

Interactive effects of adiposity and insulin resistance on the impaired lung function in asthmatic adults: cross-sectional analysis of NHANES data

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Conflict of Interest

The authors declare no conflict of interests.

Role of the Funding source

The authors received no funding from any sources.

Abbreviation List

ATS (American Thoracic Society)

BMI (body mass index)

CDC (Centers for Disease Control and Prevention)

FVC (forced vital capacity)

FEV1 (forced expiratory volume during the first second)

FEF 25-75% (forced expiratory flow between 25% and 75% of vital capacity)

HOMA-IR (Homeostasis Model Assessment of Insulin Resistance)

IR (insulin resistance)

IRB (institutional review board)

NHANES (National Health and Nutrition Examination Survey)

PFT (pulmonary function test)

WC (waist circumference)

WHtR (waist to height ratio)

Abstract

Background: Obesity is considered a risk factor for both asthma and insulin resistance in adults. Insulin resistance (IR) also influences the pulmonary function in the non-obese population.

Objective: To investigate the modifying effect of insulin resistance on the predictive role of anthropometric measures in the estimation of impaired lung function among asthmatic adults.

Methods: A cross-sectional study of 1276 adults extracted from NHANES 2009-2012 database was performed. Adjusted multivariate linear regression was conducted to analyse the contributory role of obesity and IR in predicting lung function among asthmatic adults.

Results: BMI, waist circumference (WC), and waist to height ratio (WHtR) showed significantly negative correlations with FVC ($r=-0.24, -0.18, -0.39$, respectively; $p<0.001$), FEV1 ($r=-0.24, -0.21, -0.40$, respectively; $p<0.001$), and FEF 25-75% ($r=-0.15, -0.18, -0.27$, respectively; $p<0.001$). Even after adjustment for the covariates (age, gender, smoking history, and standing height), BMI and HOMA-IR had significant relationships with FVC ($(\beta=-10.3; p<0.01)$ and $(\beta=-16.0; p<0.05)$) and FEV1 ($(\beta=-8.7; p<0.01)$ and $(\beta=-11.7; p<0.05)$). BMI could significantly predict the decreased FVC ($\beta=-13.7; p<0.01$) and FEV1 ($\beta=-10.7; p<0.01$) only in the insulin resistant asthmatics.

Conclusion: WHtR and IR predict impaired lung function in overweight/obese asthmatic adults independently. IR also modifies the association between excessive adiposity and respiratory function in asthmatic adult.

Keywords: central obesity; asthma; insulin resistance; waist to height ratio; pulmonary function

Introduction

Obesity and asthma are two contemporaneous public health concerns of the new century. In 2014, at least 600 million individuals 18 years and older were obese across the world (WHO 2000). Asthma is also a prevalent condition, affecting more than 300 million people worldwide (HSE 2013). There is now compelling evidence to suggest a sex and age-dependent contributory role of obesity to the development, severity and biological underpinning of asthma. Several observational studies have indicated a higher prevalence of asthma within the obese population (Ford, 2005; Beuther and Sutherland 2007). In prospective studies, excess adiposity, particularly visceral obesity, has been shown to be a risk factor for the development and severity of asthma in both adults and children (Mannino et al 2006; Brumpton et al. 2013; Capelo et al. 2015; Papoutsakis et al. 2015). The relationship between obesity and adult-onset asthma is further supported by weight change studies which show improvements in asthma severity and pulmonary function after weight reduction (Spivak et al. 2005). Noticeably, obese asthmatics experience more symptoms and increased or prolonged exacerbations. (Woolford et al. 2007). This obese-asthma phenotype which exhibits Th2-independent neutrophilic airway inflammation may involve other contributing elements, including metabolic syndrome (Scott et al. 2012). The impaired lung function of obese asthmatics could be due, in part, to metabolic abnormalities (Mafort et al. 2016). There is a bidirectional link between asthma and metabolic syndrome (Del-Rio-Navarro et al. 2010; Rasmussen et al. 2013). Of relevance, insulin resistance (IR) and the consequent hyperinsulinaemia also have strong molecular links with pulmonary disease, especially asthma (Singh et al. 2013). Indeed, IR has been reported to be a stronger correlate of asthma than any obesity-related anthropometric measures (Husemoen et al. 2007). IR has been shown to be inversely related to lung function among overweight or obese adolescents (Forno et al 2015). Likewise, IR increases the chance of asthma-like symptoms in the adult population (Thomsen et al. 2010). It also strengthens the association between current asthma and obesity, independent of other components of metabolic syndrome (Cardet 2016). Higher IR has also been reported to be a distinguishing factor between asthmatic versus non-asthmatic morbidly obese adults (Kim et al. 2014). Although several studies have shown a modifying effect of IR on the relationship between obesity and asthma in the paediatric population, very little

has been done to elucidate the contributory role of insulin resistance on the association of adiposity measures, particularly the waist-to-height ratio (WHtR), with the indices of lung function, especially forced vital capacity (FVC), forced expiratory volume during the first second (FEV1), and forced expiratory flow between 25% and 75% of vital capacity (FEF 25-75%) among asthmatic adults.

Aims

In view of this apparent shortcoming in the asthma-obesity research, this study set out to:

Investigate the modifying effect of insulin resistance on the association between obesity and reduced lung function in asthmatic adults.

and

to assess the contribution of insulin resistance and visceral adiposity to the functional variations of small airways in asthmatic adults.

Methods and study population

This cross-sectional study pooled 4 years (2009-2012) of NHANES data accessed via the Centers for Disease Control and Prevention (CDC) website (<http://www.cdc.gov/Nchs/Nhanes>). Two separate datasets (2009-2010 and 2011-2012) were chosen to increase the sample size and the power of study. Distinct data files were merged into the IBM SPSS statistics data editor software version 23. A total of 1276 asthmatic adults (≥ 18 years) were included in this analysis, with asthma being defined as the subject having had asthma diagnosed by a health care professional. Waist circumference (WC) and WHtR were selected as measures of central adiposity. Based on their BMI, the subjects were divided into two groups: not overweight/obese ($BMI < 25 \text{ kg/m}^2$) and overweight/obese ($BMI \geq 25 \text{ kg/m}^2$) (WHO 1995). $WHtR > 0.50$ was assigned as a cutoff for central obesity (WHO 2008). Insulin resistance was assessed by the Homeostasis Model Assessment of IR (HOMA-IR) value based on the following formula:

HOMA-IR (mmol/l × μU/ml) = (Fasting insulin (μU/ml) × Fasting glucose [mmol/l] /22:5) (Wallace et al. 2004)

Insulin resistance was defined as: HOMA-IR: > 2.5 (Singh et al. 2013)

Spirometric parameters, recorded in compliance with the American Thoracic Society (ATS) recommendations (Miller 2005), were FVC, FEV1, FEV1/FVC (Swanney et al. 2008) and FEF25-75% (Tavakol et al. 2013). (add section on sample weight).

To account for the complex sampling design of NHANES, corresponding sample weights were included in the statistical methods according to instructions provided by the CDC

(https://www.cdc.gov/nchs/tutorials/NHANES/SurveyDesign/Weighting/Task1_III.htm).

Since two survey cycles were combined in this study, fasting subsample weights (wtsaf2yr) were constructed using the NHANES formulae (<https://www.cdc.gov/nchs/tutorials/NHANES/SurveyDesign/Weighting/Task2.htm>).

Then, an analysis plan for complex samples was created in SPSS by specifying stratification and clustering variables (sdmvstra and sdmvpsu) as well as the sample weight statement.

As normality of distribution was rejected, non-parametric tests were utilised. Missing values were treated by pairwise or test by test exclusion depending on the type of analysis. Statistical significance was assigned based on a p-value < 0.05.

Spearman's correlation test was used to check for the associations among obesity, insulin resistance, and lung function. To compare the effect of insulin resistance and visceral adiposity on pulmonary function test (PFT) parameters, a Mann-Whitney U test was performed. To investigate the effect of insulin resistance on PFT variables, a hierarchical ~~multivariate~~ multiple linear regression analysis was computed on models adjusted for age, sex, standing height, ethnicity (white vs. non-white), and smoking history. Predictive variables (BMI and HOMA-IR) were standardised using mean centring to counteract the effect of multicollinearity and to investigate the interactive effect of central adiposity and insulin resistance on pulmonary function. Then, predictors were compared for their unique contribution to the model. Finally, to examine the modifying effect of insulin resistance on the association between

adiposity and lung function, an adjusted ~~multivariate~~ multiple linear regression stratified by insulin sensitivity status was performed. This study was approved by London Metropolitan University ethics review panel.

Results

The main characteristics of the study population (n=1276) are presented in Table 1. In general, female participants had significantly lower PFT values but their BMI was significantly higher compared with their male counterparts (p<0.001). Overall, majority of participants were overweight and insulin resistant. Nonetheless, they had baseline FVC and FEV 1 recordings within the normal range.

Table 1.

As shown in Table 2, BMI, WC, and WHtR were all significant negative correlates of FVC, FEV1, and FEF 25-75% (p<0.001 for all). WHtR was the strongest anthropometric correlate of all PFT parameters. After stratification by gender, a similar pattern of association was observed between proxy measures of fatness (BMI, WC, and WHtR) and FVC as well as FEV 1 in both sexes. Again, WHtR was the measure which showed greatest correlation with FEV 1 and FVC in both sexes. With respect to FEF 25-75%, all anthropometric measures of adiposity exhibited statistically significant associations in men (p<0.001). In women, however, WC, and WHtR were the measures that reached statistical significance. HOMA-IR was negatively associated with FVC (r = -0.21 for men, and r = -0.24 for women, p<0.001, respectively) and FEV 1 (r = -0.21 in men and r = -0.17 in women, p<0.001). In the analysis of all participants, insulin resistance was not associated with FEF 25-75%.

Table2.

As shown in Table 3, both insulin resistance and central obesity had significantly negative effects on FVC(p<0.001) and FEV1 (p<0.05) in both sexes. In contrast, FEF

25-75% was negatively affected by central obesity but not insulin sensitivity status ($p < 0.001$).

Table 3.

Figure 1 illustrates the multivariate multiple linear regression analysis of the relations between PFT parameters and insulin resistance among all participants. ~~This hierarchical model~~ which also included age, sex, gender, smoking history, standing height, BMI, HOMA-IR and the BMI_HOMA-IR interaction as the fixed explanatory variables, could predict approximately 71% and 67% of the variances in FVC and FEV1 among adults with asthma, respectively (Figure 1). Height exhibited the highest contribution to the variation in FVC (standardised $\beta = 0.41$, $p < 0.001$), followed by age (standardised $\beta = -0.38$, $p < 0.001$). For FEV1, however, age was the greatest contributor (standardised $\beta = -0.52$, $p < 0.001$), followed by height (standardised $\beta = 0.34$, $p < 0.001$). In this model, insulin resistance (defined by $\text{HOMA-IR} \geq 2.5$) was significantly associated with lower FVC and FEV1 (standardised $\beta = -0.06$ and -0.05 , $p < 0.05$), so that each unit increase in HOMA-IR was associated with approximately 16 and 11 ml decrease in FVC and FEV1 values, respectively. Also, for each incremental point in BMI, FVC and FEV1 could drop by approximately 10 and 8 ml, respectively. Of interest, the association between IR and lung function was independent of BMI. As such, IR-BMI interaction made no statistically significant contribution to the model. Nevertheless, IR was not significantly associated with FEF 25-75% in the regression model whereas BMI could predict 6% of the FEF 25-75% variance.

Figure1

Table 4 shows the estimated effect of adiposity measures on lung function, stratified by the insulin sensitivity status. BMI and WHtR (in separate models) contributed significantly to the prediction of FVC ($p < 0.01$) and FEV 1 ($p < 0.05$) in the insulin

resistant group, such that FVC decreased by approximately 14 ml for each point increment in BMI and by approximately 11 ml per 0.01 unit increase in WHtR. Correspondingly, FEV 1 declined by approximately 12 ml per unit increment in BMI and by 8 ml per 0.01 unit increment in WHtR. In contrast, the predictability of these adiposity measures for FVC and FEV 1 did not reach statistical significance in the insulin sensitive group.

The standardised coefficients, semi-partial correlation coefficients and r-squared changes pertaining to these variables have been presented in table 4.

The effect of IR on the relationship between central obesity and lung function in asthmatic adults is depicted in Figure [12](#).

Table 4.

Figure [12](#).

Discussion

To the best of our knowledge, this is the first study to investigate the contribution of WHtR and insulin resistance to the quantitative estimation of the absolute spirometric indices PFT parameters (FEV1, FVC, and FEF25-75%) in asthmatic adults. Overall, an inverse relationship was found between adiposity measures and pulmonary function in both sexes. Of interest, WHtR was the strongest anthropometric correlate of all described PFT parameters. In keeping with these findings, the PLATINO study results have suggested a high WHtR as a predictor of low FVC in adults (Menezes et al. 2013). Previously, the greater discriminatory power of WHtR compared with WC and BMI had been established for the adverse cardiometabolic outcomes among adults of both sexes, indicating the importance of height and other undetermined factors in this relationship (Ashwell et al. 2012). In the present study, individuals with high WHtR had significantly lower PFT values as compared to those with WHtR in healthy range, reflecting the effect of centrally distributed body fat on the large as well as small airways. Obesity, particularly of central type (Ochs-Balcom 2006), affects pulmonary function both mechanically (Koenig 2001) and metabolically as reflected in lower values for FEV1 and FVC in overweight/obese adults (Chen et al 2001). The inverse relationship between visceral adiposity and lung function could also be attributed to the low-grade systemic inflammation incited by adipokines in obesity (Rajala and Scherer 2003). Of note, IR in both sexes was negatively related to FVC and FEV1 but not FEF25–75%. FEF25-75 < 65% is suggested to be a specific predictor of bronchial responsiveness (Alberts et al. 1994) and a sensitive

marker for post-bronchodilator rise in FEV1 (Simon et al. 2010), known to be associated with poor asthma control (Rao et al. 2012). Moreover, low FEF25–75%, especially in the childhood, has been shown to predict poor asthma outcomes (Galant et al. 2011).

Of importance, this study revealed that WHtR and IR could predict the impaired pulmonary function (with greater predictive ability for FVC than FEV1) in asthmatic adults independent of their age, height, sex, ethnicity, smoking history, and BMI. Furthermore, the interactive effect of IR and BMI did not have a significant contribution to the deterioration in lung function. Nonetheless, IR significantly modified the estimated effect of obesity measures on lung function, so that insulin resistant asthmatic adults with higher BMI and WHtR had lower FVC and FEV1 compared to their more insulin-sensitive counterparts. These results concur with the findings of Forno et al. (2015), who reported a significant association of IR with FEV1 and FVC among overweight/obese US adolescents, particularly those with asthma. However, they found a modifying effect for insulin resistance in a reverse direction. This inconsistency might be a result of differing effects of obesity and/or IR on lung function in children and adolescents versus adults, or the fact that BMI is not solely a measure of fat mass but a reflection of the growth process (Bekkers et al. 2015). In contrast, a case-control study on morbidly obese non-diabetic women indicated significantly negative correlations between HOMA-IR and PFT parameters (Lecube 2010). Recently, Cardet et al. (2016) in an investigation of NHANES data, showed that IR strengthened the association of obesity and current asthma in adults by two folds, although they did not assess the contribution of IR to the association between visceral adiposity and PFT values. Nevertheless, in studies of free-living Korean males, the abdominal obesity (measured by WC) and IR (measured by) HOMA-IR were shown to be independent risk factors for reduced percentage of predicted (% pred) FVC and FEV1 (Lim et al 2010), as well as decreased absolute FVC (Kim et al. 2010), even after adjusting for age, height, and metabolic components (~~Kim et al. 2010~~). The interplay between asthma and IR in centrally obese individuals could be explained immunologically by the altered activation patterns of monocytes and T helper (Th) cells (Dixon et al. 2011; Rastogi et al. 2015), leading to the predominance of Th1 and M1 adipose tissue macrophages (Dekkers et al. 2009; Lumeng and Saltiel 2011; Gerriets and MacIver 2014). However, this study was not

able to evaluate this suggestion due to a lack of available biological data on components of the immune system. With regards to the nonsignificant contribution of IR-obesity interaction on impaired lung function, it could be argued that IR and the consequent hyperinsulinaemia may have both direct and independent effects on the proliferation and contractility of airway smooth muscle cells (Dekkers et al. 2009). Furthermore, it has been suggested that high insulin levels may also alter the diameter of small airways via central neuro-hormonal mechanisms (MacIver 2013).

Further research is warranted in this area to identify those subtypes of asthma which are most affected by insulin resistance and to determine downstream pathways mediating lung-specific changes in centrally obese asthmatics with IR.

This study was performed on a relatively large representative sample of US adults with reliable sets of data; data had been collected by uniformly trained personnel, in compliance with approved procedures and guidelines. It also included multiple anthropometric and spirometric measurements as well as indicators of insulin sensitivity. Statistically, the study gains from sample-weighted multivariate linear regression models analysing the absolute spirometric values instead of predicted PFT values, thereby facilitating the quantitative analysis of the insulin resistance contribution to pulmonary function. The models were adjusted for several confounders, including age, height and gender; this was further strengthened by choosing a hierarchical rather than a stepwise approach to find the best fitting model. The study also explored the effect of IR-obesity interaction on the lung function outcomes.

There are, however, some limitations for this study. Since the sample population is selected from the NHANES database which is a cross-sectional study, causal relationship between insulin resistance and lung function cannot be determined. The inclusion criteria relied on a history of asthma rather than a strict objective method endorsed by the ATS, which may affect the accuracy of the results. Also, exacerbations and options used to manage asthma attacks in the past year were not taken into consideration. IR indicators derived from fasting glucose-insulin concentrations should also be interpreted cautiously when comparing mixed gender and mixed ethnicity populations because of their differing insulin secretion patterns and/or clearance which may confound the analysis. In addition, a number of factors

also contribute to the variability of lung function in asthmatics, including physical activity. Estimates of physical activity in the NHANES database are based on the GPAQ - a subjective instrument which may not be a sufficiently accurate representation of the true activity levels in asthmatic adults. While the primary aim of this study was to investigate the main and interactive effects of anthropometric measures and insulin resistance on the parameters of pulmonary function in asthmatic adults, it was therefore decided not to include any PA variables in the regression model. Furthermore its inclusion could have caused a substantial rise in the number of missing values, leading to reduced statistical power and potentially misleading results.

Conclusion

This study elucidates that IR and increased WHtR are independent predictors of worsened pulmonary function in overweight/obese adults with asthma which modify the association between adiposity and lung physiology. Thus, central obesity and insulin resistance might synergistically increase asthma severity. This modifying effect could be an important factor contributing to asthma control and outcomes for asthmatic individuals.

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Figure Legends

Figure 1. Regression plots of the prediction models for lung function in asthmatic adults. The regression of baseline FVC(a) and FEV1 (b) values on a number of predicting variables, i.e., age, gender, ethnicity, smoking history, standing height, BMI, and HOMA-IR.

Figure 2. The relationship between central obesity and lung function (FVC (a) and FEV1 (b)) values in asthmatic adults based on insulin sensitivity.