

Biomarkers of the L-arginine / dimethylarginine / nitric oxide pathway in people with chronic airflow obstruction and obstructive sleep apnoea

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SUPPLEMENTARY TABLES

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Table S1. Chronic airflow obstruction, respiratory symptoms, and sleep-related symptoms in the study population by sex.

Variable	Total	Female	Male	P*
Chronic airflow obstruction¹				
Yes	78 (10.9)	46 (13.7)	32 (8.5)	0.03
Respiratory symptoms²				
Chronic cough	82 (11.5)	41 (12.2)	41 (10.9)	0.58
Chronic phlegm	67 (9.4)	28 (8.3)	39 (10.3)	0.36
Wheezing	173 (24.3)	79 (23.5)	94 (24.9)	0.66
Sleepiness				
Mean ESS score	6.1 ± 3.9	5.7 ± 3.9	6.4 ± 3.9	0.017
ESS > 10	94 (13.2)	40 (11.9)	54 (14.3)	0.34
Daytime sleepiness ≥ 3 days/week	147 (20.8)	74 (22.2)	73 (19.5)	0.38
Feeling rested < 1 time/week	99 (17.4)	46 (17.7)	53 (17.2)	0.88
OSA-related symptoms				
Loud snoring ≥ 3 nights/week	134 (26.0)	33 (15.1)	101 (34.0)	<0.001
Observed apneas ≥ 1 night/week	46 (8.7)	9 (3.6)	37 (13.2)	<0.001
Nocturnal sweating ≥ 3 nights/week	76 (10.8)	41 (12.4)	35 (9.4)	0.21
Nocturnal GER ≥ 1 night/week	40 (5.7)	21 (6.4)	19 (5.1)	0.46
MAP Index				
Mean MAP Index	0.36 ± 0.23	0.21 ± 0.16	0.50 ± 0.19	<0.001
MAP > 0.5	215 (30.2)	24 (7.1)	191 (50.7)	<0.001

Data are presented as mean ± standard deviation and as number of observations (n) with the percent value given in brackets. *p values from chi-squared test (categorical) and Student's t test (continuous) comparing males with females. ¹Chronic airflow obstruction was defined as post-bronchodilator FEV1/FVC < lower limit of the normal range as described by [7]. ²Chronic cough or phlegm was defined as positive if present for three months or more per year, wheezing was defined as positive if wheezing / whistling in the chest had been noted at any time during the preceding 12 months. Abbreviations: ESS, Epworth Sleepiness Scale; nGER, nocturnal gastroesophageal reflux; MAP, Multivariable Apnea Prediction Index; OSA, obstructive sleep apnea.

Table S2. Distribution of biomarkers of interest by age group and smoking status.

Variable	Age (years)					Smoking status			
	40-49 (n=232)	50-59 (n=220)	60-69 (n=139)	≥70 (n=122)	p-value*	Never (n=278)	Past (n=302)	Current (n=131)	p-value*
ADMA, median (IQR)	0.48 (0.42, 0.54)	0.50 (0.45, 0.55)	0.51 (0.46, 0.56)	0.54 (0.49, 0.59)	<0.001	0.50 (0.44, 0.55)	0.51 (0.45, 0.57)	0.52 (0.46, 0.57)	0.16
SDMA, median (IQR)	0.47 (0.42, 0.54)	0.48 (0.44, 0.54)	0.51 (0.46, 0.60)	0.60 (0.51, 0.69)	<0.001	0.50 (0.45, 0.58)	0.50 (0.45, 0.58)	0.46 (0.42, 0.54)	0.003
L-Arginine, median (IQR)	137.2 (125.3, 158.6)	149.9 (130.4, 164.5)	146.2 (127.9, 166.5)	140.7 (126.4, 162.0)	0.008	138.0 (123.9, 158.2)	146.2 (129.0, 165.2)	149.4 (134.5, 169.2)	<0.001
L-Citrulline, median (IQR)	36.6 (30.9, 43.3)	38.9 (32.5, 45.7)	41.8 (36.0, 49.6)	45.8 (38.4, 56.8)	<0.001	39.7 (33.6, 47.3)	39.7 (32.3, 48.0)	39.0 (32.8, 46.7)	0.97
L-Ornithine, median (IQR)	75.9 (62.1, 91.0)	79.7 (68.4, 93.4)	81.0 (66.8, 96.7)	86.3 (75.5, 102.6)	<0.001	79.1 (66.7, 92.5)	80.9 (67.3, 95.3)	81.4 (67.3, 99.5)	0.38
Arg/ADMA Ratio, median (IQR)	296.3 (252.6, 330.5)	294.8 (262.6, 345.1)	287.9 (250.2, 332.4)	269.4 (240.8, 299.4)	<0.001	284.6 (248.6, 323.8)	290.2 (255.4, 339.1)	290.7 (259.0, 326.7)	0.11
Cit/Arg Ratio, median (IQR)	0.26 (0.22, 0.31)	0.26 (0.22, 0.32)	0.28 (0.23, 0.34)	0.32 (0.26, 0.40)	<0.001	0.28 (0.24, 0.34)	0.27 (0.22, 0.33)	0.26 (0.22, 0.31)	0.05
Orn/Arg Ratio, median (IQR)	0.52 (0.44, 0.66)	0.54 (0.45, 0.65)	0.55 (0.46, 0.65)	0.60 (0.52, 0.70)	0.0001	0.57 (0.46, 0.67)	0.54 (0.46, 0.66)	0.53 (0.45, 0.65)	0.36

Data are presented as medians and inter quartile ranges. *p-value from Kruskal-Wallis test. Abbreviations: ADMA, asymmetric dimethylarginine; Arg, L-arginine; BMI, body mass index; Cit, L-citrulline; Orn, L-ornithine; SDMA, symmetric dimethylarginine.

Table S3. Chronic airflow obstruction and/or obstructive sleep apnoea risk and biomarker concentrations among the study population stratified by BMI categories.

Variable	<20	20.0-22.5	22.5-25	25-27.5	27.5-30	30-32.5	32.5-35	>35	p-value*
N (%)	13 (1.8)	57 (8.0)	131 (18.4)	167 (23.4)	145 (20.3)	97 (13.6)	50 (7.0)	53 (7.4)	-
Males (%)	4 (30.8)	18 (31.6)	57 (43.5)	95 (56.9)	93 (64.1)	58 (59.8)	29 (58.0)	23 (43.4)	<0.001
Age (years)	65 ± 13	55 ± 12	55 ± 11	58 ± 13	58 ± 12	57 ± 11	61 ± 11	55 ± 9	0.006
MAP/CAO categories									
-MAP/-CAO	7 (53.9)	47 (82.5)	100 (76.3)	122 (73.1)	91 (62.8)	45 (46.4)	16 (32.0)	11 (20.8)	<0.001
-MAP/+CAO	6 (46.2)	9 (15.7)	19 (14.5)	14 (8.4)	5 (3.5)	2 (2.1)	3 (6.0)	1 (1.9)	
+MAP/-CAO	0 (0)	0 (0)	11 (8.4)	26 (15.6)	44 (30.4)	48 (49.5)	28 (56.0)	39 (73.6)	
+MAP/+CAO	0 (0)	1 (1.8)	1 (0.8)	5 (3.0)	5 (3.5)	2 (2.1)	3 (6.0)	2 (3.8)	
Biomarker levels									
ADMA (μmol/L)	0.52 (0.49, 0.58)	0.48 (0.45, 0.55)	0.51 (0.43, 0.57)	0.50 (0.44, 0.57)	0.50 (0.45, 0.55)	0.50 (0.44, 0.54)	0.52 (0.47, 0.55)	0.53 (0.48, 0.59)	0.092
SDMA (μmol/L)	0.54 (0.48, 0.63)	0.49 (0.44, 0.55)	0.49 (0.45, 0.57)	0.52 (0.45, 0.60)	0.50 (0.45, 0.58)	0.51 (0.44, 0.55)	0.49 (0.44, 0.61)	0.47 (0.44, 0.50)	0.025
L-Arginine (μmol/L)	142.9 (125.6, 159.7)	135.9 (124.1, 158.0)	141.0 (123.5, 163.2)	142.5 (125.9, 164.1)	144.0 (132.3, 163.1)	150.1 (129.6, 167.6)	147.1 (134.9, 161.2)	147.8 (128.6, 178.8)	0.336
L-Citrulline (μmol/L)	39.1 (31.4, 54.8)	37.7 (31.6, 46.3)	39.8 (32.9, 47.2)	39.2 (34.3, 47.2)	40.7 (33.9, 50.0)	37.4 (31.1, 44.4)	44.1 (33.3, 54.0)	39.3 (33.6, 48.4)	0.089
L-Ornithine (μmol/L)	81.4 (61.6, 89.9)	70.9 (61.3, 88.4)	78.9 (65.9, 93.6)	85.0 (70.7, 98.1)	79.7 (67.4, 95.4)	76.8 (66.8, 91.5)	83.8 (66.4, 95.3)	85.5 (75.7, 102.0)	0.004
Arg / ADMA Ratio	275.0 (236.5, 295.9)	282.8 (253.7, 312.9)	293.8 (247.3, 334.6)	277.1 (246.2, 323.8)	295.1 (259.5, 333.2)	303.3 (264.5, 335.7)	294.1 (259.7, 328.7)	281.3 (244.0, 330.2)	0.128
Cit / Arg Ratio	0.26 (0.23, 0.40)	0.28 (0.23, 0.35)	0.27 (0.23, 0.33)	0.29 (0.24, 0.33)	0.28 (0.23, 0.33)	0.24 (0.21,0.30)	0.30 (0.22,0.38)	0.27 (0.23, 0.32)	0.016
Orn / Arg Ratio	0.55 (0.47, 0.60)	0.53 (0.46, 0.64)	0.55 (0.44, 0.66)	0.58 (49, 0.71)	0.53 (0.46, 0.66)	0.50 (0.44, 0.62)	0.56 (0.47, 0.67)	0.59 (0.49, 0.74)	0.012

Data are presented as mean ± standard deviation or as median with interquartile ranges in square brackets for continuous variables as appropriate. Categorical variables are presented as number of observations (N) with the percent value given in brackets. *p values from Student's t test for means, Kruskal-Wallis test for medians (continuous) and Chi-square test (categorical). Abbreviations: ADMA, asymmetric dimethylarginine; Arg, L-arginine; BMI, body mass index; CAO, Chronic airflow obstruction, Cit, L-citrulline; CVD, cardiovascular disease; MAP, Multivariable apnea prediction index, Orn, L-ornithine; SDMA, symmetric dimethylarginine.

Table S4. Distribution of biomarkers of interest based on the presence or absence of hypertension, cardiovascular disease and diabetes.

	Hypertension			Cardiovascular disease			Diabetes		
	Yes (n=177)	No (n=524)	p- value*	Yes (n=106)	No (n=606)	p-value*	Yes (n=20)	No (n=689)	p-value*
ADMA, median (IQR)	0.52 (0.46, 0.58)	0.50 (0.44, 0.55)	0.02	0.50 (0.46, 0.58)	0.51 (0.44, 0.56)	0.24	0.51 (0.43, 0.61)	0.51 (0.45, 0.56)	0.79
SDMA, median (IQR)	0.53 (0.46, 0.62)	0.49 (0.44, 0.56)	<0.001	0.54 (0.49, 0.64)	0.49 (0.44, 0.56)	<0.001	0.51 (0.47, 0.63)	0.50 (0.44, 0.57)	0.08
L-Arginine, median (IQR)	144.5 (130.0, 164.0)	143.3 (126.3, 162.8)	0.42	142.9 (125.3, 164.1)	144.2 (127.7, 163.2)	0.28	140.0 (129.4, 156.8)	144.4 (126.6, 163.2)	0.82
L-Citrulline, median (IQR)	42.8 (35.8, 52.0)	38.4 (32.0, 46.1)	<0.001	45.2 (36.0, 54.3)	39.0(32.5, 46.1)	<0.001	29.2 (22.0, 43.5)	39.6 (33.4, 47.4)	0.01
L-Ornithine, median (IQR)	83.5 (67.3, 96.4)	79.8 (66.8, 94.7)	0.29	85.5 (67.1, 101.2)	79.7 (66.8, 94.2)	0.11	83.9 (769.0, 87.8)	80.3 (66.8, 95.3)	0.95
Arg/ADMA Ratio, median (IQR)	285.0 (252.3, 327.8)	289.5(251.3, 333.5)	0.40	284.6 (240.8, 321.1)	289.7 (253.4, 333.4)	0.08	284.6 (250.3, 315.2)	288.7 (251.3, 330.2)	0.50
Cit/Arg Ratio, median (IQR)	0.29 (0.24, 0.35)	0.27 (0.22, 0.32)	<0.001	0.30 (0.25, 0.38)	0.27 (0.22, 0.32)	<0.001	0.22 (0.17, 0.30)	0.27 (0.23, 0.33)	0.01
Orn/Arg Ratio, median (IQR)	0.55 (0.47, 0.68)	0.55 (0.46, 0.66)	0.57	0.58 (0.49, 0.68)	0.55 (0.45, 0.66)	0.03	0.56 (0.49, 0.66)	0.55 (0.46, 0.67)	0.79

Data are presented as medians and inter quartile ranges. *p-value from Kruskal-Wallis test. Abbreviations: ADMA, asymmetric dimethylarginine; Arg, L-arginine; Cit, L-citrulline; Orn, L-ornithine; SDMA, symmetric dimethylarginine.

Table S5. Association of chronic airflow obstruction with biomarkers of interest. Model 1: Unadjusted. Model 2: Adjusted for age, sex and smoking status. Model 3: Model 2+BMI. Model 4: Model 2+eGFR.

ADMA quartile	Concentration in uM	N	Model 1 OR (95% CI)	p	Model 2 OR (95% CI)	p	Model 3 OR (95% CI)	p	Model 4 OR (95% CI)	p
1	0.2965-0.4475	179	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
2	0.4480-0.5065	178	0.90 (0.45-1.77)	0.74	0.70 (0.34-1.43)	0.33	0.69 (0.34-1.42)	0.32	0.70 (0.34-1.42)	0.32
3	0.5065-0.5590	179	0.83 (0.41-1.66)	0.59	0.58 (0.28-1.21)	0.15	0.65 (0.31-1.36)	0.25	0.58 (0.28-1.21)	0.15
4	0.5600-1.1335	177	1.45 (0.77-2.73)	0.25	0.94 (0.48-1.84)	0.86	0.98 (0.50-1.94)	0.96	0.94 (0.48-1.84)	0.85
SDMA quartile	Concentration in uM									
1	0.2950-0.4425	180	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
2	0.4435-0.4980	179	1.16 (0.55-2.46)	0.69	1.20 (0.56-2.59)	0.64	1.24 (0.57-2.70)	0.59	1.23 (0.57-2.66)	0.61
3	0.499-0.5740	176	1.10 (0.52-2.36)	0.80	1.10 (0.50-2.41)	0.82	1.05 (0.47-2.32)	0.91	1.13 (0.51-2.51)	0.76
4	0.5750-1.8515	178	2.70 (1.39-5.24)	0.003	2.10 (1.00-4.37)	0.049	1.99 (0.94-4.21)	0.07	2.24 (1.03-4.89)	0.042
L-Arginine quartile	Concentration in uM									
1	65.705-126.905	179	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
2	126.958-144.036	178	0.70 (0.36-1.39)	0.31	0.63 (0.31-1.27)	0.19	0.68 (0.33-1.38)	0.28	0.63 (0.31-1.27)	0.19
3	144.072-163.145	178	0.85 (0.44-1.64)	0.63	0.77 (0.39-1.51)	0.44	0.84 (0.42-1.68)	0.63	0.77 (0.39-1.51)	0.44
4	163.273-279.045	178	0.95 (0.50-1.81)	0.89	0.81 (0.41-1.57)	0.53	0.92 (0.47-1.82)	0.82	0.80 (0.41-1.56)	0.51
L-Citrulline quartile	Concentration in uM									
1	15.515-33.009	179	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
2	33.054-39.521	178	0.76 (0.37-1.59)	0.47	0.67 (0.32-1.41)	0.29	0.67 (0.29-1.33)	0.22	0.67 (0.32-1.42)	0.29
3	39.527-47.328	178	1.26 (0.65-2.44)	0.49	1.03 (0.52-2.05)	0.93	1.06 (0.53-2.12)	0.95	1.03 (0.51-2.04)	0.94
4	47-406-132.089	178	1.39 (0.73-2.67)	0.32	0.88 (0.43-1.77)	0.71	0.88 (0.43-1.80)	0.47	0.86 (0.42-1.76)	0.69
L-Ornithine quartile	Concentration in uM									
1	33.585-66.966	179	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
2	67.066-80.412	178	0.72 (0.37-1.39)	0.33	0.59 (0.30-1.18)	0.14	0.63 (0.31-1.426)	0.19	0.59 (0.30-1.18)	0.14
3	80.436-95.332	178	0.72 (0.37-1.39)	0.33	0.57 (0.29-1.16)	0.12	0.63 (0.31-1.28)	0.20	0.57 (0.28-1.15)	0.12
4	95.339-280.306	178	0.91 (0.48-1.71)	0.76	0.62 (0.32-1.21)	0.16	0.68 (0.34-1.34)	0.27	0.62 (0.32-1.21)	0.16
Arg/ADMA quartile	Ratio									
1	74.2429-251.197	179	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
2	251.326-288.691	178	0.68 (0.35-1.32)	0.26	0.60 (0.30-1.19)	0.14	0.55 (0.27-1.10)	0.09	0.60 (0.30-1.19)	0.14
3	288.877-330.143	178	0.64 (0.33-1.25)	0.19	0.66 (0.33-1.32)	0.24	0.68 (0.33-1.37)	0.28	0.66 (0.33-1.32)	0.24
4	330.197-532.619	178	0.86 (0.46-1.62)	0.65	1.02 (0.53-1.98)	0.94	1.01 (0.52-1.98)	0.97	1.02 (0.53-1.98)	0.95
Cit/Arg quartile	Ratio									
1	0.083-0.2268	179	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
2	0.2274-0.2732	178	1.07 (0.53-2.15)	0.85	1.13 (0.55-2.30)	0.74	1.03 (0.50-2.12)	0.94	1.13 (0.55-2.32)	0.73
3	0.2734-0.3279	178	1.34 (0.69-2.63)	0.39	1.26 (0.63-2.53)	0.51	1.17 (0.58-2.37)	0.66	1.27 (0.63-2.55)	0.50
4	0.3291-0.8897	178	1.27 (0.65-2.51)	0.48	0.93 (0.45-1.91)	0.45	0.83 (0.40-1.72)	0.61	0.92 (0.45-1.89)	0.82
Orn/Arg quartile	Ratio									
1	0.2392-0.4580	179	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
2	0.4582-0.5523	178	1.29 (0.64-2.58)	0.47	1.03 (0.50-2.11)	0.93	1.06 (0.52-2.18)	0.88	1.03 (0.51-2.12)	0.93
3	0.5529-0.6666	178	1.59 (0.81-3.10)	0.18	1.23 (0.61-2.47)	0.56	1.19 (0.59-2.42)	0.62	1.23 (0.61-2.48)	0.56
4	0.6678-1.8134	178	1.15 (0.56-2.33)	0.71	0.90 (0.43-1.89)	0.78	0.93 (0.44-1.97)	0.85	0.90 (0.43-1.89)	0.78

Data are presented as odds ratios and 95% confidence intervals with subjects without chronic airflow obstruction as reference. Abbreviations: ADMA, asymmetric dimethylarginine; Arg, L-arginine; CI, confidence interval; Cit, L-citrulline; OR, Odds ratio; Orn, L-ornithine; SDMA, symmetric dimethylarginine.

Table S6. Distribution of biomarkers of interest based on the presence or absence of sleepiness.

	Epworth sleepiness scale			Feeling sleepy			Feeling rested		
	ESS score ≤10 (n=619)	ESS score >10 (n=94)	p-value*	<3 times/week (n=560)	≥3 days/week (n=147)	p-value*	>1 days/week (n=469)	<1 day/week (n=99)	p-value*
ADMA	0.51 (0.45, 0.56)	0.50 (0.45, 0.55)	0.567	0.50 (0.44, 0.55)	0.53 (0.46, 0.58)	0.004	0.51 (0.44, 0.56)	0.53 (0.46, 0.59)	0.052
SDMA	0.50 (0.44, 0.58)	0.50 (0.44, 0.54)	0.229	0.49 (0.44, 0.56)	0.51 (0.46, 0.60)	0.007	0.50 (0.44, 0.58)	0.51 (0.46, 0.60)	0.137
L-Arginine	143.5 (126.4, 163.5)	146.7 (131.9, 161.7)	0.338	144.5 (127.8, 162.5)	142.4 (126.1, 166.0)	0.966	142.2 (126.1, 161.6)	150.7 (132.6, 172.9)	0.031
L-Citrulline	39.6 (33.3, 47.7)	39.1 (31.4, 46.7)	0.476	39.7 (32.9, 47.4)	38.9 (32.9, 48.4)	0.949	40.1 (33.3, 48.0)	39.4 (33.9, 48.4)	0.803
L-Ornithine	80.4 (66.8, 95.3)	80.5 (69.2, 95.0)	0.809	79.8 (66.8, 95.2)	81.4 (67.1, 95.5)	0.540	80.4 (67.3, 95.3)	81.4 (68.1, 97.2)	0.675
Arg/ADMA Ratio	287.1 (250.6, 328.8)	298.1 (255.9, 342.4)	0.251	289.7 (255.6, 333.8)	280.0 (240.0, 324.6)	0.052	288.3 (250.4, 325.8)	289.0 (250.9, 329.6)	0.634
Cit/Arg Ratio	0.27 (0.23, 0.33)	0.27 (0.22, 0.32)	0.218	0.27 (0.23, 0.33)	0.27 (0.23, 0.33)	0.921	0.28 (0.23, 0.33)	0.26 (0.22, 0.33)	0.254
Cit/Orn Ratio	0.515 (0.46, 0.67)	0.55 (0.45, 0.66)	0.473	0.55 (0.46, 0.67)	0.56 (0.46, 0.66)	0.687	0.56 (0.47, 0.67)	0.54 (0.45, 0.67)	0.374

Data are presented as medians and inter quartile ranges. *p-value from Kruskal-Wallis test. Abbreviations: ADMA, asymmetric dimethylarginine; Arg, L-arginine; Cit, L-citrulline; ESS, Epworth sleepiness scale; Orn, L-ornithine; SDMA, symmetric dimethylarginine.

Table S7. Association of high obstructive sleep apnoea risk as assessed by the MAP index ≥ 0.5 with quartiles of biomarkers of interest.

Model 1: Unadjusted. Model 2: Adjusted for eGFR

ADMA quartile	Concentration ($\mu\text{mol/L}$)	N	Model 1 OR (95% CI)	p-value	Model 2 OR (95% CI)	p-value
1	0.2965-0.4475	179	1 (Ref)		1 (Ref)	
2	0.4480-0.5065	178	1.07 (0.66, 1.72)	0.785	1.06 (0.66, 1.71)	0.806
3	0.5065-0.5590	179	1.50 (0.95, 2.38)	0.082	1.49 (0.94, 2.36)	0.089
4	0.5600-1.1335	177	1.65 (1.04, 2.60)	0.033	1.63 (1.03, 2.58)	0.037
SDMA quartile	Concentration ($\mu\text{mol/L}$)					
1	0.2950-0.4425	180	1 (Ref)		1 (Ref)	
2	0.4435-0.4980	179	1.54 (0.96, 2.47)	0.070	1.57 (0.98, 2.51)	0.063
3	0.499-0.5740	176	1.35 (0.83, 2.17)	0.224	1.38 (0.85, 2.25)	0.190
4	0.5750-1.8515	178	2.10 (1.32, 3.32)	0.002	2.23 (1.35, 3.69)	0.002
L-Arginine quartile	Concentration ($\mu\text{mol/L}$)					
1	65.705-126.905	179	1 (Ref)		1 (Ref)	
2	126.958-144.036	178	1.13 (0.71, 1.80)	0.612	1.13 (0.71, 1.80)	0.609
3	144.072-163.145	178	1.32 (0.84, 2.09)	0.231	1.33 (0.84, 2.10)	0.228
4	163.273-279.045	178	1.43 (0.91, 2.25)	0.125	1.342 (0.90, 2.24)	0.132
L-Citrulline quartile	Concentration ($\mu\text{mol/L}$)					
1	15.515-33.009	179	1 (Ref)		1 (Ref)	
2	33.054-39.521	178	1.10 (0.67, 1.74)	0.698	1.10 (0.69, 1.74)	0.701
3	39.527-47.328	178	1.10 (0.69, 1.74)	0.698	1.09 (0.69, 1.74)	0.707
4	47-406-132.089	178	1.57 (1.00, 2.46)	0.049	1.56 (0.98, 2.48)	0.059
L-Ornithine quartile	Concentration ($\mu\text{mol/L}$)					
1	33.585-66.966	179	1 (Ref)		1 (Ref)	
2	67.066-80.412	178	1.13 (0.70, 1.83)	0.604	1.13 (0.70, 1.82)	0.615
3	80.436-95.332	178	1.90 (1.21, 3.01)	0.006	1.90 (1.23, 3.00)	0.006
4	95.339-280.306	178	1.53 (0.96, 2.43)	0.073	1.52 (0.95, 2.42)	0.079
Arg/ADMA quartile	Ratio					
1	74.2429-251.197	179	1 (Ref)		1 (Ref)	
2	251.326-288.691	178	0.50 (0.32, 0.81)	0.004	0.50 (0.32, 0.81)	0.004
3	288.877-330.143	178	0.82 (0.53, 1.28)	0.391	0.82 (0.53, 1.28)	0.388

4	330.197-532.619	178	0.82 (0.53, 1.28)	0.391	0.83 (0.53, 1.29)	0.402
Cit/Arg quartile	Ratio					
1	0.083-0.2268	179	1 (Ref)		1 (Ref)	
2	0.2274-0.2732	178	0.47 (0.28, 0.75)	0.002	0.47 (0.29, 0.75)	0.002
3	0.2734-0.3279	178	0.94 (0.60, 1.44)	0.605	0.93 (0.60, 1.45)	0.760
4	0.3291-0.8897	178	0.85 (0.54, 1.31)	0.544	0.83 (0.53, 1.30)	0.414
Orn/Arg quartile	Ratio					
1	0.2392-0.4580	179	1 (Ref)		1 (Ref)	
2	0.4582-0.5523	178	1.53 (0.96, 2.43)	0.073	1.52 (0.96, 2.42)	0.076
3	0.5529-0.6666	178	1.65 (1.04, 2.62)	0.034	1.64 (1.03, 2.60)	0.037
4	0.6678-1.8134	178	1.34 (0.84, 2.15)	0.221	1.33 (0.83, 2.14)	0.229

Data are presented as odds ratios and 95% confidence intervals with subjects MAP index <0.5 as reference. Abbreviations: ADMA, asymmetric dimethylarginine; Arg, L-arginine; CI, confidence interval; Cit, L-citrulline; OR, Odds ratio; Orn, L-ornithine; SDMA, symmetric dimethylarginine.