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Association of Obesity with Quantitative Chest CT Measured Airway Wall Thickness in WTC Workers with Lower Airway Disease

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Abstract

Background—We previously reported that wall area percent (WAP), a quantitative CT (QCT) indicator of airway wall thickness and, presumably, inflammation, is associated with adverse longitudinal expiratory flow trajectories in WTC workers, but that obesity and weight gain also seemed to be independently predictive of the latter. Previous studies have reported no association between WAP and obesity, so we investigated that association in nonsmoking WTC-exposed individuals and healthy unexposed controls.

Methods—We assessed WAP using the Chest Imaging Platform QCT system in a segmental bronchus in 118 former WTC workers, and 89 COPDGene® WTC-unexposed and asymptomatic subjects. We used multiple regression to model WAP vs. body mass index (BMI) in the two groups, adjusting for important subject and CT image characteristics.

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Authors' contributions RED, RSJ, and JCC designed and oversaw the study and guided the analytical strategies. XL, JTD, and YJ performed all statistical analyses. APR and RSJ established the WTC Chest CT Imaging Archive, and RSJ performed the QCT measurements. All authors contributed to writing, and reviewed and revised the draft and the final manuscript.

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Results—Unadjusted analyses revealed significant differences between the two groups with regards to WAP, age, gender, scan pixel spacing and slice interval, but not BMI or total lung capacity. In adjusted analysis, there was a significant interaction between BMI and WTC exposure on WAP. BMI was significantly and positively associated with WAP in the WTC group, but not in the COPDGene® group, but stratified analyses revealed that the effect was significant in WTC subjects with clinical evidence of lower airway disease (LAD).

Discussion—Unlike non-diseased subjects, BMI was significantly associated with WAP in WTC workers and, in stratified analyses, the association was significant only among those with LAD. Our findings suggest that this adverse effect of obesity on airway structure and inflammation may be confined to already diseased individuals.

Keywords

Multidetector computed tomography; Computer-assisted image processing; Obesity; Bronchial disease; Smoke inhalation injury; World Trade Center Attack, 2001

Introduction

Workers and volunteers exposed to dust, gasses and fumes at the WTC disaster site present a heterogeneous group of inflammatory airway diseases [1, 2]. We previously found that wall area percent (WAP), a quantitative CT (QCT) indicator of airway wall thickness and, presumably, inflammation, is associated with adverse longitudinal expiratory flow trajectories in WTC workers, but that obesity and weight gain were also independently predictive of the latter [3]. In that study, we also observed a statistically significant correlation between WAP and body mass index (BMI). A study in asymptomatic non-diseased and never smoking subjects of the COPDGene® project reported no effect of BMI on WAP [4] and, to our knowledge, no controlled study in diseased never smoking subjects has reported that association. On the other hand, computational modeling investigations have suggested that bronchial airway wall thickness contributes to airway hyperresponsiveness, a key characteristic of asthma [5]. In this study, we investigated the relation between body mass index (BMI) and WAP in a group of WTC workers, compared to healthy, asymptomatic, and never smoking participants in the COPDGene® project.

Methods

Subjects and Clinical Data Acquisition

We had clinical and functional data, images, and QCT measurements on 207 subjects. From the COPDGene® project (clinicaltrials.gov identifier NCT00608764) [6], we obtained imaging and clinical data from a previously described [4] subgroup of 89 healthy/asymptomatic, lifetime nonsmoker, and non-Latino White individuals. From the WTC Pulmonary Evaluation Unit (WTC PEU) and its WTC chest CT Archive (clinicaltrials.gov identifier NCT03295279), we had the same data on 118 subjects who had the same nonsmoking and race/ethnicity characteristics of the subjects in the COPDGene® group. We have previously reported on the workers with images in the WTC chest CT Archive [3, 7]. All of them performed rescue, recovery, and service restoration duties at the WTC disaster site from September 11, 2001 to June 2002. This group includes all occupations, except

firefighters [8]. Beginning in July 2002, all subjects underwent a baseline screening evaluation and subsequent periodic visits, which included questionnaires on respiratory symptoms, pre-WTC- and WTC-related occupational exposures, laboratory testing, physical examination (including height and weight measurements), chest radiograph, and spirometry [9]. The Mount Sinai Program for the Protection of Human Subjects approved this study (HS12–00925).

The outcome in this investigation was wall area percent (WAP), measured in all images in this study in the 3rd bronchial generation of the right upper lobe by the Chest Imaging Platform QCT system (https://www.chestimagingplatform.org/). The Chest Imaging Platform is an open source and well-validated system that has been used in large studies [10], and different from what was used in the previous COPDGene® study [4]. The automated process starts with identification of the airways and their branch points on inspiratory scans. Airways can be followed out up to five generations, depending on the resolution of the images. Based primarily on density differences between the luminal air, airway wall, and surrounding parenchyma, the airway lumen area (A_i), total airway area (A_o), and airway wall area (A_{aw}) are measured. These cross-sectional area measurements are averaged along the length of the bronchus. Wall area percentage (WAP) is calculated as $(A_o - A_i)/A_o \times 100\%$, and was averaged over all measurable airways. A higher WAP suggests airway wall thickening, in relation to the lumen, which is in turn suggestive of airway inflammatory changes. All chest CT scans selected for this study were inspiratory, and had slice thicknesses not exceeding 3 mm.

The predictor of interest was body mass index (BMI, expressed in kg/m^2), which was assessed at the time of the spirometry, on or near the date of the CT scan study. Relevant covariates included age at the time of the CT scan study, gender, CT scan pixel size and slice thickness, and QCT-measured total lung capacity (TLC_{CT}).

For the secondary stratified analysis of the WTC group, we classified subjects according to the presence or absence of evidence of lower airway disease (LAD), as follows: (1) LAD: both abnormal spirometry, revealing at any time either fixed or reversible obstruction, low FVC, or bronchodilator response, *and* reported shortness of breath with a score of three or more in the Medical Research Council breathlessness scale (MRC, “I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level”) [11, 12]; and (2) No LAD: normal or low FVC spirometry without associated significant breathlessness.

Statistical Analysis

Descriptive statistics included means and standard deviations (SD) for normally distributed continuous variables, and counts and proportions for categorical variables. Unadjusted bivariate analyses included *t*- or Chi square tests as appropriate. We then used multiple linear regression to model WAP versus BMI, adjusting for covariates. Interaction terms, confounding and quadratic relationship were examined in the process of model selection. We included a BMI-by-group interaction term to test whether the magnitude of the BMI–WAP association differed between those with and without WTC exposure. Candidate predictors for multivariable models for both the primary and the stratified analyses included

gender, and age due to their potential confounding effect. SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyses, with a two-sided p value of < 0.05 defining statistical significance.

Results

The characteristics of the study participants ($n = 207$), stratified by group (WTC workers vs. healthy controls in COPDGene®) are presented in Table 1. Compared to the control subjects, those in the WTC group had significantly higher mean WAP, were more likely to be male and younger, and to have CT scans with both higher pixel spacing and slice thickness. While the COPDGene® lifetime nonsmokers were reported as being asymptomatic and having normal lung function, 32 (27.6%) similarly nonsmoking WTC subjects had a prevalence of dyspnea with a score ≥ 3 in the MRC questionnaire [11, 12], 48 (40.7%) had abnormal spirometry (predominantly reduced FVC in 38 or 32.3%), 27 (22.9%) had evidence of bronchodilator response, and 11 (10.2%) had shown post-bronchodilator airflow obstruction (defined as $FEV_1/FVC < 0.7$) at least once. For the stratified analysis, we classified 43 of the WTC subjects as having definite clinical evidence of lower airway disease (WTC LAD), by virtue of having both dyspnea with an MRC score ≥ 3 and spirometric abnormalities.

In the multivariable analysis of BMI and WAP, we found a significant interaction between BMI and study group on WAP (Table 2 and Supplementary Table 1, p for interaction term = 0.003). Thus, we conducted a multivariable analysis stratified by study group (Table 2). In the multivariable analysis of BMI and WAP among WTC workers, each increment of 0.5 kg/m^2 in BMI was significantly associated with 0.19% higher WAP. In this analysis, CT scan slice thickness and TLC_{CT} were positively and negatively associated with WAP, respectively. On average, each 0.25 mm increase in CT scan slice thickness would increase WAP by 0.81%, and each 1 l increase in TLC_{CT} would lower WAP by 1.69%. In contrast to our findings among WTC workers, BMI was not significantly associated with WAP among control subjects in COPDGene. In the post hoc analysis, stratifying the WTC group by the presence or absence of definite evidence of LAD, the estimated effect of BMI on WAP was larger (0.24% vs. 0.19% per 0.5 kg/m^2 BMI unit), and significant only in WTC workers with LAD, with the adjusted model improving the effect size by more than 10% over the unadjusted analysis.

To further illustrate our findings, we present a scatterplot of BMI versus WAP, comparing the WTC subgroup with LAD and the COPDGene® group (Fig. 1). The fitted regression lines show an increasing trend for higher WAP as BMI increased in the WTC–LAD subgroup, while there was no such association for the COPDGene® group. Supplementary Fig. 1 shows the scatterplot for the entire WTC group and the control subjects.

Discussion

Our study shows that BMI was positively associated with WAP among WTC workers, who have a high prevalence of lower airway diseases [2], but not in asymptomatic nonsmokers in a control group. An interaction between obesity and both airway wall thickness and lung

compliance has been proposed based on computational models [5]. Our findings suggest that the adverse effects of obesity on airway structure that lead to wall thickening (presumably because of inflammatory changes), is indeed observed in nonsmoking individuals with already compromised airways, such as WTC workers with both symptoms and functional abnormalities suggestive of lower airway disease.

We had previously identified a group of WTC-related lower airway diseases [1, 2], and investigations have suggested both proximal [3] and distal [13, 14] airway involvement. Our previous research had also suggested the significant association of obesity and weight gain with adverse longitudinal expiratory flow trajectories in this group of workers [3]. This study demonstrates that obesity is significantly associated with higher WAP in WTC workers with LAD, while we replicated the previously reported lack of such association among asymptomatic/healthy and nonsmoking subjects [4]. Given the well-known fact that the prevalence of overweight and obesity in the WTC responder cohorts exceeds national averages [15–17], and the emerging realization of the association between asthma and obesity [18, 19], our findings further the understanding of this association, and suggest that future investigations should include non-asthmatic inflammatory lower airway diseases.

To our knowledge, this is the first study to document the association of obesity with WAP among individuals with lower airway disease, to have an asymptomatic and nonsmoking control group, and to corroborate with a different QCT system the previous finding [4] of lack of association in that control group. A previous study with a smaller group of subjects, reported this association in HIV-infected asthmatic, but not in HIV-infected COPD patients [20]. Additional potential confounding in that study included a high ever-smoking prevalence (82.6%), and antiretroviral treatment in 87.6% of the subjects, which is known to be associated with substantial metabolic effects and central adiposity. Another study on second-hand tobacco-exposed COPD subjects [21] reported association in obese individuals of that exposure with adverse respiratory health outcomes such as nocturnal respiratory symptoms, chronic cough, and worse quality of life, but not with QCT metrics of airway wall thickening, including WAP. A different QCT system was used in that study, and since both comparison groups had COPD, their airway wall thickening may have not differed significantly.

Particular strengths of our study include the availability of high-quality quantitative imaging data availability in the two subgroups of subjects, and the use of similar CT scanning equipment, and the same QCT system for the WAP measurements.

Important limitations of our study include the race/ethnicity restriction, inevitable and strictly due to the characteristics of the comparator asymptomatic/healthy group. This may limit the generalizability of our findings. The chest CT scans studies of COPDGene® were obtained prospectively following a fairly uniform protocol. While there was evidence of more technical variability in the WTC Chest CT Imaging Archive studies, we feel that we were able to account satisfactorily for those differences by image selection, and adjusting our multivariable model for key technical factors. However, further studies with more diverse and closely comparable study samples, as well as technical uniformity are necessary to replicate our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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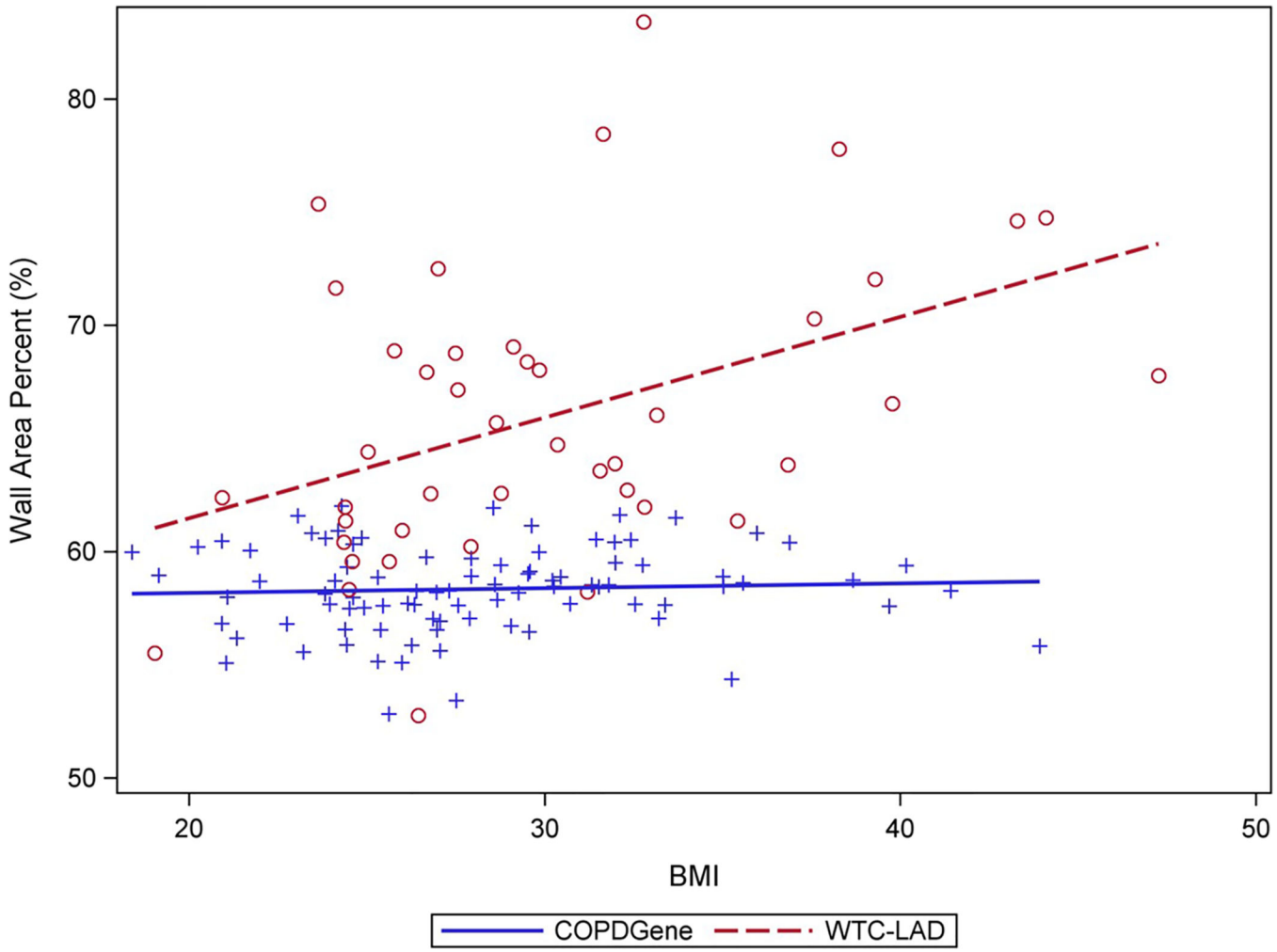

Fig. 1.
Scatterplot of WAP versus BMI, for the WTC–LAD subgroup and the COPDGene® group

Table 1

Patient and CT scan characteristics, and unadjusted bivariate comparisons (*t* test or Chi-square test, as appropriate) of the entire WTC group, and its LAD subgroup, to the healthy/asymptomatic COPDGene® group

	All (*n* = 207)	**COPDGene® group (*n* = 89)**	**WTC group (*n* = 118)**		**WTC-LAD subgroup (*n* = 43)**	
Variable	**Mean ± SD or *n* (%)**	**Mean ± SD or *n* (%)**	**Mean ± SD or *n* (%)**	***p* value[a]**	**Mean ± SD or *n* (%)**	***p* value[b]**
Wall area percent (%)	62.06 ± 6.04	58.34 ± 1.91	64.87 ± 6.56	< 0.0001	66.0 ± 6.41	< 0.0001
Age (years)	51.51 ± 13.28	62.77 ± 9.00	43.02 ± 8.98	< 0.0001	43.65 ± 10.325	< 0.0001
BMI (kg/m^2)	28.79 ± 5.03	28.16 ± 5.18	29.26 ± 4.88	0.1195	30.18 ± 5.52	0.0531
Pixel spacing (mm)	0.76 ± 0.14	0.64 ± 0.06	0.86 ± 0.09	< 0.0001	0.84 ± 0.10	< 0.0001
Slice thickness (mm)	0.86 ± 0.36	0.52 ± 0.05	1.11 ± 0.28	< 0.0001	1.14 ± 0.30	< 0.0001
Total lung capacity$_{CT}$ (l)	5.38 ± 1.30	5.49 ± 1.17	5.30 ± 1.38	0.2943	5.11 ± 1.34	0.0958
Gender (n, %)						
Female	74 (35.7)	60 (67.4)	14 (11.9)	< 0.0001	8 (18.6)	< 0.0001
Male	133 (64.3)	29 (32.6)	104 (88.1)		35 (81.4)	

[a] *p* Value for the comparison between the COPDGene® and WTC group

[b] *p* Value for the comparison between the COPDGene® group and the WTC–LAD subgroup

Table 2

Multivariate linear regression analyses for the association of WAP and BMI (per 0.5 kg/m^2 units)

Models	Coefficient estimate β	95% CI	*p*
WTC group	0.19	0.07, 0.32	0.0031
WTC-LAD subgroup	0.24	0.13, 0.35	< 0.0001
WTC-no LAD subgroup	0.11	−0.04, 0.26	0.1567

All models use the COPDGene® group as their reference for comparison. The first model compares the WTC group, and the second and third, the WTC subgroups with (n = 43) and without (n = 75) LAD, respectively. All models were adjusted for age, gender, CT scan pixel spacing and slice thickness, and CT-measured total lung capacity