

# Association between insulin resistance and lung function change: Analysis from the community-based prospective Ansan-Ansung cohort in Korea

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## Research article

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# Abstract

**Background:** Diabetes mellitus and hyperglycemia are associated with respiratory dysfunction. Although several studies have reported that insulin resistance is related to decreased lung function, the association between insulin resistance and lung function changes has been rarely studied. This study aimed to investigate the effect of insulin resistance on the annual lung function change using a large-scale prospective cohort.

**Methods:** We analyzed a community-based prospective cohort in Korea comprising 7,536 participants whose serial lung functions were assessed. Exposure was baseline insulin resistance estimated with homeostatic model assessment-insulin resistance (HOMA-IR), and outcomes were annual changes in forced expiratory volume in 1 second (FEV1), functional vital capacity (FVC), and FEV1/FVC ratio.

**Results:** In the multivariate linear regression, the increased in the logarithmic HOMA-IR was associated with a decrease in FEV1 ( $\beta$ : -0.23; 95% CI: -0.32 to -0.13;  $P < 0.001$ ), and FVC ( $\beta$ : -0.29; 95% CI: -0.39 to -0.19;  $P < 0.001$ ), but not in FEV1/FVC ratio ( $\beta$ : 0.05; 95% CI: 0.00 to 0.11;  $P = 0.051$ ). In the generalized additive model plot, L-shaped association between HOMA-IR and changes in FEV1 and FVC were observed with a HOMA-IR threshold of 2.4. Age modulated the effect of HOMA-IR on the change in FEV1, and increased HOMA-IR was associated with decreased annual FEV1 change only in the older population.

**Conclusions:** Insulin resistance was a novel risk factor for the decrease in FEV1 and FVC. The aging process may modulate the effect of insulin resistance on the decline in lung function.

## Background

Diabetes mellitus is a prevalent chronic disease in modern society, with many experiencing diabetes and its complications [1, 2]. Lung function decline has been considered a major complication of diabetes [3–5]. Several studies have found that diabetes and hyperglycemia are associated with the development of various pulmonary diseases, including chronic obstructive pulmonary disease, asthma, and interstitial lung disease [6–8]. Therefore, good control of diabetes may prevent future lung diseases.

Increased insulin resistance has been associated with the future development of obesity, diabetes [9], cardiovascular diseases [10], neurologic impairment [11], and kidney dysfunction [12]. Although several studies have reported the potential association between insulin resistance and decreased lung function, none of these studies have evaluated the longitudinal effect of insulin resistance on future lung function changes. The aging process can cause diverse physiological, immunological and structural changes in the respiratory system [13, 14]. Thus, analyzing consecutive measurements of lung function may help to interpret the effects of aging on insulin resistance and lung function changes. In addition, it can clarify a causal association between insulin resistance and lung function.

Since diabetes is associated with a future decline in lung function and insulin resistance is a fundamental pre-condition of diabetes, we hypothesized that increased insulin resistance may be

associated with future decline in lung function. Therefore, this study aimed to investigate the association between insulin resistance and lung function change using data from a community-based prospective Ansan-Ansung cohort in Korea.

## Methods

### Participants

The Ansan-Ansung cohort comprise participants aged 40–69 years who lived in Ansan (urban) and Ansung (rural) areas, and this cohort was analyzed to determine the factors affecting the incidence of chronic diseases. Baseline measurements were performed between May 2001 and February 2003, and two subsequent lung function tests were performed biennially thereafter. More detailed information about the Ansan-Ansung cohort can be obtained in previous reports [15]. Of the 10,030 participants, we excluded 134 missing smoking status, 188 missing socioeconomic status, and 316 missing metabolic disorders. Of the 9,392, participants, 1,856 with missing additional lung function test results were further excluded. Therefore, 7,536 participants were finally included in this analysis (Fig. 1).

### Exposure :insulin resistance

Insulin resistance was assessed using the homeostatic model assessment-insulin resistance (HOMA-IR). HOMA-IR was calculated using the following equation: fasting insulin ( $\mu\text{IU/mL}$ )  $\times$  fasting glucose ( $\text{mg/dL}$ )/405 [16].

### Outcomes: Changes in lung function test

Lung function tests were performed using a spirometer (VMAX2130; SensorMedics Corporation, Yorba, CA, USA). Pre-bronchodilator values were measured 3 times by trained technicians and the best scores were recorded. Predicted values of functional vital capacity (FVC) and functional expiratory volume in 1 second (FEV1) were calculated using the Korean formula [17]. The FEV1/FVC ratio was expressed as the percentage of FEV1 divided by FVC. Study outcomes were annual changes in FEV1, FVC, and FEV1/FVC ratio. These values were determined by calculating the regression coefficient using a least-square linear regression analysis, with FEV1, FVC, and FEV1/FVC ratio as functions of time in years. It was applied to all values of FEV1, FVC, and FEV1/FVC ratio that were obtained during the follow-up period.

### Measurements and other definitions

Trained investigators interviewed participants regarding their socioeconomic status and lifestyle habits using KoGES Baseline Core Questionnaire. High income was defined as the highest quintile of monthly household income ( $\geq 3$  million won a month). Blood pressure (BP) was defined as the average BP on both arms using a standard mercury sphygmomanometer (Baumanometer-Standby; W. A. Baum Co., Inc., Copiague, NY, USA). Body mass index (BMI) was defined by dividing the weight by the square of the height ( $\text{kg/m}^2$ ). Waist circumference was measured at the narrowest point between the lower rib and the iliac crest (measured to the nearest 0.1 cm). All blood samples were examined after fasting for at least 8 hours. Hemoglobin level and white blood cell (WBC) count were analyzed using enzymatic methods with

ADVIA 120 (Bayer Diagnostics, Tarrytown, NY, USA). Fasting glucose, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), triglyceride, high density lipoprotein (HDL) cholesterol, C-reactive protein (CRP), and serum creatinine levels were measured using ADVIA 1650 (Siemens, Tarrytown, NY, USA). Estimated glomerular filtration rate (eGFR) was defined using the Chronic Kidney Disease Epidemiology Collaboration equation [18].

### Statistical analyses

Normality of distribution of continuous variables was assessed using histogram and Q–Q plots. Mean  $\pm$  standard deviation (SD) was used to express normally distributed continuous variables, whereas median with interquartile range (IQR) was used for non-normally distributed continuous variables. The *P* trend was analyzed using linear regression for the normally distributed continuous variables, the Jonckheere–Terpstra test for the non-normally distributed continuous variables, and the Cochran–Armitage test for categorical variables.

The simple associations between HOMA-IR and spirometric parameters were expressed using the locally weighted scatterplot smoothing (LOWESS) function. In multivariate analyses, covariates were chosen based on clinical and statistical relevance. The non-linear association between HOMA-IR and changes in FEV1 and FVC was analyzed using the multivariate generalized additive model (GAM) for Gaussian distributions with the “mgcv” package, and calculation of Akaike information criterion (AIC) was used for the model fitting. In AIC, lower scores within the data set indicate a better model fit [19]. The threshold point of HOMA-IR was chosen based on the best fit determined by AIC among the models.

In the subgroup analysis, clinically significant variables were chosen, and participants were divided by the median of variables. The modulatory effect was confirmed by adding the interaction term of variables defining the subgroup to the multivariate linear regression analysis. To visualize potential interaction of age on the association between insulin resistance and annual lung function change, the LOWESS regression with interaction was implemented using the “predict3d” package. A *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using R version 3.6.2 (R Core Team 2019; R Foundation for Statistical Computing, Vienna, Austria).

## Results

The mean age of the 7,536 participants was 51.7 years, 49.2% were men, and 41.7% were current or past smoker. The mean  $\pm$  SD of BMI, systolic and diastolic BP, waist circumference, HDL cholesterol level, eGFR, hemoglobin level, and WBC count were  $24.6 \pm 3.1$  kg/m<sup>2</sup>,  $120.9 \pm 18.0$  mmHg,  $80.2 \pm 11.3$  mmHg,  $82.7 \pm 8.7$  cm,  $44.6 \pm 9.9$  mL/dL,  $94.1 \pm 13.3$  mL/min/1.73 m<sup>2</sup>,  $13.6 \pm 1.6$  g/dL, and  $6.5 \pm 1.8 \times 10^3/\mu\text{L}$ , respectively. Moreover, the median (IQR) of fasting glucose, HbA<sub>1c</sub>, triglyceride levels, and CRP levels were 82 (77–91) mg/dL, 5.6 (5.3–5.9) %, 135 (100–189) mg/dL, and 0.14 (0.07–0.24) mg/dL, respectively. At baseline, the mean  $\pm$  SD values of FEV1, FVC, and FEV1/FVC ratio were  $97.0 \pm 13.8\%$  predicted,  $96.9 \pm 13.0\%$  predicted, and  $80.1 \pm 7.4\%$ , respectively. The mean  $\pm$  SD values of annual change in FEV1, FVC, and FEV1/FVC ratio were  $-0.55 \pm 2.54\%$  predicted/year,  $-0.56 \pm 2.65\%$  predicted/year, and  $-0.37 \pm 1.44\%$ /year, respectively.

The clinical characteristics of the study population according to HOMA-IR quartile are shown in Table 1. Although age was not associated with HOMA-IR quartile, increased HOMA-IR quartile was associated with decreased proportion of men. Although income and educational status were not associated with HOMA-IR quartile, increased HOMA-IR quartile was associated with a decreased rate of current or past smoking. With the increase of HOMA-IR quartile, BMI, systolic and diastolic BP, waist circumference, WBC count, and fasting glucose, HbA<sub>1c</sub>, triglyceride, hemoglobin, and CRP levels increased, whereas HDL cholesterol levels decreased. With the increase of HOMA-IR quartile, baseline percent-predicted FEV1 and percent-predicted FVC decreased, but FEV1/FVC increased.

Table 1  
Clinical characteristics of the study population according to HOMA-IR quartile.

| HOMA-IR groups (n = 7536)     |                       |                          |                           |                       |         |
|-------------------------------|-----------------------|--------------------------|---------------------------|-----------------------|---------|
|                               | 1Q: < 1.05 (n = 1888) | 2Q: 1.06–1.45 (n = 1887) | 3 Q: 1.45–2.03 (n = 1882) | 4 Q: ≥2.03 (n = 1879) | P-trend |
| Age(years)                    | 52.09 ± 8.86          | 51.56 ± 8.73             | 51.43 ± 8.60              | 51.56 ± 8.63          | 0.099   |
| Male, n (%)                   | 1043 (55.24%)         | 930 (49.28%)*            | 852 (45.27%)*†            | 884 (47.05%)*         | < 0.001 |
| High income, n (%)            | 337 (17.85%)          | 343 (18.18%)             | 335 (17.80%)              | 376 (20.01%)          | 0.127   |
| College graduate, n (%)       | 261 (13.82%)          | 263 (13.94%)             | 279 (14.82%)              | 283 (15.06%)          | 0.204   |
| Current or past smoker, n (%) | 865 (45.82%)          | 781 (41.39%)*            | 723 (38.42%)*             | 775 (41.25%)*         | 0.001   |
| BMI (Kg/m <sup>2</sup> )      | 23.57 ± 2.98          | 23.96 ± 2.84*            | 24.84 ± 2.79*†            | 26.16 ± 3.08*†‡       | < 0.001 |
| Systolic BP (mmHg)            | 118.13 ± 17.31        | 118.91 ± 17.05           | 121.01 ± 17.96*†          | 125.50 ± 18.92*†‡     | < 0.001 |
| Diastolic BP (mmHg)           | 78.38 ± 11.14         | 79.00 ± 11.01            | 80.40 ± 11.14*†           | 83.10 ± 11.44*†‡      | < 0.001 |
| Waist circumference (cm)      | 79.92 ± 8.41          | 80.84 ± 8.04*            | 83.07 ± 8.15*†            | 86.89 ± 8.33*†‡       | < 0.001 |
| Fasting glucose (mg/dL)       | 79 (75–85)            | 82 (77–87)*              | 83 (78–90)*†              | 90 (82–101)*†‡        | < 0.001 |
| HbA1c (%)                     | 5.5 (5.3–5.7)         | 5.5 (5.3–5.8)            | 5.6 (5.3–5.8)* †          | 5.7 (5.5–6.3)*†‡      | < 0.001 |
| Triglyceride (mg/dL)          | 122 (93–169)          | 124 (95–171)             | 136 (101–188)*†           | 162 (118–231)*†‡      | < 0.001 |

Values are expressed as mean ± standard deviation for normally distributed continuous variables, median and interquartile range for non-normally distributed variables and percentage for categorical variables. P-trend was analyzed normally distributed continuous variables by the linear regression, for non-normally distributed continuous variable by Jonckheere-Terpstra tests, and for categorical variables by Cochran-Armitage test for trend. \*, †, and ‡ meant P < 0.05 when compared to < 1.05, 1.06–1.45, 1.45–2.03 groups of HOMA-IR, respectively, using Bonferroni post-hoc analysis of one-way ANOVA for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed continuous variable, and chi-square tests for categorical variables. Abbreviations: HOMA-IR, homeostatic model assessment for insulin resistance; BMI, body mass index; BP, blood pressure; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; WBC, white blood cell; CRP, C-reactive protein; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, functional vital capacity.

| HOMA-IR groups (n = 7536)  |                  |                  |                    |                     |         |
|--|------------------|------------------|--------------------|---------------------|---------|
| HDL cholesterol (mg/dL)  | 46.06 ± 10.17    | 45.86 ± 10.13    | 44.10 ± 9.61*†     | 42.30 ± 9.00*†‡     | < 0.001 |
| eGFR (mL/min/1.73 m <sup>2</sup> )   | 94.06 ± 12.85    | 94.49 ± 13.26    | 94.17 ± 13.36      | 93.65 ± 13.63       | 0.278   |
| Hemoglobin (g/dL)  | 13.68 ± 1.53     | 13.55 ± 1.54     | 13.55 ± 1.64       | 13.78 ± 1.55†‡      | < 0.001 |
| WBC count (× 10 <sup>3</sup> /μL)  | 6.43 ± 1.80      | 6.38 ± 1.71      | 6.46 ± 1.77        | 6.79 ± 1.81*†‡      | < 0.001 |
| CRP level (mg/dL)  | 0.12 (0.05–0.22) | 0.13 (0.06–0.23) | 0.14 (0.07–0.24)*† | 0.17 (0.09–0.27)*†‡ | < 0.001 |
| Baseline FEV1 (L)  | 2.96 ± 0.68      | 2.96 ± 0.69      | 2.92 ± 0.70        | 2.91 ± 0.69         | 0.024   |
| Baseline FVC (L)   | 3.74 ± 0.84      | 3.72 ± 0.88      | 3.66 ± 0.88*       | 3.63 ± 0.87*†       | < 0.001 |
| Baseline FEV1 (%-predicted)  | 96.82 ± 14.01    | 97.82 ± 13.84    | 97.38 ± 13.78      | 96.02 ± 13.42†‡     | < 0.001 |
| Baseline FVC (%-predicted)   | 97.45 ± 12.76    | 98.25 ± 13.25    | 97.08 ± 13.16†     | 94.61 ± 12.45*†‡    | < 0.001 |
| Baseline FEV1/FVC (%)  | 79.60 ± 7.91     | 79.97 ± 7.42     | 80.29 ± 7.26*      | 80.48 ± 6.89*       | 0.001   |
| <p>Values are expressed as mean ± standard deviation for normally distributed continuous variables, median and interquartile range for non-normally distributed variables and percentage for categorical variables. <i>P</i>-trend was analyzed normally distributed continuous variables by the linear regression, for non-normally distributed continuous variable by Jonckheere-Terpstra tests, and for categorical variables by Cochran-Armitage test for trend. *, †, and ‡ meant <i>P</i> &lt; 0.05 when compared to &lt; 1.05, 1.06–1.45, 1.45–2.03 groups of HOMA-IR, respectively, using Bonferroni post-hoc analysis of one-way ANOVA for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed continuous variable, and chi-square tests for categorical variables. Abbreviations: HOMA-IR, homeostatic model assessment for insulin resistance; BMI, body mass index; BP, blood pressure; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; WBC, white blood cell; CRP, C-reactive protein; FEV1, forced expiratory volume in 1 second; FVC, functional vital capacity.</p> |                  |                  |                    |                     |         |

We explored the association between HOMA-IR and annual changes in lung function test (Fig. 2). As HOMA-IR increased, annual FEV1 and FVC change decreased, whereas annual FEV1/FVC ratio change increased. Although the negative association between HOMA-IR and annual changes in FEV1 and FVC was statistically significant, the association between HOMA-IR and FEV1/FVC ratio was nullified in the multivariate linear regression analysis (Table 2). In the multivariate GAM plot analysis, we identified that the association between HOMA-IR and annual change in FEV1 and FVC was L-shaped, and the lowest AICs were found in HOMA-IR 2.4, in both annual FEV1 and FVC (Fig. 3).

Table 2  
Association between log-transformed HOMA-IR and the annual lung function change.

| <b>Per 1 unit increase of Log-HOMA-IR</b>   |                        |          |                        |          |                        |          |
|---|------------------------|----------|------------------------|----------|------------------------|----------|
|   | Univariate             |          | Model 1                |          | Model 2                |          |
| Outcomes  | Beta (95% CI)          | <i>P</i> | Beta (95% CI)          | <i>P</i> | Beta (95% CI)          | <i>P</i> |
| Δ FEV1 (%-predicted/year)   | -0.15 (-0.24 to -0.06) | < 0.001  | -0.15 (-0.24 to -0.07) | < 0.001  | -0.23 (-0.32 to -0.13) | < 0.001  |
| Δ FVC (%-predicted/year)  | -0.20 (-0.29 to -0.11) | < 0.001  | -0.20 (-0.29 to -0.11) | < 0.001  | -0.29 (-0.39 to -0.19) | < 0.001  |
| Δ FEV1/FVC (%/year)   | 0.07 (0.02 to 0.12)    | 0.004    | 0.06 (0.02 to 0.11)    | 0.010    | 0.05 (0.00 to 0.11)    | 0.051    |
| <p>In model 1, age and sex were added as covariates. Model 2 included high income, college graduate, smoking status, BMI, waist circumference, systolic and diastolic BP, triglyceride, HDL cholesterol, eGFR, WBC count, hemoglobin and CRP levels in addition to the covariates in the model 1. Abbreviations: HOMA-IR, homeostatic model assessment for insulin resistance; CI, confidence interval; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.</p> |                        |          |                        |          |                        |          |

There were no subgroups showing the effect modification between HOMA-IR and annual FVC change. However, participant age significantly modified the effect of HOMA-IR on annual FEV1 change (*P* for interaction < 0.001). Although HOMA-IR was not associated with annual FEV1 change in people aged < 50 years, increased HOMA-IR was significantly associated with decreased annual FEV1 change in individuals aged ≥ 50 years (Table 3). We also identified similar effect modification of age on the association between HOMA-IR and annual FEV1 change in the LOWESS regression plot with interaction (Fig. 4).

Table 3

Subgroup analysis for the effects of HOMA-IR on the annual rates of changes in FEV1 and FVC.

| Per 1 unit increase of Log-HOMA-IR   |                    |                                 |                                 |         |                          |
|--|--------------------|---------------------------------|---------------------------------|---------|--------------------------|
| Adjusted beta (95% CI, <i>P</i> )  |                    |                                 |                                 |         | <i>P</i> for interaction |
| Subgroup   | No. of people      | Δ FEV1 (%-predicted/year)       | Δ FVC (%-predicted/year)        | Δ FEV1  | Δ FVC                    |
| Age (years)  | < 50 (n = 3,755)   | -0.03 (-0.16 to 0.09, 0.597)    | -0.14 (-0.27 to 0.02, 0.026)    | < 0.001 | 0.144                    |
|  | ≥ 50 (n = 3,781)   | -0.37 (-0.51 to -0.23, < 0.001) | -0.38 (-0.53 to -0.24, < 0.001) |         |                          |
| Sex  | Male (n = 3,709)   | -0.25 (-0.37 to -0.12, < 0.001) | -0.26 (-0.39 to -0.12, < 0.001) | 0.585   | 0.306                    |
|  | Female (n = 3,827) | -0.23 (-0.37 to -0.09, 0.001)   | -0.33 (-0.47 to -0.19, < 0.001) |         |                          |
| Current or past smoker   | No (n = 4,392)     | -0.20 (-0.32 to -0.07, 0.002)   | -0.31 (-0.44 to -0.18, < 0.001) | 0.912   | 0.309                    |
|  | Yes (n = 3,144)    | -0.29 (-0.44 to -0.15, < 0.001) | -0.27 (-0.42 to -0.12, < 0.001) |         |                          |
| BMI (kg/m <sup>2</sup> )   | < 25 (n = 4,277)   | -0.25 (-0.38 to -0.13, < 0.001) | -0.30 (-0.43 to -0.17, < 0.001) | 0.289   | 0.704                    |
|  | ≥ 25 (n = 3,259)   | -0.20 (-0.34 to -0.05, 0.008)   | -0.27 (-0.42 to -0.12, < 0.001) |         |                          |
| WBC count (x10 <sup>3</sup> /μL)   | < 6.3 (n = 3,693)  | -0.19 (-0.34 to -0.04, 0.011)   | -0.29 (-0.43 to -0.14, < 0.001) | 0.683   | 0.772                    |
|  | ≥ 6.3 (n = 3,843)  | -0.26 (-0.39 to -0.14, < 0.001) | -0.29 (-0.43 to -0.16, < 0.001) |         |                          |
| Hemoglobin (mg/dL)   | < 13.6 (n = 3,668) | -0.23 (-0.38 to -0.08, 0.002)   | -0.31 (-0.47 to -0.16, < 0.001) | 0.442   | 0.389                    |
|  | ≥ 13.6 (n = 3,449) | -0.23 (-0.35 to -0.11, < 0.001) | -0.27 (-0.40 to -0.15, < 0.001) |         |                          |
| Adjusted beta and 95% CIs were analyzed using the multivariate linear regression. All covariates of model 2 shown in Table 2 were included for adjustment. The variable used to divide subgroup was excluded. Abbreviations: HOMA-IR, homeostatic model assessment for insulin resistance; CI, confidence interval; BMI, body mass index; WBC, white blood cell; FEV1, forced expiratory volume in 1 second; FVC, functional vital capacity. |                    |                                 |                                 |         |                          |

## Discussion

Recently, decreased lung function has been suggested as a complication of insulin resistance. In their large-scale cross-sectional study, Lawlor et al. found that HOMA-IR decreased by 5% and 8% for a 1 SD increase in log FEV1 and FVC, respectively [20]. Sagun et al. also showed that decreased percent-predicted FEV1 was correlated with increased insulin resistance (HOMA-IR  $\geq$  2.5) in an age-adjusted analysis (OR 0.97, 95% CI 0.94–1.00,  $P=0.028$ ) [21]. However, most previous studies were cross-sectional, and a causal association between insulin resistance and decreased lung function needed to be evaluated in a prospective cohort. Therefore, we conducted the current study using a prospective community-based cohort and found that increased insulin resistance was associated with a decline in lung function, particularly in the elderly population.

In the current study, we found that increased baseline HOMA-IR was associated with a decrease in FEV1 and FVC, but not in FEV1/FVC ratio, in the multivariate analysis after adjusting for possible confounders. We also found an L-shaped association between HOMA-IR and annual changes in FEV1 and FVC using the multivariate GAM plot, and the suggested threshold of HOMA-IR for lung function decline was 2.4. As a surrogate marker of insulin resistance, several studies have shown that the cutoff value of HOMA-IR for the risk of developing type 2 diabetes mellitus and metabolic syndrome in the Korean population is approximately 2.5 [22–24]. Our findings, consistent with those of previous studies, indicated that a decline in lung function may be metabolic complication due to the systemic effects of insulin resistance.

There were two possible explanations for the potential pulmonary hazard of insulin resistance. First, chronic low-grade inflammation in adipose tissue contributes to the development of insulin resistance [25, 26]. Levels of cytokines, such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-6, are increased with insulin resistance and cause lung fibrosis and inflammation [27, 28]. Second, respiratory muscle weakness is related to insulin resistance. With insulin resistance, TNF- $\alpha$  and interferon-gamma cause muscle wasting through the degeneration of myotubes and modulation of myogenesis [29, 30].

In subgroup analysis, age showed a statistically significant effect modification on the association between HOMA-IR and annual change in FEV1. Although HOMA-IR was not associated with annual change in FEV1 in the younger group, increased HOMA-IR was significantly related to decreased FEV1 in the older group ( $P$  for interaction  $< 0.001$ ).

Insulin resistance is associated with chronic low-grade inflammation [25]. The risk of chronic low-grade inflammation increased with the aging process [31, 32]. Lung function can decline with increased inflammation [33, 34]. Therefore, we assumed that increased chronic low-grade inflammation during the aging process may potentiate the metabolic hazard of insulin resistance in lung function decline. In this regard, early intervention to reduce insulin resistance in the elderly population may have a beneficial effect on future lung function preservation.

Several limitations should be considered when interpreting our findings. First, two or fewer additional lung function measurements were performed in this study. Therefore, the rate of change in FEV1 and FVC only reflects short-term changes in lung function. Further studies performing more spirometric tests will be needed to clarify the long-term effect of insulin resistance on lung function. Second, our study was

conducted in single ethnicity and selected areas. Therefore, the results should be elucidated cautiously in accordance with racial and regional differences. Despite these limitations, our study has several strengths. First, to the best of our knowledge, this is the first study to investigate the association between insulin resistance and lung function using a large-scale prospective cohort based on the general population. Second, we calculated the threshold of HOMA-IR for lung function decline using a nonlinear analytic method. Finally, the interaction between age and insulin resistance to lung function changes was investigated and presented using visualization.

In conclusion, increased insulin resistance was independently associated with a decrease in FEV1 and FVC, particularly in the older population. The potential pulmonary hazard of insulin resistance needs to be confirmed in future interventional studies

## Abbreviations

HOMA-IR: Homeostatic model assessment-insulin resistance; FEV1: Forced expiratory volume in 1 second; FVC: Functional vital capacity; CI: Confidence interval; BP: Blood pressure; BMI: Body mass index; WBC: White blood cell; HbA<sub>1c</sub>: Hemoglobin A<sub>1c</sub>; HDL: High density lipoprotein; CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate; SD: Standard deviation; IQR: interquartile range; LOWESS: Locally weighted scatter-plot smoothing; GAM: Generalized additive model; AIC: Akaike's information criterion; TNF- $\alpha$ : Tumor necrosis factor-alpha

## Declarations

### Ethics approval and consent to participate

Using the Ansan-Ansung cohort, this study was conducted according to the Declaration of Helsinki. The institutional review boards of the Nowon Eulji Medical Center, Eulji University approved the protocol and ethics of the study (Approval Number: 2019-06-014). Participants provided written informed consent, and all data were completely anonymized prior to access.

### Consent for publication

Not applicable.

### Availability of data and materials

The data of our study is fully available when manuscript is accepted for publication.

### Competing interests

All authors have no conflicts of interest to declare.

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### Author's contributions

S.W.L. conceptualization. S.H.K. data curation/formal analysis. H.S.K. investigation/ methodology. S.H.K. writing – original draft. H.K.M. writing – review and editing. S.W.L. supervision/validation. All authors read and approved the final manuscript.

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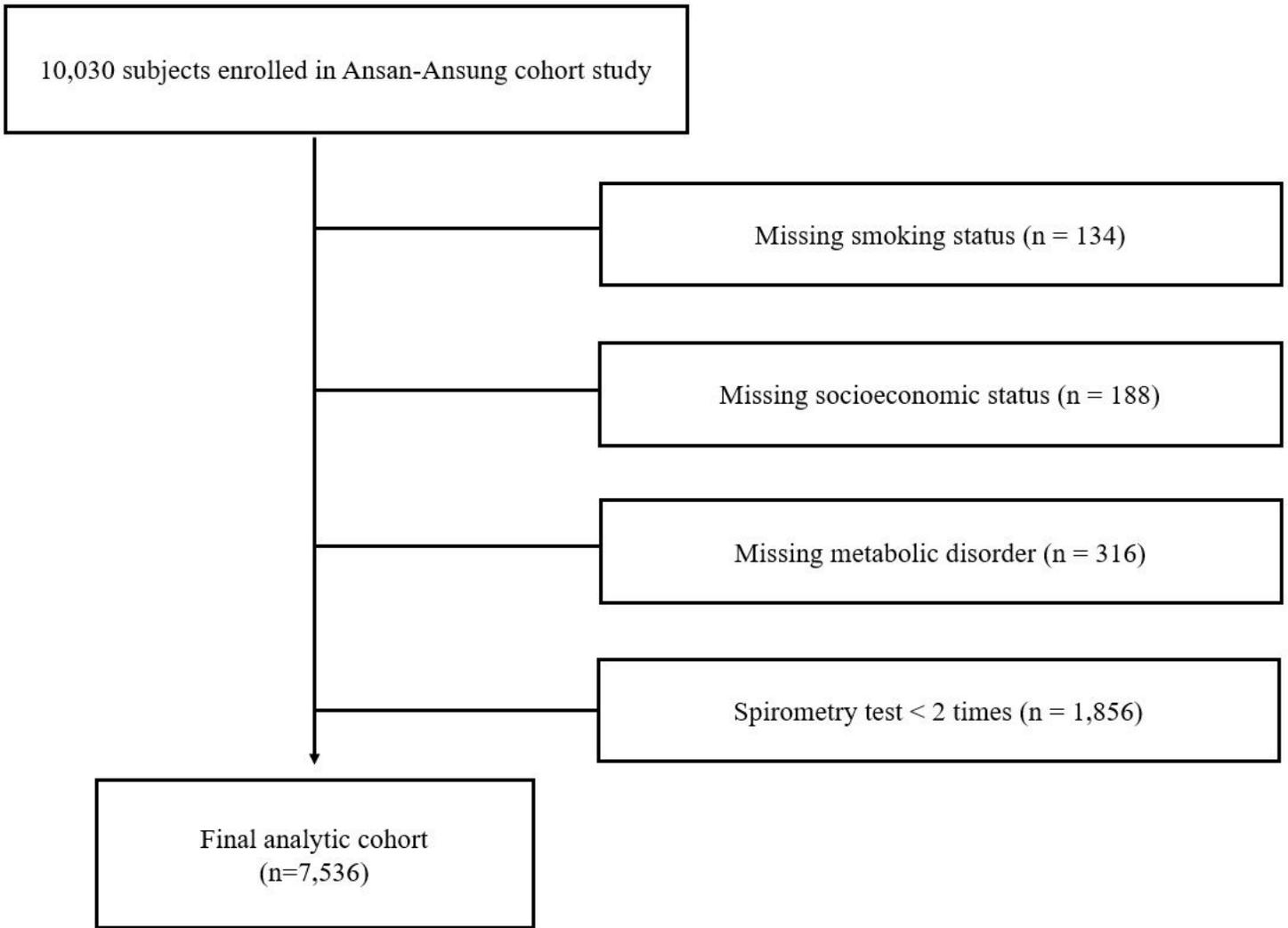
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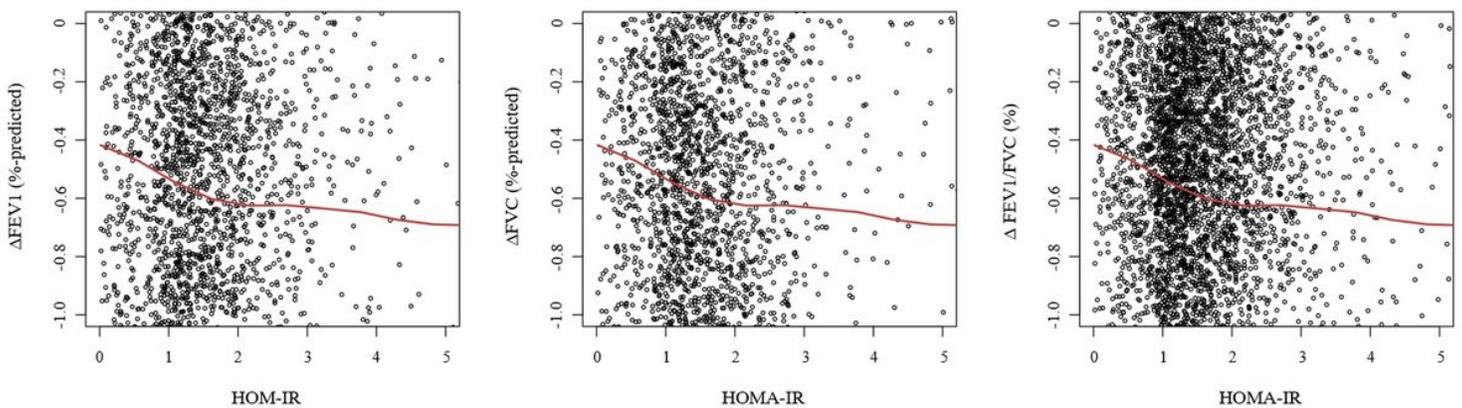
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## Figures



**Figure 1**

Flow chart of the study subject selection

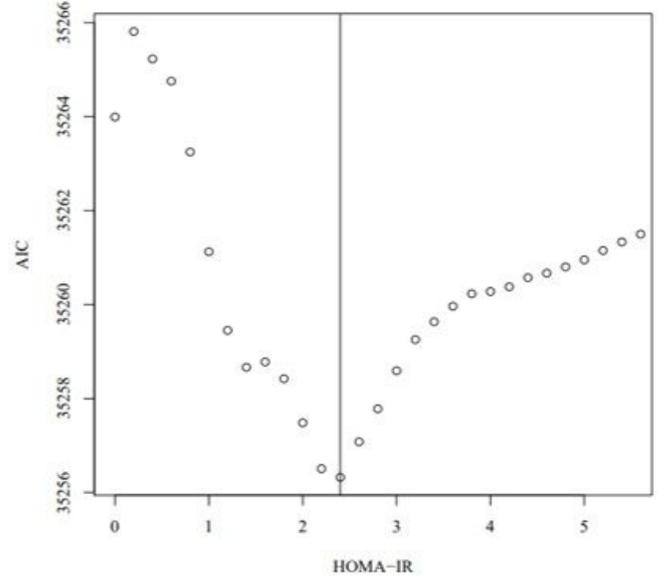
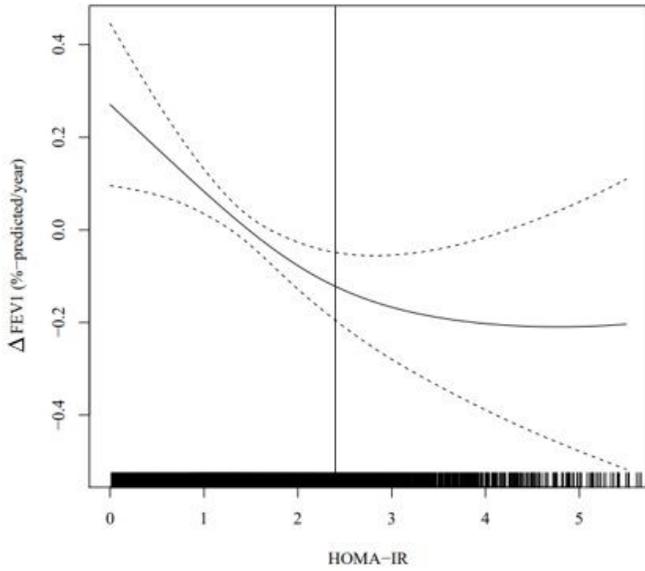


**Figure 2**

Association between HOMA-IR and lung function. The red line represented the LOWESS regression curve. Abbreviations: HOMA-IR, homeostatic model assessment-insulin resistance; LOWESS, locally weighted

scatter-plot smoothing

A. HOMA-IR and annual FEV1 change



B. HOMA-IR and annual FVC change

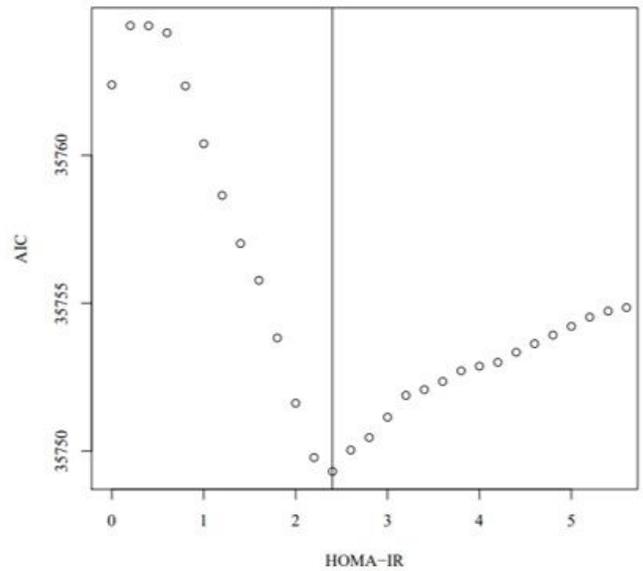
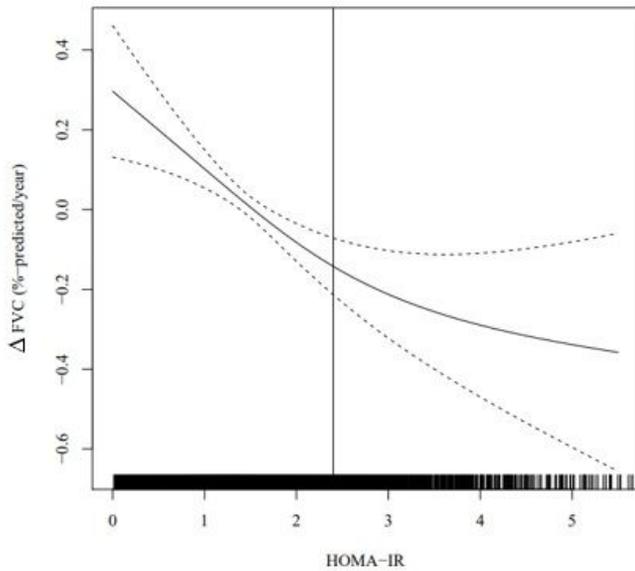
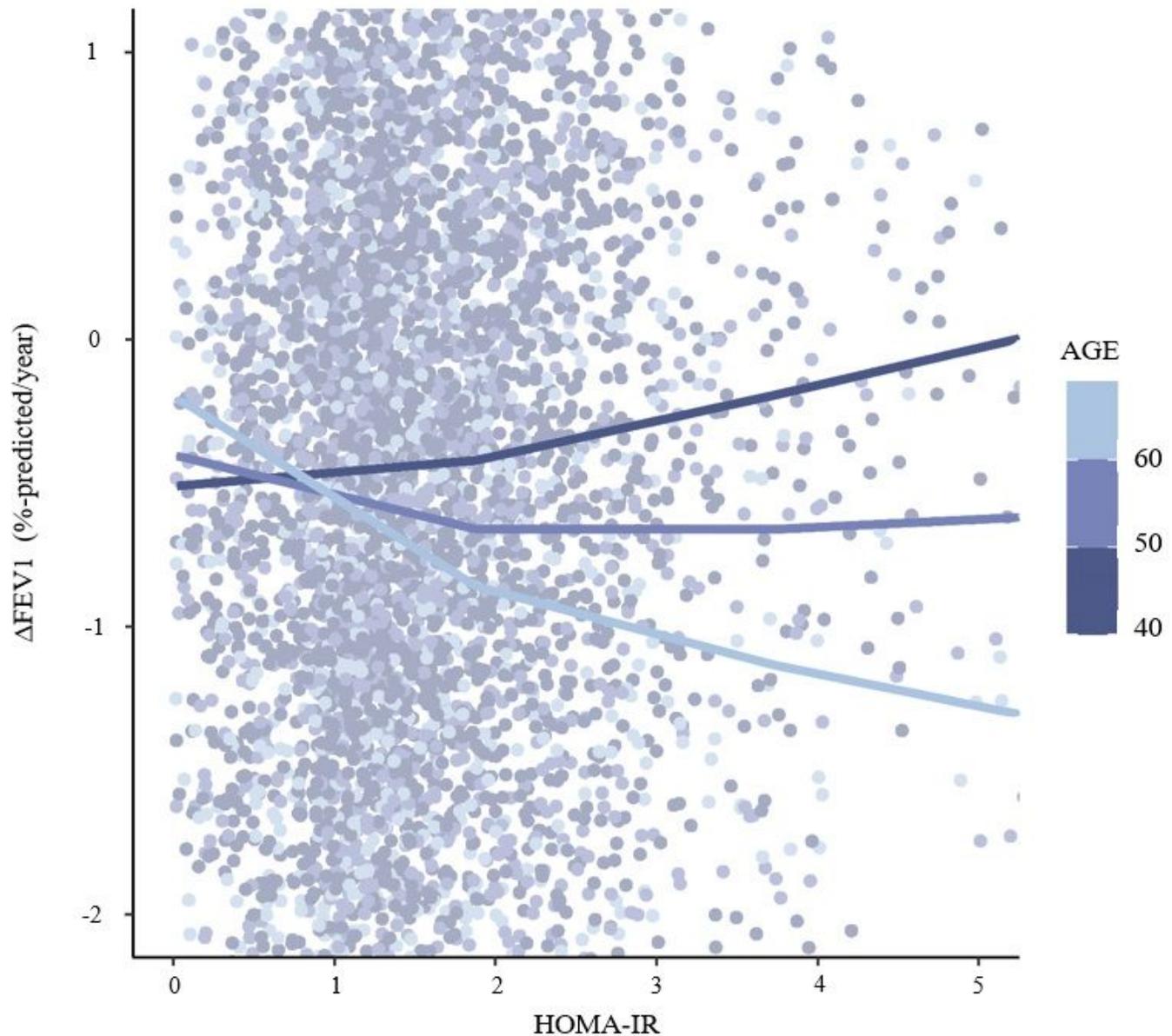


Figure 3

GAM plot between HOMA-IR and annual lung function change. The dashed lines indicate 95% CIs for values of smoothed changes in FEV1 and FVC, using the multivariate GAM analysis after adjusting for age, sex, high income, college graduate, smoking status, BMI, waist circumference, systolic and diastolic BP, triglyceride, HDL cholesterol, eGFR, WBC count, hemoglobin and CRP levels. Abbreviations: GAM, general additive model; HOMA-IR, homeostatic model assessment-insulin resistance; CI, confidence interval; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; BMI, body mass index; BP, blood pressure; HDL, high density lipoprotein; eGFR, estimated glomerular filtration rate; WBC, white blood cell; CRP, C-reactive protein



**Figure 4**

LOWESS regression plot with interaction for the effect modification of age on the association between HOMA-IR and annual FEV1 change. Solid lines represented the univariate LOWESS regression curves according to the age group. The blue, dark blue, and light blue lines represented lines of mean age (52 years), minus one SD (43 years) and plus one SD (60 years), respectively. Abbreviations: LOWESS, locally weighted scatter-plot smoothing; HOMA-IR, homeostatic model assessment-insulin resistance; FEV1, forced expiratory volume in 1 second; SD, standard deviation

## Supplementary Files

This is a list of supplementary files associated with this preprint. [Click to download.](#)

- [KoGESbaselineCoreQuestionnaire.pdf](#)