Published in final edited form as:

PM R. 2018 March ; 10(3): 276–285. doi:10.1016/j.pmrj.2017.08.437.

Plasma leptin and reduced FEV₁ and FVC in Chronic Spinal Cord Injury

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Abstract

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Background—Adipose tissue produces leptin, which is pro-inflammatory, and adiponectin, which has anti-inflammatory properties. Participants with chronic spinal cord injury (SCI) have increased body fat and are at increased risk for respiratory illness.

Objective—To assess associations between leptin and adiponectin with pulmonary function in a chronic SCI cohort.

Design—Cross-sectional study.

Setting—Veterans Affairs Medical Center.

Participants—285 participants (237 men and 48 women) with chronic SCI with mean (sd) injury duration 17.8 (13.2) years from VA Boston and the community participating in an epidemiologic study assessing factors associated with respiratory health.

Methods—Participants (24.6% Cervical AIS A, B, and C; 33.6% other AIS A, B, and C; 41.8% AIS D) provided a blood sample, completed a respiratory health questionnaire, and underwent spirometry. Linear regression methods were used to assess cross-sectional associations between plasma leptin and adiponectin with spirometric measures of pulmonary function adjusted for age, race, sex, and height. Level and severity of SCI, mobility mode, BMI, smoking, COPD, asthma, chest injury history, laboratory batch, and other potential confounders were also considered.

Main Outcome Measurements—FEV₁, FVC, and FEV₁/FVC.

Results—There was a statistically significant inverse relationship between plasma leptin assessed in quartiles or as a continuous covariate with FEV₁ and FVC. In fully adjusted models, each interquartile range (16,214 pg/mL) increase in leptin was associated with a significant decrease in FEV₁ (−93.1 mL; 95%CI: −166.2, −20.0) and decrease in FVC (−130.7 mL; 95%CI: −219.4, −42.0). There were no significant associations between leptin and FEV₁/FVC or between plasma adiponectin with FEV₁, FVC, or FEV₁/FVC.

Conclusion—Plasma leptin in individuals with chronic SCI is inversely associated with FEV₁, and FVC, independently of SCI level and severity and other covariates. This finding suggests that plasma leptin may contribute to reduced pulmonary function in chronic SCI.

Level of Evidence—Level II

Introduction

In addition to weakness and paralysis of respiratory muscles, following spinal cord injury (SCI), there is a reduction in lean tissue mass and an increase in total fat mass, including visceral fat.^{1–3} It is well known that obesity may affect the respiratory system due to loading of the upper abdomen and thorax, including a reduction in FEV₁ and FVC.⁴ However, adipose tissue also produces adipokines, including leptin,^{5–6} which is pro-inflammatory, and adiponectin, which is anti-inflammatory.^{7–8} Leptin is pro-inflammatory since it promotes neutrophil chemotaxis, the generation of reactive oxygen species, and macrophage activation.^{5–6} Leptin receptors have been found in alveolar epithelial cells^{9–10} and airway smooth muscle cells.¹¹ Adiponectin receptors have been found to be expressed in pulmonary epithelium.¹² Animal studies have shown that adiponectin deficient mice have a propensity to develop lung inflammation^{13–16} and that adiponectin down regulates pro-inflammatory

cytokines.⁸ In a mouse model of asthma, adiponectin administration suppressed allergen induced pulmonary inflammation, a finding that suggests communication between circulating adipokines and the lung.¹⁶

Although adiponectin is produced in visceral adipose tissue, its levels are reduced in obesity, and in SCI, adiponectin levels were found to be inversely proportional to waist circumference.¹⁷ Circulating concentrations of leptin are elevated in individuals with chronic SCI in proportion to the degree of adiposity.^{17–18} Although BMI underestimates the extent of adiposity in SCI, leptin concentrations are linearly related to BMI in SCI, indicating that relative differences in BMI may serve as an estimate of adiposity.¹⁹ We previously investigated the association between BMI and pulmonary function in chronic SCI. In a cross-sectional study in 339 men studied at VA Boston, a greater BMI was associated with a reduced FEV₁/FVC.²⁰ In a longitudinal study in 174 men with chronic SCI studied over a mean of 7.5 years, an increase in BMI was a significant predictor of decline in FEV₁ and FEV₁/FVC, and FVC.²¹ In addition to mechanical effects attributable to obesity, it is possible that circulating adipokines produced by fat may influence pulmonary function in SCI. Therefore, in this report, we assess the cross-sectional association between spirometric measures of pulmonary function with leptin and adiponectin, adjusting for BMI and measures of SCI severity and other potential confounders.

Methods

Study Population

Between 8/2009 and 4/2015 we recruited 360 individuals into an epidemiological study as part of ongoing work to identify factors associated with respiratory health among individuals with SCI. Participants were recruited from persons receiving care at VA Boston, from the greater Boston area through advertisement, and by direct mail to persons who had received care at Spaulding Rehabilitation Hospital or Boston University Medical Center, members of the National Spinal Cord Injury Association, and subscribers to New Mobility Magazine. Individuals were eligible if they were 22 years of age or older, were 1 or more years post-injury, had no other neuromuscular disease, did not have a tracheostomy, and were able to breathe without chronic ventilatory support. The Institutional Review Board at VA Boston Healthcare System approved the protocol and informed consent was obtained.

Pulmonary function testing

Spirometry was based on the 1994 American Thoracic Society (ATS) standards²² modified for use in SCI as we have described previously.^{23–24} Testing was done using a dry-rolling seal spirometer (CPL system, nSpire Health, Inc.; Longmont, CO) in 272 subjects or a pneumotach spirometer (Eaglet, nSpire Health, Inc.; Longmont, CO) in 13 subjects. Flow-volume and volume-time loops were electronically displayed with a goal of at least three acceptable efforts from each participant. Short expiratory efforts (less than 6 seconds) and excessive back extrapolation are common in SCI, but we have demonstrated that FVC and FEV₁ are reproducible in this population.²⁴ Therefore, we accepted excessive back extrapolation and efforts less than six seconds if the effort appeared maximal with an acceptable flow-volume loop, and at least a 0.5-second plateau at RV. The highest values of

FEV₁ and FVC from acceptable efforts were used. Percent-predicted FEV₁ and FVC were calculated based on NHANES equations.^{25–26}

Leptin and Adiponectin Assessment

Blood samples were collected using an ethylenediaminetetraacetic acid (EDTA) tube and were processed and stored on the same day as collection. Samples were centrifuged for 15 minutes at 2,600 rpm (1459 × g) at 4°C and stored at –80°C. All assays were conducted at the Clinical and Epidemiologic Research Laboratory, Children’s Hospital, Boston. Leptin was measured by an ultra-sensitive ELISA assay (R&D Systems, Minneapolis, MN). The assay has a sensitivity of 7.8 pg/mL. The day-to-day variability of the assay at concentrations of 65.7, 146 and 581 pg/mL is 5.4, 4.2 and 3.5%, respectively. Total adiponectin was measured using a similar ELISA method from ALPCO Diagnostics Inc. (Salem, NH). The day-to-day variability of the assay is 9.8% and 10.2% at 9130 and 3930 ng/mL, respectively. Samples were run in three separate batches depending on date of sample collection.

Potential Confounders

Participants completed questionnaires on respiratory health, lifestyle factors, and medical history.²⁷ Information was collected on a number of *a priori* potential confounders that were expected to be related to either pulmonary function or the fat biomarkers. Considered potential confounders included age, race, sex, height, time of blood draw (to address potential diurnal variations in leptin and adiponectin),²⁸ body mass index (BMI, kg/m²), cigarette smoking status (current, former, never) and pack-years of smoking, marijuana smoking status (current, former, never), SCI duration, SCI level and severity, current use of statins and pulmonary medications (inhaled or oral steroids, long-acting bronchodilators, and short-acting bronchodilators), doctor diagnosed chronic obstructive pulmonary disease or asthma, history of chest operation or injury, and mobility mode (motorized wheelchair, wheelchair, use of cane/walker, or able to walk unassisted). Height was obtained by measuring the body length from top of the head to the heel of the subject in a supine position. Self-reported height was used if severe contracture or bracing hindered measurement (n=27). If required, wheelchairs were weighed with and without the participant, and weight was subtracted to determine the participant’s weight. Self-reported weight was used for three participants. Body mass index was calculated from height and weight.

SCI level and severity was assessed by exam and medical record review. Motor level and completeness of injury was categorized according to the American Spinal Injury Association Impairment Scale (AIS).²⁹ Participants were classified as motor complete, no motor function below the neurological level (AIS A or B); AIS C (motor incomplete, motor function preserved below the neurological level, and more than half the key muscles below the neurological level not strong enough to overcome gravity); or AIS D (motor incomplete, motor function preserved below the neurological level, and half or more of key muscles below the neurological level strong enough to overcome gravity). Participants were grouped into cervical motor complete (AIS A or B) and cervical AIS C, high thoracic (T1–T6) motor

complete (AIS A or B) and AIS C, others with T7 or below motor complete (AIS A or B) and AIS C, and all others (AIS D's).

Statistical Analyses

We excluded those without a detectable SCI level ($n=3$), stroke history ($n=2$), with incomplete data collection ($n=6$), no information available on the biomarkers of interest ($n=37$), no acceptable spirometry or did not complete pulmonary function testing ($n=25$), and those who had previous lung resection surgery ($n=2$). In the remaining 285 participants, general linear models (PROC GLM, SAS 9.4; SAS Institute Inc., Cary, NC) were used to calculate the average (and 95% confidence interval) FEV₁ or FVC by quartile of leptin or adiponectin and assess associations using each biomarker as a continuous covariate. The statistical significance of the trends across quartiles ("p-for-trend") was assessed in models that included a variable using the median value of each biomarker quartile as a continuous exposure measure. Betas and 95% confidence intervals were calculated for an interquartile range (IQR) increase in each biomarker (PROC REG, SAS 9.4; SAS Institute Inc., Cary, NC). Basic models included adjustment for age, sex, race, height (for FEV₁ and FVC only), and laboratory batch. Each potential confounder (or group of confounders) was added to the basic model. Fully adjusted models included all *a priori* potential confounders, and parsimonious adjusted models included all potential confounders that were associated with the outcome and exposure when added to the basic models. Residual plots were examined to assess model fit.

Results

The characteristics of the 285 participants with spirometry data and fat biomarkers available are presented in Table 1. Participants were mostly male (83%), white (91%), had an average age (SD) and injury duration of 53.8 ± 14.2 years and 17.8 ± 13.2 years, respectively, and the largest number (41.8%) were AIS D. The average (SD) BMI was 27.0 ± 5.9 kg/m², and the majority of participants were ever smokers (58%) and never users of marijuana (77%). The average time of blood draw was 11:57AM with a standard deviation of 1.58 hours, with a range from 8:38AM to 3:05PM. The majority of participants (91%) had at least two or three acceptable efforts with values of FEV₁ or FVC within 200mL and an additional 7% had reproducible values of either FEV₁ or FVC. In 2%, participants had only one acceptable effort.

The associations of leptin and adiponectin with FEV₁ are presented in Table 2. In basic models, increases in leptin were associated with statistically significant decreases in FEV₁. These findings were robust to adjustment for all potential confounders, and the p-for-trends were all $<.001$. In fully adjusted models, the adjusted mean FEV₁ level in the lowest quartile of leptin was 3.05 L (95%CI: 2.86, 3.24L) and the level in the top quartile was 2.21 L (95%CI: 2.02, 2.39L). Using leptin as a continuous covariate, each IQR increase in leptin (16,214.34 pg/mL) was associated with a decrease in FEV₁ in fully adjusted models of -93.07 mL (95%CI: -166.16 , -19.98 mL; $p = .01$). Results were similar in parsimonious models that only controlled for age, sex, race, height, laboratory batch, smoking status and pack-years, marijuana smoking status, BMI (as a continuous covariate), doctor-diagnosed

COPD or asthma, current use of long-acting bronchodilators, level and severity of injury, and mobility mode (dichotomized into wheelchair vs walking aided or unaided). Increases in adiponectin were associated with small, but not statistically significant, increases in FEV₁ ($p = .11$ to $.64$).

Associations of leptin and adiponectin with FVC are presented in Table 3. Similar to our findings for FEV₁, increases in leptin were associated with statistically significant decreases in FVC. The p -values for trend for increases quartiles of leptin were $<.001$ regardless of the confounders included in the model. In fully adjusted models, each IQR increase in leptin was associated with a decrease in FVC of -130.69mL (95% CI: -219.35 , -42.02mL , $p = .004$), and there was almost a liter difference in average FVC levels comparing the highest and lowest quartiles of leptin exposure (3.94L in Q1 versus 2.93L in Q4). For both FEV₁ and FVC, there was a suggestion of larger effect estimates when leptin was modeled continuously, as opposed to in quartiles. As shown in Figures 1 and 2, this may be due to extreme values of leptin, although the residual plots did not deviate from normal.

Increases in adiponectin were associated with increases in FVC, however none of the models reached statistical significance ($p = .08$ to $.29$). Results with the FEV₁/FVC ratio are presented in Table 3. Increases in leptin and decreases in adiponectin were associated with very small decreases in the FEV₁/FVC ratio, however none of the associations reached statistical significance.

Discussion

We note for the first time in individuals with chronic SCI a significant inverse relationship between plasma leptin levels and FEV₁ and FVC. Our findings were robust to the inclusion of many other independent covariates, including demographics, BMI, smoking history, COPD and asthma history, current use of pulmonary medications, level and severity of injury, and primary means of mobility. Leptin was not associated with FEV₁/FVC, and adiponectin was not associated with any measure of pulmonary function.

There have been 4 previous reports of an inverse cross sectional association between leptin and pulmonary function in non-SCI populations. Oh et al (2015) found an inverse association, including after adjustment for BMI, between FEV₁ and leptin in 196 COPD patients participating in the Korea Obstructive Lung Disease cohort.³⁰ In 4,679 men and women in the Jackson Heart Study, Hickson et al (2011) reported a significant inverse associations between quartiles of leptin and mean FEV₁ and FVC adjusting for BMI and waist circumference. An inverse relationship between leptin and FEV₁ and FVC was also observed when the analysis was limited to persons with a normal BMI.³¹ Leptin was inversely associated with FEV₁ in 2,808 non-obese participants (BMI <26) from the Third National Health, Nutrition, and Examination Survey adjusting for BMI.³² Finally, an inverse association between leptin with FEV₁ and FVC was observed in 135 patients with heart failure adjusting for BMI.³³ These observations in a variety of different populations suggest that the effects of leptin on pulmonary function are independent of the hypothesized mechanical effects of obesity.

In our study, although leptin values tended to increase with increasing BMI (Figure 3), the correlation between BMI and leptin was only 0.47. As shown in Supplemental Tables 1 and 2, the associations between leptin and FEV₁ and FVC were similar in obese (N=84) and non-obese (N=201) participants (p-values for interaction: 0.31–0.53). These findings also support effects of leptin on pulmonary function that are separate from mechanical effects attributable to obesity.

Findings regarding adiponectin and pulmonary function have been less consistent. In two studies of COPD cohorts, adiponectin was positively associated with an accelerated decline in FEV₁.^{34–35} Van den Borst et. al (2012) also found that people with obstructive lung disease had higher adiponectin levels.³⁶ However, in a third study in COPD patients, adiponectin was not associated with FEV₁ assessed cross-sectionally or associated with longitudinal declines in FEV₁.³⁰ In a general population sample however, adiponectin was inversely associated with cross-sectional FEV₁ and declines in FEV₁ assessed over 5 to 7 years.³⁷

Since leptin is pro-inflammatory, a mechanism that could potentially account for adverse effects of leptin on pulmonary function includes effects on promoting pulmonary or systemic inflammation.^{11,38} Leptin levels in bronchoalveolar lavage (BAL) fluid are elevated in obese compared to lean mice,³⁹ and BAL leptin concentrations are significantly associated with plasma leptin concentrations in asthmatics and healthy controls.⁴⁰ However, in the same study, airway leptin levels were not correlated with BAL oxidative or inflammatory biomarkers.⁴⁰ Systemic inflammation might also adversely affect respiratory muscle performance, as systemic inflammation has been associated with muscle weakness and frailty.^{41–44} In support of this mechanism are the observations that body fat is inversely associated with less muscle and a reduction in FEV₁ and FVC in older men and women⁴⁵ and there is a negative association between muscle strength and muscle mass with systemic inflammation in patients with COPD.⁴⁶

A limitation of this study is that we were only able to include participants well enough to travel to VA Boston and perform acceptable pulmonary function tests, so it is possible we excluded persons with the most reduced pulmonary function. Therefore, although level of injury did not appear to be a confounder of our results, it is possible that our results cannot be generalized to populations with more severe levels of injury. Due to its cross-sectional nature, we only had one assessment of pulmonary function and adipokines so that temporal associations could not be assessed. However, strengths of the current study include a large cohort of persons with chronic SCI and our ability to control for many possible confounding variables. Therefore, although our results suggest that plasma leptin levels in individuals with chronic SCI are associated with impaired pulmonary function, a longitudinal assessment is needed to further assess associations between fat and adipokines in SCI with reduced pulmonary function and respiratory health.

Conclusion

Plasma leptin in individuals with chronic SCI is inversely associated with FEV₁, and FVC, independently of SCI level and severity and other covariates. This finding suggests that

plasma leptin may contribute to reduced pulmonary function in chronic SCI. Adiponectin was not associated with any measure of pulmonary function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by VA Rehabilitation Research and Development Merit Review Grant B6618R and I01 RX000792 from the U.S. Department of Veterans Affairs Rehabilitation Research and Development Service; and NIH Grant AR059270. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

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Figure 1.

Scatterplot of FEV₁ values (L) by leptin concentration (pg/mL, black dots) and association between FEV₁ and leptin and fully adjusted average FEV₁ (and 95% confidence intervals) within each quartile of leptin (red triangles).

Figure 2.

Scatterplot of FVC values (L) by leptin concentration (pg/mL, black dots) and association between FVC, and leptin and fully adjusted average FVC (and 95% confidence intervals) within each quartile of leptin (red triangles).

Figure 3.
Scatterplot of leptin concentrations (pg/mL) by body mass index (BMI, kg/m²)

Table 1

Characteristics of 285 individuals with spinal cord injury included in the analyses

Characteristic	Mean $\pm$ SD
Age (yrs)	53.8 $\pm$ 14.2
Body mass index	27.0 $\pm$ 5.9
Injury Duration (yrs)	17.8 $\pm$ 13.2
Pack years of smoking	15.4 $\pm$ 26.1
Leptin (pg/ml)	18094.3 $\pm$ 23531.2
Adiponectin (ng/ml)	5632.9 $\pm$ 3211.1
FEV ₁ (L)	2.73 $\pm$ 0.90
% – predicted FEV ₁	76.9 $\pm$ 21.1
FVC (L)	3.57 $\pm$ 1.10
% – predicted FVC	77.7 $\pm$ 20.1
FEV ₁ /FVC, %	76.8 $\pm$ 10.5
Time of blood draw	11:57AM $\pm$ 1.58 hrs
N (%)	
Males	237 (83.2)
Race	
White	258 (90.5)
African American	21 (7.4)
Other	6 (2.2)
Level of injury	
Cervical AIS A, B, and C	70 (24.6)
T1 – T6 AIS A, B, and C	40 (14.0)
Other AIS A, B, and C	56 (19.7)
AIS D	119 (41.8)
Mobility mode	
Motorized wheelchair	56 (19.7)
Wheelchair	125 (43.9)
Walk with cane/walker	48 (16.8)
Walk unassisted	56 (19.7)
Cigarette smoking status	
Current	46 (16.1)
Former	120 (42.1)
Never	119 (41.8)
Marijuana smoking status	
Current	31 (10.9)
Former	36 (12.6)
Never	218 (76.5)
Current statin use	91 (31.9)
Any pulmonary medication use	18 (6.3)
Short – acting bronchodilator within 6 hours	3 (1.1)

Characteristic	Mean $\pm$ SD
Long – acting bronchodilator within 24 hours	13 (4.6)
Current inhaled/oral steroid use	15 (5.3)
Doctor diagnosed COPD or asthma	59 (20.7)
History of chest operation or injury	86 (30.2)

Table 2

Adjusted mean levels of FEV₁ (L) within quartiles of fat biomarkers (leptin and adiponectin) and effect estimates (in ml) per interquartile range increase in leptin or adiponectin among 285 individuals with SCI

	Leptin (pg/mL)					p-for trend	β (95% CI) ml FEV ₁ per 16,214 pg/mL increase	p-value
	Q1 (366–4,936)	Q2 (4,937–10,850)	Q3 (10,851–21,151)	Q4 (21,152–184,366)	N			
N	71	76	69	69	285		285	285
Basic *	2.99 (2.81, 3.16)	2.90 (2.73, 3.06)	2.76 (2.59, 2.93)	2.28 (2.09, 2.46)	<.001		–120.47 (–187.85, –53.1)	.001
Basic + draw timing	2.98 (2.81, 3.15)	2.89 (2.73, 3.06)	2.76 (2.59, 2.94)	2.28 (2.10, 2.46)	<.001		–117.23 (–184.6, –49.86)	<.001
Basic + BMI	3.25 (3.05, 3.45)	2.94 (2.78, 3.10)	2.69 (2.53, 2.86)	2.02 (1.82, 2.23)	<.001		–167.33 (–247.42, –87.25)	<.001
Basic + statins	2.99 (2.81, 3.16)	2.89 (2.73, 3.06)	2.76 (2.59, 2.93)	2.27 (2.09, 2.46)	<.001		–121.61 (–189.62, –53.6)	.001
Basic + BDs + steroids	2.98 (2.81, 3.15)	2.89 (2.72, 3.06)	2.77 (2.60, 2.94)	2.28 (2.09, 2.46)	<.001		–117.23 (–185.24, –49.22)	.001
Basic + LOI	2.91 (2.75, 3.07)	2.89 (2.74, 3.04)	2.78 (2.62, 2.94)	2.33 (2.16, 2.50)	<.001		–88.85 (–151.14, –26.57)	.006
Basic + mobility	2.89 (2.73, 3.05)	2.87 (2.72, 3.02)	2.78 (2.62, 2.94)	2.38 (2.21, 2.55)	<.001		–77.83 (–140.75, –14.9)	.016
Basic + LOI + mobility	2.91 (2.76, 3.07)	2.89 (2.74, 3.04)	2.78 (2.63, 2.94)	2.33 (2.17, 2.50)	<.001		–87.4 (–149.68, –25.11)	.006
Basic + COPD or asthma	2.99 (2.82, 3.16)	2.87 (2.70, 3.03)	2.78 (2.61, 2.95)	2.28 (2.10, 2.46)	<.001		–119.66 (–185.76, –53.56)	.001
Basic + Chest operation	2.99 (2.81, 3.16)	2.90 (2.73, 3.06)	2.75 (2.57, 2.92)	2.28 (2.10, 2.47)	<.001		–116.74 (–183.8, –49.69)	.001
Basic + smoking	3.01 (2.84, 3.19)	2.89 (2.72, 3.05)	2.75 (2.57, 2.92)	2.27 (2.09, 2.45)	<.001		–127.28 (–194.97, –59.59)	<.001
Basic + marijuana	2.98 (2.80, 3.15)	2.89 (2.73, 3.06)	2.76 (2.59, 2.94)	2.28 (2.10, 2.46)	<.001		–115.61 (–182.98, –48.23)	.001
Fully adjusted	3.05 (2.86, 3.24)	2.89 (2.74, 3.04)	2.76 (2.60, 2.92)	2.21 (2.02, 2.39)	<.001		–93.07 (–166.16, –19.98)	.013
Parsimonious adjusted **	3.07 (2.88, 3.26)	2.88 (2.73, 3.03)	2.76 (2.61, 2.92)	2.20 (2.00, 2.39)	<.001		–85.77 (–162.05, –9.50)	.030

	Adiponectin (ng/mL)					p-for trend	β (95% CI) ml FEV ₁ per 3,738 ng/mL in adiponectin	p-value
	Q1 (1,444–3,369)	Q2 (3,370–4,817)	Q3 (4,818–7,108)	Q4 (7,109–19,900)	N			
N	68	75	71	71	285		285	285
Basic *	2.59 (2.39, 2.78)	2.85 (2.67, 3.03)	2.65 (2.47, 2.83)	2.84 (2.65, 3.02)	.20		43.14 (–69.41, 155.69)	.45
Basic + draw timing	2.59 (2.40, 2.79)	2.86 (2.68, 3.03)	2.64 (2.46, 2.82)	2.84 (2.65, 3.02)	.22		38.32 (–74.15, 150.79)	.50
Basic + BMI	2.58 (2.38, 2.78)	2.85 (2.67, 3.03)	2.65 (2.47, 2.84)	2.84 (2.65, 3.04)	.20		43.74 (–75.26, 162.73)	.47
Basic + statins	2.59 (2.39, 2.78)	2.85 (2.67, 3.03)	2.65 (2.47, 2.83)	2.84 (2.65, 3.02)	.22		41.68 (–71.82, 155.18)	.47
Basic + BDs + steroids	2.59 (2.39, 2.78)	2.85 (2.68, 3.03)	2.66 (2.48, 2.84)	2.83 (2.64, 3.02)	.24		37.53 (–75.97, 151.03)	.52
Basic + LOI	2.65 (2.47, 2.82)	2.81 (2.64, 2.97)	2.62 (2.45, 2.78)	2.86 (2.69, 3.03)	.15		45.31 (–56.69, 147.3)	.39

	Leptin (pg/mL)				p-for trend	β (95% CI)	ml FEV ₁ per 16,214 pg/mL increase	p-value
	Q1 (366–4,936)	Q2 (4,937–10,850)	Q3 (10,851–21,151)	Q4 (21,152–184,366)				
Basic + mobility	2.68 (2.50, 2.85)	2.79 (2.63, 2.95)	2.65 (2.48, 2.81)	2.82 (2.65, 2.99)	.37		24.15 (–77.41, 125.71)	.64
Basic + LOI + mobility	2.65 (2.47, 2.83)	2.80 (2.64, 2.97)	2.61 (2.45, 2.78)	2.86 (2.69, 3.03)	.16		46.39 (–55.68, 148.46)	.37
Basic + COPD or asthma	2.56 (2.37, 2.75)	2.85 (2.67, 3.02)	2.67 (2.49, 2.84)	2.85 (2.67, 3.04)	.11		61.65 (–49.58, 172.87)	.28
Basic + Chest operation	2.58 (2.39, 2.77)	2.84 (2.66, 3.02)	2.65 (2.47, 2.83)	2.86 (2.67, 3.04)	.14		61.31 (–51.24, 173.86)	.29
Basic + smoking	2.59 (2.39, 2.78)	2.84 (2.67, 3.02)	2.66 (2.48, 2.84)	2.84 (2.65, 3.03)	.20		51.74 (–61.25, 164.73)	.37
Basic + marijuana	2.59 (2.40, 2.79)	2.84 (2.66, 3.01)	2.64 (2.47, 2.82)	2.85 (2.66, 3.04)	.17		47.29 (–64.82, 159.4)	.41
Fully adjusted	2.65 (2.47, 2.84)	2.80 (2.63, 2.96)	2.63 (2.47, 2.80)	2.85 (2.67, 3.03)	.20		46.32 (–63.15, 155.79)	.41
Parsimonious adjusted**	2.66 (2.48, 2.84)	2.80 (2.64, 2.95)	2.63 (2.47, 2.79)	2.84 (2.67, 3.02)	.23		39.81 (–66.36, 145.99)	.46

* Adjusted for age, sex, race, height, and laboratory batch

** Adjusted for age, sex, race, height, laboratory batch, smoking status and pack-years, marijuana smoking status, BMI, COPD or asthma, current use of long-acting bronchodilators, level/severity of injury (LOI), and wheelchair use

Note: p-values for trend were calculated using the median values of each quartile as the exposure in the regression models

Table 3

Adjusted mean levels of FVC (L) within quartiles of fat biomarkers (leptin and adiponectin) and effect estimates in ml) per interquartile range increase of leptin or adiponectin among 285 individuals with SCI

	Leptin (pg/mL)					p-for trend	β (95% CI) ml FVC per 16,214 pg/mL increase	p-value
	Q1 (366–4,936)	Q2 (4,937–10,850)	Q3 (10,851–21,151)	Q4 (21,152–184,366)	285			
N	71	76	69	69	285		285	285
Basic*	3.90 (3.69, 4.12)	3.78 (3.57, 3.99)	3.59 (3.38, 3.81)	2.97 (2.74, 3.19)	<.001		–174.3 (–257.89, –90.72)	<.001
Basic + draw timing	3.89 (3.68, 4.11)	3.77 (3.57, 3.98)	3.60 (3.39, 3.81)	2.97 (2.75, 3.20)	<.001		–169.12 (–252.7, –85.53)	<.001
Basic + BMI	4.27 (4.03, 4.51)	3.84 (3.64, 4.04)	3.50 (3.29, 3.71)	2.62 (2.37, 2.87)	<.001		–249.54 (–348.69, –150.38)	<.001
Basic + statins	3.90 (3.69, 4.12)	3.78 (3.57, 3.99)	3.59 (3.38, 3.81)	2.97 (2.74, 3.19)	<.001		–175.11 (–259.97, –90.26)	<.001
Basic + BDs + steroids	3.91 (3.69, 4.12)	3.78 (3.57, 3.99)	3.59 (3.37, 3.80)	2.97 (2.74, 3.20)	<.001		–176.41 (–260.95, –91.88)	<.001
Basic + LOI	3.79 (3.60, 3.98)	3.76 (3.58, 3.94)	3.64 (3.45, 3.83)	3.05 (2.85, 3.25)	<.001		–126.63 (–201.32, –51.95)	.001
Basic + mobility	3.77 (3.58, 3.96)	3.73 (3.54, 3.91)	3.64 (3.45, 3.84)	3.11 (2.91, 3.31)	<.001		–110.74 (–186.06, –35.43)	.004
Basic + LOI + mobility	3.79 (3.61, 3.98)	3.75 (3.57, 3.93)	3.64 (3.45, 3.83)	3.06 (2.86, 3.26)	<.001		–122.74 (–197.11, –48.38)	.001
Basic + COPD or asthma	3.91 (3.69, 4.12)	3.77 (3.56, 3.98)	3.60 (3.38, 3.81)	2.97 (2.74, 3.20)	<.001		–179.98 (–264.2, –95.76)	<.001
Basic + Chest operation	3.91 (3.69, 4.12)	3.78 (3.58, 3.99)	3.57 (3.36, 3.79)	2.98 (2.76, 3.21)	<.001		–170.57 (–253.84, –87.31)	<.001
Basic + smoking	3.91 (3.69, 4.13)	3.78 (3.57, 3.98)	3.58 (3.36, 3.79)	2.98 (2.75, 3.20)	<.001		–174.14 (–258.36, –89.92)	<.001
Basic + marijuana	3.89 (3.67, 4.10)	3.77 (3.57, 3.98)	3.60 (3.39, 3.81)	2.98 (2.76, 3.20)	<.001		–166.2 (–249.78, –82.62)	<.001
Fully adjusted	3.94 (3.71, 4.18)	3.78 (3.59, 3.96)	3.58 (3.39, 3.79)	2.93 (2.71, 3.16)	<.001		–130.69 (–219.35, –42.02)	.004
Parsimonious adjusted**	4.00 (3.76, 4.23)	3.76 (3.58, 3.95)	3.59 (3.40, 3.79)	2.89 (2.65, 3.12)	<.001		–134.58 (–227.38, –41.78)	.005

	Adiponectin (ng/mL)					p-for trend	β (95% CI) ml FVC per 3,738 ng/mL in adiponectin	p-value
	Q1 (1,444–3,369)	Q2 (3,370–4,817)	Q3 (4,818–7,108)	Q4 (7,109–19,900)	285			
N	68	75	71	71	285		285	285
Basic*	3.33 (3.09, 3.57)	3.70 (3.48, 3.92)	3.52 (3.30, 3.75)	3.70 (3.47, 3.93)	.12		89.83 (–50.85, 230.52)	.21
Basic + draw timing	3.34 (3.10, 3.58)	3.71 (3.49, 3.93)	3.50 (3.28, 3.73)	3.70 (3.47, 3.93)	.14		82.32 (–57.92, 222.56)	.25
Basic + BMI	3.31 (3.06, 3.56)	3.69 (3.47, 3.92)	3.53 (3.30, 3.76)	3.72 (3.48, 3.97)	.10		99.44 (–49.3, 248.18)	.19
Basic + statins	3.33 (3.09, 3.57)	3.70 (3.48, 3.92)	3.52 (3.30, 3.75)	3.70 (3.46, 3.93)	.14		87.22 (–54.71, 229.15)	.23
Basic + BDs + steroids	3.33 (3.09, 3.57)	3.71 (3.48, 3.93)	3.52 (3.29, 3.75)	3.70 (3.46, 3.93)	.14		86.21 (–55.87, 228.28)	.24
Basic + LOI	3.41 (3.20, 3.62)	3.64 (3.45, 3.84)	3.48 (3.29, 3.68)	3.73 (3.52, 3.93)	.08		88.97 (–33.83, 211.78)	.16

	Leptin (pg/mL)				p-for trend	β (95% CI)	ml FVC per 16,214 pg/mL increase	p-value
	Q1 (366–4,936)	Q2 (4,937–10,850)	Q3 (10,851–21,151)	Q4 (21,152–184,366)				
Basic + mobility	3.45 (3.24, 3.67)	3.62 (3.43, 3.82)	3.51 (3.32, 3.71)	3.68 (3.47, 3.88)	.23		65.87 (–56.35, 188.09)	.29
Basic + LOI + mobility	3.42 (3.21, 3.63)	3.64 (3.45, 3.84)	3.48 (3.28, 3.67)	3.73 (3.52, 3.93)	.09		91.74 (–30.55, 214.03)	.14
Basic + COPD or asthma	3.32 (3.08, 3.56)	3.70 (3.48, 3.92)	3.53 (3.30, 3.75)	3.71 (3.48, 3.94)	.10		91.78 (–49.57, 233.12)	.18
Basic + Chest operation	3.32 (3.08, 3.56)	3.69 (3.47, 3.91)	3.52 (3.29, 3.74)	3.73 (3.50, 3.96)	.08		113.8 (–26.45, 254.04)	.11
Basic + smoking	3.33 (3.09, 3.57)	3.69 (3.47, 3.91)	3.54 (3.31, 3.76)	3.70 (3.47, 3.93)	.12		97.65 (–43.26, 238.55)	.18
Basic + marijuana	3.35 (3.11, 3.59)	3.68 (3.46, 3.90)	3.51 (3.28, 3.73)	3.72 (3.49, 3.96)	.09		96.82 (–42.76, 236.41)	.18
Fully adjusted	3.45 (3.22, 3.67)	3.63 (3.43, 3.82)	3.48 (3.28, 3.68)	3.71 (3.50, 3.93)	.16		88.15 (–44.69, 220.99)	.19
Parsimonious adjusted**	3.44 (3.22, 3.66)	3.61 (3.42, 3.81)	3.48 (3.29, 3.68)	3.72 (3.51, 3.93)	.12		92.23 (–37.17, 221.63)	.16

* Adjusted for age, sex, race, height, and laboratory batch

** Adjusted for age, sex, race, height, laboratory batch, smoking status and pack-years, marijuana smoking status, BMI, COPD or asthma, current use of long-acting bronchodilators, level/severity of injury (LOI), and wheelchair use

Note: p-values for trend were calculated using the median values of each quartile as the exposure in the regression models

Table 4

Adjusted mean levels of FEV₁/FVC (%) within quartiles of fat biomarkers (leptin and adiponectin) and effect estimates (FEV₁/FVC) per interquartile range increase of leptin or adiponectin among 285 individuals with SCI

	Leptin (pg/mL)					p-for trend	β (95% CI) FEV ₁ /FVC per 16,214 pg/mL increase	p-value
	Q1 (366–4,936)	Q2 (4,937–10,850)	Q3 (10,851–21,151)	Q4 (21,152–184,366)	N			
N	71	76	69	69	285		285	285
Basic *	76.7 (74.5, 78.9)	76.8 (74.6, 78.9)	77.2 (75.0, 79.4)	76.7 (74.4, 79.1)	> .99		0.473 (–0.354, 1.301)	.26
Basic + draw timing	76.7 (74.5, 78.9)	76.8 (74.7, 78.9)	77.2 (75.0, 79.4)	76.7 (74.4, 79.0)	.96		0.444 (–0.387, 1.274)	.30
Basic + BMI	75.8 (73.1, 78.4)	76.6 (74.5, 78.8)	77.4 (75.2, 79.7)	77.6 (74.9, 80.3)	.54		0.956 (–0.035, 1.947)	.06
Basic + statins	76.7 (74.5, 78.9)	76.7 (74.6, 78.9)	77.3 (75.0, 79.5)	76.7 (74.4, 79.1)	.99		0.471 (–0.366, 1.308)	.27
Basic + BDs + steroids	76.4 (74.2, 78.6)	76.6 (74.5, 78.7)	77.7 (75.5, 79.9)	76.7 (74.4, 79.0)	.93		0.626 (–0.19, 1.442)	.13
Basic + LOI	77.1 (75.0, 79.3)	77.0 (74.9, 79.1)	76.9 (74.7, 79.1)	76.3 (74.0, 78.6)	.59		0.283 (–0.542, 1.107)	.50
Basic + mobility	77.0 (74.8, 79.2)	77.2 (75.1, 79.3)	76.7 (74.6, 78.9)	76.4 (74.1, 78.7)	.63		0.267 (–0.566, 1.1)	.53
Basic + LOI + mobility	77.1 (74.9, 79.3)	77.2 (75.1, 79.3)	76.9 (74.7, 79.0)	76.2 (73.9, 78.5)	.53		0.229 (–0.592, 1.05)	.59
Basic + COPD or asthma	76.8 (74.7, 78.9)	76.1 (74.1, 78.1)	77.7 (75.6, 79.8)	76.9 (74.7, 79.1)	.82		0.511 (–0.271, 1.293)	.20
Basic + Chest operation	76.6 (74.4, 78.8)	76.7 (74.6, 78.9)	77.4 (75.2, 79.6)	76.7 (74.3, 79.0)	.97		0.464 (–0.359, 1.286)	.27
Basic + smoking	77.3 (75.1, 79.5)	76.6 (74.5, 78.7)	77.1 (75.0, 79.3)	76.4 (74.1, 78.6)	.64		0.257 (–0.554, 1.068)	.54
Basic + marijuana	76.8 (74.6, 79.0)	76.8 (74.7, 79.0)	77.1 (74.9, 79.3)	76.7 (74.3, 79.0)	.92		0.43 (–0.4, 1.259)	.31
Fully adjusted	77.4 (74.8, 79.9)	76.6 (74.5, 78.6)	77.7 (75.5, 79.9)	75.8 (73.3, 78.2)	.37		0.392 (–0.533, 1.318)	.38
Parsimonious adjusted **	77.1 (74.5, 79.6)	76.5 (74.5, 78.5)	77.4 (75.3, 79.6)	76.4 (73.8, 79.0)	.73		0.708 (–0.261, 1.677)	.15

	Adiponectin (ng/mL)					p-for trend	β (95% CI) FEV ₁ /FVC per 3,738 ng/mL in adiponectin	p-value
	Q1 (1,444–3,369)	Q2 (3,370–4,817)	Q3 (4,818–7,108)	Q4 (7,109–19,900)	N			
N	68	75	71	71	285		285	285
Basic *	78.1 (75.8, 80.5)	76.5 (74.3, 78.6)	75.8 (73.6, 77.9)	77.1 (74.9, 79.4)	.80		–0.613 (–1.976, 0.775)	.38
Basic + draw timing	78.1 (75.8, 80.4)	76.4 (74.3, 78.6)	75.8 (73.6, 78.0)	77.1 (74.9, 79.4)	.83		–0.576 (–1.939, 0.787)	.41
Basic + BMI	78.5 (76.1, 81)	76.6 (74.4, 78.7)	75.6 (73.4, 77.8)	76.7 (74.4, 79.1)	.55		–0.882 (–2.318, 0.554)	.23
Basic + statins	78.1 (75.8, 80.5)	76.4 (74.3, 78.6)	75.8 (73.6, 77.9)	77.1 (74.9, 79.4)	.81		–0.606 (–1.976, 0.765)	.39
Basic + BDs + steroids	78.1 (75.8, 80.5)	76.4 (74.3, 78.5)	76.0 (73.9, 78.2)	76.9 (74.6, 79.1)	.68		–0.722 (–2.062, 0.619)	.29
Basic + LOI	78.0 (75.7, 80.4)	76.5 (74.3, 78.6)	75.7 (73.6, 77.9)	77.2 (75.0, 79.4)	.88		–0.538 (–1.879, 0.803)	.43

	Leptin (pg/mL)				p-for trend	β (95% CI) FEV ₁ /FVC per 16,214 pg/mL increase	p-value
	Q1 (366–4,936)	Q2 (4,937–10,850)	Q3 (10,851–21,151)	Q4 (21,152–184,366)			
Basic + mobility	77.9 (75.6, 80.2)	76.6 (74.5, 78.7)	75.8 (73.7, 77.9)	77.1 (74.9, 79.4)	.87	–0.602 (–1.935, 0.732)	.38
Basic + LOI + mobility	78.0 (75.7, 80.3)	76.5 (74.4, 78.6)	75.8 (73.7, 78.0)	77.2 (75.0, 79.4)	.90	–0.572 (–1.906, 0.762)	.40
Basic + COPD or asthma	77.6 (75.4, 79.8)	76.4 (74.3, 78.4)	76.1 (74.0, 78.2)	77.4 (75.3, 79.6)	.82	–0.246 (–1.543, 1.051)	.71
Basic + Chest operation	78.2 (75.8, 80.5)	76.5 (74.4, 78.7)	75.8 (73.6, 78.0)	77.0 (74.7, 79.2)	.71	–0.736 (–2.092, 0.619)	.29
Basic + smoking	78.1 (75.8, 80.4)	76.5 (74.5, 78.6)	75.6 (73.5, 77.7)	77.2 (75.0, 79.4)	.85	–0.508 (–1.835, 0.818)	.45
Basic + marijuana	78.0 (75.6, 80.3)	76.6 (74.5, 78.8)	75.9 (73.7, 78.1)	77.0 (74.7, 79.2)	.74	–0.647 (–2.002, 0.709)	.35
Fully adjusted	77.5 (75.2, 79.9)	76.6 (74.6, 78.7)	76.2 (74.2, 78.3)	77.0 (74.8, 79.2)	.95	–0.613 (–1.991, 0.764)	.49
Parsimonious adjusted**	77.8 (75.5, 80.1)	76.8 (74.8, 78.8)	76.1 (74.1, 78.2)	76.7 (74.5, 78.9)	.64	–0.826 (–2.167, 0.515)	.23

* Adjusted for age, sex, race, and laboratory batch

** Adjusted for age, sex, race, laboratory batch, smoking status and pack-years, marijuana smoking status, BMI, COPD or asthma, current use of long-acting bronchodilators, level/severity of injury (LOI), and wheelchair use

Note: p-values for trend were calculated using the median values of each quartile as the exposure in the regression models