# Gender Modifies the Effect of Body Mass Index on Lung Function Decline in Mild-to-Moderate COPD Patients: A Pooled Analysis

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# Abstract

**Background:** Body weight is a poor prognostic risk factor in patients with chronic obstructive pulmonary disease (COPD). However, it is not known whether gender modifies this relationship.

**Methods:** We pooled data of 8,686 COPD patients from 7 studies. Using a longitudinal natural cubic spline regression model, we examined the dose-response relationship between body mass index (BMI) and the rate of decline in forced expiratory volume in one second ($FEV_1$) in patients with GOLD 1 and 2 disease, stratified by gender and adjusted for smoking status and cohort effects.

**Results:** There was an inverse, nearly relationship between BMI and the rate of $FEV_1$ decline in GOLD Grades 1 and 2, which was modified by gender ($p<0.001$). In male patients, an increase of BMI by 1 $kg/m^2$ reduced $FEV_1$ decline by 1.05mL/year (95% CI: 0.96, 1.14). However, in female patients, BMI status barely clinically affected $FEV_1$ decline: an increase of baseline BMI by 1 $kg/m^2$ reduced $FEV_1$ decline by 0.16 ml/year (95% CI: 0.11, 0.21). These gender-modified relationships were generally similar between GOLD 1 and 2 patients, and between current smokers and former smokers.

**Conclusion:** In mild to moderate COPD, higher BMI was associated with a less rapid decline of $FEV_1$ in male patients whereas it hardly affected females patients. This gender-specific BMI effect was independent of COPD severity and smoking status.


# Background

Chronic obstructive pulmonary disease (COPD) is a one of the leading causes of morbidity and mortality in the world(1). According to the World Health Organization, over the next 20 years COPD will rise from the fifth to third leading cause of death worldwide(2). The progression of COPD is characterized by an accelerated decline in lung function as indicated by forced expiratory volume in one second ($FEV_1$). It is now well-recognized that cachexia is a significant risk factor for poor outcomes including mortality in COPD patients (6–8). However, while multiple studies report that those with low body mass index (BMI) may be at risk of COPD progression and those who are obese may be protected (3, 4), others have shown no significant association between BMI and $FEV_1$ decline (11, 12). One reason for the controversy is the fact that a decline in lung function varies according to certain factors, most notably, smoking, gender, and disease stage (5–7). Knowing whether BMI is a significant risk factor for COPD progression in patients with mild and moderate COPD is important, because it represents a modifiable feature for COPD patients who experience rapid disease progression. Thus, we pooled individual-level data from 7 large international studies into a single, combined dataset, and examined the dose-response relationship between BMI and the rate of $FEV_1$ decline in patients with mild and moderate COPD, across gender groups and smoking status.

# Methods

# Study design and settings

This was a pooled analysis of patient-level data from 6 randomized controlled trials (RCTs) and 1 non-interventional prospective study. The RCTs were part of the Inhaled Steroids Effect Evaluation in COPD study

(ISEEC) (5) and included the Lung Health Study (LHS, n = 5 594 patients, 11 years of follow-up)(6) and the European Respiratory Society study on COPD (EUROSCOP, n = 1 039 patients, 3 years of follow-up)(7), Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE, n = 591 patients, 3 years of follow-up)(8), Copenhagen City Lung Study (CCLS, n = 225 patients, 3 years)(9), studies by Calverley et al (n = 336 patients, 12 months of follow-up)(10) and the study by Szafranski et al (n = 292 patients, 12 months of follow-up)(11). We additionally included data from a non-RCT, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study(12), which was a 3-year non-interventional study of 2 652 patients with stable COPD from 46 centers across 12 countries(13). By pooling data from these 7 cohorts, the final study sample included patients with mild and moderate COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity grades at baseline (GOLD Grade 1, $FEV_1 \geq 80$percent of predicted at 25 years of age, mild COPD; Grade 2, $FEV_1$ 50–79percent predicted, moderate COPD), who had a valid measurement of BMI ($\geq 10$ kg/$m^2$) at baseline, 3 or more measurements of $FEV_1$ across 3 or more different time points, which enabled a stable estimate of the $FEV_1$ decline slope. Of note, spirometry measurements were consistent across the ISEEC trials and ECLIPSE. Because the provision of inhaled corticosteroids (ICS) did not affect $FEV_1$ decline over time (5), the treatment intervention was not a confounder in this study. Thus, we included patients from both the treatment and placebo arms of the RCTs.

# Study variables

The primary outcome was the change in the absolute value of post-bronchodilator $FEV_1$ over time, which was assessed in all included studies through standardized spirometry measurements as described previously(5). Due to the potential difficulty in result interpretation, this study did not analyze the percent predicted $FEV_1$ value, because it was already influenced by height, and the latter was a key component of BMI.

The primary exposure, BMI at the baseline visit, was expressed as a continuous variable, and was obtained by dividing patient's weight (in kilograms) by height squared ($m^2$). We also examined the effects of gender (male, female) and their 2-way interaction effects with BMI, controlling for the confounding effect of cigarette smoking. The analyses were focused on GOLD Grades 1 and 2. For parsimony, we combined GOLD Grades 1 and 2 into one group because their $FEV_1$ decline rates were similar (see Supplementary Material –Table S1 and Figure S1–2 for the observed rate of $FEV_1$ decline between GOLD Grades 1 and 2). We excluded patients in GOLD Grades 3 and 4 because they demonstrated different $FEV_1$ trajectories over time compared with GOLD 1 and 2 patients (Table S1).

As there could be significant between-study heterogeneity in the distribution of risk factors, study design, laboratory protocols, and enrollment period across the individual studies, we included relevant patient-level covariates in the model. This included baseline age as a continuous variable, follow-up years, and a categorical variable indicating cohort membership to account for other unobserved between-study heterogeneity.

# Statistical analysis

All analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC, United States). Detailed descriptions of the statistical methods are provided in Supplementary Material – Sect. 1. Briefly, we first determined the unadjusted relationship between BMI and the rate of $FEV_1$ decline using a scatter plot, in which we fitted a linear mixed-effects model with two predictors: a random intercept (corresponding to baseline $FEV_1$ value) and a random slope of follow-up time (corresponding to the rate of $FEV_1$ decline). From this analysis, we obtained the

individual rate of $FEV_1$ decline, and plotted it against the individual's baseline BMI value. We then applied natural cubic spline models to evaluate the potentially non-linear relationship between BMI and the rate of $FEV_1$ decline. This longitudinal regression model of $FEV_1$ contained the following independent variables: a spline function of BMI (primary exposure in which knots were placed across every 5th percentile), age, gender, smoking status, follow-up years, cohort status, and 2nd -order and 3rd -oder interactions terms between BMI, gender, smoking status, and follow-up years. We did not include an interaction term between BMI and age because based on a preliminary variable selection process, we found that its inclusion reduced model fit. These natural cubic splines produced smooth curves, which took into account the nonlinear components of the relationship between the exposure variables and the outcome. To enable the construction of 95% confidence bands, which accounted for the longitudinal, correlated data structure, we applied 1,000 rounds of bootstrapping, which has been previously shown to efficiently handle correlated time-series data(14). Next, outcomes were derived as the covariate-adjusted dose-response curves of BMI-rate of FEV1 decline using a robust causal inference technique named the G-computation(15). The primary results are reported according to gender. In a secondary analysis, the results were further stratified by smoking status to determine the impact of smoking on the relationship between BMI and $FEV_1$ decline.

## Results

# Characteristics of the study population

This pooled analysis comprised of 8,686 COPD patients (Fig. 1, cohort selection). Table 1 presents the baseline characteristics of the study population. The mean baseline age was 51.9 years (SD = 9.1); 37% were women; and 56% were current smokers. The average BMI at baseline was 25.8 $kg/m^2$ (SD = 4.3). The median follow-up time was 2 years. A total of 3,674 (42%) patients were in GOLD Grade 1; 5,012 (58%) were in GOLD Grade 2.

Table 1
Baseline characteristics of the study population

| | Total | Calverley | CCLS | ECLIPSE | EUROSCOPE | ISOLDE | LHS | Szafranski |
|---|---|---|---|---|---|---|---|---|
| Patient, N(%) | 8,686 (100) | 90 (1.0) | 231 (2.7) | 1,500 (17.3) | 982 (11.3) | 260 (3.0) | 5,591 (64.4) | 32 (0.4) |
| Age, y (SD) | 51.9 (9.1) | 62.4 (9.4) | 58.9 (9.1) | 60.2 (9.0) | 52.5 (7.6) | 63.9 (8.0) | 48.4 (6.8) | 66.3 (8.5) |
| Women, N(%) | 3,229 (37.2) | 25 (27.8) | 94 (40.7) | 665 (44.3) | 276 (28.1) | 81 (31.2) | 2,085 (37.3) | 3 (9) |
| Current smoker, N(%) | 4,849 (55.9) | 29 (32.2) | 175 (75.8) | 426 (28.7) | 982 (100) | 126 (48.5) | 3,096 (55.4) | 15 (46.9) |
| GOLD grade, N(%) | | | | | | | | |
| 1 | 3,674 (42.3) | 12 (13.3) | 105 (45.5) | 575 (38.3) | 354 (36.0) | 9 (3.5) | 2,619 (46.8) | 0 (0) |
| 2 | 5,012 (57.7) | 78 (86.7) | 126 (54.5) | 925 (61.7) | 628 (64.0) | 251 (96.5) | 2,972 (53.2) | 32 (100) |
| $FEV_1$ | | | | | | | | |
| Absolute, Litre | 2.62 (0.73) | 1.84 (0.48) | 2.54 (0.80) | 2.35 (0.96) | 2.60 (0.62) | 1.83 (0.44) | 2.75 (0.63) | 1.62 (0.29) |
| % predicted | 77.8 (14.4) | 63.7 (13.5) | 79.6 (15.6) | 81.6 (25.6) | 74.6 (11.6) | 61.9 (8.6) | 78.4 (9.1) | 56.0 (6.0) |
| BMI, $kg/m^2$ | 25.7 (4.3) | 25.9 (5.3) | 25.5 (4.2) | 27.3 (5.4) | 24.5 (3.3) | 25.2 (4.3) | 25.5 (3.9) | 26.0 (5.3) |
| BMI category, N(%) | | | | | | | | |
| Underweight (BMI < 19.0) | 163 (1.9) | 5 (5.6) | 3 (1.3) | 30 (2.0) | 21 (2.1) | 13 (5.0) | 90 (1.6) | 1 (3.1) |
| Normal (BMI 19.1–25.0) | 3,945 (45.4) | 41 (45.6) | 118 (50.1) | 510 (34.0) | 555 (56.5) | 118 (45.4) | 2,589 (46.3) | 14 (43.8) |

BMI, body mass index, CCLS, City Lung Study, ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Study, EUROSCOPE, European Respiratory Society study on COPD, GOLD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric grades, ISOLDE, Inhaled Steroids in Obstructive Lung Disease in Europe, LHS, Lung Health Study, mo, moth, N, number, SD, standard deviation, y, year.

| | Total | Calverley | CCLS | ECLIPSE | EUROSCOPE | ISOLDE | LHS | Szafranski |
|---|---|---|---|---|---|---|---|---|
| Overweight (BMI 25.1–30.0) | 3,340 (38.5) | 27 (30.0) | 71 (30.7) | 589 (39.3) | 354 (30.0) | 93 (35.8) | 2,194 (39.2) | 12 (37.5) |
| Obese (BMI > 30.1) | 1,238 (14.3) | 17 (18.9) | 39 (16.9) | 371 (24.7) | 52 (5.3) | 36 (13.8) | 718 (12.8) | 5 (15.6) |
| Follow-up, mo | 36 (median) | | | | | | | |

BMI, body mass index, CCLS, City Lung Study, ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints Study, EUROSCOPE, European Respiratory Society study on COPD, GOLD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric grades, ISOLDE, Inhaled Steroids in Obstructive Lung Disease in Europe, LHS, Lung Health Study, mo, moth, N, number, SD, standard deviation, y, year.

Table 2 presents the gender-specific baseline characteristics and the observed rate of $FEV_1$ decline of the combined GOLD Grades 1 and 2 samples. Male patients experienced a significantly faster decline in absolute $FEV_1$ values compared to female patients (mL/year, -36.6 vs -29.2, p-value < 0.001). Male and female patients had similar mean ages (51.8 vs. 51.9 years) and proportionality of current smokers (54% vs. 57%). However, the majority of males had normal body weight (58% of BMI between 19.1 and 25.0), whereas the majority of females were more likely to be overweight or obese (60% of had a BMI above 25.1). Supplemental Material Table S2 further shows the observed decline of $FEV_1$ by smoking status and BMI level. Current smokers had a much more rapid decline than ex-smokers (mL/year, -40.9 vs -24.9), while obese individuals (BMI $\geq$ 30 kg/$m^2$) had a slower rate of decline than those who were overweight (BMI 25–30 kg/$m^2$), normal (BMI 19–25 kg/$m^2$) or underweight (BMI < 19 kg/$m^2$) (mL/year, -27.5 vs -34.4, -35.3, -34.6, respectively).

Table 2
Observed rate of $FEV_1$ decline according to GOLD subgroups, gender, smoking status and BMI category.

| | GOLD Grades 1 and 2 | | |
|---|---|---|---|
| | Male (N = 5,457) | Female (N = 3,229) | p-value* |
| Rate of $FEV_1$ decline, mean (95% CI), *mL/year* | -36.6 (-37.6, -35.6) | -29.2 (-30.2, -28.1) | p < 0.001 |
| Age, y, mean (SD) | 51.8 (8.8) | 51.9 (9.3) | p = 0.51 |
| BMI, $kg/m^2$, mean(SD) | 26.3 (3.9) | 24.8 (4.7) | p < 0.001 |
| BMI category, n(%) | | | |
| *Underweight (BMI < 19.0)* | 109 (3.4) | 54 (1.0) | p < 0.001 |
| *Normal (BMI 19.1–25.0)* | 1,863 (57.7) | 2,082 (38.2) | |
| *Overweight (BMI 25.1–30.0)* | 863 (26.7) | 2,477 (45.4) | |
| *Obese (BMI > 30.1)* | 394 (12.2) | 844 (15.5) | |
| Smoking status, n(%) | | | |
| *Ex-smoker* | 1,472 (45.7) | 2,350 (43.1) | p = 0.02 |
| *Current smoker* | 1,750 (54.3) | 3,099 (56.9) | |

BMI, body mass index, GOLD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric grades, N, number, SD, standard deviation.

*p-values were obtained from t test for continuous variables and chi-square test for categorical variables.

# Gender-modified the non-linear effects of BMI on the rate of $FEV_1$ decline

Figures 2 illustrates the fitted dose-response relationship between BMI (x-axis) and the rate of decline in absolute $FEV_1$values (y-axis, with confidence intervals shown in error bars) in combined GOLD Grades 1 and 2. The confidence interval of the curve was wider at both ends of the BMI scale, suggesting that the dose-response relationship have greater variance at the more extreme BMI values.

Gender significantly modified the relationship between BMI and $FEV_1$ decline($p < 0.001$). In male patients, the dose-response curve depicted a reverse association between BMI and rate of decline in absolute $FEV_1$ values. This relationship was mostly linear, except for a negligible fluctuation in the line at BMI of 25 $kg/m^2$ (Figs. 2). The slope of this nearly linear curve showed that, an increase of BMI by 1 $kg/m^2$ reduced $FEV_1$ decline by approximately 1.05 mL/year (95% CI: 0.96, 1.14). In female patients, although the dose-response curve still depicted a nearly linear association between BMI and rate of $FEV_1$ decline, the slope of the curve showed that BMI

had a very small (and clinically insignificant) effect: An increase of BMI of 1 kg/$m^2$ reduced $FEV_1$ decline by only 0.16 ml/year (95% CI: 0.11, 0.21).

In a secondary analysis, the effects of BMI were stratified by GOLD Grades and smoking status (Fig. 3, upper panel, male patients [left, GOLD 1; right, GOLD 2], lower panel, female patients [left, GOLD 1, right, GOLD 2]). The dose-response curves of BMI on $FEV_1$ decline were similar between GOLD Grades 1 and 2 for both males and females, and were generally in parallel between current smokers and ex-smokers within GOLD Grades and gender, despite that statistically they were different ($p < 0.001$). This suggests that, conditional on COPD severity and gender, the additional impact of smoking on the relationship between BMI and $FEV_1$ decline was small (though statistically significant). Of note, the highest risk of decline was observed in underweight male smokers with GOLD 1 disease, who experienced, on average > 70 ml/year decline in FEV1 (Fig. 3).

# Discussion

In a large pooled analysis of seven multinational prospective studies, we showed that the relationship between BMI and $FEV_1$ decline in mild to moderate COPD was significantly modified by gender. In females, BMI had no material impact on $FEV_1$ decline; whereas in males, a 1 kg/$m^2$ increase in BMI was associated with a reduction of approximately 1 mL/year in the rate of decline in absolute $FEV_1$ values. Of note, underweight male current smokers in GOLD 1 were at highest risk of disease progression. We did not include percent of predicted $FEV_1$ as an outcome given that it was derived from height.

Previous studies have largely focused on effects of smoking as a risk factor for COPD disease progression. Consistent with previous findings, we found that smokers experienced over 10 mL/year faster decline in $FEV_1$ compared with sustained quitters (16). Our findings are also consistent with a recent observation that female smokers are at increased risk of COPD compared to male smokers(17). We extend these previous findings in this large pooled analysis by showing that BMI significantly impacts $FEV_1$ decline in males but has no or only a minimal effect in females with mild to moderate COPD. For example, the annual decline of $FEV_1$ was at least 6 mL/year faster in underweight (BMI < 19 kg/$m^2$) male patients than those who were overweight (BMI ≥ 25 kg/$m^2$).

The mechanisms by which BMI modifies $FEV_1$ decline have not been fully elucidated. High BMI may represent better nutrition status(18), increased body fat, muscle mass, and/or bone mineral density(19), while lower BMI may indicate poor nutrition and skeletal muscle loss that leads to accelerated lung function loss (20). BMI may also be a biomarker for smoking intensity as heavy smokers tend to have lower BMI than those who smoke intermittently. In addition, emphysema might have also played a role, because emphysema is strongly associated with reduced BMI(21), and is also more common in male patients, especially among those with mild or moderate disease(22). Due to concerns regarding reverse causality, we were unable to study the effects of dynamic changes in BMI (i.e., increased lung burden caused weight loss). Notwithstanding these important mechanistic issues, BMI is easy to measure, accurate and reproducible. As such, BMI may be used clinically to identify COPD patients (particularly males) at risk for rapid disease progression.

A major strength of this analysis was that it pooled individual-level data from seven high-quality long-term studies, which reduced heterogeneity and yielded more reliable results than the previously reported meta-

analysis(23). The inclusion of ECLIPSE, a real-world prospective cohort, added to the external validity and generalisability of results. Another strength was the use of a robust and powerful statistical approach, which adapted longitudinal analyses to principles of restricted cubic splines. This enabled us to extend measures of static, cross-sectional dose-response relationship to more pragmatic metrics representing the impact of BMI on the progression of COPD (ie., the rate of $FEV_1$ decline). Importantly, our analyses were stratified by gender and adjusted for various confounders including GOLD grades of severity, cohort and calendar effects, smoking status and its interactions with BMI. This enabled us to tease out the differential effects of BMI between gender, which were not well known previously.

Our findings need to be interpreted within the context of certain limitations. First, BMI is an approximate measure for nutritional status, because it is unable to distinguish between fat and fat-free mass or its distribution. Future studies should consider other anthropometric measurements in female patients with mild to moderate COPD and investigate the potential roles of muscle and fat mass in the gender-specific progression of COPD. Second, we assessed BMI at baseline and weight may change dynamically over time. This was not necessarily a limitation, because this “intention-to-treat” approach protects against reverse causality and provides more valid inference to our research question. Third, this analysis could not adjust for unrecorded potential confounders such as comorbidities and exacerbations. However, while the comorbidities of low BMI COPD patients are different from those of patients with a high BMI(24), the direct impact of comorbidities on lung function decline is largely unknown.

# Conclusion

We conclude that reduced BMI is a significant risk factor for accelerated decline in lung function but is modified by gender. Underweight male smokers with GOLD 1 disease are at the highest risk of rapid COPD progression and thus should be followed closely and be strongly counseled for smoking cessation.

# Declarations

**Ethics approval and consent to participate:** Not applicable

**Availability of data and materials:** The data that support the findings of this pooled study are available from the individual trials, including CCLS, ECLIPSE , EUROSCOP, ISOLDE, LHS, and studies conducted by Calverley et al, Szafranski et al, , but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of these trials.

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

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**Author’s contributions:** DS, MS, WC and JMF conceived and designed the study. DS contributed to acquisition of data, WC contributed to quality assessment. WC cleaned the data, designed and carried out the statistical analysis, and wrote the first draft of the manuscript. MS contributed to the design of statistical analysis. DS, JMF

provided clinical insights into data interpretation. WC and DS had full access to the data in the study, and takes responsibility for the integrity of the data and the accuracy of the analyses. All authors contributed to critical revision of the paper for important intellectual content and approval of the final version to be published.

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# Figures

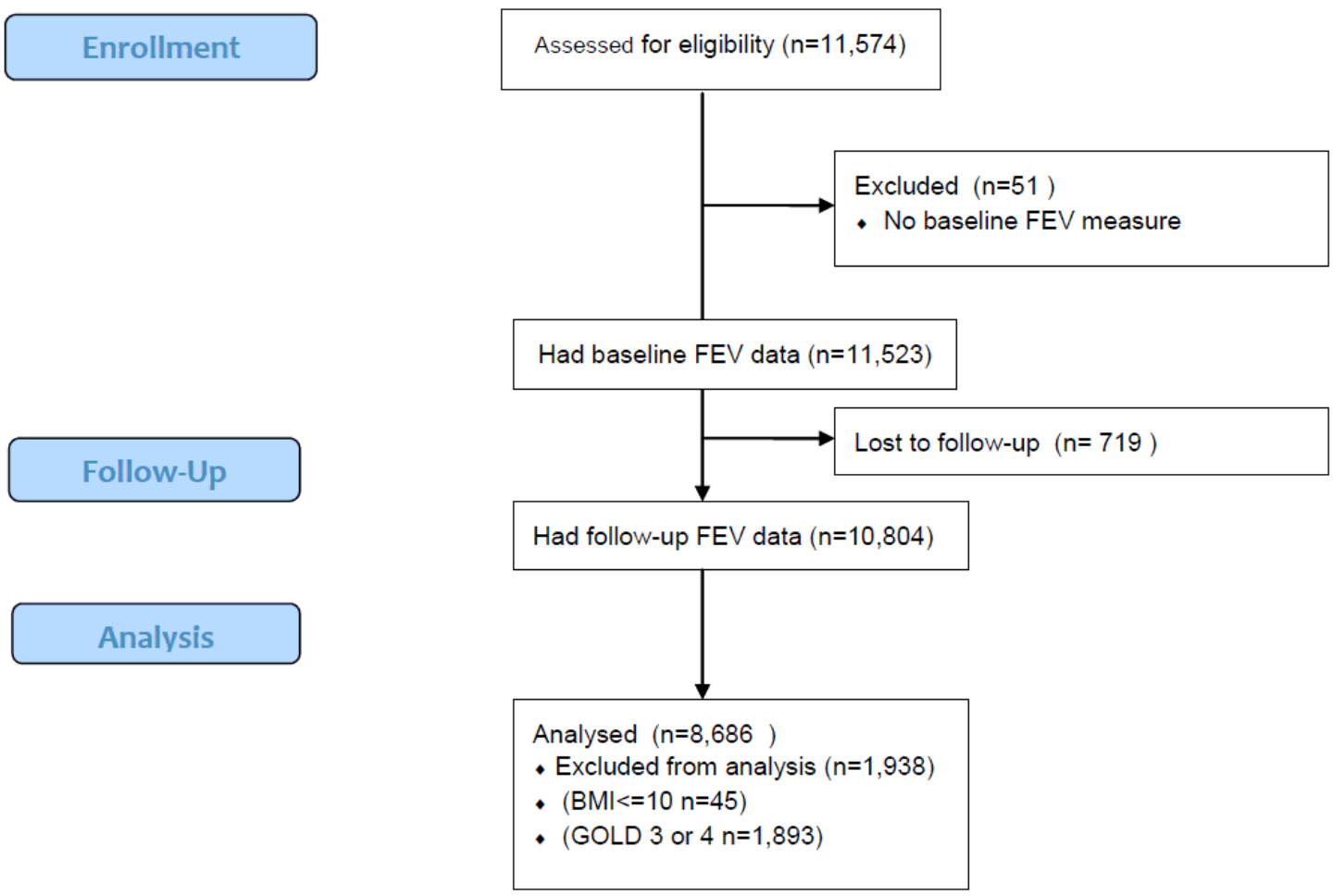


**Figure 1**

Flowchart of cohort selection.

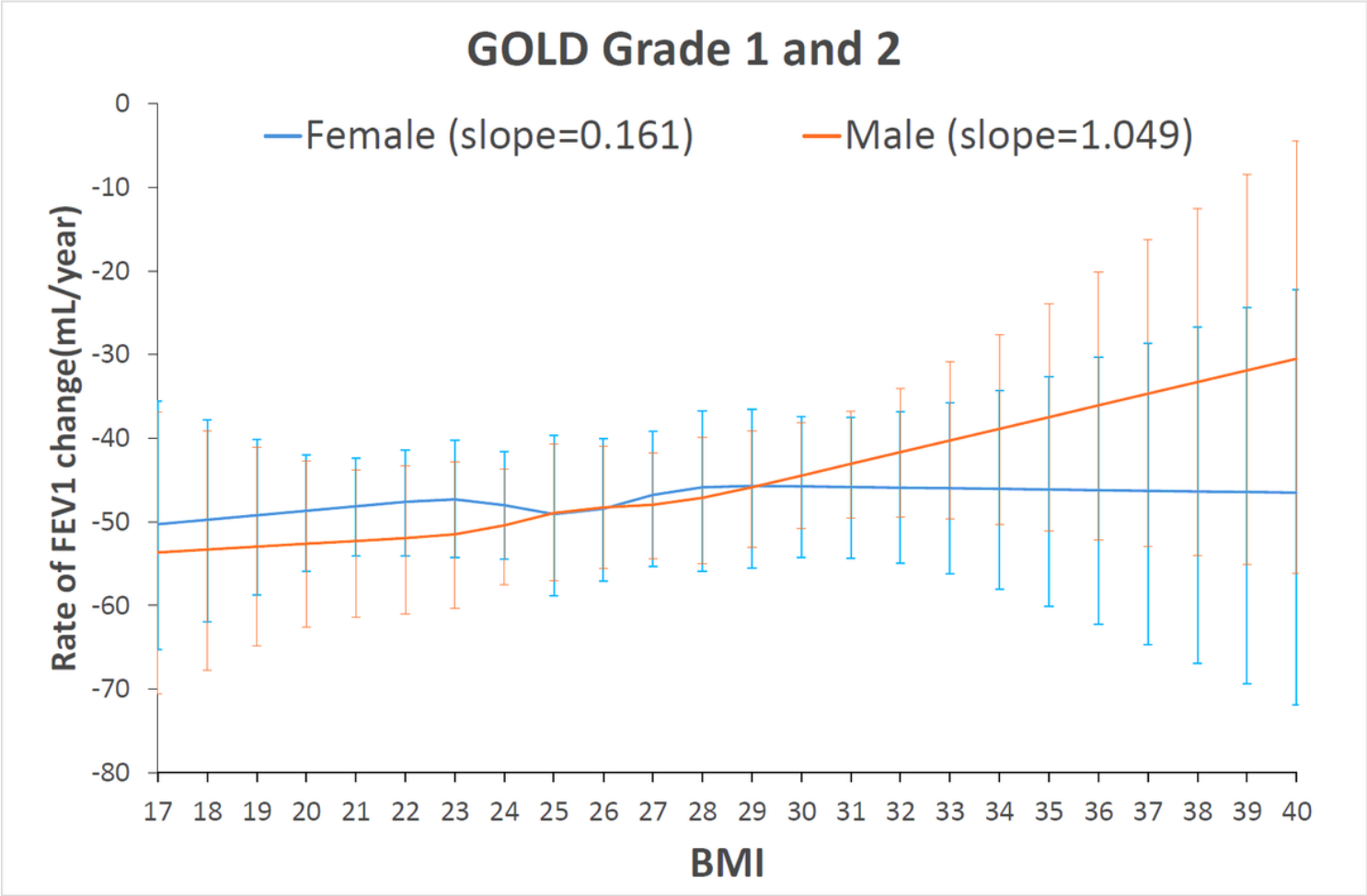


**Figure 2**

Estimated association between BMI and rate of FEV1 decline in absolute values (mL/year).

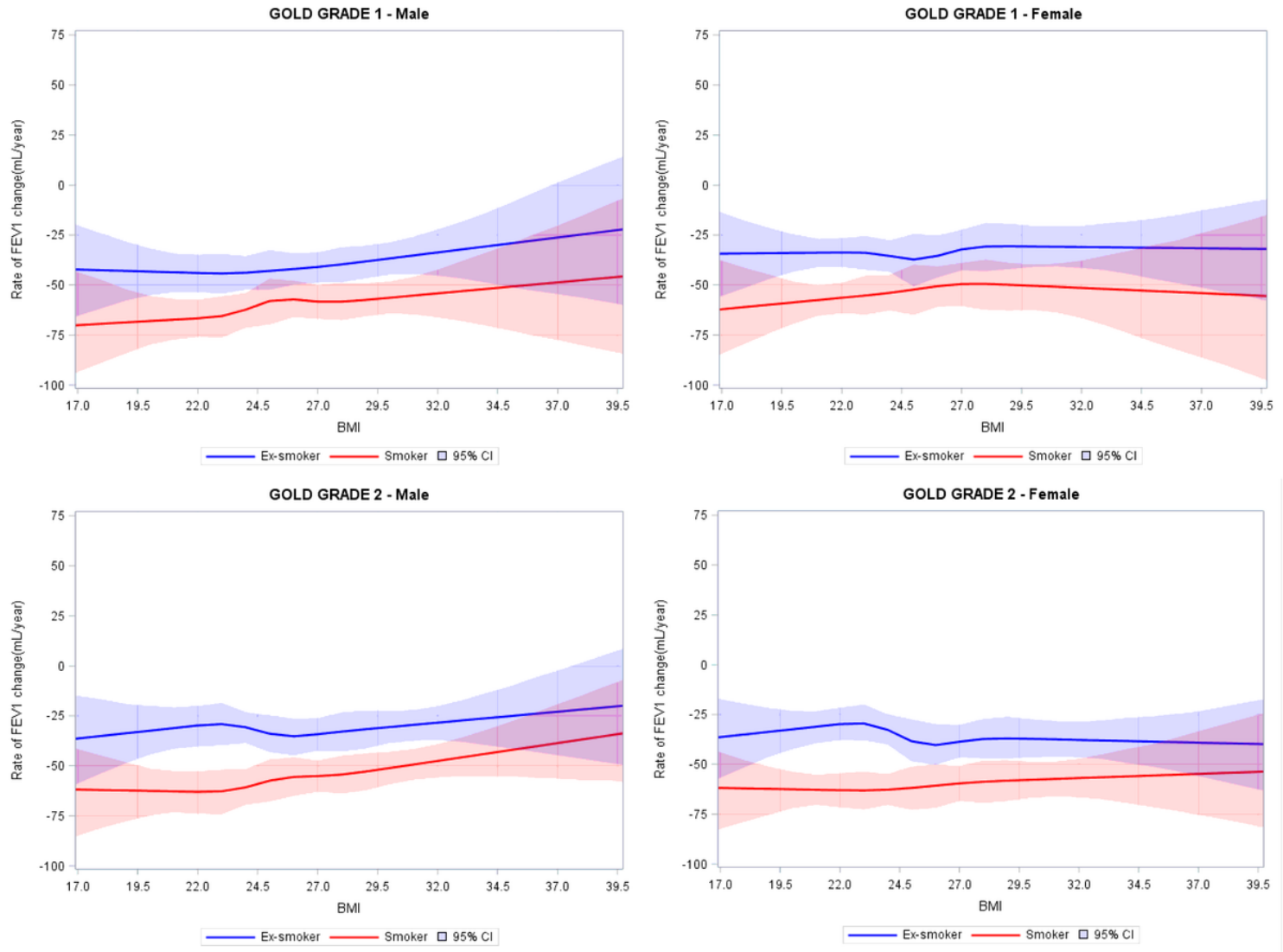


**Figure 3**

Association between BMI and rate of FEV1 decline across GOLD grades, gender, and smoking status.

# Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementarymaterialRR.docx