

Online Supplement

Original Research

Psychobiologic Correlates of Stress in Individuals With COPD

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Supplemental Table 1a. Baseline Characteristics of Low vs. High Perceived Stress (Median = 12)

Variables	Low Perceived Stress (<12)	High Perceived Stress (>12)
Demographics		
Age, mean (SD)	65.30 (7.62)	63.87 (8.55)
Female sex, N (%)	6 (26.1)	15 (55.6)
Race, N(%)		
Non-Hispanic White	12 (52.2)	18 (66.7)
Black	9 (39.1)	9 (33.3)
Other	2 (8.7)	0 (0)
Smoking History, N(%)		
Never	2 (8.7)	0 (0)
Former	13 (56.5)	13 (48.1)
Current	8 (34.8)	14 (51.9)
Financial Insecurity, N(%)	1 (4.3)	6 (22.2)
Clinical Characteristics		
FEV1%, mean (SD)	49.46 (18.36)	49.97 (15.46)
FEV1, L, mean (SD)	1.43 (0.61)	1.34 (0.52)
FVC, L, mean (SD)	3.07 (0.91)	2.67 (0.66)
FEV1/FVC, mean (SD)	0.46 (0.12)	0.50 (0.13)
Severity of airflow obstruction n(%)		
FEV1% >80%	1 (4.5)	0 (0)
FEV1% 50-79%	10 (45.5)	11 (47.8)
FEV1% 30-49%	6 (27.3)	9 (39.1)
FEV1% <30%	5 (22.7)	3 (13)
Long-term Oxygen Therapy, N(%)	6 (27.3)	3 (12)
MMRC score, mean (SD)	2.00 (1.17)	1.78 (1.12)
Moderate AECOPD in the prior 12 months, mean (SD)	0.70 (1.06)	0.96 (1.45)
≥1 moderate AECOPD in the prior 12 months, n(%)	10 (43.5)	13 (48.1)
ED visit for AECOPD in the prior 12 months, mean (SD)	0.26 (0.54)	0.41 (1.22)
≥1 ED visit for AECOPD in the prior 12 months, n(%)	5 (21.7)	5 (18.5)
Hospitalization for AECOPD in the prior 12 months, mean (SD)	0.04 (0.21)	0.44 (0.93)
≥1 Hospitalization for AECOPD in the prior 12 months, n(%)	1 (4.3)	6 (22.2)
≥1 Severe exacerbation (ED or hospitalization) in the prior 12 months, n (%)	5 (21.7)	9 (33.3)
≥1 any exacerbations in the prior 12 months (moderate or severe) n (%)	10 (43.5)	14 (51.9)
CAT score, mean (SD)	16.09 (6.36)	22.74 (8.10)
Comorbidities, N(%)		
Coronary artery disease	6 (26.1)	5 (18.5)
Congestive heart failure	4 (17.4)	3 (11.1)
Stroke	3 (13)	1 (3.7)
Acid reflux	12 (52.2)	13 (48.1)
Anxiety	6 (26.1)	13 (48.1)

Depression	5 (21.7)	13 (48.1)
Hypertension	3 (13)	1 (3.7)
Osteoporosis	2 (8.7)	3 (11.1)
Sleep apnea	3 (13)	5 (18.5)
Lung cancer	1 (4.3)	0 (0)
Osteoarthritis	6 (26.1)	5 (18.5)
Health status, N(%)		
Excellent/Very good/Good	18 (78.3)	13 (48.1)
Fair/Poor	5 (21.7)	14 (51.9)
Stress-related Measurements		
Nail cortisol, nmol/g, mean (SD); median (IQR)	0.06 (0.11)	0.05 (0.08)
Serum cortisol, mcg/dl, mean (SD); median (IQR)	9.74 (4.68)	8.19 (3.49)
Fibrinogen, mg/dl, mean (SD) (n=49)	397.41 (96.65)	392.44 (81.13)
C-reactive protein, mg/L, mean (SD)	5.21 (6.37)	4.82 (4.93)
IL-1B, ng/ml, mean (SD) (n=46)	8.14 (28.44)	11.13 (29.14)
IL-6, ng/ml mean (SD) (n=46)	18.91 (68.67)	22.74 (65.31)
Grit score, mean (SD)	4.00 (0.40)	3.32 (0.60)
Total negative life events, mean (SD)	1.13 (1.29)	3.04 (2.46)
Social interactions with close friends, N (%)		
0-2x per week	4 (17.4)	6 (22.2)
3-5x per week	7 (30.4)	6 (22.2)
>5x per week	12 (52.2)	15 (55.6)
PHQ-2, mean (SD)	0.74 (1.21)	2.04 (1.93)
PHQ-2 score 3-6 (depression likely), N(%)	1 (4.3)	6 (22.2)

Abbreviations: AECOPD – acute exacerbation of COPD; CAT – COPD Assessment Test; IL-1B – interleukin 1 beta; IL-6 – interleukin 6; MMRC – modified medical research council; Nmole/g – nanomole per gram; Ng/ml – nanogram per milligram; PHQ-2 – Patient health questionnaire 2; SD – standard deviation.

*Bold font indicates p value <0.05 for differences between high and low groups

Supplemental Table 1b. Baseline Characteristics of Low vs. High Serum Cortisol (Median 9.1 mcg/dl)

Variables	Low Serum Cortisol (<9.1)	High Serum Cortisol (≥9.1)
Demographics		
Age, mean (SD)	63.53 (7.38)	65.53 (8.77)
Female sex, N (%)	14 (56)	7 (28)
Race, N(%)		
Non-Hispanic White	16 (64)	14 (56)
Black	9 (36)	9 (36)
Other	0 (0)	2 (8)
Smoking History, N(%)		
Never	0 (0)	2 (8)
Former	13 (52)	13 (52)
Current	12 (48)	10 (40)
Financial Insecurity, N(%)	4 (16)	3 (12)
Clinical Characteristics		
FEV1%, mean (SD)	47.89 (15.57)	51.64 (18.06)
FEV1, L, mean (SD)	1.27 (0.49)	1.51 (0.61)
FVC, L, mean (SD)	2.76 (0.73)	2.97 (0.88)
FEV1/FVC, mean (SD)	0.46 (0.13)	0.50 (0.12)
Severity of airflow obstruction n(%)		
FEV1% >80%	0 (0)	1 (4.5)
FEV1% 50-79%	10 (43.5)	11 (50)
FEV1% 30-49%	9 (39.1)	6 (27.3)
FEV1% <30%	4 (17.4)	4 (18.2)
Long-term Oxygen Therapy, N(%)	5 (20)	4 (18.2)
MMRC score, mean (SD)	1.68 (1.07)	2.08 (1.19)
Moderate AECOPD in the prior 12 months, mean (SD)	0.92 (1.26)	0.76 (1.33)
≥1 moderate AECOPD in the prior 12 months, n(%)	12 (48)	11 (44)
ED visit for AECOPD in the prior 12 months, mean (SD)	0.52 (1.29)	0.16 (0.37)
≥1 ED visit for AECOPD in the prior 12 months, n(%)	6 (24)	4 (16)
Hospitalization for AECOPD in the prior 12 months, mean (SD)	0.36 (0.91)	0.16 (0.47)
≥1 Hospitalization for AECOPD in the prior 12 months, n(%)	4 (16)	3 (12)
≥1 Severe exacerbation (ED or hospitalization) in the prior 12 months, n (%)	8 (32)	6 (24)
≥1 any exacerbations in the prior 12 months (moderate or severe) n (%)	13 (52)	11 (44)
CAT score, mean (SD)	21.16 (7.49)	18.20 (8.39)
Comorbidities, N(%)		
Coronary artery disease	2 (8)	9 (36)
Congestive heart failure	3 (12)	4 (16)
Stroke	2 (8)	2 (8)
Acid reflux	12 (48)	13 (52)

Anxiety	12 (48)	7 (28)
Depression	11 (44)	7 (28)
Hypertension	1 (4)	3 (12)
Osteoporosis	2 (8)	3 (12)
Sleep apnea	1 (4)	7 (28)
Lung cancer	1 (4)	0 (0)
Osteoarthritis	4 (16)	7 (28)
Health status, N(%)		
Excellent/Very good/Good	18 (72)	13 (52)
Fair/Poor	7 (28)	12 (48)
Stress-related Measurements		
Nail cortisol, nmol/g, mean (SD); median (IQR)	0.05 (0.10)	0.05 (0.09)
Fibrinogen, mg/dl, mean (SD) (n=49)	364.68 (73.61)	425.92 (91.28)
C-reactive protein, mg/L, mean (SD)	4.43 (4.96)	5.57 (6.19)
IL-1B, ng/ml, mean (SD) (n=46)_	8.03 (27.19)	11.35 (30.22)
IL-6, ng/ml mean (SD) (n=46)	24.08 (69.45)	18.16 (64.33)
Perceived stress, mean (SD), median (IQR)	13.84 (6.09)	10.88 (5.45)
Grit score, mean (SD)	3.43 (0.56)	3.85 (0.61)
Total negative life events, mean (SD)	2.60 (2.55)	1.72 (1.74)
Social interactions with close friends, N (%)		
0-2x per week	3 (12)	7 (28)
3-5x per week	5 (20)	8 (32)
>5x per week	17 (68)	10 (40)
PHQ-2, mean (SD)	1.84 (1.91)	1.04 (1.51)
PHQ-2 score 3-6 (depression likely), N(%)	6 (24)	1 (4)

Abbreviations: AECOPD – acute exacerbation of COPD; CAT – COPD Assessment Test; IL-1B – interleukin 1 beta; IL-6 – interleukin 6MMRC – modified medical research council; Nmol/g – nanomole per gram; Ng/ml – nanogram per millimeter; PHQ-2 – Patient health questionnaire 2; SD – standard deviation.

*Bold font indicates p value <0.05 for differences between high and low groups

Supplemental Table 1c. Baseline Characteristics of Low vs. High Nail Cortisol (Median = 0.016 nmol/g)

Variables	Low Nail Cortisol (<0.016)	High Nail Cortisol (≥0.016)
Demographics		
Age, mean (SD)	64.36 (6.83)	64.70 (9.32)
Female sex, N (%)	12 (48)	9 (36)
Race, N(%)		
Non-Hispanic White	18 (72)	12 (48)
Black	6 (24)	12 (48)
Other	1 (4)	1 (4)
Smoking History, N(%)		
Never	2 (8)	0 (0)
Former	11 (44)	15 (60)
Current	12 (48)	10 (40)
Financial Insecurity, N(%)	4 (16)	3 (12)
Clinical Characteristics		
FEV1%, mean (SD)	45.35 (17.26)	54.30 (15.25)
FEV1, L, mean (SD)	1.30 (0.58)	1.48 (0.53)
FVC, L, mean (SD)	2.84 (0.94)	2.87 (0.63)
FEV1/FVC, mean (SD)	0.45 (0.12)	0.51 (0.13)
Severity of airflow obstruction n(%)		
FEV1% >80%	0 (0)	1 (4.5)
FEV1% 50-79%	9 (39.1)	12 (54.5)
FEV1% 30-49%	7 (30.4)	8 (36.4)
FEV1% <30%	7 (30.4)	1 (4.5)
Long-term Oxygen Therapy, N(%)	5 (21.7)	4 (16.7)
MMRC score, mean (SD)	1.72 (1.14)	2.04 (1.14)
Moderate AECOPD in the prior 12 months, mean (SD)	1.24 (1.56)	0.44 (0.77)
≥1 moderate AECOPD in the prior 12 months, n(%)	15 (60)	8 (32)
ED visit for AECOPD in the prior 12 months, mean (SD)	0.60 (1.29)	0.08 (0.28)
≥1 ED visit for AECOPD in the prior 12 months, n(%)	8 (32)	2 (8)
Hospitalization for AECOPD in the prior 12 months, mean (SD)	0.44 (0.96)	0.08 (0.28)
≥1 Hospitalization for AECOPD in the prior 12 months, n(%)	5 (20)	2 (8)
≥1 Severe exacerbation (ED or hospitalization) in the prior 12 months, n (%)	10 (40)	4 (16)
≥1 any exacerbations in the prior 12 months (moderate or severe) n (%)	16 (64)	8 (32)
CAT score, mean (SD)	19.84 (6.72)	19.52 (9.27)
Comorbidities, N(%)		
Coronary artery disease	6 (24)	5 (20)
Congestive heart failure	4 (16)	3 (12)
Stroke	3 (12)	1 (4)
Acid reflux	16 (64)	9 (36)

Anxiety	11 (44)	8 (32)
Depression	9 (36)	9 (36)
Hypertension	0 (0)	4 (16)
Osteoporosis	4 (16)	1 (4)
Sleep apnea	5 (20)	3 (12)
Lung cancer	0 (0)	1 (4)
Osteoarthritis	2 (8)	9 (36)
Health status, N(%)		
Excellent/Very good/Good	17 (68)	14 (56)
Fair/Poor	8 (32)	11 (44)
Stress-related Measurements		
Serum cortisol, mcg/dl, mean (SD); median (IQR)	8.08 (4.55)	9.72 (3.52)
Fibrinogen, mg/dl, mean (SD) (n=49)	378.40 (86.69)	411.63 (86.91)
C-reactive protein, mg/L, mean (SD)	4.49 (4.57)	5.51 (6.50)
IL-1B, ng/ml, mean (SD) (n=46)_	7.35 (17.62)	11.98 (36.05)
IL-6, ng/ml mean (SD) (n=46)	22.07 (68.84)	20.00 (65.03)
Perceived stress, mean (SD), median (IQR)	12.60 (6.04)	12.12 (5.90)
Grit score, mean (SD)	3.57 (0.52)	3.71 (0.71)
Total negative life events, mean (SD)	2.52 (1.94)	1.80 (2.43)
Social interactions with close friends, N (%)		
0-2x per week	8 (32)	2 (8)
3-5x per week	7 (28)	6 (24)
>5x per week	10 (40)	17 (68)
PHQ-2, mean (SD)	1.64 (1.73)	1.24 (1.79)
PHQ-2 score 3-6 (depression likely), N(%)	3 (12)	4 (16)

Abbreviations: AECOPD – acute exacerbation of COPD; CAT – COPD Assessment Test; IL-1B – interleukin 1 beta; IL-6 – interleukin 6MMRC – modified medical research council; Nmol/g – nanomole per gram; Ng/ml – nanogram per millimeter; PHQ-2 – Patient health questionnaire 2; SD – standard deviation.

*Bold font indicates p value <0.05 for differences between high and low groups

Supplemental Table 2. Univariate Analysis of Serum Cortisol (continuous), Nail cortisol (continuous) and Perceived Stress (continuous) with Co-variates of Interest

	Perceived Stress		Serum Cortisol		Nail Cortisol	
	Beta (SE)	P value	Beta (SE)	P value	Beta (SE)	P value
Age	-0.0567 (0.105)	0.5924	0.0551 (0.073)	0.4535	0.001 (0.002)	0.5590
Male Sex	-4.4696 (1.586)	0.0069	1.4374 (1.172)	0.2261	0.0122 (0.027)	0.6519
White Race vs Other	2.9333 (1.672)	0.0857	-1.4363 (1.181)	0.2299	-0.0407 (0.026)	0.1305
Current Smoking Status	1.3864 (1.69)	0.4162	-0.2849 (1.183)	0.8106	-0.0184 (0.027)	0.4936
≥1 Moderate Exacerbations vs none	0.2995 (1.695)	0.8604	-0.6211 (1.175)	0.5996	0.0089 (0.027)	0.7394
≥1 ED Exacerbations vs none	0.175 (2.112)	0.9343	-1.3165 (1.457)	0.3705	-0.0208 (0.033)	0.5325
≥1 Hospitalized Exacerbations vs none	4.2326 (2.357)	0.0788	-1.3492 (1.682)	0.4264	-0.0296 (0.038)	0.4393
FEV1 % predicted	-0.0076 (0.054)	0.8888	0.0384 (0.038)	0.3190	-0.0001 (0.001)	0.9053
FEV1 L	-1.0797 (1.585)	0.4992	1.5359 (1.108)	0.1726	-0.0302 (0.024)	0.2094
FVC L	-1.5471 (1.108)	0.1696	0.3642 (0.803)	0.6524	-0.0208 (0.017)	0.2247
FEV1/FVC ratio	4.1328 (7.14)	0.5656	7.3298 (4.971)	0.1474	-0.0435 (0.108)	0.6905
CAT score	0.3659 (0.093)	0.0002	-0.0703 (0.073)	0.3425	-0.0007 (0.002)	0.6905
MMRC	0.2712 (0.75)	0.7192	0.4987 (0.517)	0.3398	0.0153 (0.012)	0.1923
PHQ2	1.81 (0.411)	<0.0001	-0.4531 (0.332)	0.1793	-0.0055 (0.008)	0.4772
Grit	-5.1214 (1.168)	<0.0001	1.4969 (0.937)	0.1165	0.0154 (0.022)	0.4794
Health status (poor, fair vs Excellent/very good/good)	3.1545 (1.68)	0.0665	-0.2938 (1.21)	0.8091	0.0006 (0.027)	0.9823
Fibrinogen	-0.0009 (0.01)	0.9286	0.0131 (0.007)	0.0517	0.0001 (0.0002)	0.3802
CRP	-0.022 (0.153)	0.8859	0.059 (0.106)	0.5803	-0.0017 (0.002)	0.4677
IL-1b	0.0272 (0.029)	0.3524	0.0129 (0.02)	0.5235	-0.0005 (0.001)	0.3705
IL-6	0.0002 (0.013)	0.9867	0.0074 (0.009)	0.3962	-0.0002 (0.0002)	0.3731
Income						
Tertile1 (<= 12,200) vs Tertile3 (> 24,000)	3 (2.303)	0.2013	1.5333 (1.646)	0.3582	0.0401 (0.036)	0.2774
Tertile2 (>12,200-24,000) vs Tertile3(> 24,000)	-0.6026 (2.258)	0.7911	1.3931 (1.614)	0.3942	0.0718 (0.036)	0.0515
Financial insecurity Yes vs No	5.5615 (2.299)	0.0194	-0.3027 (1.693)	0.8588	-0.001 (0.038)	0.9786
Social interactions with close friends						
0-2x/week vs ≥5x/ week	2.1481 (2.213)	0.3365	1.4927 (1.509)	0.3277	-0.0492 (0.034)	0.1523
3-5x/week vs ≥5x/ week	0.302 (2.018)	0.8816	2.1974 (1.376)	0.1170	-0.0498 (0.031)	0.1132
Total negative events	1.2488 (0.342)	0.0006	-0.1782 (0.268)	0.5087	-0.0119 (0.006)	0.0467

Beta coefficient (standard error) from regression models(glm) provided

Supplemental Figure 1

The SAS System

