Original Research
Urine and Plasma Markers of Platelet Activation and Respiratory Symptoms in COPD

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Supplemental Table 1: Baseline characteristics by study enrollment

Characteristic [mean ± SD or N (%)]	CLEAN AIR Study N = 113	CURE COPD Study N = 56
Age (years)	65.6 ± 8.3	68.4 ± 7.6
Female	57 (50.4)	30 (53.6)
Black Race	34 (30.1)	34 (60.7)
Education (> high school)	67 (59.3)	26 (46.4)
Annual Income		
<$20,000	44 (38.9)	27 (48.2)
$20,000-$39,999	31 (27.4)	13 (23.2)
≥ $40,000	27 (23.9)	11 (19.6)
Don't Know / Refused	11 (9.7)	5 (8.9)
BMI	32.2 ± 8.3	31.1 ± 7.7
Underweight (<18.5)	2 (1.8)	1 (1.8)
Normal/Overweight (18.5 to <30)	43 (38.1)	26 (46.4)
Obese (≥30)	68 (60.2)	29 (51.8)
Smoking pack-years	52.5 ± 33.1	37.4 ± 20.9
FEV1 % Predicted	54.6 ± 16.8	52.1 ± 17.8
History of Cardiac or Vascular Disease	54 (47.8)	25 (44.6)
Heart Attack	16 (14.2)	9 (16.1)
Percutaneous Coronary Angiography	16 (14.2)	10 (17.9)
Congestive Heart Failure	20 (17.7)	11 (19.6)
Circulatory Disease / Claudication	25 (22.1)	11 (19.6)
Stroke	11 (9.7)	7 (12.5)
History of Diabetes	25 (22.1)	10 (17.9)
Antiplatelet Therapy	62 (54.9)	25 (44.6)
Aspirin	62 (54.9)	25 (44.6)
Clopidogrel	7 (6.2)	5 (8.9)
Coronary Artery Calcium (Agatston Score)	683 ± 1429	800 ± 1225
No Coronary Artery Disease (Agatston=0)	21 (22.6)	8 (18.6)
Any Coronary Artery Disease (Agatston>0)	72 (77.5)	35 (81.4)
Urine 11-dehydro-thromboxane B2 (pg/mg Creatinine)	5500 ± 2748	3503 ± 1991
Plasma Soluble CD40L (pg/mL)	241.8 ± 323	N/A
Plasma Soluble P-selectin (ng/mL)	39.8 ± 12.3	N/A

Supplemental Table 2: Sample availability and biomarker distribution including baseline comparisons by history of cardiovascular disease, presence of subclinical coronary artery disease (defined as coronary artery calcium [Agatston] score >0), and antiplatelet therapy using Wilcoxon rank-sum test. Asterisk (*) represents visits and biomarkers performed only in the CLEAN AIR study (N=113).

	Urine 11-dehydro-thromboxane B2 (pg/mg Creatinine)		***p-value***	***Plasma Soluble CD40L (pg/mL)****		***p-value***	***Plasma Soluble P-selectin (ng/mL)****		***p-value***
Samples Available (N) | Missing (N [%])									
All Visits	630	103 (16.3%)		505	60 (11.9%)		505	60 (11.9%)	
3-Month Pre-Randomization*	111	2 (1.8%)		106	7 (6.2%)		106	7 (6.2%)	
Baseline / Randomization	163	6 (3.6%)		107	6 (5.3%)		107	6 (5.3%)	
1 Week Follow-Up*	103	10 (8.8%)		104	9 (8%)		104	9 (8%)	
3 Month Follow-Up	131	38 (22.5%)		95	18 (15.9%)		95	18 (15.9%)	
6 Month Follow-Up	122	47 (27.8%)		93	20 (17.7%)		93	20 (17.7%)	
Biomarker Distributions (median [IQR] unless otherwise specified)									
All Visits (mean ± SD)	5231 ± 5811.3			219 ± 323.5			40.6 ± 13.1		
All Visits	4439 (2921, 6296)			140.6 (106.1, 205.2)			39.4 (32.7, 46.4)		
3-Month Pre-Randomization*	5433 (3481, 7930)			134.3 (98.4, 219.8)			40.6 (33.1, 46.6)		
Baseline / Randomization	4443 (2785, 6138)			146.8 (108.7, 251.7)			39.0 (31.5, 46.1)		
1 Week Follow-Up*	4689 (3318, 6368)			140.6 (108.2, 207.3)			38.5 (32.9, 45.3)		
3 Month Follow-Up	3775 (2399, 5486)			151.1 (107.2, 222.8)			40.2 (33.6, 48.0)		
6 Month Follow-Up	4269 (2724, 5560)			141.1 (108.9, 174.9)			39.2 (31.4, 46.3)		
Baseline Biomarker Distribution by Subgroups (median [IQR])									
History of Cardiovascular Disease	4406 (2834, 5925)		0.9	162.0 (110.9, 263.1)		0.2	39.4 (32.7, 45.1)		0.7
No History of Cardiovascular Disease	4595 (2739, 6264)			140.5 (108.7, 207.3)			38.5 (29.3, 47.4)		
Subclinical Coronary Artery Disease Present (Agatston>0)	4136 (2767, 6043)		0.3	162.0 (120.1, 257.7)		0.2	38.7 (32.6, 46.9)		0.1
Subclinical Coronary Artery Disease Absent (Agatston=0)	5082 (2781, 6202)			135.3 (104.4, 211.1)			32.8 (28.1, 42.3)		
Antiplatelet Therapy User	3284 (2141, 4996)		<0.0001	159.9 (111.4, 263.3)		0.3	38.7 (31.9, 45.1)		0.7
Antiplatelet Therapy Non-User	5483 (3865, 7298)			138.7 (108.7, 216.0)			39.6 (30.5, 46.9)		

Supplemental Table 3: Disaggregated between-person and within-person associations between urinary 11-dehydro-thromboxane B2 and respiratory outcomes

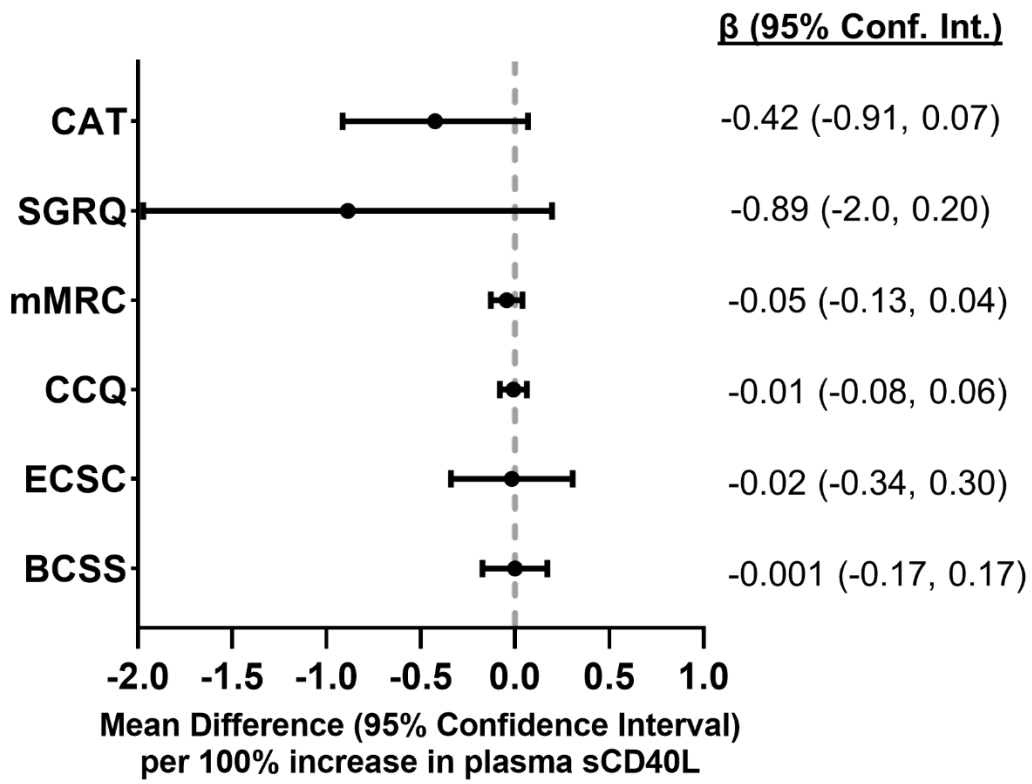
Outcome	Between-Person Effect	Within-Person Effect
CAT	1.1 (-1.6, 3.9)	0.74 (0.04, 1.4)
SGRQ	2.9 (-3.7, 9.5)	1.8 (0.28, 3.4)
mMRC	0.10 (-0.14, 0.35)	0.09 (-0.03, 0.20)
CCQ	0.13 (-0.22, 0.48)	0.13 (0.02, 0.24)
ECSC	0.84 (-0.41, 2.1)	0.76 (0.35, 1.2)
BCSS	-0.04 (-0.75, 0.66)	0.38 (0.02, 0.73)

CAT = COPD Assessment Test; SGRQ = St. George's Respiratory Questionnaire; mMRC = Modified Medical Research Council Questionnaire; CCQ = Clinical COPD Questionnaire: ECSC: Ease of Cough and Sputum Clearance Questionnaire; BCSS = Breathlessness, Cough and Sputum Scale

Supplemental Table 4: Biomarker distribution by history of cardiovascular disease and presence of subclinical coronary artery disease (defined as coronary artery calcium [Agatston] score >0) among antiplatelet therapy non-users using Wilcoxon rank-sum test.

Subgroup	Urine 11-dehydro-thromboxane B2 (pg/mg Creatinine)			Plasma Soluble CD40L (pg/mL)			Plasma Soluble P-selectin (ng/mL)		
	N	Median (IQR)	p-value	N	Median (IQR)	p-value	N	Median (IQR)	p-value
History of Cardiovascular Disease	29	5102 (3865, 7840)	0.7	17	135.3 (105.9, 216.0)	0.8	17	39.4 (35.9, 46.1)	0.8
No History of Cardiovascular Disease	52	5512 (3913, 6667)		33	140.4 (114.4, 212.6)		33	39.8 (29.0, 46.9)	
Subclinical Coronary Artery Disease Present (Agatston>0)	48	5531 (4053, 7579)	0.4	29	151.2 (120.1, 228.5)	0.4	29	41.8 (35.8, 50.1)	0.03
Subclinical Coronary Artery Disease Absent (Agatston=0)	16	5102 (3498, 6567)		11	127.3 (105.9, 179.4)		11	31.5 (27.2, 36.4)	

Supplemental Figure 1: Association between plasma soluble CD40L and respiratory outcomes among individuals with COPD



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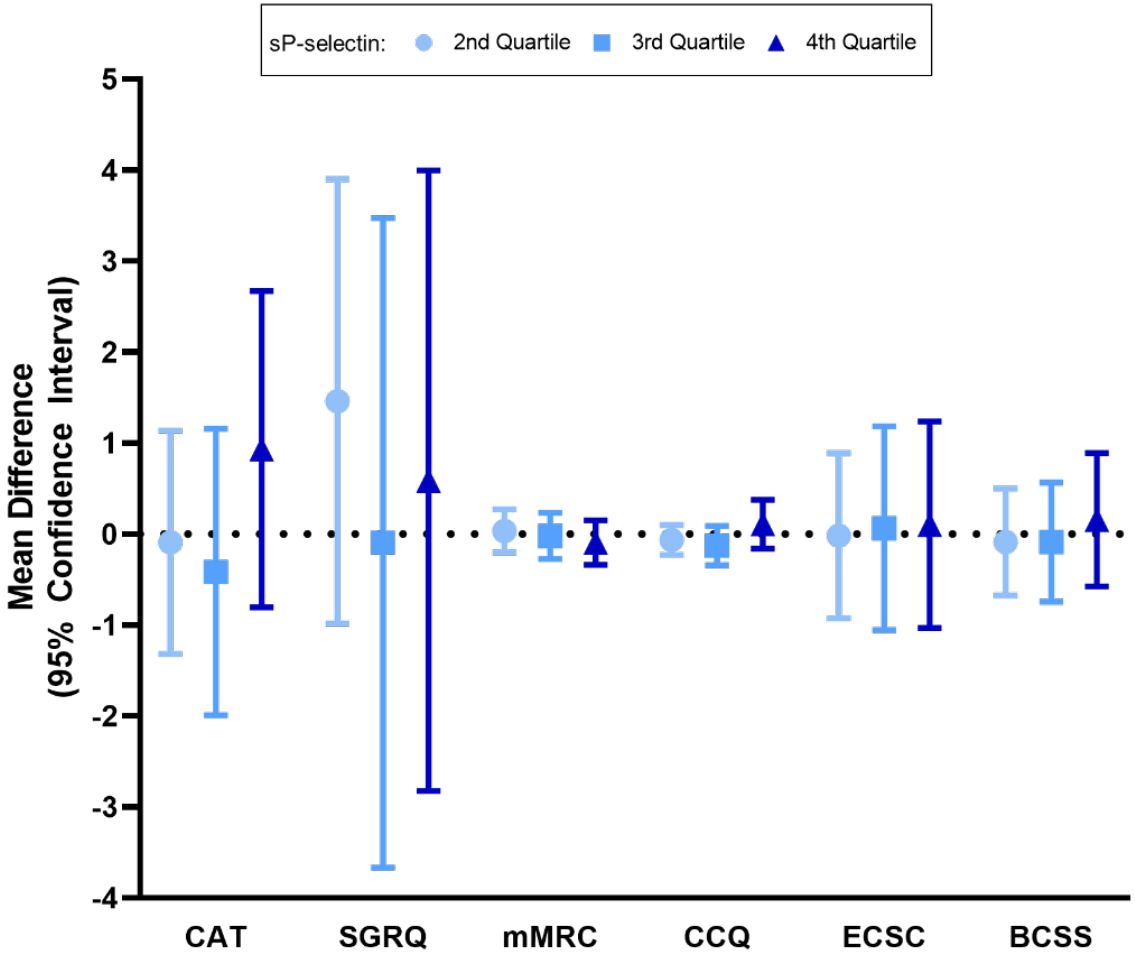
Supplemental Figure 2: Association between plasma soluble P-selectin and respiratory outcomes among individuals with COPD



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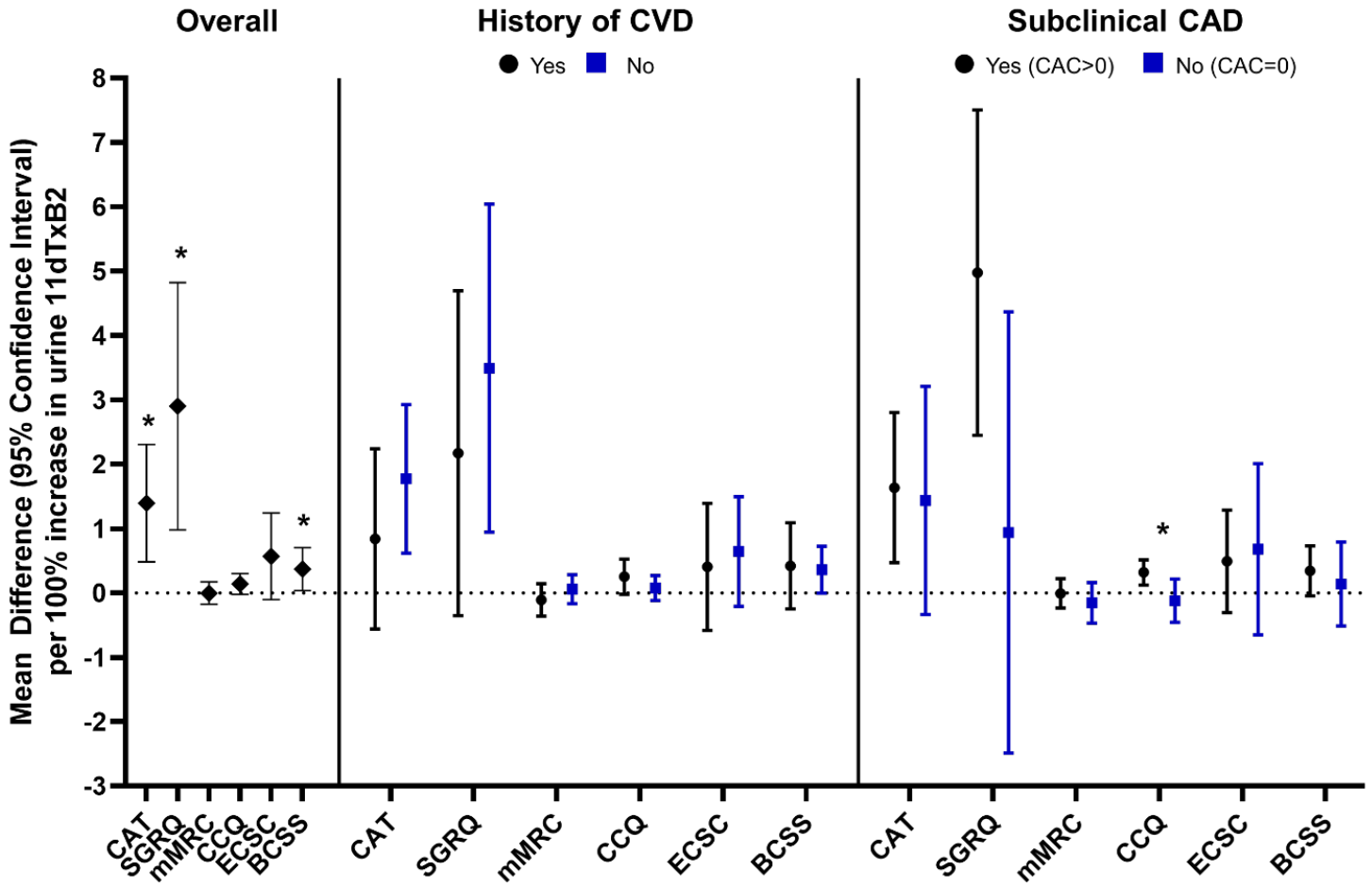
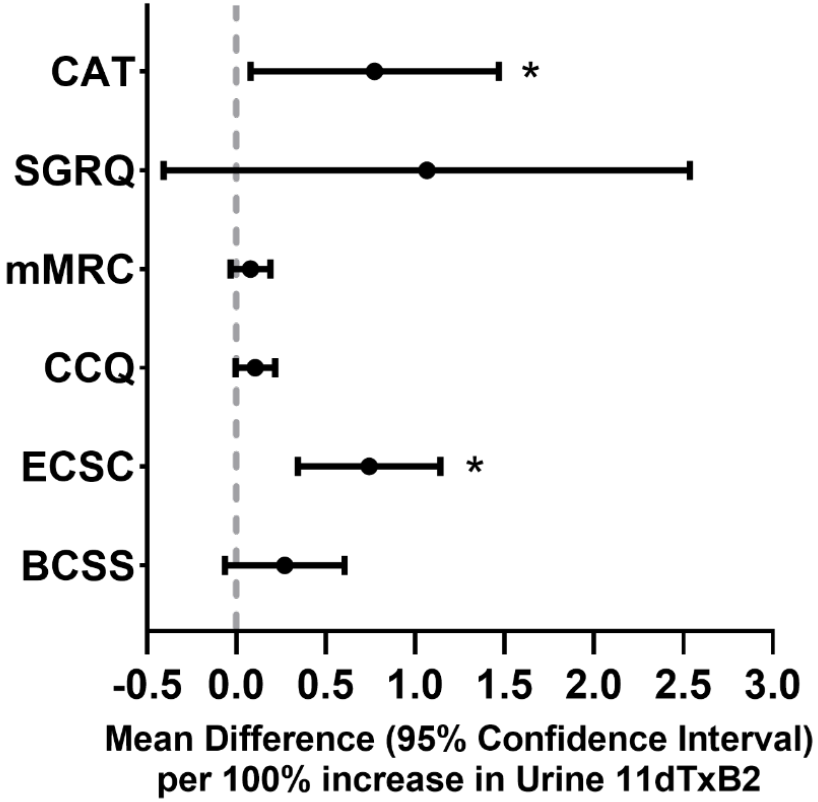
Supplemental Figure 3: Association between urine 11-dehydro-thromboxane B2 and respiratory outcomes limited to antiplatelet therapy non-users unstratified and with subgroup analyses by history of cardiovascular disease (CVD) and subclinical coronary artery disease (CAD) defined based on coronary artery calcium (CAC) Agatston score. For overall analysis asterisk denotes p-value < 0.05 and for subgroup analyses asterisk denotes p-interaction < 0.05.



Supplemental Figure 4: Association between urine 11-dehydro-thromboxane B2 and respiratory outcomes in a limited sample of participants and study visits where plasma biomarker results were also available. Asterisk denotes a statistically significant association ($p<0.05$).



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