposity measures BMI, total body fat, waist circumference, abdominal subcutaneous adipose tissue and visceral fat as independent variables and FEV_1 (% predicted), FVC (% predicted) and the FEV_1/FVC ratio as dependent variables. The different measures of adiposity were standardized to a mean of 0 and a standard deviation of 1. Analyses were corrected for age, sex, and additionally for education, ethnicity, smoking history, pulmonary disease, physical activity and menopausal status. To investigate whether the associations were specific for visceral fat and not merely representing associations of total body fat, we adjusted the associations for total body fat and for waist circumference, as measures of total and abdominal subcutaneous fat. To examine the multicollinearity between the measures of body fat we calculated variance inflation factors (VIF), which were under 10 and therefore considered acceptable [31]. We examined potential effect modification by sex by including an interaction term for sex and visceral fat in the models.

We performed two additional linear regression analyses to investigate the specific association of visceral fat with lung function and minimize the influence of the other adiposity measures. First, we grouped visceral fat into six categories based on percentiles (<50th percentile [reference], 50th-70th, 70th-90th, 95th-99th, and >99th percentile) and used it as a categorical variable in the multivariate regression model. Because the amount of visceral fat differs by sex, we created this variable separately for men and women. Second, with the aim to further distinguish associations of abdominal subcutaneous and visceral fat, we used linear regression analysis to calculate the difference in lung function in participants with and without excess visceral fat, defined by ≥100 cm^2 compared with <100 cm^2 [32] in participants with low and high waist circumference using WHO cut-offs [33] (102 cm for men and 88 cm for women).

To examine the mediating role of markers of inflammation in the associations between visceral fat and lung function, we performed a mediation analysis according to Baron and Kenny and evaluated the assumptions [34]. The distribution of the mediators CRP, GlycA, Fe_{NO}, leptin and adiponectin was skewed and therefore the mediators were log transformed using natural logarithm [10,35]. Linear regression models were constructed to estimate the direct and indirect effects of visceral fat on lung function. The assumption of no interaction between the exposure and the mediators [34] was checked by including an interaction term of visceral fat with the mediators in the linear regression models. An additional assumption is that there is no unmeasured confounding between the mediator and the outcome, hence we aimed to correct for all potential confounding factors and adjusted for age, sex, education, ethnicity, smoking history, pulmonary disease, physical activity, menopausal status, total body fat and waist circumference. To examine the extent of mediation, we included the mediators in the multivariate model of the association between visceral fat and lung function and used structural equation modeling [36] to obtain the percentage of mediation with 95% confidence intervals. As sensitivity analyses, we repeated the main analyses after exclusion of participants with a pulmonary history of asthma or COPD, and after exclusion of participants with a measured CRP >10.0 mg/L, as this level of CRP could indicate the presence of an acute infection instead of a chronic low-grade inflammatory state.

3. Results

3.1. Characteristics of the study population

Of the 6,671 participants in the NEO study, 2,569 participants underwent an assessment of visceral fat by MRI. Participants with MRI measurements were similar to participants without an MRI, except for BMI (25.9 kg/m^2 versus 26.6 kg/m^2) and leptin (15.8 ug/L versus 18.0 ug/L). Participants with missing data were consecutively excluded ($n = 308$, Figure 2). As a result, 2,261 individuals (52% women) were analyzed in the present study. Mean (SD) age was 56 (6) years, BMI 25.9 (4.0) kg/m^2, visceral fat of 90 (56) cm^2, Forced Expiratory Volume in 1 second (FEV_1) of 108 (16) % predicted and Forced Vital Capacity (FVC) of 117 (16) % predicted.

Characteristics of the study population stratified by sex are presented in Table 1. Overall, men had a higher BMI, larger waist circumference and more visceral adipose tissue than women, whereas women had more total body fat and abdominal subcutaneous adipose tissue.

3.2. Associations between measures of adiposity and lung function

The estimated differences in lung function per standard deviation in measure of body fat adjusted for potential confounding factors are shown in Table 2. All measures of adiposity were negatively associated with FEV_1 and FVC. In the multivariate model including total body fat and waist circumference, visceral fat was most strongly associated with FEV_1 and FVC (both −3.6% predicted per SD visceral fat).

3.3. Association between visceral fat and lung function

Crude scatterplots showed a negative linear association between visceral fat on the x-axis and measures of lung function on the y-axis (Figure 3). After adjustment for confounding factors including total body fat and waist circumference, each SD in visceral fat (56 cm^2) was associated with a 3.6% lower FEV_1 (95% CI: −4.9,-2.4) and a 3.6% lower FVC (95% CI: −4.6,-2.6) (Figure 4). There was no evidence for interaction between visceral fat and sex in the associations between visceral fat and FEV_1, FVC and the FEV_1/FVC ratio (p-value for interaction term 0.46, 0.75 and 0.52, respectively).

The results in Table 3 show a dose–response relation between percentiles groups with increasing amounts of visceral fat and decreased lung function, both in men and women (Table 3). Compared with men and women with an amount of visceral fat below the median (50th percentile), the adjusted mean FEV_1 % predicted in participants with visceral fat > 99th percentile was 20% (95% CI −27,-13) lower in men and 12% (95% CI −21,-3) lower in women. Compared with men and women with an amount of visceral fat below the 50th percentile, the adjusted mean FVC % predicted in participants with visceral fat in the 99th percentile was 14% (95% CI −20,-8) lower in men and 11% (95% CI −18,-4) lower in women, and the adjusted mean difference in FEV_1/FVC ratio was −5% (95% CI −8,-1) in men and −2% (95% CI −7,2) in women.

Table 4 shows that, despite small groups and wide confidence intervals, both in men and women with high and low waist circumference, excess visceral fat (here, >100 cm^2) was associated with lower lung function than in those without excess visceral fat.

3.4. Mediation of the association between visceral fat and lung function by CRP, GlycA, Fe_{NO}, leptin and adiponectin

Per standard deviation of visceral fat (56 cm^2), visceral fat was associated with higher levels of CRP and leptin (Supplemental

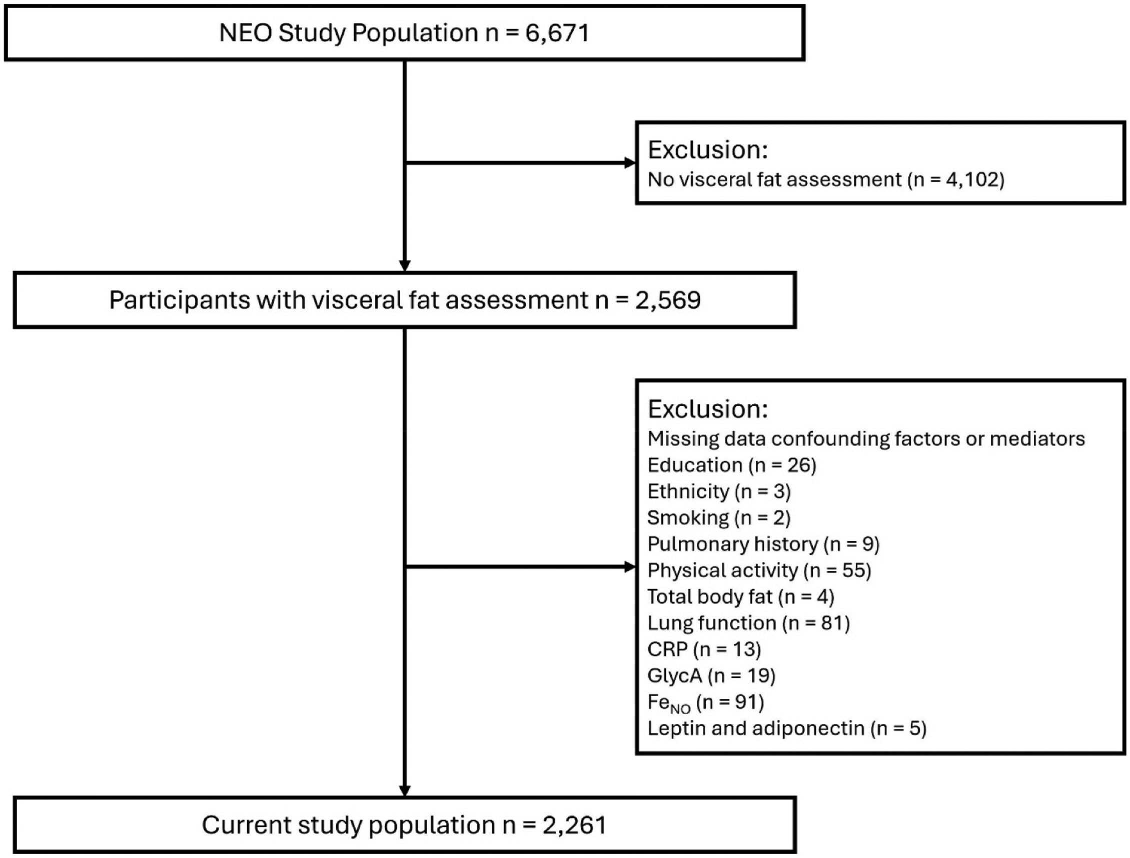

Figure 2. Flow chart of the study population. Abbreviations: CRP, c-reactive protein; Fe_{NO}, fractional exhaled nitric oxide; GlycA, glycoprotein acetylation; NEO: Netherlands epidemiology of obesity.

Table S1) and lower levels of adiponectin. Inspection of scatterplots of visceral fat and the mediators showed no deviation from linearity. GlycA, $Fe_{NO,}$and adiponectin were not associated with lung function (Supplemental Table S2) and could not be investigated further as mediators. CRP and leptin were negatively associated with lung function (Supplemental Table S2). There was no interaction between visceral fat and CRP and leptin (Supplemental Table S3).

After adjustment for the potential mediators CRP and leptin, the association between visceral fat and FEV_1 attenuated to −2.8% (CI −4.0,-1.5) per standard deviation of visceral fat (56 cm^2), reflecting22% mediation by CRP and leptin, the association of FVC attenuated to −2.9% (CI −3.9,-1.8), reflecting 19% mediation by CRP and leptin (Figure 4). Separately, 15% (95% CI 7,23) of the association with FEV_1 was mediated by CRP and 11% (95% CI 3,20) by leptin. The association with FVC was for 12% (95% CI 5,19) mediated by CRP and for 10% (95% CI 2,18) by leptin.

All associations between visceral fat and lung function remained similar after exclusion of participants with asthma or COPD (*n* = 231) and after exclusion of participants with a CRP level above 10 mg/L (*n* = 292).

4. Discussion

In the present study, we investigated the specific association between visceral fat and lung function in a general population of middle-aged men and women with a mean lung function within the normal range, and examined to what extent this association was mediated by inflammatory markers CRP, GlycA, and Fe_{NO}, and by leptin and adiponectin. After adjustment for confounding factors including total body fat and waist circumference, visceral fat was specifically associated with a reduction in lung function, i.e. with 3.6% lower FEV_1 and FVC predicted per 56 cm^2 visceral fat. This association showed a dose–response relation, with even an up to 20% lower FEV_1 % predicted in men with excess visceral fat than men with an amount of visceral fat below the median. There was no relation between the amount of visceral fat and the FEV_1/FVC ratio. Despite large sex differences in the amount of visceral fat, the association between visceral fat and lung function was similar in men and women, and even in participants with a low waist circumference excess visceral fat was associated with a reduced lung function. The associations between visceral fat and FEV_1 and FVC were for approximately 20% mediated by CRP and leptin and not by GlycA, Fe_{NO}, or adiponectin.

There have only been a few previous studies reporting on the association between visceral adipose tissue and lung function [14–16]. Findings of our study are consistent with previous studies that showed that visceral adiposity is associated with a lower lung function. The associated reduction in lung function we observed was stronger than described earlier in men with the metabolic syndrome: 3.6% FEV1 per 56 cm^2 visceral fat versus 4.6% FEV1 per 200 cm^2 visceral fat in men

Table 1. Baseline characteristics of the participants in the Netherlands epidemiology of obesity study, aged 45–65 years, stratified by sex ($n = 2{,}261$).

Characteristic	Total	Men (48%)	Women (52%)
Demographic/anthropometric			
Age (y)	56 (0.6)	56 (0.7)	55 (0.6)
Ethnicity (% white)	96	97	96
BMI (kg/m^2)	25.9 (4.0)	26.6 (3.6)	25.3 (4.1)
Total body fat (%)	30.7 (8.3)	24.7 (5.8)	36.2 (6.1)
Waist circumference (cm)	91.4 (12.8)	97.7 (10.8)	85.5 (11.6)
Visceral adipose tissue (cm^2)	89.8 (56.0)	115.3 (60.5)	66.5 (40.7)
Abdominal subcutaneous adipose tissue (cm^2)	235.1 (97.0)	209.9 (84.8)	258.0 (99.3)
Tobacco smoking (% former)	46	48	45
Tobacco smoking (% current)	14	16	13
Pack years	8 (0.13)	10 (0.15)	7 (0.12)
Alcohol intake (g/d)	15 (0.16)	20 (0.19)	10 (0.11)
Physical activity (MET-hours/week)	39 (0.34)	40 (0.39)	37 (0.28)
Education level (% high)	47	50	44
Comorbidity			
Asthma (%)	4	4	5
COPD (%)	4	4	4
Diabetes (%)	3	4	2
Cardiovascular disease (%)	4	4	4
Metabolic Syndrome (%)	23	29	18
Postmenopausal (%)			57
Potential mediators			
CRP (mg/L)	1.9 (2.6)	1.7 (2.4)	2.1 (2.7)
GlycA (mmol/l)	1.2 (0.2)	1.3 (0.2)	1.2 (0.2)
Fe_{NO} (ppb)	18.8 (11.5)	21.3 (13.8)	16.5 (8.9)
Leptin (ug/L)	15.8 (14.4)	8.9 (7.6)	22.1 (15.5)
Adiponectin (ug/L)	9.1 (4.7)	6.6 (3.1)	11.4 (4.7)
Lung function			
FEV_1 (% predicted)	108 (0.16)	106 (0.17)	110 (0.15)
FVC (% predicted)	117 (0.16)	111 (0.15)	122 (0.15)
FEV_1 (L)	3.4 (0.8)	3.9 (0.7)	2.9 (0.5)
FVC (L)	4.4 (1.0)	5.2 (0.9)	3.7 (0.6)
FEV_1/FVC ratio (%)	76 (0.7)	76 (0.8)	77 (0.6)

Values are presented as mean (SD) or percentage. Results are based on analyses weighted towards the BMI distribution of the general population (n = 2,261). Availability of variables: Pack years n = 2,214, comorbidity of cardiovascular disease n = 2,252, comorbidity of diabetes 2 n = 2,251, metabolic syndrome n = 2,255 fasting glucose n = 2,253, HbA1C n = 2,252, triglycerides, HDL and LDL n = 2,255. Abbreviations aSAT, abdominal subcutaneous adipose tissue; BMI, Body mass index; COPD, Chronic Obstructive Pulmonary Disease; CRP, c-reactive protein; Fe_{NO}, fractional exhaled nitric oxide; FEV_1, forced expiratory volume; FVC, forced vital capacity; GlycA, Glycoprotein acetylation; HbA1C, haemoglobin A1C; HDL, high density lipoprotein; LDL, low density lipoprotein; MET, Metabolic equivalent; VAT, visceral adipose tissue.

Table 2. Difference in measure of lung function per standard deviation of measure of body fat in the netherlands epidemiology of obesity study.

	FEV_1 (% predicted)	FVC (% predicted)	FEV_1/FVC ratio (%)
Measures of body fat	Regression coefficient (95% confidence interval)		
BMI age + sex	−2.2 (−3.0,-1.4)	−3.5 (−4.3,-2.8)	0.8 (0.5,1.1)
multivariate^1	−1.6 (−2.5,-0.8)	−3.2 (−4.0,-2.4)	1.0 (0.6,1.3)
TBF age + sex	−4.0 (−5.2,-2.7)	−5.3 (−6.4,-4.2)	0.8 (0.2,1.3)
multivariate^1	−3.4 (−4.7,-2.2)	−5.1 (−6.2,-3.9)	1.1 (0.5,1.6)
WC age + sex	−3.6 (−4.5,-2.7)	−4.5 (−5.4,-3.7)	0.5 (0.1,0.8)
multivariate^1	−3.1 (−4.1,-2.1)	−4.4 (−5.3,-3.4)	0.7 (0.3,1.2)
aSAT age + sex	−3.0 (−3.8,-2.1)	−4.0 (−4.8,-3.3)	0.6 (0.2,0.9)
multivariate^1	−2.6 (−3.4,-1.7)	−3.8 (−4.6,-3.0)	0.7 (0.4,1.1)
VAT age + sex	−4.4 (−5.3,-3.6)	−5.0 (−5.8,-4.3)	0.1 (−0.3,0.5)
multivariate^1	−4.0 (−4.9,-3.1)	−4.9 (−5.7,-4.1)	0.4 (−0.0,0.8)
multivariate^1 TBF+WC	−3.6 (−4.9, −2.4)	−3.6 (−4.6, −2.6)	−0.3 (−0.9, 0.3)

Results are based on linear regression analyses weighted towards the BMI distribution of the general population (n = 2,261 and expressed as differences in lung function per standard deviation of measure of body fat). Standard deviation BMI = 4 kg/m^2, standard deviation WC = 13 cm, standard deviation TBF = 8%, standard deviation aSAT = 97 cm^2, standard deviation VAT = 56 cm^2. ^{1}Multivariate models are adjusted for age, sex, education, ethnicity, smoking history, pulmonary disease, physical activity, menopausal status of women, in addition to TBF and WC in the final model of VAT. Abbreviations: aSAT, abdominal subcutaneous adipose tissue; BMI, Body mass index; CI, confidence interval; FEV_1, forced expiratory volume; FVC, forced vital capacity; TBF, total body fat; VAT, visceral adipose tissue; WC, waist circumference.

with the metabolic syndrome [16]. Our study adds to the current literature that these associations of visceral fat and lung function remained after adjustment for total body fat and waist circumference and therefore are specific for visceral fat. This suggests that reduced lung function in those with abdominal obesity is not solely due to mechanical pressure, but that the amount of visceral fat specifically plays a role in reducing lung function.

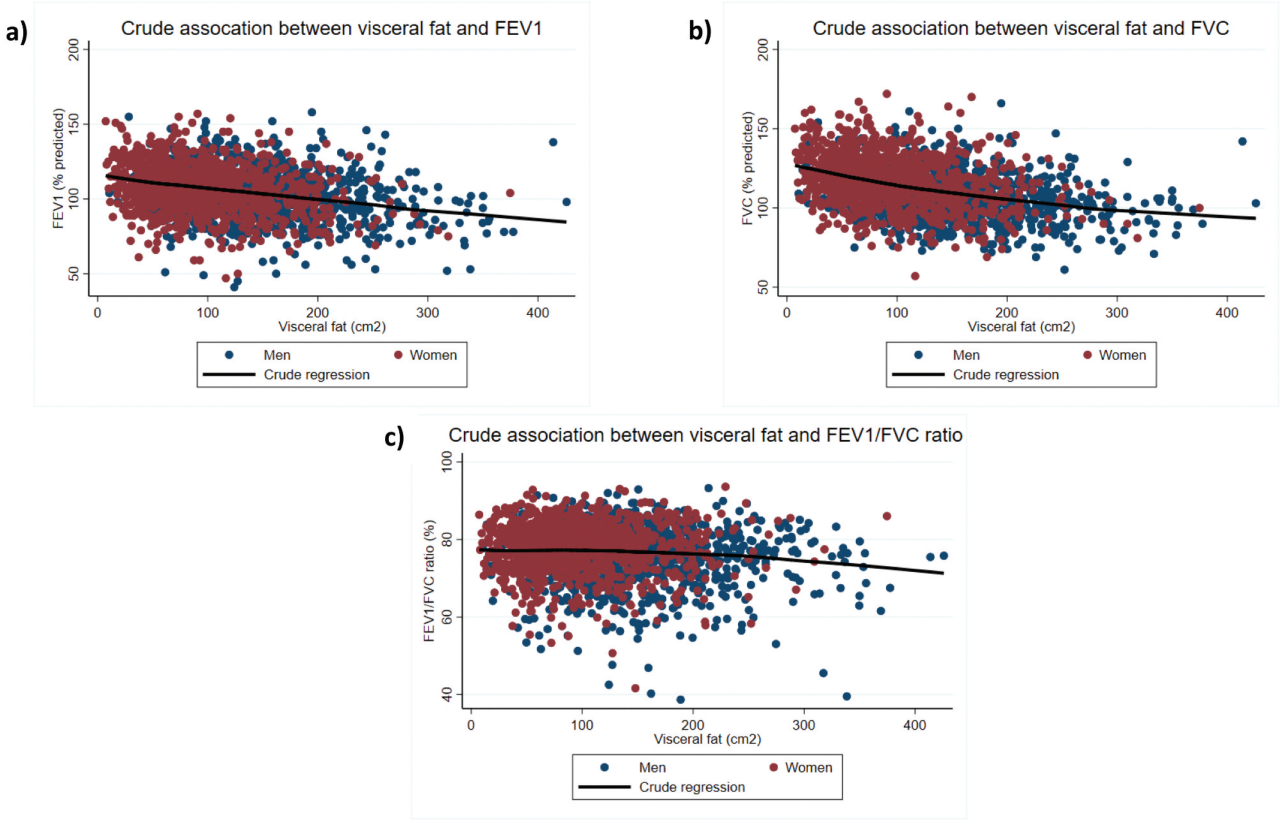

Figure 3. Scatterplots of the crude association between visceral fat and (a) FEV_1, (b) FVC and (c) the FEV_1/FVC ratio in the Netherlands epidemiology of obesity study in men (n = 1,197) and women (n = 1,064). The lines represent nonlinear associations between visceral fat and FEV_1, FVC and the FEV_1/FVC ratio. Correlation coefficients: a) ρ=-0.26, b) ρ=-0.38, c) ρ= −0.05. Abbreviations: FEV_1: forced expiratory volume; FVC: forced vital capacity.

Whereas there was no mediation of the association between visceral fat and lung function by GlycA, FeNO and adiponectin, CRP and leptin together mediated 22% of the association with FEV_1 and 19% with FVC. We hypothesized that the underlying mechanism of this observation is the release of IL-6 and TNF-α by visceral fat, in view of their role in the regulation of CRP synthesis [37–39]. Leptin is also secreted by visceral fat and known to act as a proinflammatory cytokine [40]. Although the underlying mechanism linking inflammation and visceral fat remains unclear, research has shown elevated leptin levels during COPD exacerbation [41]. It has been suggested that leptin may regulate the infiltration and survival of inflammatory cells in the submucosa [41]. Nevertheless, the total mediation by CRP and leptin of approximately 20% may seem marginal, and possibly other pro-inflammatory hormones and cytokines that are directly secreted by the visceral adipocytes, like IL-6 and TNF-α [8], may more strongly mediate the association between visceral fat and lung function. While part of the underlying mechanism of the association between visceral fat and lung function still may be mechanical, this seems unlikely due to the small volume of visceral fat in comparison with the volume of subcutaneous fat (~95% of total body fat). Thus, the underlying mechanism of the total effect of obesity on lung function is a combination of mechanical and metabolic.

The presence of airflow obstruction is often measured with the FEV_1/FVC ratio [42,43]. Whereas other studies showed that visceral fat was also negatively associated with the FEV_1/FVC ratio, we only observed this in the highest percentiles of visceral fat [14]. The lack of association between visceral fat and the FEV_1/FVC ratio in our study suggests that obstruction is not part of the association between visceral fat and reduced lung function.

Strengths of this study include the large population, information on potential confounding factors and the assessment of abdominal subcutaneous and visceral adipose tissue by MRI. A major limitation of this study is the observational cross-sectional design, and therefore temporal relations cannot be inferred. Despite the extensive phenotyping of the NEO study, we cannot exclude the possibility of residual confounding [44]. Our analyses showed that participants with an MRI scan to assess visceral fat had a somewhat lower BMI, lower CRP and leptin concentrations than those without assessment of visceral fat. Although we have no reason to think this may have influenced our results, our results pertain those who are eligible to undergo MRI. The majority of our study population was white, and whereas our findings confirm a previous observation that increased visceral fat was involved in the development of obstructive lung disease in young Japanese men [14], the susceptibility to the accumulation of visceral fat may differ between ethnicities [45], and it therefore remains unclear to what extent these findings can be extrapolated to other populations [8]. Another limitation is that pro-inflammatory cytokines that are directly secreted by the visceral adipocytes, predominantly IL-6 and TNF-α [8], were not measured in this study and could therefore not be investigated as potential mediators. Furthermore, Fe_{NO} as well may not truly reflect

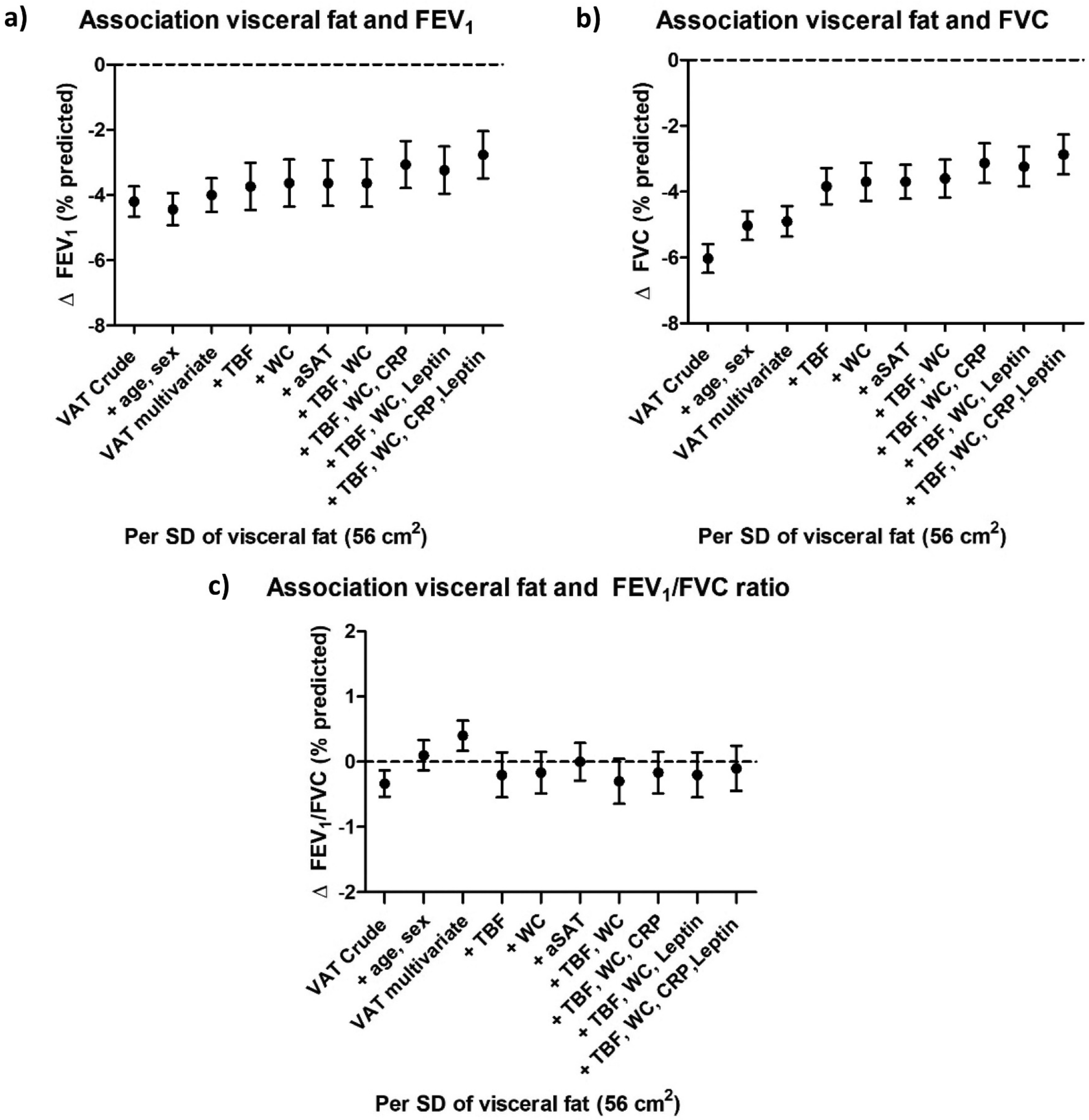

Figure 4. The association between visceral fat (VAT) and (a) FEV_1, (b) FVC and (c) the FEV_1/FVC ratio adjusted for different combinations of potential confounders and mediators in the Netherlands epidemiology of obesity study. results were based on analyses weighted towards the BMI distribution of the general population (n=2,261) and presented as the relative change in FEV_1, FVC and the FEV_1/FVC ratio per standard deviation of visceral fat ($56cm^2$) with 95% confidence intervals. Multivariate models are adjusted for age, sex, education, ethnicity, smoking history, pulmonary disease, physical activity, menopausal status of women. Abbreviations: aSAT, abdominal subcutaneous adipose tissue; CRP, c-reactive protein; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; TBF, total body fat; VAT, visceral adipose tissue; WC, waist circumference.

inflammation related to visceral fat. Fe_{NO} is enhanced by sputum eosinophils and airway eosinophilia in bronchial biopsies but not with neutrophilic inflammation [46,47]. For example, asthma in people with obesity is associated with higher sputum neutrophil instead of eosinophil counts [48,49]. This is supported by the fact that several previous studies did not observe an association between BMI and Fe_{NO} [50,51]. The possible airway inflammation related to visceral fat is also accompanied by higher neutrophil instead of eosinophil counts, which is not detected by Fe_{NO}. Finally, we assessed subcutaneous and visceral fat with MRI by measuring three transverse slices at the level of the fifth vertebra instead of total visceral fat volume [44,52]. However, cross-sections at that level are highly correlated to total volumes (correlation coefficients around 0.8) [53,54].

We acknowledge that we observed the association between excess visceral fat and reduced lung function in a population with normal lung function, which may have limited clinical implications. Nevertheless, people with excess visceral fat may be more susceptible to impairment of lung function by other, for example, infectious causes. As an example, it was recently suggested that abdominal obesity was related to the severity of SARS-CoV-2 infection [55–57]. In addition, for those with chronic respiratory diseases, the additional reduction in lung function might be relevant. Because of the lack of association with FEV_1/FVC, the use of lung medication to reduce obstruction may not be useful for people who suffer from reduced lung function mainly related to visceral fat. Instead, adopting a healthy lifestyle should be encouraged to reduce the hazardous effects of overall and visceral obesity, possibly in

Table 3. Differences in measures of lung function per percentile group of visceral fat compared with those with visceral fat below the 50th percentile in men and women participating in the Netherlands epidemiology of obesity study.

Percentile group	FEV$_1$ (% predicted)	FVC (% predicted)	FEV$_1$/FVC ratio (%)
	Regression coefficient (95% confidence interval)		
Men			
50th-70th percentile (VAT ranges, 107–135 cm^2)	−5.6 (−8.8,-2.3)	−4.8 (−7.6,-2.0)	−0.7 (−2.4,1.0)
70th-90th percentile (VAT ranges, 135–191 cm^2)	−4.3 (−7.9,-0.7)	−4.7 (−7.3,-2.1)	−0.2 (−1.9,1.6)
90th-95th percentile (VAT ranges, 191–222 cm^2)	−7.6 (−12.5,-2.8)	−8.0 (−11.3,-4.7)	0.0 (−3.0,3.0)
95th-99th percentile (VAT ranges, 222–292 cm^2)	−9.5 (−14.3,-4.8)	−9.9 (−14.0,-5.8)	−0.3 (−2.6,1.9)
>99th percentile (VAT ranges, 292–426 cm^2)	−20.1 (−27.0,-13.2)	−14.0 (−20.4,-7.6)	−4.7 (−8.5,-0.9)
Women			
50th-70th percentile (VAT ranges, 56–80 cm^2)	1.8 (−2.2,5.8)	1.8 (−2.1,5.8)	0.1 (−1.5,1.7)
70th-90th percentile (VAT ranges, 80–121 cm^2)	−1.7 (−6.1,2.6)	−2.3 (−6.6,2.0)	0.0 (−1.5,1.6)
90th-95th percentile (VAT ranges, 121–151 cm^2)	−6.0 (−11.0,-1.0)	−5.9 (−10.8,-1.0)	−0.9 (−2.8,1.1)
95th-99th percentile (VAT ranges, 151–207 cm^2)	−7.9 (−13.3,-2.5)	−9.5 (−14.8,-4.1)	0.5 (−1.6,2.7)
>99th percentile (VAT ranges, 207–374.7 cm^2)	−11.7 (−20.5,-2.8)	−10.8 (−18.1,-3.6)	−2.1 (−6.5,2.3)

Results are based on linear regression analyses weighted towards the BMI distribution of the general population (n = 1,197 men and n = 1,064 women) and expressed as differences in lung function compared with lung function in those with visceral fat below the 50 percentile. Adjusted for age, education, ethnicity, smoking history, pulmonary disease, physical activity, total body fat and waist circumference. Abbreviations: CI, confidence interval; FEV$_1$, forced expiratory volume; FVC, forced vital capacity; VAT, visceral adipose tissue.

Table 4. Difference with 95% confidence intervals in measures of lung function in those with ≥100 cm^2 visceral fat compared with those <100 cm^2 visceral fat in men and women participating in the netherlands epidemiology of obesity study stratified by sex-specific cutoffs of waist circumference [31].

	Lung function	VAT <100 cm^2 Reference mean (SD)	VAT ≥100 cm^2 Difference from reference (95% CI)
Men WC < 102 cm			
	FEV$_1$ (% predicted)	109 (0.16)	−2.4 (−5.4,0.6)
	FVC (% predicted)	115 (0.14)	−2.4 (−4.9,0.1)
	FEV$_1$/FVC ratio (%)	75 (0.7)	0.1 (−1.5,1.6)
Men WC ≥102 cm			
	FEV$_1$ (% predicted)	108 (0.15)	−1.5 (−4.8,1.9)
	FVC (% predicted)	113 (0.12)	−2.4 (−5.3,0.4)
	FEV$_1$/FVC ratio (%)	76 (0.7)	0.6 (−0.9,2.2)
Women WC <88 cm			
	FEV$_1$ (% predicted)	112 (0.16)	−3.0 (−11.8,5.8)
	FVC (% predicted)	125 (0.15)	−1.6 (−8.4,5.3)
	FEV$_1$/FVC ratio (%)	77 (0.6)	−2.0 (−5.1,1.0)
Women WC ≥88 cm			
	FEV$_1$ (% predicted)	108 (0.15)	−4.2 (−7.3,-1.2)
	FVC (% predicted)	119 (0.14)	−5.5 (−8.6,-2.4)
	FEV$_1$/FVC ratio (%)	78 (0.6)	0.3(−0.9,1.6)

Results are based on linear regression analyses weighted towards the BMI distribution of the general population (n = 1,197 men and n = 1,064 women). Adjusted for age, education, ethnicity, smoking history, pulmonary disease, physical activity, total body fat and waist circumference. Weighted proportion of men present in each subgroup: WC <102 cm, VAT <100 cm^2 = 18%, VAT ≥100 cm^2 = 16%, WC ≥102 cm, VAT <100 cm^2 = 6%, VAT ≥100 cm^2 = 59%. Proportion of women present in each subgroup: WC <88 cm, VAT <100 cm^2 = 24%, VAT ≥100 cm^2 = 1%, WC ≥88 cm, VAT <100 cm^2 = 35%, VAT ≥100 cm^2 = 41%. Abbreviations: CI, confidence interval; FEV$_1$, forced expiratory volume; FVC, forced vital capacity; VAT, visceral adipose tissue; WC, waist circumference.

combination with obesity medication. This is increasingly important given the growing prevalence of overall and abdominal obesity and obesity-related diseases world-wide [58].

In conclusion, in a middle-aged general population with a lung function within the normal range, excess visceral fat was specifically related with reduced lung function, also after taking into account measures of total and abdominal subcutaneous fat. This association was for 20% mediated by CRP and leptin. Future research should explore cytokines such as IL-6 and TNF-α as potential mediating variables as these are directly affected by visceral fat. This may contribute to the understanding of the potential mechanisms underlying the association between visceral fat and lung function.

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Declarations of interest

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Author contributions

MJP Oosterom-Eijmael: designed and performed statistical analyses and drafted manuscript. S le Cessie: supervised statistical analyses. AM Slats, PS Hiemstra, W Thijs, HLJ Lamb, and K Willems van Dijk: contributed to study design and data collection. FR Rosendaal: designed the NEO study. R de Mutsert: designed and conducted the NEO study, supervised the statistical analyses and writing. All authors critically revised the manuscript and read and approved the final version.

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Ethical approval

Approved by the medical ethics committee of the Leiden University Medical Centre P08.109

References

1. Brumpton B, Langhammer A, Romundstad P, et al. General and abdominal obesity and incident asthma in adults: the HUNT study. Eur Respir J. 2013;41(2):323–329. doi: 10.1183/09031936.00012112
2. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med. 2007;175(7):661–666. doi: 10.1164/rccm.200611-1717OC
3. Assad N, Qualls C, Smith LJ, et al. Body mass index is a stronger predictor than the metabolic syndrome for future asthma in women. The longitudinal CARDIA study. Am J Respir Crit Care Med. 2013;188(3):319–326. doi: 10.1164/rccm.201303-0457OC
4. Stefan N, Häring HU, Hu FB, et al. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol. 2013;1(2):152–162. doi: 10.1016/S2213-8587(13)70062-7
5. de Oliveira PD, Wehrmeister FC, Horta BL, et al. Visceral and subcutaneous abdominal adiposity and pulmonary function in 30-year-old adults: a cross-sectional analysis nested in a birth cohort. BMC Pulm Med. 2017;17(1):157. doi: 10.1186/s12890-017-0510-7
6. Rasslan Z, Stirbulov R, Junior RS, et al. The impact of abdominal adiposity measured by sonography on the pulmonary function of pre-menopausal females. Multidiscip Respir Med. 2015;10(1):23. doi: 10.1186/s40248-015-0018-z
7. Dixon AE, Peters U. The effect of obesity on lung function. Expert Rev Respir Med. 2018;12(9):755–767. doi: 10.1080/17476348.2018.1506331
8. de Mutsert R, Gast K, Widya R, et al. Associations of abdominal subcutaneous and visceral fat with insulin resistance and secretion differ between men and women: the Netherlands epidemiology of obesity study. Metab Syndr Relat Disord. 2018;16(1):54–63. doi: 10.1089/met.2017.0128
9. Brooks GC, Blaha MJ, Blumenthal RS. Relation of C-reactive protein to abdominal adiposity. Am J Cardiol. 2010;106(1):56–61. doi: 10.1016/j.amjcard.2010.02.017
10. Christen T, Trompet S, Rensen PCN, et al. The role of inflammation in the association between overall and visceral adiposity and subclinical atherosclerosis. Nutr Metab Cardiovasc Dis. 2019;29(7):728–735. doi: 10.1016/j.numecd.2019.03.010
11. Al Khathlan N, Salem AM. The effect of adiposity markers on fractional exhaled nitric oxide (FeNO) and pulmonary function measurements. Int J Gen Med. 2020;13:955–962. doi: 10.2147/IJGM.S280395
12. Sin DD, Man SF. Impaired lung function and serum leptin in men and women with normal body weight: a population based study. Thorax. 2003;58(8):695–698. doi: 10.1136/thorax.58.8.695
13. Garcia P, Sood A. Adiponectin in pulmonary disease and critically ill patients. Curr Med Chem. 2012;19(32):5493–5500. doi: 10.2174/092986712803833263
14. Kawabata R, Soma Y, Kudo Y, et al. Relationships between body composition and pulmonary function in a community-dwelling population in Japan. PLOS ONE. 2020;15(11):e0242308. doi: 10.1371/journal.pone.0242308
15. Park YS, Kwon HT, Hwang SS, et al. Impact of visceral adiposity measured by abdominal computed tomography on pulmonary function. J Korean Med Sci. 2011;26(6):771–777. doi: 10.3346/jkms.2011.26.6.771
16. Thijs W, Alizadeh Dehnavi R, Hiemstra PS, et al. Association of lung function measurements and visceral fat in men with metabolic syndrome. Respir Med. 2014;108(2):351–357. doi: 10.1016/j.rmed.2013.10.003
17. Seidell JC, Bouchard C. Visceral fat in relation to health: is it a major culprit or simply an innocent bystander? Int J Obes Relat Metab Disord. 1997;21(8):626–631. doi: 10.1038/sj.ijo.0800467
18. de Mutsert R, den Heijer M, Rabelink TJ, et al. The Netherlands epidemiology of obesity (NEO) study: study design and data collection. Eur J Epidemiol. 2013;28(6):513–523. doi: 10.1007/s10654-013-9801-3
19. Wendel-Vos GC, Schuit AJ, Saris WH, et al. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56(12):1163–1169. doi: 10.1016/S0895-4356(03)00220-8
20. Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol. 1990;13(8):555–565. doi: 10.1002/clc.4960130809
21. Knopfholz J, Disserol CC, Pierin AJ, et al. Validation of the friedewald formula in patients with metabolic syndrome. Cholesterol. 2014;2014:1–5. doi: 10.1155/2014/261878
22. Otvos JD, Shalaurova I, Wolak-Dinsmore J, et al. GlycA: a composite nuclear magnetic resonance biomarker of systemic inflammation. Clin Chem. 2015;61(5):714–723. doi: 10.1373/clinchem.2014.232918
23. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/national heart, lung, and blood institute scientific statement. Circulation. 2005;112(17):2735–2752. doi: 10.1161/CIRCULATIONAHA.105.169404
24. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Am J Respir Crit Care Med. 2019;200(8):e70–e88. doi: 10.1164/rccm.201908-1590ST
25. Miller A, Enright PL. PFT interpretive strategies: American thoracic society/European respiratory society 2005 guideline gaps. Respir Care. 2012;57(1):127–133. discussion 33–35. doi: 10.4187/respcare.01503
26. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–338. doi: 10.1183/09031936.05.00034805
27. Thijs W, de Mutsert R, le Cessie S, et al. Reproducibility of exhaled nitric oxide measurements in overweight and obese adults. BMC Res Notes. 2014;7(1):775. doi: 10.1186/1756-0500-7-775
28. Cole SR. Analysis of complex survey data using SAS. Comput Methods Programs Biomed. 2001;64(1):65–69. doi: 10.1016/S0169-2607(00)00088-2

29. Korn EL, Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. Am J Public Health. 1991;81(9):1166–1173. doi: 10.2105/AJPH.81.9.1166
30. VWS. Hoeveel mensen hebben overgewicht? 2013 [cited 2021 Dec 10]. Available from: https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/huidige-situatie
31. Kim JH. Multicollinearity and misleading statistical results. Korean J Anesthesiol. 2019;72(6):558–569. doi: 10.4097/kja.19087
32. Examination Committee of Criter Japan ECoCfODi, Obesity JSftSo. New criteria for 'obesity disease' in Japan. Circ J. 2002;66(11):987–992. doi: 10.1253/circj.66.987
33. WHO. Waist circumference and waist-hip ratio: a report of a WHO expert consultation. [cited 2021 Dec 10]. Available from: https://www.who.int/publications/i/item/9789241501491
34. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986;51(6):1173–1182. doi: 10.1037/0022-3514.51.6.1173
35. Noordam R, Boersma V, Verkouter I, et al. The role of C-reactive protein, adiponectin and leptin in the association between abdominal adiposity and insulin resistance in middle-aged individuals. Nutr Metab Cardiovasc Dis. 2020;30(8):1306–1314. doi: 10.1016/j.numecd.2020.04.021
36. Gunzler D, Chen T, Wu P, et al. Introduction to mediation analysis with structural equation modeling. Shanghai Arch Psychiatry. 2013;25(6):390–394. doi: 10.3969/j.issn.1002-0829.2013.06.009
37. Saijo Y, Kiyota N, Kawasaki Y, et al. Relationship between C-reactive protein and visceral adipose tissue in healthy Japanese subjects. Diabetes Obes Metab. 2004;6(4):249–258. doi: 10.1111/j.1462-8902.2003.0342.x
38. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. Biochem J. 1990;265(3):621–636. doi: 10.1042/bj2650621
39. Warren RS, Starnes HF, Gabrilove JL, et al. The acute metabolic effects of tumor necrosis factor administration in humans. Arch Surg. 1987;122(12):1396–1400. doi: 10.1001/archsurg.1987.01400240042007
40. Tian YF, Chang WC, Loh CH, et al. Leptin-mediated inflammatory signaling crucially links visceral fat inflammation to obesity-associated β-cell dysfunction. Life Sci. 2014;116(1):51–58. doi: 10.1016/j.lfs.2014.07.039
41. Malli F, Papaioannou AI, Gourgoulianis KI, et al. The role of leptin in the respiratory system: an overview. Respir Res. 2010;11(1):152. doi: 10.1186/1465-9921-11-152
42. Bhatt SP, Kim YI, Wells JM, et al. FEV 1 /FEV 6 to diagnose airflow obstruction. Comparisons with computed tomography and morbidity indices. Ann Am Thorac Soc. 2014;11(3):335–341. doi: 10.1513/AnnalsATS.201308-251OC
43. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347–365. doi: 10.1164/rccm.201204-0596PP
44. Elffers TW, de Mutsert R, Lamb HJ, et al. Body fat distribution, in particular visceral fat, is associated with cardiometabolic risk factors in obese women. PLOS ONE. 2017;12(9):e0185403. doi: 10.1371/journal.pone.0185403
45. Tchernof A, Després JP. Pathophysiology of human visceral obesity: an update. Physiol Rev. 2013;93(1):359–404. doi: 10.1152/physrev.00033.2011
46. Jatakanon A, Lim S, Kharitonov SA, et al. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. Thorax. 1998;53(2):91–95. doi: 10.1136/thx.53.2.91
47. Payne DN, Adcock IM, Wilson NM, et al. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. Am J Respir Crit Care Med. 2001;164(8):1376–1381. doi: 10.1164/ajrccm.164.8.2101145
48. Scott HA, Gibson PG, Garg ML, et al. Airway inflammation is augmented by obesity and fatty acids in asthma. Eur Respir J. 2011;38(3):594–602. doi: 10.1183/09031936.00139810
49. Telenga ED, Tideman SW, Kerstjens HA, et al. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. Allergy. 2012;67(8):1060–1068. doi: 10.1111/j.1398-9995.2012.02855.x
50. Singleton MD, Sanderson WT, Mannino DM. Body mass index, asthma and exhaled nitric oxide in U.S. Adults, 2007–2010. J Asthma. 2014;51(7):756–761. doi: 10.3109/02770903.2014.912302
51. Kim SH, Kim TH, Lee JS, et al. Adiposity, adipokines, and exhaled nitric oxide in healthy adults without asthma. J Asthma. 2011;48(2):177–182. doi: 10.3109/02770903.2010.529223
52. Demerath EW, Shen W, Lee M, et al. Approximation of total visceral adipose tissue with a single magnetic resonance image. Am J Clin Nutr. 2007;85(2):362–368. doi: 10.1093/ajcn/85.2.362
53. Han TS, Kelly IE, Walsh K, et al. Relationship between volumes and areas from single transverse scans of intra-abdominal fat measured by magnetic resonance imaging. Int J Obes Relat Metab Disord. 1997;21(12):1161–1166. doi: 10.1038/sj.ijo.0800530
54. Shen W, Chen J, Gantz M, et al. A single MRI slice does not accurately predict visceral and subcutaneous adipose tissue changes during weight loss. Obesity (Silver Spring). 2012;20(12):2458–2463. doi: 10.1038/oby.2012.168
55. Loef B, Boer JMA, Beekman M, et al. The association of overweight, obesity, and long-term obesity with SARS-CoV-2 infection: a meta-analysis of 9 population-based cohorts from the Netherlands cohorts consortium. Int J Obes (Lond). 2024;49(4):586–595. doi: 10.1038/s41366-024-01660-x
56. Chandarana H, Dane B, Mikheev A, et al. Visceral adipose tissue in patients with COVID-19: risk stratification for severity. Abdom Radiol (NY). 2021;46(2):818–825. doi: 10.1007/s00261-020-02693-2
57. Petersen A, Bressem K, Albrecht J, et al. The role of visceral adiposity in the severity of COVID-19: highlights from a unicenter cross-sectional pilot study in Germany. Metabolism. 2020;110:154317. doi: 10.1016/j.metabol.2020.154317
58. WHO. Fact sheet obesity and overweight. [cited 2024 Nov 10]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight