Online Supplement

Perceived Stress is Associated with Health Outcomes, Platelet Activation, and Oxidative Stress in COPD

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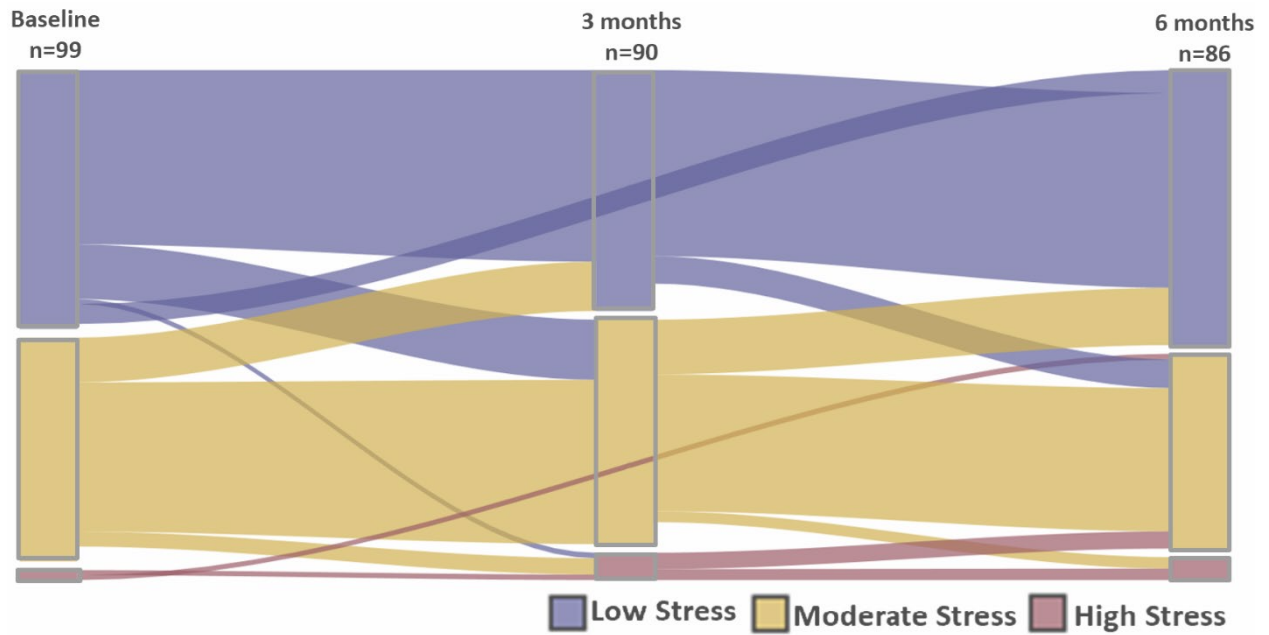
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Supplemental Figure 1: Flow of participants between perceived stress score categories low (0-13), medium (14-26), and high (27-40) during the 6-month study period

Baseline
n=99

3 months
n=90

6 months
n=86

Low Stress   Moderate Stress   High Stress

Supplemental Table 1. Effect Estimates of the Association Between a 4-point increment in Perceived Stress Score with COPD Morbidity

	All Participants	GOLD≤2	GOLD≥3
Respiratory symptoms	**Mean Difference (95% CI)**	**Mean Difference (95% CI)**	**Mean Difference (95% CI)**
CAT	**0.91 (0.40, 1.43)**	0.49 (-0.15, 1.12)	**1.50 (0.74, 2.25)**
mMRC	0.03 (-0.05, 0.10)	0.01 (-0.08, 0.09)	**0.11 (0.01, 0.22)**
SGRQ	**2.17 (1.21, 3.13)**	1.07 (-0.03, 2.18)	**3.95 (2.39, 5.52)**
CCQ	**0.11 (0.05, 0.17)**	0.03 (-0.03, 0.10)	**0.22 (0.13, 0.32)**
ECSC	**0.36 (0.11, 0.61)**	0.17 (-0.17, 0.51)	**0.64 (0.38, 0.56)**
Exacerbations*	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
Any	1.17 (0.96, 1.42)	1.28 (0.92, 1.78)	1.04 (0.81, 1.33)
Moderate/Severe	1.11 (0.90, 1.37)	1.32 (1.00, 1.76)	1.01 (0.75, 1.35)

CAT = COPD Assessment Test; mMRC = Modified Medical Research Council Questionnaire; SGRQ = St. George's Respiratory Questionnaire; CCQ = Clinical COPD Questionnaire; ECSC: Ease of Cough and Sputum Clearance Questionnaire. *Exacerbations assessed as having at least 1 exacerbation over the 12-month study period (yes/no) using repeated measures of PSS scores collected at each study visit.

Supplemental Table 2. Effect Estimates of the Association Between Perceived Stress Score Categories with COPD Morbidity

	All Participants		GOLD≤2		GOLD≥3	
	Moderate Stress	High Stress	Moderate Stress	High Stress	Moderate Stress	High Stress
	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)
Respiratory Symptoms						
CAT	**2.39 (0.80, 3.97)**	**7.86 (5.10, 10.63)**	0.84 (-1.05, 2.74)	**6.04 (3.06, 9.02)**	**3.87 (1.47, 6.27)**	**14.60 (11.72, 17.48)**
mMRC	0.20 (-0.05, 0.44)	0.18 (-0.31, 0.68)	0.02 (-0.25, 0.29)	0.35 (-0.15, 0.86)	**0.53 (0.16, 0.90)**	0.25 (-0.64, 1.15)
SGRQ	3.38 (-0.02, 6.78)	**12.04 (5.60, 18.47)**	-0.60 (-4.68, 3.49)	**6.89 (0.16, 13.63)**	**9.16 (4.38, 13.93)**	**29.96 (23.38, 36.54)**
CCQ	**0.29 (0.07, 0.52)**	**0.70 (0.38, 1.02)**	0.02 (-0.23, 0.27)	**0.48 (0.22, 0.74)**	**0.60 (0.232, 0.97)**	**1.62 (1.17, 2.08)**
ECSC	**1.46 (0.63, 2.28)**	**3.20 (1.41, 4.99)**	0.95 (-0.22, 2.12)	2.35 (0.04, 4.65)	**2.00 (0.99, 3.01)**	**5.19 (4.00, 6.38)**
Exacerbations*	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Any	0.95 (0.52, 1.74)	3.90 (0.83, 18.2)	0.90 (0.35, 2.28)	2.95 (0.21, 41.13)	0.74 (0.31, 1.76)	2.03 (0.14, 28.61)
Moderate/Severe	0.77 (0.37, 1.57)	**4.15 (1.28, 13.47)**	1.10 (0.29, 4.19)	2.45 (0.28, 21.63)	0.45 (0.18, 1.12)	5.89 (0.93, 37.37)

Reference group is Low Stress (PSS 0-13). CAT = COPD Assessment Test; mMRC = Modified Medical Research Council Questionnaire; SGRQ = St. George's Respiratory Questionnaire; CCQ = Clinical COPD Questionnaire; ECSC: Ease of Cough and Sputum Clearance Questionnaire. *Exacerbations assessed as having at least 1 exacerbation over the 12-month study period (yes/no) using repeated measures of PSS scores collected at each study visit.

Supplemental Table 3. Sensitivity Analysis of the individual and combined effects of symptoms of Depression or Anxiety, Food insecurity and Area Deprivation index on the Association of Perceived Stress Score on Respiratory Outcomes

Respiratory symptoms	Depression or Anxiety Mean Difference (95% CI)	Food insecurity Mean Difference (95% CI)	Area Deprivation Index Mean Difference (95% CI)	Combined Effects Mean Difference (95% CI)
CAT	**0.84 (0.28, 1.40)**	**0.89 (0.37, 1.41)**	**0.91 (0.40, 1.43)**	**0.80 (0.24, 1.37)**
mMRC	0.01 (-0.06, 0.09)	0.02 (-0.06, 0.09)	0.03 (-0.04, 0.10)	0.004 (-0.07, 0.08)
SGRQ	**1.96 (0.93, 2.99)**	**2.14 (1.16, 3.12)**	**2.21 (1.24, 3.17)**	**1.99 (0.95, 3.04)**
CCQ	**0.09 (0.02, 0.15)**	**0.11 (0.04, 0.17)**	**0.11 (0.05, 0.17)**	**0.08 (0.02, 0.15)**
ECSC	**0.30 (0.03, 0.58)**	**0.36 (0.10, 0.61)**	**0.37 (0.11, 0.62)**	**0.30 (0.03, 0.58)**
Exacerbations*	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Any	1.17 (0.95, 1.44)	1.15 (0.94, 1.40)	1.19 (0.98, 1.45)	1.14 (0.96, 1.37)
Moderate/Severe	1.16 (0.93, 1.45)	1.08 (0.87, 1.34)	1.13 (0.92, 1.38)	1.12 (0.98, 1.27)

CAT = COPD Assessment Test; mMRC = Modified Medical Research Council Questionnaire; SGRQ = St. George's Respiratory Questionnaire; CCQ = Clinical COPD Questionnaire; ECSC: Ease of Cough and Sputum Clearance Questionnaire. *Exacerbations assessed as having at least 1 exacerbation over the 12-month study period (yes/no) using repeated measures of PSS scores collected at each study visit.

Supplemental Table 4. Mean Difference with 95% confidence intervals and interaction p-values of the Association Between a 4-point increment in Perceived Stress Score with Biomarkers stratified by COPD severity.

	All Participants	Mild-Moderate COPD (GOLD≤2)	Severe COPD (GOLD≥3)	Interaction P-value
Platelet activation				

Urine 11-dehydro-Thromboxane B2 (pg/mg Creatinine)	2.8 (-0.5, 6.3)	**6.0 (1.6, 10.6)**	-1.3 (-6.3, 4.0)	0.14
Oxidative stress				
Urine TBARS (um/mg Creatinine)	-2.1 (-5.8, 1.6)	1.1 (-3.4, 5.8)	**-6.5 (-11.6, -1.0)**	0.07
Urine 8OHDG (ng/mg Creatinine)	-0.3 (-3.8, 3.3)	2.0 (-3.1, 7.4)	-3.4 (-9.4, 3.0)	0.13
Urine 8-Isoprostane (pg/mg Creatinine)	1.9 (-1.6, 5.5)	**4.9 (-0.7, 9.3)**	-2.6 (-7.7, 2.8)	0.06
Inflammation				
TNF-α (pg/ml)	0.7 (-0.6, 1.9)	0.7 (-1.0, 2.5)	0.1 (-1.6, 1.8)	0.99
Interleukin 6 (pg/ml)	2.8 (-3.5, 9.6)	2.8 (-6.8, 13.3)	5.1 (-1.8, 12.5)	0.52
Interleukin 8 (pg/ml)	-0.7 (-3.2, 1.8)	0.2 (-2.7, 3.2)	-2.5 (-6.6, 1.9)	0.17
IFN-γ (pg/ml)	-0.6 (-5.6, 4.7)	2.2 (-10.2, 6.5)	-2.2 (-6.4, 5.7)	0.39

TBARS= Thiobarbituric acid reactive species; 8-OHdG= 8-hydroxydeoxyguanosine

Supplemental Table 5. Effect Estimates of the Association Between Perceived Stress Score Categories with Biomarkers.

	All Participants		GOLD≤2		GOLD≥3	
	Moderate Stress	High Stress	Moderate Stress	High Stress	Moderate Stress	High Stress
	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)
Platelet activation						
Urine Thromboxane B2 (pg/mg Creatinine)	8.7 (-6.3, 26.1)	25.1 (-0.3, 56.9)	**20.1 (3.1, 40.0)**	**52.9 (22.1, 91.6)**	-10.7 (-31.9, 17.1)	-11.6 (-30.9, 13.2)
Oxidative Stress						
Urine TBARS (um/mg Creatinine)	0.3 (-12.9, 15.5)	**-25.5 (-43.8, -1.2)**	-2.2 (-19.6, 19.0)	-9.0 (-33.8, 25.2)	3.0 (-13.1, 22.1)	**-53.9 (-64.8, -39.7)**
Urine 8OHDG (ng/mg Creatinine)	-6.1 (-18.9, 8.8)	-0.2 (-28.7, 39.5)	-3.0 (-20.9, 19.0)	5.5 (-37.1, 76.9)	-13.8 (-31.6, 8.7)	-0.8 (-30.5, 41.7)
Urine 8-Isoprostane (pg/mg Creatinine)	-3.9 (-16.2, 10.1)	**40.1 (11.5, 76.0)**	6.7 (-8.3, 24.3)	**59.4 (20.6, 110.8)**	-18.5 (-35.2, 2.5)	16.7 (-10.9, 52.9)
Inflammation						
TNF-α (pg/ml)	1.6 (-3.7, 7.2)	0.8 (-8.4, 10.9)	4.3 (-2.3, 11.4)	1.6 (-9.3, 13.8)	-1.2 (-8.0, 6.0)	-2.3 (-20.1, 19.6)
Interleukin 6 (pg/ml)	7.3 (-12.4, 31.5)	12.9 (-34.7, 95.2)	1.6 (-24.8, 37.2)	-3.4 (-49.9, 86.5)	15.6 (-13.6, 54.6)	47.9 (-11.8, 147.8)
Interleukin 8 (pg/ml)	0.3 (-9.0, 10.6)	6.7 (-8.5, 24.3)	3.6 (-6.9, 15.3)	11.5 (-5.5, 31.5)	-7.4 (-24.4, 13.5)	-15.1 (-30.1, 3.1)
IFN-γ (pg/ml)	-4.7 (-21.3, 15.3)	-13.9 (-44.5, 33.5)	-0.9 (-21.4, 24.9)	2.7 (-40.9, 78.6)	-5.6 (-33.8, 34.6)	-18.7 (-65.4, 91.1)

Reference group is Low Stress (PSS 0-13). TBARS= Thiobarbituric acid reactive species; 8-OHdG= 8-hydroxydeoxyguanosine