Association between HOMA-IR and Lung Function in Korean Young Adults based on the Korea National Health and Nutrition Examination Survey

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Metabolic syndrome, including obesity and insulin resistance, has been reported to lower lung function in elderly subjects with asthma or chronic obstructive lung disease. This study aimed to find the association between lung function and insulin resistance in Korean young adults. This study used data from the Korean National Health and Nutrition Examination Survey 2011–2013, which is a representative sample of the Korean population. A total of 1,922 young adults aged 19 to 40 were included in the analysis. The association between lung function test and insulin resistance was evaluated. Weighted logistic regression analyses showed a significant negative correlation of insulin resistance with FVC% predicted (correlation coefficient $\gamma = -0.130, P < 0.0001$), FEV1% predicted ($\gamma = -0.074, P = 0.004$) and FEV1/FVC ratio ($\gamma = -0.059, P = 0.019$) in young adults, especially in subjects without asthma ($\gamma$ for FVC% predicted, FEV1% predicted and FEV1/FVC ratio $= -0.138, -0.092$, and $-0.061$, respectively). This study demonstrates an inverse correlation between insulin resistance and lung function in Korean young adults. Young adults with preclinical insulin resistance have a higher risk of impaired lung function.

Insulin resistance is defined as a condition in which higher than normal insulin concentrations are needed to achieve normal metabolic responses or normal insulin concentrations fail to achieve a normal metabolic response1. The failure of insulin to stimulate glucose transport into its target cells plays a central etiological role in metabolic syndrome, which includes abdominal obesity, hypertriglyceridemia, low high-density lipoprotein-cholesterol, elevated blood pressure, and hyperglycemia1.

A negative correlation between lung function and metabolic syndrome has recently been proposed in several studies. In Forno’s study, adolescents with asthma and metabolic syndrome showed significantly decreased pulmonary function compared to adolescents with asthma alone2. Yeh et al. reported that subjects with metabolic syndrome had lowered lung function3. Obesity, a component of metabolic syndrome, was reported as a risk factor for decreased pulmonary function in asthma patients24. However, the metabolic components playing a key role in lower lung function have not been clearly elucidated.

The correlation between lung function and insulin resistance that is an underlying pathophysiology leading to metabolic syndrome remains unclear. Forno et al. reported that insulin resistance is associated with lower lung function in adolescents2. Yamamoto et al. reported that impaired lung function was associated with higher risk of metabolic syndrome independent of insulin in middle aged Japanese population5. In another study, Paek et al. reported that Korean patients with chronic obstructive pulmonary disease (COPD) had higher risk of metabolic syndrome; however, glucose level was not associated with low lung function6. In another Korean study, Park et

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The coefficient for FEV1% predicted (r coefficient for FVC% predicted) group showed stronger negative association between lung function and insulin resistance than total population (HOMA-IR, P value was significantly associated with lower FVC% predicted (r coefficient was not statistically significant in the asthma group. Each unit increase in serum level of insulin and HOMA-IR, the no-asthma group (Table 2). However, the inverse correlation between insulin resistance and lung function group, and the asthma group are shown in Table 2. The levels of insulin and insulin resistance (HOMA-IR) were observed between the asthma and non-asthma groups regarding mean age, sex, exercise, area of residence, household income, weight, height, BMI, waist circumference, energy intake, serum levels of glucose and insulin, HOMA-IR, and energy intake. However, the percentage of current smokers was significantly lower in the non-asthma group (34.9 ± 0.8%, P = 0.0635) than in the asthma group (53.7 ± 3.7%, P < 0.0001). The prevalence of atopic dermatitis and allergic rhinitis were significantly higher (13.1 ± 0.9%, P = 0.0029) and FEV1/FVC ratio (r coefficient was not statistically significant in the asthma group.

### Results

#### Demographics.

The characteristics of the study participants are summarized in Table 1. Among 1,922 participants aged 19 to 40 years with lung function test, 216 had a medical history of asthma. No significant differences were observed between the asthma and non-asthma groups regarding mean age, sex, exercise, area of residence, household income, weight, height, BMI, waist circumference, energy intake, serum levels of glucose and insulin, HOMA-IR, and energy intake. However, the percentage of current smokers was significantly lower in the no-asthma group (34.9 ± 0.8%) than in the asthma group (53.7 ± 3.7%). The percentage of heavy current alcohol users (>30 g/day) was significantly higher in the asthma group (21.2 ± 3.0%) than in the no-asthma group (13.1 ± 0.9%, P = 0.0029). The prevalence of atopic dermatitis and allergic rhinitis were significantly higher in the asthma group (P < 0.0001). This finding was expected as atopic dermatitis and allergic rhinitis are known to be common in asthma patients.

#### Association between lung function and insulin resistance.

The results of multivariate analysis of the relationships between insulin resistance and lung function measurements in total population, the no-asthma group, and the asthma group are shown in Table 2. The levels of insulin and insulin resistance (HOMA-IR) negatively correlated with FVC% predicted, FEV1/FVC ratio in total population and the no-asthma group (Table 2). However, the inverse correlation between insulin resistance and lung function was not statistically significant in the asthma group. Each unit increase in serum level of insulin and HOMA-IR value was significantly associated with lower FVC% predicted (r coefficient = −0.130 for insulin level and −0.133 for HOMA-IR, P < 0.0001 for both), FEV1% predicted (r coefficient = −0.074 for insulin level and −0.078 for HOMA-IR, P = 0.004 and P = 0.0025, respectively) and FEV1/FVC ratio (r coefficient = −0.058 for insulin level and −0.045 for HOMA-IR, P = 0.0019 and P = 0.0744, respectively) in the total population group. The no-asthma group showed stronger negative association between lung function and insulin resistance than total population (r coefficient for FVC% predicted = −0.138 for insulin level and −0.128 for HOMA-IR, P < 0.0001 for both, r coefficient for FEV1% predicted = −0.092 for insulin level and −0.084 for HOMA-IR, P = 0.0019 and P = 0.0041, respectively, and r coefficient for FEV1/FVC ratio = −0.061 for insulin level −0.081 and for HOMA-IR, P = 0.0269 and P = 0.0026, respectively).

| Sex (Male, %) | No-asthma group n = 1706 | Asthma group n = 216 | P value |
|--------------|--------------------------|----------------------|---------|
| 57.2 ± 1.3   | 64 ± 3.7                 | 0.0635               |
| Age (Years)  | 31.2 ± 0.2               | 30.7 ± 0.5           | 0.2868  |
| Exercise (Yes, %) | 26.8 ± 1.3           | 22.3 ± 2.9           | 0.1641  |
| Place (Rural, %) | 12.0 ± 2.1               | 14.6 ± 3.2           | 0.3827  |
| Current smoker (Yes, %) | 34.9 ± 1.3              | 53.7 ± 3.7           | <0.0001 |
| Current alcohol use (>30 g/day, %) | 13.1 ± 0.9             | 21.2 ± 3.1           | 0.0029  |
| Income (Less than 25%, %) | 7.1 ± 0.8              | 4 ± 1.5              | 0.1104  |
| Atopic dermatitis (Yes, %) | 4.2 ± 0.5               | 8.1 ± 2.3            | <0.0001 |
| Allergic rhinitis (Yes, %) | 30.8 ± 1.6              | 53.6 ± 4.4           | <0.0001 |
| Height (cm)  | 167.7 ± 0.2              | 168.7 ± 0.6          | 0.1     |
| Weight (kg)  | 68.5 ± 0.3               | 68.8 ± 1             | 0.7494  |
| Body mass index (kg/m²) | 24.2 ± 0.1              | 24.1 ± 0.3           | 0.6181  |
| Waist circumference (cm) | 82.1 ± 0.3              | 82.4 ± 0.9           | 0.7356  |
| FVC (L)      | 4.2 ± 0.0                | 4.3 ± 0.1            | 0.6624  |
| FVC % predicted | 95.1 ± 0.3              | 93.8 ± 0.7           | 0.0891  |
| FEV1 (L)     | 3.5 ± 0.0                | 3.5 ± 0.1            | 0.3009  |
| FEV1 % predicted | 93.8 ± 0.3              | 90 ± 0.8             | <0.0001 |
| FEV1/FVC ratio | 0.84 ± 0.00             | 0.8 ± 0              | 0.0002  |
| Glucose (mg/dL) | 91.0 ± 0.2              | 90 ± 0.6             | 0.1355  |
| Insulin (µU/mL) | 9.6 (9.4, 9.9)        | 9.5 (8.9–10.1)       | 0.4318  |
| HOMA IR      | 2.2 (2.1, 2.2)           | 2.1 (2–2.2)          | 0.644   |
| Energy intake (kcal/day) | 2039.9 ± 26.8        | 2123.2 ± 74.9        | 0.2826  |
| Fat intake (% of calorie) | 20.8 ± 0.3              | 20.5 ± 0.7           | 0.695   |

Table 1. Demographics of participants. HOMA-IR, homeostasis model of assessment of insulin resistance; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.
We next performed multiple logistic regression analyses between HOMA-IR and lung function in comparison with the asthma group and no-asthma group (Table 3). The no-asthma group showed that each unit increase of HOMA-IR was significantly associated with FEV₁% predicted (β coefficient = 3.656, P < 0.0001) and FVC% predicted (β coefficient = 3.892, P < 0.0001) after adjustment for age, sex, and BMI in Model 1. After fully adjusting for age, sex, BMI, smoking status, drinking status (>30 mg/day), and exercise status, HOMA-IR, homeostasis model of assessment of insulin resistance; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second.

### Table 3. Regression coefficients of dependent variables of lung function. Data are presented as β coefficients and SE (standard error). Model 1: adjusted for age, sex, and BMI; Model 2: adjusted for age, sex, BMI, smoking status (current smoker), drinking status (>30 mg/day), and exercise status. HOMA-IR, homeostasis model of assessment of insulin resistance; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second.

| Insulin | Total population | No-asthma group | Asthma group | P value for interaction |
|---------|------------------|-----------------|--------------|------------------------|
| FVC     | 0.02246 (0.0272, 0.0675) | 0.3622 (0.13 (0.0349, 0.0608) | 0.6145 (−0.04 (−0.1738, 0.0953) | 0.5528 (0.4472) |
| FVC% predicted | −0.13689 (−0.1748, −0.0861) | <0.0001 (−0.138 (−0.1846, −0.0907) | <0.0001 (−0.107 (−0.2383, 0.0282) | 0.175 (0.7497) |
| FEV₁    | 0.00286 (0.0422, 0.048) | 0.9122 (−0.007 (−0.0548, 0.0409) | 0.8077 (−0.028 (−0.1612, 0.1072) | 0.6549 (0.7504) |
| FEV₁% predicted | −0.07418 (−0.1189, −0.0292) | 0.004 (−0.092 (−0.1393, −0.0443) | 0.0019 (0 (−0.1348, 0.1348) | 0.9981 (0.2927) |
| FEV₁/FVC ratio | −0.05889 (−0.1037, −0.0138) | 0.019 (−0.061 (−0.1096, −0.0132) | 0.0269 (0.031 (−0.1042, 0.1651) | 0.6889 (0.3393) |
| HOMA-IR | 0.00736 (−0.0378, 0.0524) | 0.7641 (0.032 (−0.0159, 0.0797) | 0.2241 (−0.053 (−0.1864, 0.0823) | 0.4191 (0.224) |
| FVC     | 0.00303 (−0.0778, 0.0884) | <0.0001 (−0.128 (−0.1748, −0.0806) | <0.0001 (−0.162 (−0.2904, −0.0279) | 0.0313 (0.6112) |
| FEV₁    | −0.0085 (−0.0536, 0.0366) | 0.7432 (0.007 (−0.0409, 0.0548) | 0.8074 (−0.033 (−0.167, 0.1023) | 0.6062 (0.5597) |
| FEV₁% predicted | −0.07843 (−0.1231, −0.0334) | 0.0025 (−0.084 (−0.1313, −0.0363) | 0.0041 (−0.025 (−0.1592, 0.1101) | 0.7272 (0.5217) |
| FEV₁/FVC ratio | −0.04549 (−0.0964, −0.0004) | 0.0744 (−0.081 (−0.1284, −0.0333) | 0.0026 (0.049 (−0.0863, 0.1825) | 0.5216 (0.1724) |

### Linear correlation between HOMA-IR and lung function in the no-asthma group.

We next stratified participants into four quartiles according to HOMA-IR level in both no-asthma and asthma groups (Table 4). In the no-asthma group, the mean value of FEV₁% predicted was 96.2026% for HOMA-IR quartile 1, 94.8399% for HOMA-IR quartile 2, 92.7097% for HOMA-IR quartile 3, and 91.8195% for HOMA-IR quartile 4. The negative linear correlation was statistically significant between HOMA-IR and FEV₁% predicted (P < 0.0001). The mean values of FVC% predicted according to HOMA-IR quartiles were 97.4197%, 95.8775%, 94.2153%, and 93.1292%, respectively (P < 0.0001) in the no-asthma group. Although the P value for interactions between the two groups was not statistically significant, the difference was observed that there was no significant linear correlation between lung function and HOMA-IR in the asthma group (Table 4).

### Discussion

To the best of our knowledge, this study is the first to demonstrate a negative correlation between insulin resistance and lung function in a representative sample of Korean young adults. This study showed that HOMA-IR is associated with lower FEV₁% predicted, FVC% predicted and FEV₁/FVC ratio. In addition, lung function was significantly affected by HOMA-IR level; individuals with higher HOMA-IR (greater insulin resistance) had significantly lower lung function. This study has a unique point in that it revealed an independent association between subclinical insulin resistance and lung function based on a database of young adults.

There have been several studies documenting the association between overt diabetes mellitus and impaired lung function. Several studies have evaluated the association between insulin resistance and lung function in adult
and elderly participants. Kim et al. reported that insulin resistance was associated with low FVC in both obese and non-obese middle-aged Koreans over 30 years (mean age >50 years). Lawlor et al. demonstrated that HOMA score was inversely associated with FEV1 and FVC in British women between 60 and 79 years of age. Lazarus et al. also reported inverse associations between insulin resistance and FEV1 and FVC in males aged 21 to 80 in Boston, Massachusetts area. However, age is a very important determining factor in lung function. Decrease in muscle mass with age results in muscle weakness and decreases in FVC and FEV1. The high prevalence of COPD in elderly individuals might also have acted as a confounding factor in the previous studies. Thus, the association between lung function and insulin resistance without comorbidities needs to be evaluated in young adults.

Asthma is characterized by airway obstruction like COPD and is common in people under 35 years of age, unlike COPD, which is an elderly disease. In a previous study, an inverse correlation between metabolic syndrome and lung function was observed in asthma patients. However, in this study, the asthma group did not show a significant inverse correlation between lung function and insulin resistance. This discrepancy might be explained by the difference in subjects. Unlike previous studies in which asthma subjects were included by medical chart review, the asthma group in this study was collected by questionnaire survey with self-reported asthma. Although the FEV1% predicted and FEV1/FVC ratio of the asthma group were lower than those of the no-asthma group, the FVC, FEV1, FVC% predicted, FEV1% predicted, and FEV1/FVC ratio in both groups were within the normal range, without any evidence of impaired lung function. Another possible explanation is that the remaining confounding factors could affect lung function in the asthma group, such as smoking, drinking status, and the presence of allergic diseases. Impaired lung function seemed to have a negative correlation with insulin resistance in the asthma group; however, no statistical significance was found, likely due to the other confounding factors.

Until now, the mechanisms of lower lung function by insulin resistance have not been clearly elucidated. Several possible mechanisms have been reported. Kim et al. demonstrated that HOMA-IR was significantly associated with bronchial hyper-reactivity. In an in vitro study, Dekkers et al. evaluated that insulin-induced hypercontractility after eight days of tissue culture of bovine smooth muscle cells. Conversely, the influence of lung function on systemic insulin resistance has also been reported. Sarlus et al. revealed the brain gene expression toward induction of insulin resistance that was induced by airway-associated inflammation. Thuesen et al. reported that insulin resistance was a predictor of asthma-like symptoms in adults. The mechanisms that link insulin resistance with impaired lung function should be elucidated in future studies.

Obesity is a well-known risk factor for impaired lung function and is associated with insulin resistance. Higher BMI might be a confounding factor between insulin resistance and lung function. BMI has a positive correlation with FEV1/FVC and a negative correlation with FEV1. One possible mechanism to explain decreased lung function caused by obesity is decreased lung volume, especially expiratory reserve volume and functional residual capacity. The ineffectiveness of respiratory muscles in obesity also results in decreased lung function. Obesity is considered a chronic inflammatory state and is associated with insulin resistance, endothelial dysfunction, systemic arterial hypertension, and dyslipidemia. However, Thuesen's study demonstrated that the effect of insulin resistance was stronger than that of obesity.

Our study has several limitations. First, the definition of no-asthma was based on a self-reported system. Second, the present study did not compare other components of metabolic syndrome such as diabetes mellitus and obesity in association with lung function. The relationship between insulin resistance and lung function could be strengthened by including these variables in future studies.

In conclusion, data from the Korean National Health and Nutrition Examination Survey revealed that insulin resistance is negatively correlated with lung function in young Korean adults. This study is important in understanding the association between insulin resistance and lung function in the young Korean population. Our results suggest the importance of early management and education on metabolic syndrome for preservation of pulmonary function, one of the most important determinants of comorbidity and mortality.

Materials and Methods
Study population and data collection. We used data from the Fifth Korean National Health and Nutrition Examination Survey (KNHANES V-2, V-3, and VI-1), which was conducted from January 2011 to December 2013, by the Korea Centers for Disease Control and Prevention. The study design followed the tenets of the Declaration of Helsinki for biomedical research. This survey was conducted after approval from the Institutional Review Board of the Korea Centers for Disease Control and Prevention (IRB No. 2011-02CON-06-C, 2012-01EXP-01-2C, and

| HOMA-IR | FEV1% predicted | FVC% predicted | FEV1/FVC ratio |
|---------|----------------|----------------|----------------|
| No-asthma | Asthma | No-asthma | Asthma | No-asthma | Asthma |
| Quartile 1 | 96.2 ± 0.5 | 88.1 ± 1.5 | 97.4 ± 0.5 | 93.9 ± 1.6 | 0.841 ± 0.003 | 0.803 ± 0.014 |
| Quartile 2 | 94.8 ± 0.6 | 90.6 ± 1.4 | 95.9 ± 0.6 | 94.8 ± 1.4 | 0.841 ± 0.003 | 0.814 ± 0.010 |
| Quartile 3 | 92.7 ± 0.6 | 91.4 ± 1.6 | 94.2 ± 0.5 | 93.8 ± 1.4 | 0.837 ± 0.003 | 0.828 ± 0.008 |
| Quartile 4 | 91.8 ± 0.6 | 88.9 ± 1.6 | 93.1 ± 0.5 | 92.3 ± 1.5 | 0.838 ± 0.003 | 0.820 ± 0.010 |
| P value | <0.0001 | 0.4004 | <0.0001 | 0.7446 | 0.7131 | 0.4019 |
| P value for interaction | 0.187 | 0.8567 | 0.35 |
2013-07CON-03-4C). It was performed using a rolling sampling design involving a complex, stratified, multi-
stage, probability cluster survey of a representative sample of the civilian population of South Korea. A total of 192
sampling units were randomly selected from primary sampling units encompassing the target population. Each
sampling unit contained 20 households, with a total of 3800 households surveyed in one year. The Korean National
Health and Nutrition Examination Survey V-2, V-3, and VI-1 were conducted by four survey teams. The survey
consisted of three components: a health interview, a nutrition interview, and health examination.

All questionnaires were administered in person either by physicians or by trained interviewers at the partic-
ipants’ homes. Participants had the right to refuse participation according to the National Health Enhancement
Act. All participants who agreed to take part provided written informed consent. The Korea Centers for Disease
Control and Prevention obtained agreement from participants to use blood samples collected during the health
interview survey for further research.

We excluded participants younger than 19 years or older than 40 years and participants without a pulmonary
function test. A total of 1,922 participants were included in this analysis.

**Anthropometry and laboratory measurements.** Trained medical staff performed the physical exami-
nations according to standardized procedures. The health interview and health behavior surveys included
well-established questions to determine the demographic and socioeconomic characteristic of the subjects. The
surveys included questions on age, residence, family income, education level, occupation, marital status, smoking
habit, alcohol consumption, exercise, previous and current disease, and family disease history. Smoking status
was divided into three categories: current smoker, ex-smoker, or nonsmoker. A heavy alcohol consumer was
categorized as one who drinks more than 30 g per day. Exercise status was divided into yes or no (regular exer-
cise ≥ once a week). Residential area was categorized as urban or rural. Body weight was measured to the nearest
0.1 kg with subjects wearing light indoor clothing and height was measured to the nearest 0.1 cm without shoes.
Body mass index (BMI) was calculated as the ratio of weight in kilograms to height in square meters. After over-
night fasting, blood samples were obtained from participants’ antecubital veins. Levels of glucose and insulin were
measured enzymatically using a Hitachi Automatic Analyzer 7600 (Hitachi, Chiyoda-ku, Japan). Daily calorie
intake was monitored by 24-h food recall and analyzed using CAN-Pro 3.0 software (Korean Nutrition Society,
Seoul, Korea).

**Definition of asthma.** Asthma was defined as a self-reported diagnosis by a physician in the health interview
surveys. The questionnaire contained questions on physician-diagnosed asthma, wheezing, and use of asthma
medication. We used the following survey questions in this study: “Have you ever been diagnosed with asthma
by a doctor?”?, “Have you experienced wheezing or whistling in your chest at any time in the last 12 months”?,
“Are you currently taking any medicine (including inhalers, aerosols or tablets) for asthma”? Participants who
answered “Yes” to these questions were considered to have been diagnosed with asthma by a doctor. The ques-
tionnaire was validated and is generally used in epidemiologic studies of asthma.21–23.

**Lung function tests.** Lung function was measured using a dry rolling seal spirometer (model 2130, SensorMedics, Yorba Linda, CA) according to the American Thoracic Society/European Respiratory Society criteria for standardization. Best forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) values were selected for data analysis. Spirometric data were obtained on site by clinical technicians. The percentage of predicted values for FEV₁ and FVC were calculated from the following equations obtained in a representative Korean population:25

\[
\text{Predicted FVC in men} = -4.8434 - (0.00008633 \times \text{age}^2 \times \text{year}) + (0.05292 \times \text{height} \times \text{cm})
\]
\[
+ (0.01095 \times \text{weight} \times \text{kg})
\]

\[
\text{Predicted FVC in women} = -3.0006 - (0.0001273 \times \text{age}^2 \times \text{year}) + (0.03951 \times \text{height} \times \text{cm})
\]
\[
+ (0.006892 \times \text{weight} \times \text{kg})
\]

\[
\text{Predicted FVC in men} = -3.4132 - (0.0002484 \times \text{age}^2 \times \text{year}) + (0.04578 \times \text{height} \times \text{cm})
\]

\[
\text{Predicted FVC in women} = -2.4114 - (0.0001920 \times \text{age}^2 \times \text{year}) + (0.03558 \times \text{height} \times \text{cm})
\]

**Measurement of insulin resistance.** The homeostasis model assessment of insulin resistance (HOMA-IR)
value was used as a measure of insulin resistance and was defined as (fasting insulin [µIU/mL] × fasting glucose
[mg/dL])/405.26.

**Statistical analysis.** All continuous variables are presented as means and standard deviations. Analysis of
variance (ANOVA) was used to compare mean values for continuous variables. All multivariate analyses were
performed with linear regression and multiple logistic regression within the SURVEY procedure in SAS software
(Statistical Analysis System, Version 9.3, SAS Institute Inc., Cary, NC, USA). Statistical significance was set at
P < 0.05.
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Author Contributions

Y.L., S.J. and H.C designed the study. Y.K., D.L., H.K., J.L., H.A., and T.S edited the manuscript. T.L., J.S., C.Y., M.H., and K.H. performed statistical analysis. All authors reviewed the manuscript and approved the manuscript for publication.

Additional Information

Competing Interests: The authors declare that they have no competing interests.

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