CrossMark

# FEV$_1$ and FVC and systemic inflammation in a spinal cord injury cohort

Jaime E. Hart[1,2,3*], Rebekah Goldstein[4,8], Palak Walia[4,9], Merilee Teylan[4,8,10], Antonio Lazzari[5,11], Carlos G. Tun[6,8] and Eric Garshick[1,3,7,8]

## Abstract

**Background:** Systemic inflammation has been associated with reduced pulmonary function in individuals with and without chronic medical conditions. Individuals with chronic spinal cord injury (SCI) have clinical characteristics that promote systemic inflammation and also have reduced pulmonary function. We sought to assess the associations between biomarkers of systemic inflammation with pulmonary function in a chronic SCI cohort, adjusting for other potential confounding factors.

**Methods:** Participants (n = 311) provided a blood sample, completed a respiratory health questionnaire, and underwent spirometry. Linear regression methods were used to assess cross-sectional associations between plasma C-reactive protein (CRP) and interleukin-6 (IL-6) with forced expiratory volume in one second (FEV$_1$), forced vital capacity (FVC), and FEV$_1$/FVC.

**Results:** There were statistically significant inverse relationships between plasma CRP and IL-6 assessed in quartiles or continuously with FEV$_1$ and FVC. In fully adjusted models, each interquartile range (5.91 mg/L) increase in CRP was associated with a significant decrease in FEV$_1$ (−55.85 ml; 95% CI: -89.21, −22.49) and decrease in FVC (−65.50 ml; 95% CI: -106.61, −24.60). There were similar significant findings for IL-6. There were no statistically significant associations observed with FEV$_1$/FVC.

**Conclusion:** Plasma CRP and IL-6 in individuals with chronic SCI are inversely associated with FEV$_1$ and FVC, independent of SCI level and severity of injury, BMI, and other covariates. This finding suggests that systemic inflammation associated with chronic SCI may contribute to reduced pulmonary function.

**Keywords:** CRP, Il-6, Systemic inflammation, Pulmonary function, Chronic spinal cord injury

## Background

A growing literature supports inverse associations between levels of inflammatory markers and reductions in measures of pulmonary function in both the general population and among populations with chronic disease (e.g. chronic obstructive pulmonary disease (COPD), asthma, end-stage-renal disease) [1–17]. The majority of these studies have been cross-sectional; however, these findings have also been reported in some, but not all,

longitudinal studies [18–24]. The consistency of observations across study populations suggests that systemic inflammation, and not pulmonary inflammation alone, may play a role in reductions in pulmonary function.

SCI is a chronic medical condition that is associated with a number of clinical characteristics that promote systemic inflammation, including increases in central fat, decreased mobility due to muscle paralysis, and recurrent infection mainly associated with skin ulcers and urinary tract infections [25–32]. In two reports (n = 59 and n = 137 persons with chronic SCI) from an SCI cohort with data collected between 2003 and 2007 [13, 14], we observed inverse associations between systemic inflammatory biomarkers and forced expiratory volume in one second (FEV$_1$) and forced vital capacity (FVC), but not the FEV1/FVC ratio. Due to the smaller sample sizes

* Correspondence: rejch@channing.harvard.edu
[1]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, 401 Park Drive, Landmark Center 3rd Floor West, Boston, MA 02215, USA
[2]Department of Environmental Health, Harvard T.H. Chan School of Public Health, 401 Park Drive, Landmark Center 3rd Floor West, Boston, MA 02215, USA
Full list of author information is available at the end of the article

Hart *et al. BMC Pulmonary Medicine* (2017) 17:113

Page 2 of 9

of our previous studies, we were unable to adjust for large numbers of potential confounders simultaneously and lacked information on others, leaving concerns regarding residual confounding. Our objective was to determine if these findings were generalizable to another SCI cohort with a larger sample size and information on additional potential confounders.

## Methods

### Study population
As part of ongoing work to identify predictors of adverse health outcomes among individuals with SCI, 360 individuals with chronic SCI were recruited between 8/2009 and 4/2015. 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. Participants provided informed consent at the beginning of the study and the study protocol was approved by the Institutional Review Board at VA Boston.

### Outcome assessment
Spirometry was based on the 1994 American Thoracic Society (ATS) standards [33] modified for use in SCI as described previously [34]. After demonstrating the maneuver, participants were instructed to exhale maximally and sustain the effort for at least 6 s. Efforts were made to obtain at least three acceptable efforts from each participant. Short expiratory efforts (less than 6 s) and excessive back extrapolation are common in SCI, but we have demonstrated that FVC and $FEV_1$ are reproducible in this population [34]. Therefore, we accepted excessive back extrapolation and efforts less than six seconds if the effort was maximal with an acceptable flow-volume loop, and at least a 0.5-s plateau at RV. The highest values of $FEV_1$ and FVC from acceptable efforts were used. Percent-predicted $FEV_1$ and FVC were calculated based on NHANES equations [35, 36].

### Inflammatory biomarkers
Blood samples were collected using an ethyle-diamine-tetraacetic acid tube and were processed and stored on the same day as collection. Samples were stored at −80 °C until ready for analysis. High-sensitivity plasma CRP was determined by an immunoturbidimetric assay and IL-6 was determined by an ultra-sensitive enzyme linked immunosorbent assay at the Clinical and Epidemiologic Research Laboratory, Children's Hospital, Boston.

### Potential confounders
Information was collected on a number of *a priori* potential confounders, including age, race, sex, height, body mass index (BMI), cigarette smoking status (current, former, never) and pack-years of smoking, marijuana smoking status (current, former, never), SCI duration, level, and severity, current use of statins and pulmonary medications (inhaled or oral steroids, long-acting bronchodilators, and short-activing bronchodilators), doctor diagnosed chronic obstructive pulmonary disease (COPD) or asthma, history of chest operation or chest injury, and mobility mode (motorized wheelchair, wheelchair, use of cane/walker, or able to walk unassisted). BMI was calculated from measured height and weight for each participant (self-reported weight was used for 4 participants and self-reported height was used for 28 participants).

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) [37]. Participants were classified as motor complete, (i.e. no motor function below the neurological level (AIS A or B)); AIS C (i.e. 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 (i.e. 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 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
Participants were excluded from the current analyses if their SCI level could not be determined ($n = 3$), they had a history of prior stroke ($n = 2$), did not provide a blood sample ($n = 6$) or sufficient blood sample for biomarker assessment ($n = 7$), they did not perform spirometry or did not have an acceptable spirometry effort ($n = 27$), or they had a previous lung resection ($n = 4$), leaving a final analytical sample of 311 participants. There were 62 participants who were recruited from our previous SCI cohort (2003–2007) [14] who were retested. General linear models (PROC GLM, SAS 9.4; SAS Institute Inc., Cary, NC) were used to calculate the average (and 95% confidence interval) FEV1, FVC, or FEV1/FEV ratio within each quartile of CRP or IL-6. The significance of the trends across quartiles was

Hart et al. BMC Pulmonary Medicine (2017) 17:113

Page 3 of 9

assessed using the median value of each inflammatory biomarker within each quartile. Betas and 95% confidence intervals were calculated for an interquartile range (IQR) increase in each biomarker (PROC GLM, SAS 9.4; SAS Institute Inc., Cary, NC). Basic models included adjustment for age, sex, race, and height ($FEV_1$ and FVC models only). 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. In sensitivity analyses, we adjusted our final models for laboratory batch to assess potential differences in the biomarker measures over time.

## Results

Participants were mostly male (84%) and white (91%) with a mean age of 54 years, had a wide range of injury levels, with a median injury duration of 14.1 years (Table 1). Most were current or former cigarette smokers with a median of 18 pack-years and were overweight. The majority of participants (90%) had at least two or three acceptable efforts with values of $FEV_1$ or FVC within 200 mL and an additional 7% (*n* = 21) had reproducible values of either $FEV_1$ or FVC. In 3% (*n* = 9), participants had only one acceptable effort.

The associations of CRP and IL-6 with $FEV_1$ are presented in Table 2. In basic models, increases in either inflammatory biomarker were associated with statistically significant reductions in FEV1. Although all adjusted models were attenuated relative to the basic model (Additional file 1: Table S1), the associations were robust to adjustment for potential confounders. In fully adjusted continuous models, each IQR increase in CRP (5.91 mg/L) was associated with a 55.85 (95% CI:-89.21, −22.49, *p*-value = 0.0012) mL decrease in FEV1, and each IQR increase in IL-6 (3.18 pg/mL) was associated with a 61.39 (95% CI: -115.47, −7.30, *p*-value = 0.027) mL decrease. Associations were similar in parsimonious adjusted models that included only age, sex, race, height, cigarette smoking status and pack-years, marijuana smoking status, doctor diagnosed COPD or asthma, level of injury and mobility mode (dichotomized into wheelchair vs walking aided or unaided), and use of inhaled steroids or long-acting bronchodilators.

Similar results were observed in models examining the associations of the inflammatory biomarkers with FVC (Table 3), although the models were slightly more sensitive to adjustment for potential confounders, especially mobility mode (Additional file 2: Table S2). In fully adjusted models, each IQR increase in CRP was associated with a 65.50 (95% CI: -106.61, −24.60, *p*-value = 0.0019)

**Table 1** Characteristics of 311 individuals included in the analyses

| Characteristic | Mean ± SD or Median (25th percentile – 75th percentile) |
|---|---|
| Age (yrs) | 54.0 ± 14.1 |
| Body mass index (kg/m²) | 26.9 (22.8–31.2) |
| Injury duration (yrs) | 14.1 (5.3–25.4) |
| Pack years of smoking[a] | 18.0 (5.0–37.2) |
| CRP (mg/L) | 2.4 (1.0–6.9) |
| IL-6 (pg/mL) | 2.1 (1.3–4.4) |
| $FEV_1$ (L) | 2.8 ± 0.9 |
| % predicted $FEV_1$ | 77.6 ± 20.9 |
| FVC (L) | 3.6 ± 1.1 |
| % predicted FVC | 78.3 20.1 |
| FEV1/FVC | 0.77 ± 0.11 |
| Characteristic | N (%) |
| Males | 260 (83.6) |
| Race | |
| White | 282 (90.7) |
| African American | 23 (7.4) |
| Asian | 3 (1.0) |
| American Indian/Alaskan Native | 3 (1.0) |
| Level of injury | |
| Motor complete cervical & AIS C | 76 (24.4) |
| Motor complete high thoracic & AIS C | 42 (13.5) |
| Motor complete low thoracic & AIS C | 61 (19.6) |
| All AIS D | 132 (42.4) |
| Mobility mode | |
| Motorized wheelchair | 60 (19.3) |
| Wheelchair | 135 (43.4) |
| Walk with cane/walker | 54 (17.4) |
| Walk unassisted | 62 (19.9) |
| Cigarette smoking status | |
| Current | 52 (16.7) |
| Former | 132 (42.4) |
| Never | 127 (40.8) |
| Marijuana smoking status | |
| Current | 37 (11.9) |
| Former | 38 (12.2) |
| Never | 236 (75.9) |
| Current statin use | 97 (31.2) |
| Any pulmonary medication use | 19 (6.1) |
| Short-acting bronchodilator within 6 h | 3 (1.0) |
| Long-acting bronchodilator within 24 h | 13 (4.2) |
| Current inhaled/oral steroid use | 16 (5.1) |
| Doctor diagnosed COPD or asthma | 30 (9.7) |
| History of chest operation or injury | 90 (28.9) |

[a]Among current and former smokers only (*N* = 184)

**Table 2** Adjusted mean levels of FEV1 by quartile of inflammatory biomarkers and associations per IQR change

CRP (mg/L)

| | Q1 (0.07–0.99) | Q2 (1.00–2.41) | Q3 (2.42–6.91) | Q4 (6.92–161.56) | p-for trend | β (95% CI) mL FEV1 per 5.91 mg/L CRP | p-value |
|---|---|---|---|---|---|---|---|
| N | 77 | 78 | 78 | 78 | 311 | 311 | 311 |
| Basic[a] | 3.05 (2.89, 3.22) | 2.84 (2.68, 3.00) | 2.59 (2.43, 2.75) | 2.55 (2.39, 2.71) | 0.0002 | −63.71 (−99.27,−28.15) | 0.0005 |
| Fully adjusted | 2.93 (2.76, 3.10) | 2.82 (2.67, 2.97) | 2.66 (2.51, 2.82) | 2.62 (2.46, 2.78) | 0.0346 | −55.85 (−89.21,−22.49) | 0.0012 |
| Parsimonious adjusted[b] | 2.93 (2.77, 3.09) | 2.81 (2.66, 2.96) | 2.67 (2.52, 2.82) | 2.62 (2.47, 2.77) | 0.0183 | −51.83 (−83.92,−19.74) | 0.0017 |

IL-6 (pg/mL)

| | Q1 (0.30–1.26) | Q2 (1.27–2.12) | Q3 (2.13–4.44) | Q4 (4.45–46.8) | p-for trend | β (95% CI) mL FEV1 per 3.18 pg/mL IL-6 | p-value |
|---|---|---|---|---|---|---|---|
| N | 77 | 83 | 76 | 75 | 311 | 311 | 311 |
| Basic[a] | 2.98 (2.81, 3.15) | 2.82 (2.66, 2.98) | 2.71 (2.54, 2.88) | 2.51 (2.34, 2.68) | 0.0003 | −101.28 (−156.74,−45.83) | 0.0004 |
| Fully adjusted | 2.90 (2.74, 3.07) | 2.75 (2.60, 2.90) | 2.77 (2.61, 2.92) | 2.61 (2.44, 2.77) | 0.0388 | −61.39 (−115.47,−7.30) | 0.027 |
| Parsimonious adjusted[b] | 2.90 (2.75, 3.06) | 2.75 (2.60, 2.89) | 2.77 (2.61, 2.92) | 2.61 (2.45, 2.76) | 0.0240 | −61.48 (−112.64,−10.33) | 0.0192 |

[a] Adjusted for age, sex, race, and height
[b] Adjusted for age, sex, race, height, smoking status and pack-years, marijuana smoking status, COPD or asthma, current use of steroids and long-acting bronchodilators, level/severity of injury (LOI), and wheelchair use

Hart *et al. BMC Pulmonary Medicine* (2017) 17:113

Page 5 of 9

**Table 3** Adjusted mean levels of FVC by quartile of inflammatory biomarkers and associations per IQR change

| CRP (mg/L) | Q1 (0.07–0.99) | Q2 (1.00–2.41) | Q3 (2.42–6.91) | Q4 (6.92–161.56) | p-for trend | β (95% CI) L FEV1 per 5.91 mg/L CRP | p-value |
|---|---|---|---|---|---|---|---|
| N | 77 | 78 | 78 | 78 | 311 | 311 | 311 |
| Basic[a] | 4.02 (3.82, 4.23) | 3.68 (3.47, 3.88) | 3.42 (3.21, 3.62) | 3.27 (3.07, 3.48) | <.0001 | −82.09 (−126.69,−37.49) | 0.0004 |
| Fully adjusted | 3.84 (3.63, 4.05) | 3.65 (3.46, 3.83) | 3.52 (3.33, 3.71) | 3.39 (3.20, 3.59) | 0.014 | −65.50 (−106.61,−24.60) | 0.0019 |
| Parsimonious adjusted[b] | 3.83 (3.64, 4.02) | 3.63 (3.45, 3.82) | 3.53 (3.34, 3.71) | 3.40 (3.22, 3.59) | 0.007 | −60.22 (−99.61,−20.84) | 0.003 |
| IL-6 (pg/mL) | Q1 (0.30–1.26) | Q2 (1.27–2.12) | Q3 (2.13–4.44) | Q4 (4.45–46.8) | p-for trend | β (95% CI) mL FEV1 per 3.18 pg/mL IL-6 | p-value |
| N | 77 | 83 | 76 | 75 | 311 | 311 | 311 |
| Basic[a] | 3.85 (3.63, 4.06) | 3.69 (3.49, 3.89) | 3.55 (3.33, 3.76) | 3.29 (3.08, 3.50) | 0.0004 | −125.13 (−194.85,−55.40) | 0.0005 |
| Fully adjusted | 3.73 (3.53, 3.93) | 3.62 (3.44, 3.80) | 3.61 (3.42, 3.81) | 3.43 (3.23, 3.63) | 0.0481 | −77.69 (−143.93,−11.46) | 0.0222 |
| Parsimonious adjusted[b] | 3.73 (3.54, 3.92) | 3.62 (3.44, 3.80) | 3.62 (3.43, 3.81) | 3.42 (3.23, 3.61) | 0.0307 | −76.87 (−139.55,−14.19) | 0.0169 |

[a]Adjusted for age, sex, race, and height
[b]Adjusted for age, sex, race, height, smoking status and pack-years, marijuana smoking status, COPD or asthma, current use of steroids and long-acting bronchodilators, level/severity of injury (LOI), and wheelchair use

Hart *et al. BMC Pulmonary Medicine* (2017) 17:113

Page 6 of 9

mL decrease in FVC and each IQR increase in IL-6 was associated with a 77.69 (95% CI: -143.93, −11.46, $p$-value = 0.0222) ml decrease. Adjustment for level of injury and mobility mode led to the largest attenuations in the effect estimates. Increases in CRP and IL-6 were not associated with the $FEV_1/FVC$ ratio (Table 4), and adjustment for individuals confounders or groups of confounders had little impact (Additional file 3: Table S3) (all $p$-values > 0.34). In sensitivity analyses, adjusting for laboratory batch had no impact on the interpretation of any the final models (data not shown).

## Discussion

In this cohort of individuals with SCI, biomarkers of systemic inflammation (CRP, IL-6) were associated with decreases in $FEV_1$ and FVC, but not $FEV_1/FVC$. These findings were robust to adjustment for a number of potential confounders, including demographics and anthropometrics (age, race, sex, height, and BMI), lifestyle characteristics (cigarette and marijuana smoking status, medication use, and usual mobility mode), and disease characteristics (level of injury, history of COPD or asthma, history of chest operations or chest injuries).

In our previous analyses of 59 and 137 participants with SCI studied between 2003 and 2007, we observed similar associations between measures of inflammation and pulmonary function [13, 14]. In our pilot study of 59 individuals, IL-6 was inversely associated with percent-predicted $FEV_1$ (mean percent-predicted $FEV_1$ 92.4% in the least exposed quartile and 69.8% in the most exposed) and percent-predicted FVC (mean percent-predicted FVC 86.9% in the least exposed quartile and 71.5% in the most exposed) in unadjusted models, and in models adjusted for either SCI level, history of doctor diagnosed COPD, cigarette smoking status, or BMI (multivariable models were not possible). Similar decreases that did not reach statistical significance were observed between CRP and percent-predicted $FEV_1$ or percent-predicted FVC, and no associations were observed with $FEV_1/FVC$ [13]. In a larger study of 137 individuals (54 of whom were also participants in the pilot study), we observed similar findings, even in multivariable models simultaneously adjusted for level of injury, BMI, cigarette smoking, statin use, and doctor-diagnosed COPD [14]. In our current study conducted in a larger SCI cohort enrolled between 2009 and 2015, we observed little confounding, and our parsimonious models included a different set of confounders than our previous studies (age, sex, race, height, cigarette smoking status and pack-years, marijuana smoking status, doctor diagnosed COPD, level or injury and mobility mode (dichotomized into wheelchair vs walking aided or unaided), and use of inhaled steroids or long-acting bronchodilators). Overall, we have observed consistent decreases in $FEV_1$ and FVC with increases in CRP and IL-6 among populations of individuals with SCI.

Our findings are also consistent with most other cross-sectional studies [1–17]. Across a wide variety of populations, including individuals with and without chronic illnesses, increases in markers of systemic inflammation have been associated with declines in measures of pulmonary function. Similar to our study, the majority of the literature has focused on the impacts of CRP and IL-6 on $FEV_1$ and FVC.

This study has a number of limitations. First, due to its cross-sectional nature, we cannot determine the temporality of the associations between increased inflammation and decreased pulmonary function. A recent longitudinal study among a group of younger adults studied at ages 32 and 38 has suggested that reductions in pulmonary function lead to subsequent increases in inflammation, but that inflammation did not predict future decreases in lung function [24]. This is contrary to another longitudinal study that found CRP measured in young adults was predictive of pulmonary function measured 7 years later, and other studies that have suggested inflammation may be related to subsequent pulmonary function [18–20].

Second, although we have considered an extensive number of potential confounders that were risk factors for pulmonary function and shown that our associations are robust to adjustment, residual confounding is always a concern in epidemiologic studies. Thirdly, the mechanism whereby systemic inflammation could influence pulmonary function in SCI is uncertain. Since chronic SCI is not known to be a condition characterized by pulmonary inflammation, it is likely that systemic inflammation following SCI is a function of decreased mobility, pressure ulcers, bladder dysfunction, and increased adipose tissue [32, 38]. Once these factors that occur after SCI are accounted for, we have previously found that level and completeness of SCI is not associated with CRP [32, 38]. However, since systemic inflammation is associated with muscle weakness and frailty, it is possible that systemic inflammation could adversely affect respiratory muscle performance and contribute to reduced pulmonary function [39–42].

Lastly, our study population may not be broadly generalizable. We have small numbers of female and minority participants, reflecting the distribution in the population served at VA Boston. However, associations between inflammation and pulmonary function have been observed across a wide spectrum of populations.

## Conclusions

Plasma CRP and IL-6 in individuals with chronic SCI is inversely associated with $FEV_1$ and FVC, independent of SCI severity, BMI, and other covariates. This finding suggests that systemic inflammation may contribute to reduced pulmonary function in chronic SCI.

Hart *et al. BMC Pulmonary Medicine* (2017) 17:113

Page 7 of 9

**Table 4** Adjusted mean levels of FEV1/FVC(%) by quartile of inflammatory biomarkers and associations per IQR change

| CRP (mg/L) | Q1 (0.07–0.99) | Q2 (1.00–2.41) | Q3 (2.42–6.91) | Q4 (6.92–161.56) | p-for trend | β (95% CI) FEV1/FVC per 5.91 mg/L CRP | p-value |
|---|---|---|---|---|---|---|---|
| N | 77 | 78 | 78 | 78 | 311 | 311 | |
| Basic[a] | 76.0 (73.8, 78.2) | 77.2 (75.0, 79.4) | 76.2 (74.0, 78.4) | 78.4 (76.2, 80.6) | 0.14 | −0.068 (−0.536,0.40) | 0.78 |
| Fully adjusted | 76.4 (74.1, 78.7) | 77.3 (75.2, 79.3) | 76.3 (74.3, 78.4) | 77.8 (75.6, 79.9) | 0.43 | −0.19 (−0.643,0.262) | 0.41 |
| Parsimonious adjusted[b] | 76.8 (74.7, 79.0) | 77.3 (75.3, 79.4) | 76.0 (74.0, 78.1) | 77.6 (75.5, 79.6) | 0.59 | −0.216 (−0.65,0.217) | 0.33 |
| **IL-6 (pg/mL)** | Q1 (0.30–1.26) | Q2 (1.27–2.12) | Q3 (2.13–4.44) | Q4 (4.45–46.8) | p-for trend | β (95% CI) FEV1/FVC per 3.18 pg/mL IL-6 | |
| N | 77 | 83 | 76 | 75 | 311 | 311 | |
| Basic[a] | 77.6 (75.3, 79.8) | 76.9 (74.7, 79.0) | 77.1 (74.9, 79.4) | 76.2 (74.0, 78.5) | 0.47 | −0.13 (−0.859,0.599) | 0.73 |
| Fully adjusted | 77.5 (75.3, 79.7) | 76.6 (74.6, 78.6) | 77.5 (75.4, 79.6) | 76.2 (74.0, 78.4) | 0.50 | 0.069 (−0.654,0.791) | 0.85 |
| Parsimonious adjusted[b] | 77.9 (75.8, 79.9) | 76.5 (74.5, 78.4) | 77.4 (75.3, 79.5) | 76.1 (74.0, 78.2) | 0.38 | −0.041 (−0.726,0.645) | 0.91 |

[a]Adjusted for age, sex, and race
[b]Adjusted for age, sex, race, smoking status and pack-years, marijuana smoking status, COPD or asthma, current use of steroids and long-acting bronchodilators, level/severity of injury (LOI), and wheelchair use

Hart *et al. BMC Pulmonary Medicine* (2017) 17:113

Page 8 of 9

## Additional files

**Additional file 1: Table S1.** Univariate adjusted mean levels of FEV1 by quartile of inflammatory biomarkers and associations per IQR change. (DOCX 48 kb)

**Additional file 2: Table S2.** Univariate Adjusted mean levels of FVC by quartile of inflammatory biomarkers and associations per IQR change. (DOCX 49 kb)

**Additional file 3: Table S3.** Univariate adjusted mean levels of FEV1/FVC(%) by quartile of inflammatory biomarkers and associations per IQR change. (DOCX 48 kb)

### Abbreviations

AIS: American spinal injury association impairment scale; ATS: American Thoracic Society; BMI: Body mass index; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; IL-6: Interleukin-6; IQR: Interquartile range; NSCIA: National Spinal Cord Injury Association; RV: Residual volume; SCI: Spinal cord injury; VA: Veteran Affairs

### Availability of data and materials

Data relating to this study is available from the Author on request.

### Authors' contributions

EG, AL, CEG contributed to study conception and design. Data analysis and the draft manuscript was prepared by JEH, and EG & PW edited and revised the manuscript. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The present study was approved by a local institutional review board of Boston Veteran Affairs Hospital (IRB No. 2232, 2417, 2751). Written informed consent was obtained from all study participants.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

### Author details

[1]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, 401 Park Drive, Landmark Center 3rd Floor West, Boston, MA 02215, USA. [2]Department of Environmental Health, Harvard T.H. Chan School of Public Health, 401 Park Drive, Landmark Center 3rd Floor West, Boston, MA 02215, USA. [3]Harvard Medical School, Boston 02115, MA, USA. [4]Research and Development Service, VA Boston Healthcare System, Boston, MA, USA. [5]Divison of Primary Care and Rheumatology Section, VA Boston Healthcare System, Boston University School of Medicine, Boston, MA, USA. [6]Department of Physical Medicine and Rehabilitation, VA Boston Healthcare System, Boston, MA, USA. [7]Pulmonary, Allergy, Sleep, and Critical Care Medicine Section, Medical Service, VA Boston Healthcare System, Boston, MA, USA. [8]VA Boston Healthcare System- West Roxbury Campus, 1400 VFW Parkway, Building 88, Room 18, West Roxbury, MA 02132, USA. [9]VA Boston Healthcare System- Jamaica Plain Campus, 151C- SCI Research, 150 South Huntington Avenue, Jamaica Plain, MA 02130, USA. [10]Department of Epidemiology, University of Washington, 4311 11th Avenue NE, Suite 300, Seattle, WA 98105, USA. [11]Primary Care Clinic, 2nd Floor, Rm, F2-10, 150 South Huntington Avenue, Jamaica Plain, MA 02130, USA.

### References

1. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax. 2004;59(7):574–80.
2. Yende S, Waterer GW, Tolley EA, et al. Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects. Thorax. 2006;61(1):10–6.
3. Walter RE, Wilk JB, Larson MG, et al. Systemic inflammation and COPD: the Framingham heart study. Chest. 2008;133(1):19–25.
4. Aronson D, Roterman I, Yigla M, et al. Inverse association between pulmonary function and C-reactive protein in apparently healthy subjects. Am J Respir Crit Care Med. 2006;174(6):626–32.
5. Thorleifsson SJ, Margretardottir OB, Gudmundsson G, et al. Chronic airflow obstruction and markers of systemic inflammation: results from the BOLD study in Iceland. Respir Med. 2009;103(10):1548–53.
6. Kuhlmann A, Ólafsdóttir IS, Lind L, Sundstrom J, Janson C. Association of biomarkers of inflammation and cell adhesion with lung function in the elderly: a population-based study. BMC Geriatr. 2013;13:82.
7. Duprez DA, Hearst MO, Lutsey PL, et al. Associations among lung function, arterial elasticity, and circulating endothelial and inflammation markers: the multiethnic study of atherosclerosis. Hypertension. 2013;61(2):542–8.
8. Agarwal R, Zaheer MS, Ahmad Z, Akhtar J. The relationship between C-reactive protein and prognostic factors in chronic obstructive pulmonary disease. Multidiscip Respir Med. 2013;8(1):63.
9. Aksu F, Capan N, Aksu K, et al. C-reactive protein levels are raised in stable chronic obstructive pulmonary disease patients independent of smoking behavior and biomass exposure. J Thorac Dis. 2013;5(4):414–21.
10. Ólafsdóttir IS, Gíslason T, Gudnason V, et al. CRP is associated with lung function decline in men but not women: a prospective study. Respir Med. 2013;107(1):91–7.
11. Emami Ardestani M, Zaerin O. Role of serum interleukin 6, albumin and C-reactive protein in COPD patients. Tanaffos. 2015;14(2):134–40.
12. Hancox RJ, Poulton R, Greene JM, et al. Systemic inflammation and lung function in young adults. Thorax. 2007;62(12):1064–8.
13. Garshick E, Stolzmann KL, Gagnon DR, Morse LR, Brown R. Systemic inflammation and reduced pulmonary function in chronic spinal cord injury. PM R. 2011;3(5):433–9.
14. Hart JE, Morse L, Tun CG, Brown R, Garshick E. Cross-sectional associations of pulmonary function with systemic inflammation and oxidative stress in individuals with chronic spinal cord injury. J Spinal Cord Med. 2016;39(3):344–52.
15. Gläser S, Ittermann T, Koch B, et al. Airflow limitation, lung volumes and systemic inflammation in a general population. Eur Respir J. 2012;39(1):29–37.
16. Rasmussen F, Mikkelsen D, Hancox RJ, et al. High-sensitive C-reactive protein is associated with reduced lung function in young adults. Eur Respir J. 2009;33(2):382–8.
17. Zhang P, Wu HM, Shen QY, Liu RY, Qi XM. Associations of pulmonary function with serum biomarkers and dialysis adequacy in patients undergoing peritoneal dialysis. Clin Exp Nephrol. 2016;20(6):951–9.
18. Shaaban R, Kony S, Driss F, et al. Change in C-reactive protein levels and FEV1 decline: a longitudinal population-based study. Respir Med. 2006;100(12):2112–20.
19. Kalhan R, Tran BT, Colangelo LA, et al. Systemic inflammation in young adults is associated with abnormal lung function in middle age. PLoS One. 2010;5(7):e11431.
20. Ahmadi-Abhari S, Kaptoge S, Luben RN, Wareham NJ, Khaw KT. Longitudinal association of C-reactive protein and lung function over 13 years: the EPIC-Norfolk study. Am J Epidemiol. 2014;179(1):48–56.
21. Donaldson GC, Seemungal TA, Patel IS, et al. Airway and systemic inflammation and decline in lung function in patients with COPD. Chest. 2005;128(4):1995–2004.
22. Fogarty AW, Jones S, Britton JR, Lewis SA, McKeever TM. Systemic inflammation and decline in lung function in a general population: a prospective study. Thorax. 2007;62(6):515–20.
23. Jiang R, Burke GL, Enright PL, et al. Inflammatory markers and longitudinal lung function decline in the elderly. Am J Epidemiol. 2008;168(6):602–10.
24. Hancox RJ, Gray AR, Sears MR, Poulton R. Systemic inflammation and lung function: a longitudinal analysis. Respir Med. 2016;111:54–9.

Hart *et al. BMC Pulmonary Medicine* (2017) 17:113

Page 9 of 9

25. Frost F, Roach MJ, Kushner I, Schreiber P. Inflammatory C-reactive protein and cytokine levels in asymptomatic people with chronic spinal cord injury. Arch Phys Med Rehabil. 2005;86(2):312–7.

26. Jones LM, Legge M, Goulding A. Healthy body mass index values often underestimate body fat in men with spinal cord injury. Arch Phys Med Rehabil. 2003;84(7):1068–71.

27. Maggioni M, Bertoli S, Margonato V, Merati G, Veicsteinas A, Testolin G. Body composition assessment in spinal cord injury subjects. Acta Diabetol. 2003;40(Suppl 1):S183–6.

28. Myers J, Lee M, Kiratli J. Cardiovascular disease in spinal cord injury: an overview of prevalence, risk, evaluation, and management. Am J Phys Med Rehabil. 2007;86(2):142–52.

29. Nelson MD, Widman LM, Abresch RT, et al. Metabolic syndrome in adolescents with spinal cord dysfunction. J Spinal Cord Med. 2007;30(Suppl 1):S127–39.

30. Segal JL, Gonzales E, Yousefi S, Jamshidipour L, Brunnemann SR. Circulating levels of IL-2R, ICAM-1, and IL-6 in spinal cord injuries. Arch Phys Med Rehabil. 1997;78(1):44–7.

31. Spungen AM, Adkins RH, Stewart CA, et al. Factors influencing body composition in persons with spinal cord injury: a cross-sectional study. J Appl Physiol. 2003;95(6):2398–407.

32. Morse LR, Stolzmann K, Nguyen HP, et al. Association between mobility mode and C-reactive protein levels in men with chronic spinal cord injury. Arch Phys Med Rehabil. 2008;89(4):726–31.

33. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med. 1995;152(3):1107–36.

34. Kelley A, Garshick E, Gross ER, Lieberman SL, Tun CG, Brown R. Spirometry testing standards in spinal cord injury. Chest. 2003;123(3):725–30.

35. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999;159(1):179–87.

36. Redlich CA, Tarlo SM, Hankinson JL, Townsend MC, Eschenbacher WL. Official American Thoracic Society technical standards: spirometry in the occupational setting. Am J Respir Crit Care Med. 2014;189(8):984–94.

37. Kirshblum SC, Waring W, Biering-Sorensen F, et al. Reference for the 2011 revision of the international standards for neurological classification of spinal cord injury. J Spinal Cord Med. 2011;34(6):547–54.

38. Goldstein RL, Walia P, Teylan M, et al. Clinical factors associated with C-reactive protein in chronic spinal cord injury. *Spinal Cord.* 1 August 2017; doi:10.1038/sc.2017.81.

39. Ferrucci L, Penninx BW, Volpato S, et al. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. J Am Geriatr Soc. 2002;50(12):1947–54.

40. Schaap LA, Pluijm SM, Deeg DJ, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. Am J Med. 2006;119(6):526 e9–17.

41. Drummond MJ, Timmerman KL, Markofski MM, et al. Short-term bed rest increases TLR4 and IL-6 expression in skeletal muscle of older adults. Am J Physiol Regul Integr Comp Physiol. 2013;305(3):R216–23.

42. Aleman H, Esparza J, Ramirez FA, Astiazaran H, Payette H. Longitudinal evidence on the association between interleukin-6 and C-reactive protein with the loss of total appendicular skeletal muscle in free-living older men and women. Age Ageing. 2011;40(4):469–75.