

**Supplemental Table 1. Associations of secretory solute clearance with eGFR decline after truncating extreme solute clearance values.<sup>a</sup>**

	Median (IQR) clearance		Model 1		Model 2	
	Controls	Cases	OR (95% CI)	p-value	OR (95% CI)	p-value
Cinnamoylglycine	151.8 (94.9-309.0)	170.7 (95.5-289.2)	0.89 (0.72, 1.10)	0.28	0.88 (0.70, 1.10)	0.25
Isovalerylglycine	715.8 (521.5-1221.0)	632.5 (445.0-997.3)	1.69 (1.14, 2.52)	0.0097**	1.91 (1.23, 2.96)	0.004**
Kynurenic acid	403.4 (273.7-588.3)	324.3 (243.1-456.9)	1.93 (1.18, 3.16)	0.0086**	2.26 (1.33, 3.87)	0.0028**
P-cresol sulfate	34.9 (24.4-51.6)	30.7 (20.5-48.0)	1.14 (0.88, 1.48)	0.33	1.25 (0.93, 1.68)	0.13
Xanthosine	68.2 (47.4-106.2)	63.1 (40.7-88.8)	1.39 (1.00, 1.93)	0.052	1.48 (1.02, 2.13)	0.037*
Summary score	55.5 (47.9-62.5)	51.9 (43.7-58.7)	1.43 (1.06, 1.92)	0.019*	1.57 (1.13, 2.18)	0.0076**

<sup>a</sup>Cutoffs in ml/min are cinnamoylglycine >2000, isovalerylglycine >3000, p-cresol sulfate >500, xanthosine >450; no cutoff was defined for kynurenic acid.

Odds ratios are per 50% lower secretory clearance for individual solutes and per 10 point decrement for summary score. Model 1 adjusts for age, baseline eGFR, diabetes, flexibly modeled A1c, and sex; Model 2 further adjusts for log-transformed 24-hour urine albumin, SBP, BMI, and current smoking.

\*Significant at  $p < 0.05$

\*\*Significant at  $p < 0.01$  accounting for multiple comparisons

**Supplemental Table 2. Associations of secretory solute clearance with cystatin C-eGFR decline.**

	Median (IQR) clearance (mL/min)		Model 1		Model 2	
	Controls	Cases	OR (95% CI)	p-value	OR (95% CI)	p-value
Cinnamoylglycine	151.8 (94.9-309.0)	170.7 (95.5-289.2)	0.90 (0.74, 1.11)	0.32	0.88 (0.71, 1.09)	0.24
Isovalerylglycine	715.8 (521.5-1221.0)	632.5 (445.0-997.3)	1.69 (1.14, 2.52)	0.0094**	1.93 (1.25, 3.00)	0.0031**
Kynurenic acid	403.4 (273.7-588.3)	324.3 (243.1-456.9)	1.96 (1.20, 3.21)	0.007**	2.33 (1.36, 3.98)	0.0021**
P-cresol sulfate	34.9 (24.4-51.6)	30.7 (20.5-48.0)	1.14 (0.88, 1.48)	0.32	1.22 (0.92, 1.63)	0.17
Xanthosine	68.2 (47.4-106.2)	63.1 (40.7-88.8)	1.45 (1.04, 2.02)	0.028*	1.56 (1.08, 2.25)	0.018*
Summary score	50.8 (43.6-57.0)	47.2 (39.6-53.4)	1.45 (1.08, 1.94)	0.014*	1.59 (1.15, 2.21)	0.0055**

Odds ratios are per 50% lower secretory clearance for individual solutes and per 10-point decrement for summary score. Model 1 adjusts for age, baseline eGFR (2012 CKD-EPI cystatin C), diabetes, flexibly modeled A1c, and sex; Model 2 further adjusts for log-transformed 24-hour urine albumin, SBP, BMI, and current smoking.

\*Significant at  $p < 0.05$

\*\*Significant at  $p < 0.01$  accounting for multiple comparisons

**Supplemental Table 3. Associations of secretory solute clearance with eGFR decline, including further adjustment Model 3 including smoking, RAAS inhibitors, diuretics, and HbA1c.**

	Model 1		Model 2		Model 3	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	p-value	OR (95% CI)	p-value
Cinnamoylglycine	0.89 (0.72, 1.10)	0.29	0.88 (0.71, 1.09)	0.25	0.85 (0.67, 1.06)	0.15
Isovalerylglycine	1.69 (1.14, 2.52)	0.0091**	1.91 (1.23, 2.96)	0.0038**	1.96 (1.25, 3.07)	0.0035**
Kynurenic acid	1.93 (1.18, 3.16)	0.0086**	2.26 (1.33, 3.87)	0.0028**	2.42 (1.38, 4.26)	0.0022**
P-cresol sulfate	1.12 (0.87, 1.45)	0.38	1.22 (0.92, 1.62)	0.16	1.24 (0.93, 1.65)	0.15
Xanthosine	1.39 (1.00, 1.93)	0.052	1.48 (1.02, 2.13)	0.037*	1.55 (1.06, 2.27)	0.023*
Summary score	1.43 (1.06, 1.92)	0.019*	1.57 (1.13, 2.18)	0.0076**	1.6 (1.14, 2.24)	0.0063**

Odds ratios are per 50% lower secretory clearance for individual solutes and per 10-point decrement for summary score. Model 1 adjusts for age, baseline eGFR (2012 CKD-EPI creatinine), diabetes, and sex; Model 2 further adjusts Model 1 for log-transformed 24-hour urine albumin, SBP, BMI, and current smoking; Model 3 further adjusts Model 2 for RAASi, diuretics, and HbA1c.

\*Significant at  $p < 0.05$

\*\*Significant at  $p < 0.01$  accounting for multiple comparisons

**Supplemental Table 4. Associations of secretory fractional excretion with eGFR decline.**

	Median (IQR) FE		Model 1		Model 2	
	Controls	Cases	OR (95% CI)	p-value	OR (95% CI)	p-value
Cinnamoylglycine	1.2 (0.8-2.3)	1.4 (0.9-2.4)	0.90 (0.73, 1.11)	0.32	0.87 (0.70, 1.08)	0.21
Isovalerylglycine	6.6 (4.8-9.0)	5.6 (3.7-7.4)	1.73 (1.16, 2.58)	0.0073**	1.84 (1.19, 2.85)	0.0064**
Kynurenic acid	3.4 (2.6-4.3)	2.8 (2.2-3.5)	2.21 (1.27, 3.82)	0.0049**	2.44 (1.33, 4.47)	0.0041**
P-cresol sulfate	0.3 (0.2-0.4)	0.3 (0.2-0.4)	1.14 (0.87, 1.49)	0.33	1.20 (0.90, 1.60)	0.21
Xanthosine	0.6 (0.4-0.9)	0.5 (0.3-0.8)	1.42 (1.01, 1.99)	0.044*	1.45 (1.00, 2.11)	0.053

Odds ratios are per 50% lower secretory clearance for individual solutes. Model 1 adjusts for age, baseline eGFR (2012 CKD-EPI creatinine), diabetes, flexibly modeled A1c, and sex; Model 2 further adjusts for log-transformed 24-hour urine albumin, SBP, BMI, and current smoking.

\*Significant at  $p < 0.05$

\*\*Significant at  $p < 0.01$  accounting for multiple comparisons

**Supplemental Table 5: Comparison of case-control population to all Jackson Heart Study participants that completed 24-hour urine collection**

	Case-control (N = 254)	All 24-hour urine patients (N = 1,027)
Age*	60.4 (10.3)	58.9 (11.3)
Female*	192 (75.5%)	698 (67.9%)
BMI (kg/m <sup>2</sup> )	32.5 (6.4)	31.9 (6.9)
eGFR* (ml/min/1.73m <sup>2</sup> )	93.9 (19.7)	84.8 (17.9)
Diabetes*	79 (31%)	253 (24.6%)
HbA1c	6.15 (1.32)	6.1 (1.24)
BP medications	181 (71.3%)	614 (59.8%)
SBP (mmHg)	128.5 (17.6)	127.7 (17.4)
DBP (mmHg)	76.9 (10.2)	77.9 (10.2)
Urine albumin (mg/24hr)**	7.9 (5.5-15.4)	7.6 (5.3-15.4)

\* Matching variable. \*\* Albuminuria derived from 24-hour urine collection; presented as median (IQR)

Entries are mean (SD) for continuous variables or N (%) for categorical variables, except as noted.

Cases and controls were matched on age ( $\pm 7$  years), eGFR ( $\pm 10$  mL/min/1.73m<sup>2</sup>), and diabetes status; cases and controls were further matched on sex, when possible.