Spirometry and Health Status Worsen with Weight Gain in Obese Smokers but Improve in Normal-Weight Smokers

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Abstract

Rationale: The literature on the effect of obesity and weight gain on respiratory outcomes in smokers is contradictory.

Objective: To examine the cross-sectional effect of body mass index (BMI) and the longitudinal effect of change in BMI upon spirometry and health status among smokers at risk for and with milder chronic obstructive pulmonary disease (COPD).

Methods: Participants from the Lovelace Smokers' Cohort were followed for a median period of 6 years, 75% of whom were at risk and 25% of whom had COPD at baseline examination. BMI and gain in BMI were examined as continuous independent variables overall and after stratification into three categories (normal-weight, overweight, and obese) determined on the basis of baseline weight. Spirometry and health status (as assessed by St. George Respiratory Questionnaire total and subscale scores) were dependent variables. Covariates included age, sex, ethnicity, pack-years of smoking, and current smoking status. Cross-sectional analysis used linear and logistic regression; longitudinal analysis used a mixed model approach.

Measurements and Main Results: In cross-sectional analyses, higher BMI was associated with worse health status among obese smokers but with better health status among normal-weight smokers. In longitudinal analyses, weight gain was associated with a decrease in

FEV₁ and health status among obese smokers and with an increase in these outcomes among normal-weight smokers.

Conclusions: Weight gain affects respiratory outcomes differently between obese and normal-weight smokers. Whereas FEV₁ and health status decrease with weight gain among obese smokers, they improve among normal-weight smokers. The nonlinear relationship between weight gain and respiratory outcomes suggests that this effect of excess weight is unlikely to be mechanical alone.

At a Glance Commentary

Scientific Knowledge on the Subject: The effect of weight as well as gain in weight upon spirometry and health status among smokers at risk for and with milder chronic obstructive pulmonary disease has not been adequately studied. The limited literature in this field has contradictory findings.

What This Study Adds to the Field: Weight gain affects respiratory outcomes differently between obese and normal-weight smokers. Spirometric function and health status decrease with weight gain among obese smokers but improve among normal-weight smokers. The nonlinear relationship between weight gain and respiratory outcomes suggests that this effect of excess weight is unlikely to be mechanical alone.

The worldwide prevalence of obesity has more than doubled between 1980 and 2008 (1). During the period 2009–2010, more

than one-third of American adults were obese, and the prevalence was even higher among women (2). Excess weight was likely

responsible for about 18% of all adult deaths in the United States between 1986 and 2006; this rate was higher for women

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than for men (3, 4). Obesity evokes systemic inflammatory processes and oxidative stress, both of which are aggravated by cigarette smoking (5). Additionally, obesity and cigarette smoking increase airway inflammation and oxidant stress (6–8). Therefore, it seems plausible that obesity should be particularly detrimental for airway disease among smokers. Yet, the current literature on the effect of obesity or gain in weight on respiratory outcomes in subjects at risk for or having smoking-related lung disease is contradictory (9–14). Although ever-smokers constitute 41.4% of the United States population (15), the effect of obesity on respiratory outcomes among smokers has been inadequately studied. Our study objective was to examine the cross-sectional effect of obesity and the longitudinal effect of weight gain on respiratory outcomes among smokers at risk for or having milder chronic obstructive pulmonary disease (COPD) with a view toward prevention strategies. Given our study objective and the findings from the Copenhagen Heart Study (11), we excluded patients with advanced COPD because they already show a linear inverse relationship of outcomes on body mass index (BMI). We hypothesized that the relationships between obesity and weight gain on spirometry and health status among smokers at risk for or having milder COPD were nonlinear, with opposing effects at the opposite ends of the BMI spectrum.

Methods

Study Population

Our study population was drawn from eligible participants, primarily women, from a dynamic cohort of current and former smokers in New Mexico (Lovelace Smokers' Cohort) recruited since March 2001 with a median follow-up period of 6 years. The Lovelace Smokers' Cohort disproportionately enrolled women ever-smokers to study the susceptibility to the development of smoking-related lung diseases because women are underrepresented in most such studies in the United States (16). The catchment area for this cohort is Albuquerque, New Mexico and its surrounding communities, comprising a diverse population of approximately 700,000 persons. Most participants were recruited through newspaper or television advertisements and were paid a small stipend for their

participation. At initial examination visit and on regular follow-up examination visits that occurred at 18-month intervals, subjects underwent questionnaires, phlebotomy, anthropometry, and spirometry by trained study personnel, as published previously (17, 18). BMI was calculated using standard methods.

Inclusion and Exclusion Criteria

Participants were included if they were 40 to 75 years of age and if they were former or current smokers with ≥ 20 pack-years of smoking history at baseline examination. Subjects with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 4 COPD (FEV_1/FVC ratio $< 70\%$ and $FEV_1 < 30\%$ of the ethnicity-specific predicted values) or with self-reported history of asthma at baseline examination were excluded. We excluded patients with advanced COPD on the basis of the findings from the Copenhagen Heart Study (11) that show a linear inverse relationship of outcomes on BMI in this population. On the other hand, we were interested in exploring nonlinear relationships in individuals at risk for or with milder disease with a view toward future prevention strategies. We excluded subjects with GOLD stage 4 COPD also because of their very small numbers in our study ($n = 12$). Subjects with asthma were excluded because obesity/weight gain is an established risk factor for asthma prevalence, incidence, and disease severity (19–25).

Questionnaires

Demographic information, including age, smoking history, environmental exposure history, and history of respiratory disease, was obtained using the adult American Thoracic Society (ATS)-DLD-78 questionnaire (26). The St. George's Respiratory Questionnaire (SGRQ) was used to evaluate respiratory health status, with higher scores indicating worse health status (27). The SGRQ consists of a total score and scores on three subscales of the impact of disease, activity limitation, and symptoms. A difference of four points on the total SGRQ score indicates a clinically meaningful difference (28). Although this questionnaire was originally developed for use in subjects with COPD, it has been successfully used to study smokers without COPD (29–32).

Spirometry

Trained registered respiratory therapists administered all spirometry tests using the Vmax Encore 22 (Viasys Respiratory Care, Yorba Linda, CA) or the KoKo (Ferraris Respiratory, Louisville, CO) spirometers that met the ATS guidelines (33). Therapists were monitored and recertified periodically per the standardized laboratory proficiency device testing plan. Devices were calibrated daily and verified on three different injection speeds (33). Pre- and postbronchodilator spirometry were obtained on all subjects (33). Postbronchodilator spirometry was obtained after the administration of two inhalations of albuterol (90 $\mu\text{g}/\text{spray}$ via metered dose inhaler) via a Lite Aire, dual valve spacer (Thayer Medical Corporation, Tucson, AZ). Tests meeting the ATS criteria (33) were used in the final analysis.

Independent (Predictor) Variable

For the cross-sectional analysis, baseline BMI was examined as a continuous independent variable overall and after stratification into the following three baseline weight categories: normal-weight ($\text{BMI} < 25 \text{ kg}/\text{m}^2$), overweight ($\text{BMI} 25$ to $< 30 \text{ kg}/\text{m}^2$), and obese ($\text{BMI} \geq 30 \text{ kg}/\text{m}^2$). For the longitudinal analysis, change in BMI was examined as a continuous independent variable overall and after stratification into the three baseline weight categories. Fourteen underweight smokers ($\text{BMI} < 18.5 \text{ kg}/\text{m}^2$) were included in the normal weight category; their exclusion in a subsequent sensitivity analysis did not change the results of the study.

Dependent (Outcome) Variable

Two sets of dependent variables were studied. These included baseline spirometry and health status for the cross-sectional analysis. Spirometry measures included absolute postbronchodilator values of FVC, FEV_1 , FEV_1/FVC percent ratio, and forced midexpiratory flow rate ($FEF_{25-75\%}$). Baseline health status was assessed by SGRQ total score and disease impact, activity limitation, and symptom subscales. Time-dependent changes in these variables were studied as dependent variables for the longitudinal analysis.

Statistical Approach

Summary statistics, including means, SD, and SE, were obtained for continuous

variables, and proportions were obtained for categorical variables. Cross-sectional analyses used logistic and linear regression techniques for categorical and continuous dependent variables, respectively. Longitudinal analysis used mixed model analyses for continuous and categorical variables. The analyses were performed overall and after stratification into the three baseline weight categories. All statistical analyses were done using the Statistical Analysis Software package version 9.3 (SAS, Cary, NC). A two-sided *P* value of <0.05 was considered statistically significant.

Covariates

Covariates included self-reported age, sex, Hispanic ethnicity, pack-years of smoking, and current smoking status. Age and smoking variables were included as time-varying covariates in the longitudinal mixed model analysis. Height was not included as a covariate because its square term was included in the definition of BMI. Socioeconomic status was studied initially as a covariate but was dropped from final analytic run to retain a more parsimonious statistical model. Formal tests of interaction between independent variables and extreme categories of baseline weight on dependent variables were also performed.

Institutional Review Board Approval

This study was approved by the Western Institutional Review Board (Olympia, WA), and all subjects gave informed consent for their participation.

Results

Of the 1,641 eligible smokers studied over a median follow-up duration of 6 years, 36, 36, and 28% were normal-weight, overweight, and obese at baseline examination visit, respectively. Although 35, 23, and 17% of smokers in the normal-weight, overweight, and obese categories, respectively, had spirometry-defined COPD, the remainder was considered at risk for COPD. Of the 417 subjects with COPD overall, 175 subjects were in GOLD stage 1, 211 subjects were in GOLD stage 2, and 31 subjects were in GOLD stage 3 disease. The mean weight gain in this cohort was -0.1 ± 4.1 lb per year, suggesting that there was nearly equal distribution of weight gain and loss in this population.

This is consistent with the expected BMI change in this age group (34).

Obese smokers were more likely to be hypertensive or diabetic at baseline examination than other smokers (Table 1). Consistent with their lower prevalence of spirometry-defined COPD, obese smokers had higher values of FEV₁/FVC but lower FVC percent predicted values than other smokers, and obese smokers had higher SGRQ total and higher subscale scores (i.e., worse health status) than other smokers. Although obese smokers were more likely to report shortness of breath and tended to wheeze more frequently, they were not different from their counterparts in other BMI categories regarding the prevalence of cough, excess phlegm production, or chronic bronchitis.

In a multivariable, cross-sectional analysis, higher BMI at baseline was associated with significantly worse health status (i.e., greater SGRQ total and subscale scores) among obese smokers. On the other hand, higher BMI was associated with significantly better health status among normal-weight smokers (Table 2). This suggested a U-shaped association of health status on BMI between the extreme categories of weight (*P* values for interaction tests between BMI and extreme categories of weight on health status measures were <0.001 for all analyses) (Table 2). Similarly, an inverted U-shaped association was suggested for spirometric function on BMI across the extreme weight categories. Generally speaking, the cross-sectional associations of health status or of spirometric function on BMI among the middle category of overweight smokers were similar to those seen among obese smokers (Table 2).

In a univariate longitudinal analysis, gain in weight was associated with a decline in FVC, FEV₁, and FEF_{25–75%} values among smokers who were obese at baseline (Table 3). On the contrary, these spirometric parameters increased with weight gain among smokers who were normal-weight at baseline. FEV₁/FVC increased with weight gain in all categories of smokers, but the increase did not reach significance among smokers who were obese at baseline. Gain in weight was also associated with a worsening of health status (i.e., increases in SGRQ total and subscale scores) among smokers who were obese at baseline, but an improvement in health status was seen among smokers who were

in the normal-weight category at baseline. The *P* values for interaction tests between gain in BMI and extreme weight categories at baseline on longitudinal change in these parameters were significant (≤ 0.001). Generally speaking, the longitudinal associations of change in health status or of spirometric function on gain in BMI among the middle category of smokers who were overweight at baseline were similar to those seen among normal-weight smokers (Table 3).

When adjusted for covariates in a multivariable analysis, the results largely remained unchanged. The longitudinal association between gain in weight and changes in FVC or FEF_{25–75%} in normal-weight smokers lost statistical significance, but the interaction results remained significant (Table 4). This confirms that the differences seen between the extreme BMI categories regarding longitudinal changes in respiratory outcomes were not explained by smoking behavior or the apparently different ethnic distribution.

Discussion

Baseline weight and longitudinal gain in weight affect respiratory outcomes differently between obese and normal-weight smokers at risk for or having early COPD. Weight gain may worsen spirometric function and health status among baseline obese smokers but may improve FEV₁ and health status among baseline normal-weight smokers. This nonlinear relationship of change in respiratory outcomes on gain in BMI among smokers at risk for or with milder COPD suggests that the effect of weight is unlikely to be a linear mechanical effect but may involve regulated inflammatory mechanisms.

Smokers develop chronic bronchitis and/or emphysema, but these two traditional phenotypes of COPD are not always easily distinguishable (35). Although obesity is typically described as seen with chronic bronchitis, emphysema is typically associated with a low BMI value (36–38). In our study population, chronic bronchitis was not differentially prevalent among obese smokers. One possible explanation is that the association of obesity with chronic bronchitis originates from studies of male smokers and may not adequately reflect

Table 1: Univariate Analysis of the Cross-Sectional Association between Body Mass Index Category and Characteristics Measured at Baseline Examination

Characteristics	All Smokers (n = 1,641)	Normal-Weight Smokers* (n = 586)	Overweight Smokers (n = 595)	Obese Smokers (n = 460)	P Value across Three BMI Categories†
Demographic characteristics					
Women	73.4‡	77.0	69.4	74.1	0.19
Age, yr	55.6 ± 9.4	55.4 ± 9.5	56.3 ± 9.6	55.9 ± 9.0	0.31
Hispanic ethnicity	16.9	13.0	19.3	18.9	0.006 ^{a,c}
Smoking pack-years	40.8 ± 20.1	40.8 ± 20.6	41.0 ± 21.1	40.5 ± 18.3	0.88
BMI, kg/m ²	27.8 ± 6.0	22.2 ± 1.9	27.4 ± 1.4	35.3 ± 5.0	NA
Annual weight gain, lb	−0.1 ± 4.1	0.5 ± 2.7	−0.3 ± 3.2	−0.6 ± 6.0	<0.001 ^{a,c}
History of hypertension	32.5	23.9	31.9	44.3	<0.001 ^{a,b,c}
History of diabetes mellitus	7.7	4.4	5.9	14.1	<0.001 ^{b,c}
COPD [§]	25.4	34.5	23.0	17.0	<0.001 ^{a,b,c}
History of chronic bronchitis	30.0	29.2	32.4	27.8	0.77
Spirometry					
FVC, % predicted¶	94.3 ± 14.4	96.2 ± 14.8	95.3 ± 14.5	90.6 ± 13.1	<0.001 ^{b,c}
FEV ₁ , % predicted¶	89.2 ± 16.6	88.1 ± 17.9	90.5 ± 16.2	89.0 ± 15.1	0.31
FEV ₁ /FVC percent ratio	73.9 ± 9.4	71.6 ± 10.5	74.2 ± 8.9	76.6 ± 7.5	<0.001 ^{a,b,c}
Bronchodilator reversibility	20.3	20.8	19.0	21.3	0.93
Health status					
SGRQ total score**	19.3 ± 16.0	16.8 ± 14.8	18.7 ± 16.0	23.4 ± 16.6	<0.001 ^{a,b,c}
SGRQ symptom score**	28.5 ± 22.0	26.9 ± 20.9	28.8 ± 22.7	30.2 ± 22.4	0.02 ^c
SGRQ impact score**	9.9 ± 12.4	8.4 ± 11.4	9.5 ± 12.3	12.1 ± 13.6	<0.001 ^{b,c}
SGRQ activity score**	28.8 ± 23.4	23.8 ± 21.4	27.2 ± 23.2	37.4 ± 23.9	<0.001 ^{a,b,c}
Cough**	49.7	51.4	49.9	47.3	0.20
Phlegm**	42.2	42.4	44.5	38.9	0.33
Shortness of breath**	27.1	23.6	24.5	34.7	<0.001 ^{b,c}
Wheeze**	11.5	9.7	12.0	13.2	0.07

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; NA = not available; SGRQ = St. George's Respiratory Questionnaire.

Note 1: Exclusion criteria: COPD GOLD stage 4 and those with history of asthma. Inclusion criteria: ≥20 pack-years of smoking and age 40–75 yr.

Note 2: Data from individuals with COPD only (including stage 4 COPD) are presented in Table E3.

**Normal-weight" was defined as BMI 18.5 to <25, "overweight" was defined as BMI 25 to <30, and "obese" was defined as ≥30 kg/m². Fourteen underweight smokers with BMI < 18.5 kg/m² were included in the normal-weight category.

†P values for frequencies of categorical variables were based on the Jonckheere-Terpstra test of ordered alternatives and for means of continuous variables were based on multivariate ANOVA. Post hoc testing was performed when P values across three BMI categories were significant using Fisher's least significant difference method, and significant differences (P < 0.05) are shown in the last column as follows: a = difference between normal-weight and overweight, b = difference between overweight and obese, and c = difference between normal-weight and obese.

‡Values are % mean ± SD.

§COPD was defined by an absolute postbronchodilator value of FEV₁/FVC < 70%. Of the 417 subjects with COPD included in this analysis, 175, 211, and 31 subjects had stage 1, 2, and 3 disease, respectively.

||Chronic bronchitis was defined as the presence of at least two of the following three criteria: (1) doctor diagnosis of chronic bronchitis, (2) phlegm production over the previous 4 wk, and (3) phlegm production for most days for at least three consecutive months during the year.

¶Percent predicted values are based on the NHANES-III reference values by Hankinson and colleagues (49).

**These data were obtained from the SGRQ, including its component activity, impact, and symptom subscales or from its individual items that were coded for presence or absence.

population studies of primarily female smokers who have different prevalence rates of chronic bronchitis and obesity than men (39). Furthermore, in our study, smokers with spirometry-defined COPD were overall less likely to be obese than those without (18.7% vs. 31.2%, respectively; *P* < 0.001). Although our finding among smokers is consistent with the existing literature (36–38), a recent Canadian national survey including smokers and nonsmokers demonstrated the opposite: subjects who self-reported a diagnosis of COPD (including chronic bronchitis and/or emphysema) were more

likely to be obese than the general population who did not report that diagnosis (40). Given that self-report is considered a valid marker of COPD in epidemiologic studies (41), it is possible that the natural history of COPD is changing in the face of the obesity epidemic.

Most epidemiological data suggest that overweight or obese smokers are "protected" from developing airflow obstruction (9–11, 42). This may be a tautology because weight gain raises the FEV₁/FVC ratio, and airflow obstruction is defined by a low ratio. It is possible that

weight gain primarily affects small airways by causing edema, inflammation, and closure and that the FEV₁/FVC ratio increases due to consequent air-trapping (43). Our study demonstrates that this increase in FEV₁/FVC ratio due to weight gain occurs primarily among normal-weight or overweight smokers. Patients already obese at baseline show only a modest increment in their FEV₁/FVC ratio with further weight gain (Tables 3 and 4).

Potential reasons why obesity has been associated with better respiratory outcomes in some epidemiological studies include

Table 2: Multivariable Analysis of the Cross-Sectional Associations of Respiratory Outcomes on Body Mass Index within Weight Categories, All Measured at Baseline Examination

Outcomes	All Smokers (n = 1,641)		Normal-Weight Smokers* (n = 586)		Overweight Smokers (n = 595)		Obese Smokers (n = 460)		Interaction P Value [†]
	PE ± SE	P Value	PE ± SE	P Value	PE ± SE	P Value	PE ± SE	P Value	
FVC, ml	−6 ± 2	0.01	6 ± 12	0.61	−5 ± 15	0.76	−9 ± 5	0.10	0.24
FEV ₁ , ml	−2 ± 3	0.47	8 ± 14	0.55	1 ± 18	0.96	−8 ± 6	0.19	0.26
FEV ₁ /FVC % ratio	0.004 ± 0.001	<0.001	0.004 ± 0.003	0.09	0.008 ± 0.003	0.03	0.001 ± 0.001	0.60	0.12
FEF _{25–75%} , ml	7 ± 3	0.02	13 ± 17	0.43	10 ± 20	0.62	−7 ± 7	0.32	0.24
Total SGRQ score [‡]	0.26 ± 0.01	<0.001	−0.53 ± 0.05	<0.001	0.24 ± 0.07	<0.001	0.28 ± 0.02	<0.001	<0.001
SGRQ symptom score [‡]	0.11 ± 0.01	<0.001	−0.39 ± 0.04	<0.001	0.02 ± 0.05	0.65	0.10 ± 0.02	<0.001	<0.001
SGRQ impact score [‡]	0.30 ± 0.01	<0.001	−0.73 ± 0.07	<0.001	0.22 ± 0.09	0.02	0.36 ± 0.02	<0.001	<0.001
SGRQ activity score [‡]	0.33 ± 0.01	<0.001	−0.45 ± 0.04	<0.001	0.41 ± 0.06	<0.001	0.32 ± 0.01	<0.001	<0.001

Definition of abbreviations: PE = parameter estimate; SE = standard error; SGRQ = St. George's Respiratory Questionnaire.

Note 1: Covariates adjusted for in this model include age, sex, current smoking, pack-years, and ethnicity (all measured at baseline examination).

Note 2: Exclusion criteria: COPD GOLD stage 4 (n = 12) and those with history of asthma. Inclusion criteria: ≥20 pack-years of smoking and age 40–75 yr.

Note 3: Of the 417 subjects with COPD included in this analysis, 175, 211, and 31 subjects had stage 1, 2, and 3 disease, respectively.

*"Normal-weight" was defined as body mass index (BMI) 18.5 to <25, "overweight" was defined as BMI 25 to <30, and "obese" was defined as ≥30 kg/m². Fourteen underweight smokers of BMI < 18.5 kg/m² were included in the normal-weight category.

[†]For interaction analyses, overweight smokers were excluded, and the P value for the test of interaction between BMI and extreme weight categories (i.e., normal-weight vs. obese status) on each respiratory outcome is presented.

[‡]Data obtained from SGRQ, including its component activity, impact, and symptom subscales, were presented for every 10 score units.

bias from linear modeling and inadequate stratified analyses separating overweight and obese categories or different classes of obesity (9–11, 44). If BMI associations with respiratory outcomes are U-shaped, bias from linear modeling would be particularly manifest in analyses of study populations with limited numbers of obese subjects. In support of that statement, our longitudinal data suggest that the detrimental effect of weight gain on respiratory outcomes is seen

in obese smokers and not in smokers who are not obese. Another potential reason why obesity has been associated with better respiratory outcomes in some studies is the focus on clinical populations of advanced disease. In advanced COPD, greater BMI is associated with lower resting lung hyperinflation (12), an effect that may simulate lung volume reduction surgery. This may explain why studies of severe COPD may show relationships different

from those seen among at-risk smokers and milder COPD. In support of this hypothesis, the Copenhagen Heart Study showed a significant linear inverse effect of BMI on all-cause mortality in subjects with advanced COPD but not in subjects with milder COPD, where plots suggest U-shaped relationships (11). Because our study involves an "upstream" cohort (i.e., 75% of the participants are at risk for COPD and almost all of those with COPD

Table 3: Univariate Analysis of the Longitudinal Associations of Change in Respiratory Outcomes on Gain in Body Mass Index within Baseline Body Mass Index Categories

Outcomes	All Smokers (n = 1,187)		Normal-Weight Smokers* (n = 413)		Overweight Smokers (n = 441)		Obese Smokers (n = 333)		Interaction P Value [†]
	PE ± SE	P Value	PE ± SE	P Value	PE ± SE	P Value	PE ± SE	P Value	
ΔFVC, ml	−17 ± 2	<0.001	20 ± 10	0.04	−11 ± 10	0.27	−34 ± 4	<0.001	<0.001
ΔFEV ₁ , ml	−1 ± 2	0.45	28 ± 8	<0.001	13 ± 8	0.08	−24 ± 3	<0.001	<0.001
ΔFEV ₁ /FVC % ratio	0.35 ± 0.02	<0.001	0.50 ± 0.11	<0.001	0.58 ± 0.10	<0.001	0.06 ± 0.05	0.18	<0.001
ΔFEF _{25–75%} , ml	19 ± 3	<0.001	27 ± 11	0.01	43 ± 12	<0.001	−14 ± 6	0.01	0.001
Δ Total SGRQ score [‡]	20.3 ± 0.40	<0.001	−5.84 ± 1.50	<0.001	−4.81 ± 1.77	0.007	6.42 ± 0.97	<0.001	<0.001
Δ SGRQ symptom score [‡]	−0.90 ± 0.57	0.12	−6.34 ± 2.22	0.004	−9.64 ± 2.63	<0.001	3.11 ± 1.31	0.02	<0.001
Δ SGRQ impact score [‡]	1.11 ± 0.28	<0.001	−3.97 ± 1.05	<0.001	−3.59 ± 1.22	0.003	4.39 ± 0.67	<0.001	<0.001
Δ SGRQ activity score [‡]	5.24 ± 0.60	<0.001	−8.08 ± 2.22	<0.001	−3.44 ± 2.66	0.20	11.19 ± 1.46	<0.001	<0.001

Definition of abbreviations: PE = parameter estimate; SE = standard error; SGRQ = St. George's Respiratory Questionnaire.

Note 1: In a mixed model, respiratory outcomes and BMI were used as time-varying variables.

Note 2: Data obtained from the SGRQ, including its component activity, impact, and symptom subscales, were presented for every 10 score units.

Note 3: Of the 283 subjects with COPD included in this analysis, 115, 141, and 27 subjects had stage 1, 2, and 3 disease, respectively.

*"Normal-weight" was defined as body mass index (BMI) 18.5 to <25, "overweight" was defined as BMI 25 to <30, and "obese" was defined as ≥30 kg/m². Fourteen underweight smokers of BMI <18.5 kg/m² were included in the normal-weight category.

[†]For interaction analyses, overweight smokers were excluded, and the P value for the test of interaction between gain in BMI and extreme weight categories at baseline (i.e., normal-weight vs. obese status) on longitudinal change in each respiratory outcome is presented.

Table 4: Multivariable Analysis of the Longitudinal Association of Change in Respiratory Outcomes on Gain in Body Mass Index within Baseline Body Mass Index Categories

Outcomes	All Smokers (n = 1,187)		Normal-Weight Smokers* (n = 413)		Overweight Smokers (n = 441)		Obese Smokers (n = 333)		Interaction P Value [†]
	PE ± SE	P Value	PE ± SE	P Value	PE ± SE	P Value	PE ± SE	P Value	
ΔFVC, ml	-21 ± 1	<0.001	-1 ± 6	0.83	-28 ± 7	<0.001	-34 ± 3	<0.001	<0.001
ΔFEV ₁ , ml	-5 ± 1	<0.001	10 ± 5	0.04	-4 ± 5	0.45	-24 ± 2	<0.001	0.03
ΔFEV ₁ /FVC % ratio	0.32 ± 0.02	<0.001	0.44 ± 0.10	<0.001	0.44 ± 0.09	<0.001	0.03 ± 0.04	0.54	<0.001
ΔFEF _{25-75%} , ml	14 ± 2	<0.001	14 ± 9	0.11	15 ± 9	0.10	-18 ± 5	<0.001	0.001
Δ Total SGRQ score [‡]	2.36 ± 0.39	<0.001	-4.73 ± 1.44	0.001	-3.80 ± 1.72	0.03	6.58 ± 0.93	<0.001	<0.001
Δ SGRQ symptom score [‡]	-0.46 ± 0.55	0.40	-5.03 ± 2.13	0.02	-8.28 ± 2.50	0.001	3.37 ± 1.25	0.007	0.001
Δ SGRQ impact score [‡]	1.25 ± 0.27	<0.001	-3.24 ± 1.02	0.002	-3.26 ± 1.20	0.007	4.47 ± 0.65	<0.001	<0.001
ΔSGRQ activity score [‡]	5.79 ± 0.58	<0.001	-6.44 ± 2.14	0.003	-1.50 ± 2.61	0.57	11.42 ± 1.42	<0.001	<0.001

Definition of abbreviations: PE = parameter estimate; SE = standard error; SGRQ = St. George's Respiratory Questionnaire.

Note 1: Covariates adjusted for in this model include age, sex, current smoking, pack-years, and ethnicity—all measured at baseline examination (with age and current smoking as repeated measures).

Note 2: Exclusion criteria: COPD GOLD stage 4 and those with history of asthma. Inclusion criteria: ≥20 pack-years of smoking and age 40–75 yr.

Note 3: In a mixed model, change in respiratory outcomes, BMI, age, and current smoking status were used as time-varying variables.

Note 4: Of the 283 subjects with COPD included in this analysis, 115, 141, and 27 subjects had stage 1, 2, and 3 disease, respectively.

**“Normal-weight” was defined as body mass index (BMI) 18.5 to <25, “overweight” was defined as BMI 25 to <30, and “obese” was defined as ≥30 kg/m². Fourteen underweight smokers of BMI < 18.5 kg/m² were included in the normal-weight category.

[†]For interaction analyses, overweight smokers were excluded. The P value for the test of interaction between gain in BMI and extreme weight categories at baseline (i.e., normal-weight vs. obese status) on longitudinal change in each respiratory outcome is presented.

[‡]Data obtained from the SGRQ, including its component activity, impact, and symptom subscales, were presented for every 10 score units.

have GOLD stages 1 and 2), our findings are relevant to subjects at risk for or having milder COPD.

Cross-sectional studies indicate that obese patients have greater symptoms, activity limitation, medication use, and health care use than normal-weight patients with COPD (40). Using a cohort of smokers at risk for or having milder COPD, our data confirm those cross-sectional findings and add that weight gain in obese smokers worsens their health status, including symptoms, activity limitation, and disease impact. Our study also shows that weight gain in normal-weight or overweight smokers improves their health status. This improvement cannot be explained by the mechanical effect of weight gain on truncal compliance. Although a likely explanation involves regulated inflammatory mechanisms, our study did not find correlations between baseline serum leptin, IL-6, or IL-10 concentrations with decline in lung function overall or within normal weight or obese categories in a measured subset (data not shown).

Our study has several limitations. One limitation is our inability to differentiate fat from lean mass in our measure of BMI. In a study of mostly men with moderate to severe COPD, lean mass predicted survival (45). Greater lean mass (i.e., primarily muscle mass) is also associated with greater

FEV₁ and FVC, particularly among men (46, 47). Therefore, it is possible that high BMI in studies of mostly men reflects their greater lean mass (and not excess fat mass), which may explain their survival advantage. Sutherland and colleagues, in their study of pulmonary function, suggested that although lean mass was a measure of muscle bulk in men, excess lean mass in women was a measure of obesity (47). Studies of women (such as ours) where BMI does not reflect the disproportionate contribution of muscle mass may therefore reveal different findings with respiratory outcomes than studies enrolling primarily men. In support of this hypothesis, we present cross-sectional data in Table E1 in the online supplement that the opposing associations of SGRQ symptom subscale score on BMI between the extreme weight categories (i.e., normal-weight vs. obese) were stronger among women than men. In other words, there was a significant three-way interaction noted between sex, BMI, and extreme weight categories on SGRQ symptom subscale score (interaction $P < 0.001$; all measured at baseline examination visit). This is proof-of-concept that BMI may affect respiratory outcomes differently between men and women smokers.

It is possible that gain in BMI reflects primarily accumulation of muscle mass in normal-weight smokers but accumulation

of fat mass in obese smokers. The U-shaped relationships seen could be explained by such a dichotomy. Particularly in overweight and obese smokers, loss in BMI may represent depletion of muscle mass, whereas gain in BMI may reflect accumulation of fat mass. We have studied change in BMI variable (which measures gain and loss of BMI) as a linear predictor variable. It is possible that subgroups that gain BMI may have different relationships than subgroups that lose BMI. We present data in Table E2 that demonstrate that the relationships are similar between these subgroups and that our analytic plan is correct.

Another limitation is that some effect sizes, although statistically significant, may be small and possibly not clinically significant. However, statistical pooling of data may hide individual smokers in whom the effect size may be larger and clinically significant.

Smoking behavior is a complex variable that may not be completely captured by measures such as pack years and current smoking status. It is difficult to account for factors such as type of cigarettes, depth of inhalation, or number of puffs per cigarette. Also, we did not adjust for differences in occupational and environmental exposures and in dietary habits between the various baseline weight categories. Finally, because our cohort participants were recruited from

the community using newspaper and radio advertisements, our study cohort may not be representative of all smokers in New Mexico and in other parts of the United States. However, smoking behaviors in our study are consistent with those observed in representative state surveys of smokers in New Mexico (48).

Our study has several strengths. These include its focus on women, the fact that it examines a question of tremendous public health impact, its use of postbronchodilator spirometric values, its strict adherence to the ATS guidelines in the performance of

spirometry, its use of longitudinal data, and its evaluation of nonlinear relationships during statistical modeling.

In summary, using a longitudinal cohort of smokers at risk for or having early COPD, our study demonstrates that baseline weight and longitudinal gain in weight have nonlinear associations with spirometric function and health status. Being nonlinear, the effect of weight is unlikely to be a mechanical effect alone and may involve carefully regulated inflammatory pathways that need further research. Although not studied, weight loss intervention is likely to

be beneficial only among obese smokers at risk for or having early COPD but may not be beneficial among their normal-weight or overweight counterparts. ■

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