

SUPPLEMENTAL TABLES AND FIGURES

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Supplemental Table 1: Pearson's Correlation Coefficients between log-transformed clearance of each uremic solute at baseline

	Cinnamoylglycine	Indoxyl Sulfate	Isovalerylglycine	Kynurenic Acid	P-Cresol Sulfate	Pyridoxic Acid	Tiglylglycine	Xanthosine
Cinnamoylglycine	1	0.46	0.39	0.46	0.45	0.37	0.51	0.33
Indoxyl Sulfate		1	0.60	0.69	0.74	0.58	0.59	0.43
Isovalerylglycine			1	0.70	0.52	0.56	0.73	0.44
Kynurenic Acid				1	0.60	0.66	0.69	0.50
P-Cresol Sulfate					1	0.50	0.54	0.40
Pyridoxic Acid						1	0.55	0.44
Tiglylglycine							1	0.47
Xanthosine								1

Supplemental Table 2: Pearson's Correlation Coefficients between log-transformed baseline plasma levels of each uremic solute

	Cinnamoylglycine	Indoxyl Sulfate	Isovalerylglycine	Kynurenic Acid	P-Cresol Sulfate	Pyridoxic Acid	Tiglylglycine	Xanthosine
Cinnamoylglycine	1	0.19	0.32	0.17	0.30	0.13	0.39	0.03
Indoxyl Sulfate		1	0.33	0.43	0.56	0.18	0.30	0.18
Isovalerylglycine			1	0.36	0.32	0.21	0.73	0.08
Kynurenic Acid				1	0.30	0.31	0.32	0.28
P-Cresol Sulfate					1	0.19	0.30	0.11
Pyridoxic Acid						1	0.17	0.10
Tiglylglycine							1	0.08
Xanthosine								1

Supplemental Table 3: Associations of secretory biomarker clearance and sustained cognitive decline >5 points AND drop below threshold for cognitive impairment (<75, <80, or <85 for age >80, 65-80, and <65 years, respectively), per 50% lower biomarker clearance (N of events = 78)

Biomarker	HR (95% CI)				Model 3 p-value
	Unadjusted	Model 1	Model 2	Model 3	
Cinnamoylglycine	1.25 (1.07, 1.46)	1.20 (1.02, 1.41)	1.18 (1.00, 1.40)	1.14 (0.95, 1.37)	0.17
Indoxyl sulfate	1.57 (1.24, 1.98)	1.44 (1.13, 1.85)	1.37 (1.06, 1.78)	1.30 (0.96, 1.77)	0.09
Isovalerylglycine	1.87 (1.51, 2.32)	1.63 (1.30, 2.04)	1.65 (1.30, 2.10)	1.63 (1.26, 2.11)	<0.001*
Kynurenic acid	1.91 (1.51, 2.42)	1.74 (1.35, 2.22)	1.67 (1.28, 2.18)	1.71 (1.25, 2.32)	<0.001*
p-cresol sulfate	1.26 (1.07, 1.49)	1.22 (1.00, 1.49)	1.17 (0.94, 1.46)	1.09 (0.84, 1.41)	0.53
Pyridoxic acid	1.51 (1.26, 1.82)	1.32 (1.07, 1.64)	1.29 (1.02, 1.63)	1.22 (0.93, 1.60)	0.16
Tiglylglycine	1.55 (1.32, 1.82)	1.32 (1.12, 1.55)	1.25 (1.04, 1.50)	1.21 (0.98, 1.49)	0.07
Xanthosine	1.42 (1.20, 1.69)	1.24 (1.04, 1.48)	1.25 (1.05, 1.50)	1.21 (1.00, 1.47)	0.05
Summary Score (per 10 point decrement)	2.00 (1.57, 2.54)	1.68 (1.30, 2.18)	1.65 (1.24, 2.19)	1.69 (1.20, 2.39)	0.00268

Model 1: Adjusted for age, sex, and race/ethnicity, education, and baseline 3MS

Model 2: Adjusted for the components of Model 1, diabetes, coronary artery disease, peripheral arterial disease, systolic blood pressure, BMI, HDL, LDL, hemoglobin, log-transformed CRP, and use of statins, aspirin, beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers

Model 3: Adjusted for the components of Model 2, as well as eGFR and log-transformed 24-hour proteinuria

*Indicates significance when controlling false discovery rate at 5%

Supplemental Table 4: Associations of secretory biomarker clearance and unrepeated cognitive decline >5 points, per 50% lower biomarker clearance (N of events = 704)

Biomarker	HR (95% CI)				Model 3 p-value
	Unadjusted	Model 1	Model 2	Model 3	
Cinnamoylglycine	1.12 (1.06, 1.18)	1.10 (1.04, 1.17)	1.11 (1.05, 1.17)	1.10 (1.03, 1.16)	0.00271*
Indoxyl sulfate	1.15 (1.06, 1.25)	1.15 (1.05, 1.25)	1.16 (1.06, 1.27)	1.14 (1.02, 1.26)	0.0165*
Isovalerylglycine	1.28 (1.18, 1.38)	1.21 (1.12, 1.32)	1.22 (1.12, 1.32)	1.20 (1.10, 1.32)	6.92E-05*
Kynurenic acid	1.22 (1.12, 1.33)	1.18 (1.08, 1.30)	1.19 (1.08, 1.31)	1.17 (1.05, 1.31)	0.0053*
p-cresol sulfate	1.09 (1.02, 1.16)	1.08 (1.00, 1.15)	1.08 (1.01, 1.16)	1.04 (0.96, 1.13)	0.301
Pyridoxic acid	1.12 (1.05, 1.21)	1.09 (1.01, 1.17)	1.09 (1.01, 1.18)	1.06 (0.97, 1.16)	0.186
Tiglylglycine	1.20 (1.12, 1.29)	1.15 (1.07, 1.24)	1.15 (1.07, 1.24)	1.13 (1.04, 1.23)	0.00412*
Xanthosine	1.10 (1.04, 1.18)	1.07 (1.00, 1.14)	1.07 (1.00, 1.14)	1.04 (0.97, 1.12)	0.246
Summary Score (per 10 point decrement)	1.28 (1.17, 1.40)	1.23 (1.11, 1.36)	1.25 (1.13, 1.38)	1.25 (1.11, 1.42)	4.23E-04

Model 1: Adjusted for age, sex, and race/ethnicity, education, and baseline 3MS

Model 2: Adjusted for the components of Model 1, diabetes, coronary artery disease, peripheral arterial disease, systolic blood pressure, BMI, HDL, LDL, hemoglobin, log-transformed CRP, and use of statins, aspirin, beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers

Model 3: Adjusted for the components of Model 2, as well as eGFR and log-transformed 24-hour proteinuria

*Indicates significance when controlling false discovery rate at 5%

Supplemental Table 5: Associations of secretory biomarker clearance and sustained cognitive decline, per 50% lower biomarker clearance, accounting for competing risk of death with Fine-Gray approach

Biomarker	HR (95% CI)				Model 3 p-value
	Unadjusted	Model 1	Model 2	Model 3	
Cinnamoylglycine	1.13 (1.03, 1.24)	1.12 (1.01, 1.23)	1.12 (1.01, 1.23)	1.12 (1.01, 1.25)	0.03
Indoxyl sulfate	1.11 (0.96, 1.27)	1.08 (0.94, 1.25)	1.12 (0.96, 1.29)	1.13 (0.95, 1.35)	0.15
Isovalerylglycine	1.18 (1.04, 1.34)	1.08 (0.95, 1.24)	1.13 (0.99, 1.30)	1.14 (0.98, 1.33)	0.08
Kynurenic acid	1.21 (1.05, 1.40)	1.14 (0.98, 1.33)	1.18 (1.01, 1.39)	1.23 (1.02, 1.48)	0.03
p-cresol sulfate	1.04 (0.93, 1.17)	1.01 (0.89, 1.14)	1.03 (0.91, 1.17)	1.03 (0.89, 1.19)	0.71
Pyridoxic acid	1.11 (0.99, 1.25)	1.04 (0.92, 1.19)	1.07 (0.94, 1.22)	1.08 (0.93, 1.25)	0.29
Tiglylglycine	1.14 (1.02, 1.28)	1.04 (0.92, 1.18)	1.07 (0.94, 1.22)	1.07 (0.93, 1.24)	0.34
Xanthosine	1.09 (0.98, 1.22)	1.05 (0.94, 1.17)	1.08 (0.96, 1.21)	1.08 (0.96, 1.22)	0.20
Summary Score (per 10 point decrement)	1.22 (1.05, 1.43)	1.13 (0.96, 1.33)	1.19 (1.00, 1.41)	1.26 (1.02, 1.55)	0.0313

Model 1: Adjusted for age, sex, and race/ethnicity, education, and baseline 3MS

Model 2: Adjusted for the components of Model 1, diabetes, coronary artery disease, peripheral arterial disease, systolic blood pressure, BMI, HDL, LDL, hemoglobin, log-transformed CRP, and use of statins, aspirin, beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers

Model 3: Adjusted for the components of Model 2, as well as eGFR and log-transformed 24-hour proteinuria

Supplemental Table 6: Association of secretory biomarker clearance and sustained cognitive decline or death, per 50% lower biomarker clearance (N of events = 843)

Biomarker	Unadjusted	Model 1	Model 2	Model 3	Model 3 p-value
Cinnamoylglycine	1.17 (1.11, 1.23)	1.15 (1.10, 1.21)	1.16 (1.10, 1.22)	1.08 (1.02, 1.14)	0.00645*
Indoxyl sulfate	1.38 (1.29, 1.49)	1.37 (1.27, 1.49)	1.35 (1.24, 1.46)	1.16 (1.06, 1.28)	0.00174*
Isovalerylglycine	1.42 (1.33, 1.52)	1.36 (1.27, 1.46)	1.32 (1.23, 1.42)	1.20 (1.11, 1.30)	1.06E-05*
Kynurenic acid	1.46 (1.35, 1.58)	1.42 (1.30, 1.54)	1.37 (1.26, 1.49)	1.17 (1.06, 1.30)	0.00246*
p-cresol sulfate	1.24 (1.18, 1.31)	1.25 (1.18, 1.33)	1.23 (1.15, 1.30)	1.09 (1.01, 1.17)	0.0312*
Pyridoxic acid	1.33 (1.25, 1.41)	1.30 (1.22, 1.39)	1.27 (1.19, 1.36)	1.14 (1.05, 1.23)	0.0014*
Tiglylglycine	1.37 (1.30, 1.45)	1.32 (1.24, 1.41)	1.31 (1.22, 1.39)	1.17 (1.09, 1.26)	2.74E-05*
Xanthosine	1.22 (1.16, 1.29)	1.19 (1.12, 1.27)	1.18 (1.11, 1.25)	1.08 (1.01, 1.15)	0.0178*
Summary Score (per 10 point decrease)	1.59 (1.47, 1.73)	1.56 (1.43, 1.70)	1.52 (1.39, 1.67)	1.31 (1.17, 1.47)	2.74E-06

Model 1: Adjusted for age, sex, and race/ethnicity, education, and baseline 3MS

Model 2: Adjusted for the components of Model 1, diabetes, coronary artery disease, peripheral arterial disease, systolic blood pressure, BMI, HDL, LDL, hemoglobin, log-transformed CRP, and use of statins, aspirin, beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers

Model 3: Adjusted for the components of Model 2, as well as eGFR and log-transformed 24-hour proteinuria

*Indicates significance when controlling false discovery rate at 5%

Supplemental Table 7: Average decrease in Trails A, Trails B, and Buschke Selective Reminding Test Scores per 10-point increase in summary score over median (IQR) of 2 (1.9, 2.1) years

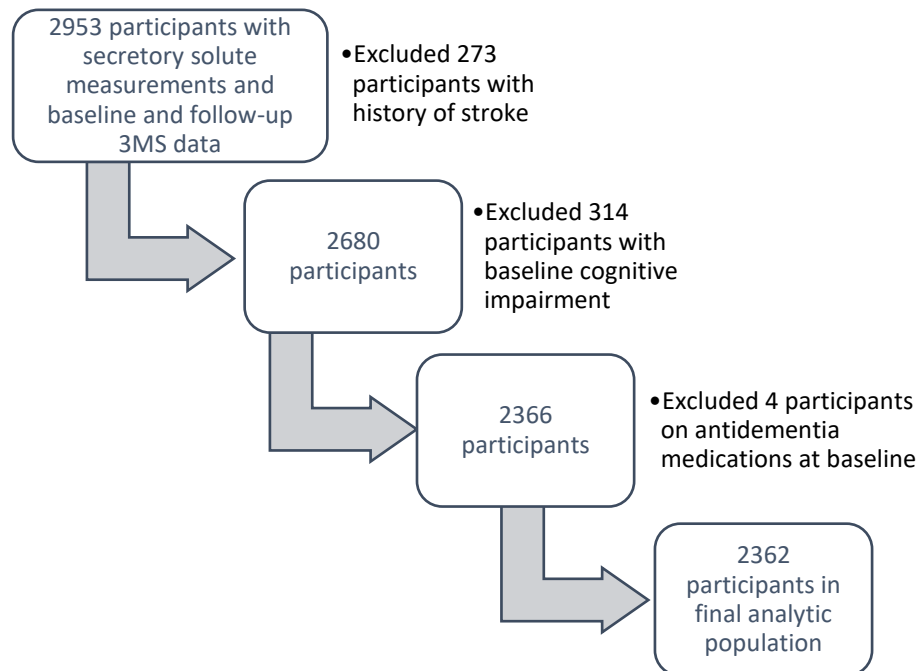
Test	Unadjusted	Model 1	Model 2	Model 3	Model 3 p-value
Trails A time (in seconds) (N = 1566)	-0.4 (-2.8, 2.0)	-0.3 (-2.5, 1.9)	-0.3 (-2.4, 1.7)	-0.3 (-2.2, 1.6)	0.76
Trails B time (in seconds) (N = 1565)	0.6 (-4.3, 5.6)	0.1 (-4.3, 4.5)	0.1 (-4.1, 4.3)	-1.9 (-6.3, 2.5)	0.41
Buschke SRT score (N = 1569)	-0.2 (-0.4, 0.1)	-0.1 (-0.4, 0.1)	-0.1 (-0.3, 0.1)	-0.2 (-0.3, 0.0)	0.10

Model 1: Adjusted for age, sex, race/ethnicity, education, and baseline 3MS

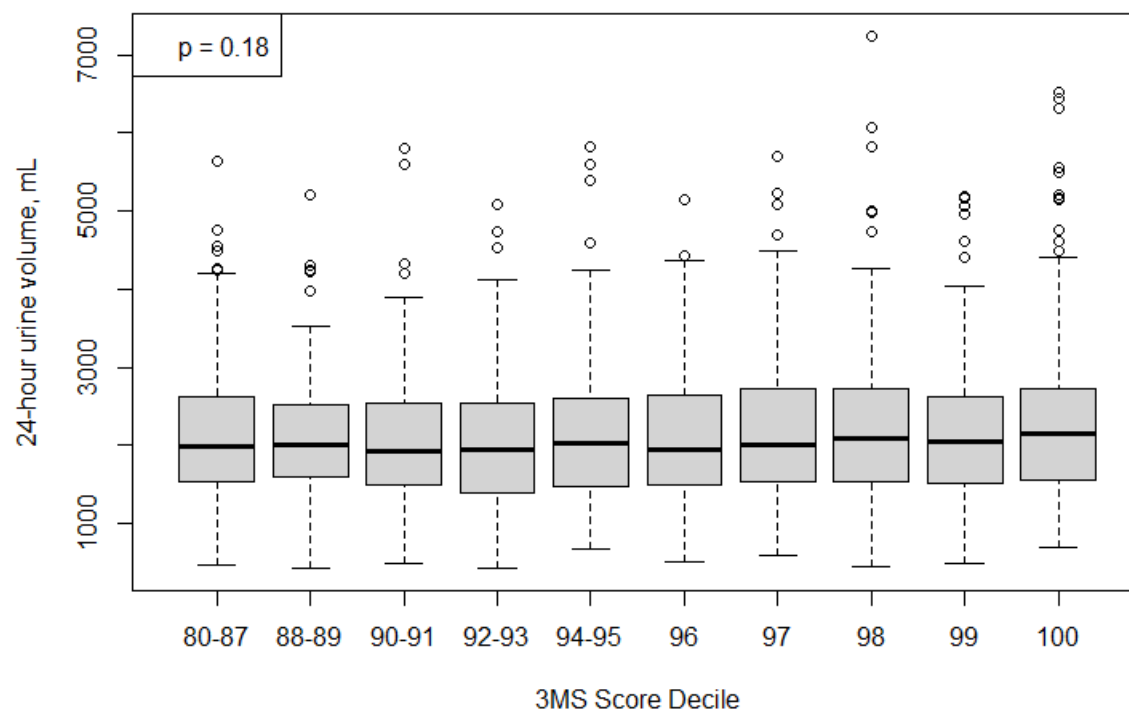
Model 2: Adjusted for the components of Model 1, diabetes, coronary artery disease, peripheral arterial disease, systolic blood pressure, BMI, HDL, LDL, hemoglobin, log-transformed CRP, and use of statins, aspirin, beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers

Model 3: Adjusted for the components of Model 2, as well as eGFR and log-transformed 24-hour proteinuria

Supplemental Figure 1: CONSORT diagram



Supplemental Figure 2: 24-hour urine volume by baseline 3MS score deciles



Supplemental Figure 3: Creatinine excretion by baseline 3MS score deciles

