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Cite this article as: H-J Kim, J-H Park, J-y Min, K-b Min, Y-S Seo, J M Yun, H Kwon, J-I Kim, B Cho, Abdominal adiposity intensifies the negative effects of ambient air pollution on lung function in Korean men, *International Journal of Obesity* accepted article preview 25 April 2017; doi: 10.1038/ijo.2017.97.

Received 12 December 2016; revised 24 February 2017; accepted 14 March 2017; Accepted article preview online 25 April 2017

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Abdominal adiposity intensifies the negative effects of ambient air pollution on lung function in Korean men

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Running title: Adiposity and air pollution on lung function

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ABSTRACT

BACKGROUND: Some studies have provided the possibility that adipose tissue may mediate air pollution-induced lung dysfunction. Studies using quantified fat mass data are needed to understand the biological mechanisms between adipocyte and air pollution in lung function. We aimed to investigate whether abdominal adiposity measured by computed tomography (CT) modifies the effects of air pollution on lung function in Korean men.

METHODS: A total of 1,876 men who visited one of two health checkup centers were recruited for this study. Adiposity traits such as visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and total adipose tissue (TAT) areas were measured by CT. We used the annual mean concentrations of ambient air pollutants including nitrogen dioxide (NO_2) and particulate matter with an aerodynamic diameter ≤10 μm (PM_{10}).

RESULTS: Interquartile range (IQR) increase in annual mean concentration of NO_2 was significantly associated with a 2.5% lower forced expiratory volume in 1 second (FEV_1) and 2.9% lower forced vital capacity (FVC) (both $p < 0.05$). The decrease in lung function was more strongly associated with adiposity traits than with body mass index. In a stratified analysis of adiposity, compared with subjects with low-VAT area (VAT ≤ 200 cm^2), those with high-VAT area (VAT > 200 cm^2) showed a rapid decrease in FEV_1 with each IQR increase in PM_{10} (β = –0.0812; 95% confidence interval [CI] = –0.1590, –0.0035) and NO_2 (β = –0.0979; 95% CI = –0.1611, –0.0346). In the high-VAT group, each IQR increase in NO_2 content was significantly associated with a 10.6% decrease (β = –0.1056; 95% CI = –0.1770, –0.0343) in FVC. SAT and TAT areas showed similar patterns.

CONCLUSIONS: We report the first finding that abdominal adiposity intensifies the inverse relationship between air pollution and lung function.

INTRODUCTION

Ambient air pollution is one of the most important global health issues because it increases the risk of and aggravates many diseases, such as asthma, lung disease, stroke, and certain cancers.[1-5] Air pollution has been shown to have negative effects on respiratory health, and acute or repeated exposure to air pollution is associated with a reduced lung function. [6-9]

A recent genome-wide interaction study based on the SAPALDIA (Swiss Cohort Study on Air Pollution and Lung Disease in Adults) cohort reported that particulate matter with an aerodynamic diameter ≤10 μm (PM_{10}) was significantly associated with lung function decline by interacting with the certain variants of *CDH13*.[10] Our previous study also replicated this *CDH13* gene-by-PM_{10} interaction effect on lung function in Korean men.[11] *CDH13* (also known as T-cadherin) is closely related to adiponectin which is secreted exclusively from fat tissue.[10] These findings indicate that there might be a potential connection between air pollution, fat tissue, and lung function. In fact, several plausible hypotheses have been proposed to explain this connection, including the roles of oxidative stress and inflammation because of their shared mechanisms; that is, both obesity-induced inflammation and oxidative stress are related to excess adipose tissue.[12] Increased adipose tissue produces predominantly proinflammatory cytokines, including leptin, visfatin, resistin, TNF-α and IL-6. Activated reactive oxygen species (ROS) produced by accumulated adipose tissue increases systemic oxidative stress.

Although previous reports have shown significant synergistic effects of obesity and exposure to ambient air pollutants such as nitrogen dioxide (NO_2) and PM_{10} content on lung function using an indirect measurement of obesity including body mass index (BMI),[6, 13, 14] accurate quantitative measurement of adipose tissue mass by computed tomography (CT) is needed to understand the plausible mechanisms between adipose tissue and air pollution in lung function. However, to our knowledge, no studies have investigated whether there is an additive effect of fat accumulation in

adipose tissue on the relationship between ambient air pollution and lung function. In addition, most epidemiological studies regarding negative impacts of air pollution on lung function have focused mainly on children or specific populations such as Europeans, and there are few studies of these associations in Asian adults.

This study was to investigate the chronic effects of ambient air pollutants such as PM_{10} and NO_2 on lung function in Korean men and to identify whether these effects are mediated by abdominal adiposity in particular visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and total adipose tissue (TAT) areas measured by CT. We provide the first evidence that adiposity may mediate the effects of air pollution on lung function in Asian adults.

SUBJECTS AND METHODS

Subjects

The participants in this study were recruited at the two Healthcare centers at Seoul National University Hospital from 2009 to 2014.[11] They visited the center to have periodic comprehensive screening health checkups. During this period, we enrolled a total of 2,761 subjects, 885 of whom were excluded because they met the following exclusion criteria: 1) age ≤40 years; 2) lacking the necessary phenotypic information such as adiposity-related traits, lung function, and smoking status; 3) lacking zip code information for estimating exposure to air pollution; or 4) missing air pollution values. Therefore, a total of 1,876 subjects were included in the final analysis. This study was approved by the institutional review board of the Seoul National University Hospital Biomedical Research Institute (approval number, H-0911-010-299; C-1511-114-723).

Assessment of lung function

Pulmonary function was assessed in each subject using a 1022 digital spirometer (SensorMedics, Anaheim, CA, USA).[15] After each measurement, each flow–volume curve was examined to ensure that it satisfied the acceptability and reproducibility criteria, and the same measurement process was repeated at least three times for forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) values. The highest absolute values for FVC and FEV_1 were chosen as the outcome variables in this study.

Adiposity-related traits assessment

The details of the methods to measure abdominal adiposity have been described in a previous study.[16] Briefly, abdominal adiposity, including VAT, SAT, and TAT, was measured using CT scanner (Somatom Sensation 16 CT scanner, Siemens AG, Erlangen, Germany), and the areas of the fat

compartments were estimated with Rapidia 2.8 CT software (Infinitt, Seoul, Korea). To define the visceral obesity group, an optimal cut-off criterion in Korean men (VAT $\geq$ 136 cm^2) was first considered. However, we could not observe the significant effect of visceral obesity group. Therefore, we classified into three groups according to VAT level: subjects with low VAT level (VAT $\leq$ 100 cm^2), subjects with moderate VAT level (100 cm^2 < VAT $\leq$ 200 cm^2), and subjects with high VAT level (VAT > 200 cm^2). Similar to VAT, the subjects were categorized into three subgroups according SAT and TAT level, because of absence of optimal cut-off criterion in Korean men for SAT or TAT.

Lifestyle and anthropometric variables

To examine the associations between adiposity, exposure to ambient air pollution, and lung function, we collected data about lifestyle factors and anthropometric markers. Health-related behaviors such as smoking status and physical activity were assessed using a structured questionnaire and classified as categorical variables as follows: cigarette smoking status (current, former, or never smoker) and moderate activity (yes or no). Anthropometric data including height and weight were also measured.

Assessment of air pollution exposure

To assess exposure to ambient air pollution, we obtained the monitoring data (2009–2014) for 24-hour concentrations of ambient PM_{10} and NO_2 from the Ministry of the Environment of Korea (https://www.airkorea.or.kr). These concentrations were measured at about 300 nationwide monitoring sites in Korea. The annual average concentrations of air pollutants at each monitoring site were calculated to identify the effects of air pollutants on lung function. Residential zip codes were used to link each subject to the annual average concentrations from the nearest monitoring site.

Statistical analysis

Correlation coefficients between air pollutants and adiposity measures were estimated using Pearson's correlational analysis. Multiple linear regression analysis was performed to evaluate the associations between ambient air pollution, adiposity traits, and lung function. To identify the effects of adiposity traits on the relationship between air pollution and lung function, we performed a stratified analysis using the cutoff for the definition of high adiposity group for each adiposity trait. The results are presented as beta coefficients and 95% confidence intervals (CIs) for lung function after adjustment for covariates such as the site of recruitment, age, age^2, height, BMI, smoking status (never, past, or current), pack years, and moderate activity (yes or no). These estimates were converted by scale to the interquartile range (IQR) for each pollutant (9.2 μg/m^3 for PM_{10} and 13.9 ppb for NO_2). All analyses were implemented in SAS 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

The detailed characteristics of the study subjects are shown in Table 1. A total of 1,876 subjects (recruitment site A, n = 1,405; recruitment site B, n = 471) were included in the final association analyses. All subjects were men, and most were aged 50–60 years. The mean SAT area (139.8 ± 53.1 cm^2) was slightly higher than the VAT area (131.4 ± 53.6 cm^2). All adiposity-related traits were significantly intercorrelated ($p < 0.001$), and the correlation between VAT and TAT areas was the strongest of these correlations (r = 0.880) (see Supplemental Material, Table S1). The percentages of former and current smokers were 42.4% (n = 796) and 32.3% (n = 605), respectively. The mean FEV_1 and FVC were 3.3 ± 0.5 L and 4.1 ± 0.6 L. The median PM_{10} and NO_2 concentrations were 49.0 μg/m^3 and 31.5 ppb, respectively, and their IQRs were 9.2 μg/m^3 and 13.9 ppb, respectively. There was significant positive correlation between PM_{10} and NO_2 values (r = 0.430, $p < 0.001$) (see Supplemental Material, Table S1). The concentrations of PM_{10} and NO_2 in each subgroup of VAT, SAT and TAT were also demonstrated at Table S2. There was no significant difference in air pollutant concentrations among the subgroups (all $p > 0.05$) (see Supplemental Material, Table S2). In addition, we have investigated the associations of moderate activity and smoking status with lung function. As a result, smoking status and pack years were associated with decreased FEV_1, although no significant association between smoking status and FVC was observed. However, moderate activity was not significantly associated with FEV_1 and FVC (Data not shown).

Table 2 shows the results of the analysis of the associations between air pollution or adiposity-related traits and lung function including FEV_1 and FVC. NO_2 concentration was significantly associated with FEV_1 ($p = 0.0131$); there was a 2.5% decrease in FEV_1 (95% CI = –4.6%, –0.5%) with IQR (13.9 ppb) increase in NO_2 concentration. Similarly, FVC was significantly associated with NO_2 concentration ($p = 0.0102$); there was a 2.9% decrease in FVC (95% CI = –5.1%, –0.7%) for IQR (13.9 ppb) increase in NO_2 concentration. However, PM_{10} was not significantly

associated with a reduction in FEV_1 or FVC (both $p > 0.05$). Analysis of the associations between adiposity-related traits and lung function showed that BMI was not significantly associated with FEV_1 or FVC (bothn $p > 0.05$). However, overall obesity, defined as a BMI ≥ 25 kg/m^2, was significantly associated with FVC ($p = 0.0230$). All abdominal adiposity traits such as VAT, SAT, and TAT were significantly associated with both FEV_1 and FVC (all $p < 0.0001$). Compared with BMI, the adiposity variables quantified using CT, including VAT area, were more strongly related to FEV_1 and FVC.

To examine the effects of air pollution on lung function according to the degree of adiposity, we performed subgroup analysis by classifying the adiposity traits VAT, SAT, and TAT into three levels (Figure 1). The effects of air pollutants on FEV_1 and FVC were much greater in the high-fat group with a VAT > 200 cm^2. Similar to VAT, the negative association between air pollution and lung function was stronger in the high-fat group with an SAT area > 200 cm^2 than in the group with an SAT area ≤ 200 cm^2. For TAT area, the negative associations between air pollution and FEV_1 and FVC were strongest in the high-fat group with a TAT area > 300 cm^2. The negative association between TAT and FEV_1 was smaller in the moderate fat group than in the low- and high-fat groups, whereas the relationship between TAT and FVC was smaller in the low-fat group than in the other two groups.

Table 3 shows the results of the regression analysis in the low- and high-adiposity groups with cutoff points of 200 cm^2, 200 cm^2, and 300 cm^2 for VAT, SAT, and TAT areas, respectively. Similar to the results for obesity classified by BMI (see Supplemental Material, Table S3), the effects of air pollution on lung function were much stronger in the high- than in the low-adiposity group. In the low-adiposity group, none of the air pollutants showed significant effects on FEV_1, whereas in the high-adiposity group, PM_{10} and NO_2 concentrations were significantly associated with decreased FEV_1 (both $p < 0.05$). In the high-VAT group (VAT area > 200 cm^2), FEV_1 decreased 8.1% ($\beta = -0.0812$; 95% CI = –0.1590, –0.0035) and 9.8% ($\beta = -0.0979$; 95% CI = –0.1611, –0.0346) for each IQR increase in PM_{10} and NO_2, respectively. The high-SAT group (SAT area > 200 cm^2) showed a pattern similar to the high-VAT group. In the high-TAT group (TAT area > 300 cm^2), FEV_1 decreased

4.3% (β = –0.0426; 95% CI = –0.0810, –0.0042) and 5.5% (β = –0.0545; 95% CI = –0.0864, –0.0226) for each IQR increase in PM_{10} and NO_2 concentration, respectively.

In the high-adiposity group, air pollution was also associated with decreased FVC. In the high-VAT group, FVC decreased 10.6% (β = –0.1056; 95% CI = –0.1770, –0.0343) for each IQR increase in NO_2 concentration. PM_{10} (p = 0.0262) and NO_2 (p = 0.0198) concentration were also significantly associated with a decrease in FVC in the high-SAT group; FVC decreased 8.7% (β = –0.0868; 95% CI = –0.1629, –0.0108) and 7.5% (β = –0.0752; 95% CI = –0.1379, –0.0125) for each IQR increase in PM_{10} and NO_2 concentration. Overall, the effects of NO_2 were greater than those of PM_{10} when analyzed according to VAT area, whereas the effects of PM_{10} were greater than those of NO_2 when analyzed according to SAT area. In the high-TAT group (TAT area > 300 cm^2), FVC decreased 6.1% (β = –0.0607; 95% CI = –0.0967, –0.0248) for IQR increase in NO_2 concentration.

DISCUSSION

This study investigated the associations between exposure to ambient air pollution, as shown by the PM_{10} and NO_2 levels, and lung function in Korean men, and whether these associations are modified by adiposity level. We observed a significant negative relationship between annual average concentration of NO_2 and lung function ($p < 0.05$), showing 2.5% (β = –0.0254; 95% CI = –0.0455, –0.0053) FEV_1 and 2.9% (β = –0.0292; 95% CI = –0.0514, –0.0070) FVC decrease per IQR (13.9 ppb) increase in the NO_2 concentration. Interestingly, in the subgroup analyses, the associations of PM_{10} and NO_2 concentrations were much stronger in the high- than in the low-adiposity group. In the high-VAT group, each IQR increase in PM_{10} and NO_2 concentration was associated with a decrease in FEV_1 (β [95% CI] for PM_{10} = –0.0812 [–0.1590, –0.0035] and β [95% CI] for NO_2 = –0.0979 [–0.1611, –0.0346]), compared with the low-VAT group. In the high-VAT group, FVC was also negatively associated with NO_2 concentration; there was a 10.6% (β = –0.1056; 95% CI = –0.1770, –0.0343) decrease in FVC for increase in IQR. This pattern was similar in the subgroups classified according to subcutaneous and total abdominal fat.

Considering the negative impacts of air pollution on health, the increase in air pollution in South Korea has become an inevitable social issue. A recent report documented that Korea is expected to experience the greatest increase in premature deaths and economic damage caused by air pollution among the Organization for Economic Cooperation and Development (OECD) countries, if Korea's air pollution continues its current trend by 2060.[17] The median values of PM_{10} (μg/m^3) and NO_2 (ppb) concentrations estimated in our study were 49 and 31.5, respectively. In particular, the level of PM_{10} concentration is considerably higher compared to other European studies.[6,18] This was even higher than the measured PM_{10} concentration near the busy road in Germany.[19] However, when compared to the average concentrations of 31 major provincial cities in China (average concentration for PM_{10} in 2014 =109.8 μg/m^3), the level of PM_{10} concentration in our study was much lower.[20]

Epidemiological studies have reported significant associations between exposure to air pollutants and a decreased lung function in adults.[18,19,21] In 1997, significant relationships between the annual mean levels of air pollutants such as PM_{10}, NO_2, and SO_2 and lung function were observed in adults aged 18–60 years residing in Switzerland.[21] In 2005, Schikowski et al. found that chronic exposure to PM_{10} and NO_2 was related with increased risk of chronic obstructive pulmonary disease in 55-year-old women in Germany.[19] Forbes et al. reported a significant association between chronic exposure to air pollution and FEV_1 in a large English population, and reported a 3% decline in FEV_1 per 10 $\mu g/m^3$ increase in PM_{10} concentration.[18] However, these effects of air pollution on lung function in adults were found in specific European populations.

More recent evidence has suggested an additive effect of air pollution and obesity on lung function decline.[6, 13, 14] In 2013, Schikowski et al. investigated whether the effect of improved air quality on lung function is modified by obesity status.[14] They reported significant interactions between a change in PM_{10} concentration and BMI; after a decrease in PM_{10} concentration, the annual rates of decline in lung function were smaller in the groups with low or normal BMI compared with those defined as obese according to BMI. Dong et al. found that the risks for asthma and respiratory symptoms including cough were greater in obese children than in normal-weight children.[13] In particular, the interaction effects with obesity on cough and phlegm were significant for NO_2 and PM_{10} concentrations. One European adult study based on the multicenter cohorts in the European Study of Cohorts for Air Pollution Effects (ESCAPE) identified a larger effect of exposure to air pollution including PM_{10} and NO_2 on lung function in the obese group.[6]

To date, the mechanisms underlying the synergistic effects of obesity on the link between ambient air pollution and lung function remain unclear, but several possible physiological mechanisms linked to adipocyte have been suggested. One plausible mechanism is the inflammatory pathway. Exposure to ambient air pollution promotes airway inflammation, which can lead to a decline in lung function and/or lung injury.[22] Similarly, a significant correlation between obesity and systemic inflammation has been reported.[23] Adipokines such as leptin and adiponectin, which mediate

the inflammatory response, are produced mainly in adipose tissue. Inflammatory cytokines including TNF-α and IL-6 are also released by adipocytes. These molecules are directly linked to the inflammatory process. In addition, macrophage migration inhibitory factor, a pro-inflammatory protein, is known to be a crucial factor in inflammation of chronic adipose tissue.[24] Immune cells including macrophages can also infiltrate adipose tissue. The macrophages within adipose tissue not only contribute to the production of inflammatory cytokines, but also lead to increased local inflammation.[25] Both air pollution and high-adiposity are closely related to increased inflammation, and the synergistic effect of air pollution and adiposity in the high-fat group may be explained by the combined effects of adipose tissue and ambient air pollution on airway and/or systemic inflammation. Another possible explanation is that air pollution and high-adiposity can both increase oxidative stress.[12, 26, 27] Many components of ambient air pollutants cause lung damage through oxidative stress, either by acting directly on ROS production or by the indirect induction of local inflammation.[28] Accumulated adipose tissue also promotes the production of proinflammatory adipokines, which trigger the production of ROS.[26] Oxidative stress is significantly associated with the decline in lung function.[29-31] These plausible hypotheses are supported by present findings in adipose tissue as well as the *CDH13* gene-by-PM_{10} interaction effect identified previously.[10, 11]

Most studies have primarily focused on short-term or acute effects in a restricted region or a specific population, particularly children. The present study showed significant associations between abdominal adipose tissue, as well as the negative effects of air pollution on FEV_1 and FVC using nationwide data in Korean adults. To our knowledge, we have shown for the first time that high adiposity strengthens an inverse relationship between air pollution and lung function in Asian men. However, our study does have some limitations. First, the study design was cross-sectional, which means that no causal inferences can be made about the observed effects of adiposity on the relationship between air pollution and lung function. Second, we did not measure the exposure time to ambient air pollutants in individuals.

CONCLUSION

Our study identified a synergistic effect of adiposity on the relationship between prolonged exposure to air pollution and FEV_1 and FVC decreases in Asian men. Our findings provide the first evidence that accumulated abdominal fat intensifies the adverse effects of air pollutants on lung function.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ACKNOWLEDGEMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (grant number, 2015R1D1A1A01057619, 2015R1A1A3A04000923, and 2015R1D1A1A01059048). This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2012R1A5A2A44671346).

REFERENCES

1. Boffetta P, Nyberg F. Contribution of environmental factors to cancer risk. Brit Med Bull 2003; **68**:71-94.

2. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. Lancet 2014; **383**:1581-1592.

3. Hong YC, Lee JT, Kim H, Kwon HJ. Air pollution - A new risk factor in ischemic stroke mortality. Stroke 2002; **33**:2165-2169.

4. Ko FWS, Hui DSC. Outdoor air pollution: impact on chronic obstructive pulmonary disease patients. Curr Opin Pulm Med 2009; **15**:150-157.

5. Leikauf GD. Hazardous air pollutants and asthma. Environ Health Perspect 2002; **110 Suppl 4**:505-526.

6. Adam M, Schikowski T, Carsin AE, Cai YT, Jacquemin B, Sanchez M et al. Adult lung function and long-term air pollution exposure. ESCAPE: a multicentre cohort study and meta-analysis. Eur Respir J 2015; **45**:38-50.

7. Gehring U, Gruzieva O, Agius RM, Beelen R, Custovic A, Cyrys J et al. Air Pollution Exposure and Lung Function in Children: The ESCAPE Project. Environ Health Persp 2013; **121**:1357-1364.

8. Min JY, Min KB, Cho S, Paek D. Lag effect of particulate air pollution on lung function in children. Pediatr Pulm 2008; **43**:476-480.

9. Sunyer J. Lung function effects of chronic exposure to air pollution. Thorax 2009; **64**:645-646.

10. Imboden M, Kumar A, Curjuric I, Adam M, Thun GA, Haun M et al. Modification of the Association between PM10 and Lung Function Decline by Cadherin 13 Polymorphisms in the SAPALDIA Cohort: A Genome-Wide Interaction Analysis. Environ Health Persp 2015; **123**:72-79.

11. Kim HJ, Min JY, Min KB, Seo YS, Sung J, Yun JM et al. CDH13 gene-by-PM10 interaction effect on lung function decline in Korean men. Chemosphere 2016; e-pub ahead of print 10 November 2016; doi: 10.1016/j.

12. Fernandez-Sanchez A, Madrigal-Santillan E, Bautista M, Esquivel-Soto J, Morales-Gonzalez A, Esquivel-Chirino C et al. Inflammation, oxidative stress, and obesity. Int J Mol Sci 2011; **12**:3117-

3132.

13. Dong GH, Qian Z, Liu MM, Wang D, Ren WH, Fu Q et al. Obesity enhanced respiratory health effects of ambient air pollution in Chinese children: the Seven Northeastern Cities study. Int J Obes 2013; **37**:94-100.

14. Schikowski T, Schaffner E, Meier F, Phuleria HC, Vierkotter A, Schindler C et al. Improved air quality and attenuated lung function decline: modification by obesity in the SAPALDIA cohort. Environ Health Perspect 2013; **121**:1034-1039.

15. AT. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995; **152**:1107-1136.

16. Kim HJ, Park JH, Lee S, Son HY, Hwang J, Chae J et al. A Common Variant of NGEF Is Associated with Abdominal Visceral Fat in Korean Men. PLoS One 2015; **10**:e0137564.

17. OECD. The economic consequences of outdoor air pollution. Published on June 09, 2016.

18. Forbes LJ, Kapetanakis V, Rudnicka AR, Cook DG, Bush T, Stedman JR et al. Chronic exposure to outdoor air pollution and lung function in adults. Thorax 2009; **64**:657-663.

19. Schikowski T, Sugiri D, Ranft U, Gehring U, Heinrich J, Wichmann HE et al. Long-term air pollution exposure and living close to busy roads are associated with COPD in women. Respir Res 2005; **6**:152.

20. He J, Gong S, Yu Y, Yu L, Wu L, Mao H et al. Air pollution characteristics and their relation to meteorological conditions during 2014-2015 in major Chinese cities. Environ Pollut 2017; e-pub ahead of print 22 January 2017; doi: 10.1016/j.envpol.2017.01.050.

21. Ackermann-Liebrich U, Leuenberger P, Schwartz J, Schindler C, Monn C, Bolognini G et al. Lung function and long term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. Am J Respir Crit Care Med 1997; **155**:122-129.

22. Esposito S, Tenconi R, Lelii M, Preti V, Nazzari E, Consolo S et al. Possible molecular mechanisms linking air pollution and asthma in children. BMC Pulm Med 2014; **14**:31.

23. Mancuso P. Obesity and lung inflammation. J Appl Physiol (1985) 2010; **108**:722-728.

24. Kim BS, Rongisch R, Hager S, Grieb G, Nourbakhsh M, Rennekampff HO et al. Macrophage Migration Inhibitory Factor in Acute Adipose Tissue Inflammation. PLoS One 2015; **10**:e0137366.

25. Surmi BK, Hasty AH. Macrophage infiltration into adipose tissue: initiation, propagation and remodeling. Future Lipidol 2008; **3**:545-556.

26. Marseglia L, Manti S, D'Angelo G, Nicotera A, Parisi E, Di Rosa G et al. Oxidative stress in obesity: a critical component in human diseases. Int J Mol Sci 2015; **16**:378-400.

27. Yang W, Omaye ST. Air pollutants, oxidative stress and human health. Mutat Res-Gen Tox En 2009; **674**:45-54.

28. Ghio AJ, Carraway MS, Madden MC. Composition of air pollution particles and oxidative stress in cells, tissues, and living systems. J Toxicol Environ Health B Crit Rev 2012; **15**:1-21.

29. Ben Moussa S, Sfaxi I, Tabka Z, Ben Saad H, Rouatbi S. Oxidative stress and lung function profiles of male smokers free from COPD compared to those with COPD: a case-control study. Libyan J Med 2014; **9**.

30. Ochs-Balcom HM, Grant BJ, Muti P, Sempos CT, Freudenheim JL, Browne RW et al. Oxidative stress and pulmonary function in the general population. Am J Epidemiol 2005; **162**:1137-1145.

31. Waseem SMA, Hussain M, Islam N. Oxidative Stress in Mild and Moderate COPD: Assessment of Oxidant Anti-Oxidant Imbalance. Biomed Res-India 2014; **25**:115-119.

Figure Legend

Fig. 1. The effect estimates of each air pollutant for lung function such as FEV_1 and FVC according to categories of adiposity-related traits including VAT, SAT, and TAT.

Table 1. Characteristics of study participants

Characteristics	Site A of recruitment	Site B of recruitment	Total
n	1,405	471	1,876
Age years	51.9 (5.8)	50.7 (5.3)	51.6 (5.7)
Height (cm)	169.3 (6.7)	170.7 (5.2)	169.6 (6.4)
Weight (kg)	70.4 (10.1)	72.0 (8.7)	70.8 (9.8)
Adiposity measures			
BMI(kg/m^2)	24.5 (2.8)	24.7 (2.6)	24.6 (2.7)
VAT (cm^2)	128.1 (54.5)	141.2 (49.8)	131.4 (53.6)
SAT (cm^2)	140.2 (54.4)	138.5 (49.1)	139.8 (53.1)
TAT (cm^2)	268.4 (95.3)	279.7 (89.0)	271.2 (93.8)
Smoking status, n (%)			
Never	372 (26.5)	103 (21.9)	475 (25.3)
Former	574 (40.9)	222 (47.1)	796 (42.4)
Current	459 (32.7)	146 (31.0)	605 (32.3)
Pack years	14.2 (18.0)	15.5 (16.9)	14.5 (17.7)
Moderate activity, n (%)			
Yes	614 (43.7)	263 (55.8)	877 (46.8)
No	791 (56.3)	208 (44.2)	999 (53.2)
Lung function test			
FEV_1 (L)	3.3 (0.6)	3.4 (0.5)	3.3 (0.5)
FVC (L)	4.0 (0.6)	4.3 (0.6)	4.1 (0.6)
Air pollutants (annual average concentration)			
PM_{10} ($\mu g/m^3$)			
Mean	48.0 (7.2)	52.7 (6.7)	49.2 (7.4)
Median	47.3	52.3	49.0
IQR	9.3	6.1	9.2
NO_2 (ppb)			
Mean	29.8 (12.5)	35.0 (13.3)	31.1 (12.9)
Median	30.0	34.4	31.5
IQR	14.6	12.4	13.9

BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 μm; NO_2, nitrogen dioxide; IQR, interquartile range

Data are presented as mean (standard deviation) for continuous variables, or n (%) for categorical variables.

Table 2. Regression results for the association between air pollution, adiposity-related traits, and lung function level

	FEV_1 (L)		FVC (L)	
Exposure	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Air pollution				
PM_{10} ($\mu g/m^3$)	-0.0097 (-0.0335, 0.0141)	0.4259	0.0042 (-0.0222, 0.0305)	0.7556
NO_2 (ppb)	-0.0254 (-0.0455, -0.0053)	0.0131	-0.0292 (-0.0514, -0.0070)	0.0102
Adiposity measures				
BMI(kg/m^2)	-0.0051 (-0.0118, 0.0017)	0.1430	-0.0061 (-0.0135, 0.0014)	0.1114
BMI≥25 kg/m^2	-0.0204 (-0.0578, 0.0171)	0.2876	-0.0480 (-0.0894, -0.0067)	0.0230
VAT (cm^2)	-0.0013 (-0.0017, -0.0010)	<0.0001	-0.0015 (-0.0019, -0.0012)	<0.0001
SAT (cm^2)	-0.0011 (-0.0014, -0.0007)	<0.0001	-0.0013 (-0.0017, -0.0010)	<0.0001
TAT (cm^2)	-0.0008 (-0.0010, -0.0006)	<0.0001	-0.0009 (-0.0011, -0.0007)	<0.0001

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; CI, confidence interval; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 μm; NO_2, nitrogen dioxide; BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TAT, total adipose tissue

These results were adjusted for site of recruitment, age, age^2, height, smoking status (never, past, or current), pack years, and moderate activity (yes or no).

The beta coefficients and 95% confidence intervals in air pollution were scaled to the interquartile range for each pollutant (9.2 $\mu g/m^3$ for PM_{10} and 13.9 ppb for NO_2).

Table 3. Results of stratified analyses by abdominal adiposity traits for the association between lung function and exposure to ambient air pollution

			Low adiposity group		**High adiposity group**	
Adiposity	Trait	Exposure	β (95% CI)	*p*-value	β (95% CI)	*p*-value
VAT (VAT cut-off point for low and high adiposity groups = 200 cm^2)						
	FEV_1 (L)	PM_{10} ($\mu g/m^3$)	-0.0013 (-0.0264, 0.0237)	0.9172	-0.0812 (-0.1590, -0.0035)	0.0417
		NO_2 (ppb)	-0.0164 (-0.0375, 0.0047)	0.1267	-0.0979 (-0.1611, -0.0346)	0.0028
	FVC (L)	PM_{10} ($\mu g/m^3$)	0.0110 (-0.0165, 0.0386)	0.4339	-0.0490 (-0.1372, 0.0391)	0.2774
		NO_2 (ppb)	-0.0199 (-0.0431, 0.0033)	0.0941	-0.1056 (-0.1770, -0.0343)	0.0042
SAT (SAT cut-off point for low and high adiposity groups = 200 cm^2)						
	FEV_1 (L)	PM_{10} ($\mu g/m^3$)	0.0024 (-0.0231, 0.0278)	0.8557	-0.0948 (-0.1627, -0.0268)	0.0069
		NO_2 (ppb)	-0.0164 (-0.0379, 0.0051)	0.1334	-0.0828 (-0.1390, -0.0267)	0.0041
	FVC (L)	PM_{10} ($\mu g/m^3$)	0.0164 (-0.0114, 0.0441)	0.2494	-0.0868 (-0.1629, -0.0108)	0.0262
		NO_2 (ppb)	-0.0210 (-0.0446, 0.0027)	0.0819	-0.0752 (-0.1379, -0.0125)	0.0198
TAT (TAT cut-off point for low and high adiposity groups = 300 cm^2)						
	FEV_1 (L)	PM_{10} ($\mu g/m^3$)	0.0027 (-0.0272, 0.0327)	0.8583	-0.0426 (-0.0810, -0.0042)	0.0305
		NO_2 (ppb)	-0.0073 (-0.0328, 0.0181)	0.5727	-0.0545 (-0.0864, -0.0226)	0.0009
	FVC (L)	PM_{10} ($\mu g/m^3$)	0.0188 (-0.0137, 0.0512)	0.2588	-0.0337 (-0.0771, 0.0098)	0.1291
		NO_2 (ppb)	-0.0086 (-0.0361, 0.0189)	0.5417	-0.0607 (-0.0967, -0.0248)	0.0010

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; CI, confidence interval; PM_{10}, particulate matter with aerodynamic diameter ≤ 10 μm; NO_2, nitrogen dioxide; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TAT, total adipose tissue

These results were adjusted for site of recruitment, age, age^2, height, smoking status (never, past, or current), pack years, and moderate activity (yes or no).

The beta coefficients and 95% confidence interval were scaled to the interquartile range for each pollutant (9.2 $\mu g/m^3$ for PM_{10} and 13.9 ppb for NO_2.