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Table S1. Laboratory characteristics and variability of secretory solutes.[a]

	Molecular weight (g/mol)	Intra-assay CV plasma (%)	Inter-assay CV plasma (%)	Intra-assay CV urine (%)	Inter-assay CV urine (%)	Diurnal CV (%)[b]
Hippurate	179	3.8	5.1	5.4	4.7	47.4
Pyridoxic acid	183	3.4	4.7	5.7	5.8	8.5
Dimethyluric acid	196	4.5	5.4	4.9	4.5	39.0
Trimethyluric acid	210	7.1	7.4	7.8	7.8	49.2
Isovalerylglycine	159	7.1	7.3	5.4	5.9	30.2
Tiglylglycine	157	7.0	14.7	6.0	5.5	22.4
Kynurenic acid	189	4.1	5.5	5.6	8.6	14.9
Xanthosine	284	11.1	14.5	9.8	10.1	13.0
Cinnamoylglycine	205	4.5	5.4	4.9	4.5	26.8
Indoxyl sulfate	213	4.3	6.0	6.1	9.4	21.0
p-cresol sulfate	188	3.9	5.2	5.6	5.2	26.6

[a] CV: coefficient of variation.

[b] Diurnal CV was calculated in normal healthy individuals using plasma samples drawn at 8 AM, 12 PM, 5:30 PM, 6:30 PM, 10 PM, 2 AM, and 8 AM the following day in 29 participants from the baseline study visit of a completed clinical trial of dietary n-3-polyunsaturated fatty acids. Participants were men and women who had a body mass index of 28-33 kg/m^2, but otherwise healthy at entry and stable weight over the previous six months.

Table S2. Kidney clearance and plasma concentration of secretory solutes by quartiles of the estimated glomerular filtration rate[a]

	Estimated GFR (ml/min/1.73m^2)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
	eGFR < 32.4	eGFR 32.4 – 43.1	eGFR 43.1 – 55.4	eGFR > 55.4
Hippurate				
Clearance	309 (194, 514)	438 (275, 754)	525 (320, 907)	644 (393, 1098)
Plasma concentration	1008 (583, 1456)	694 (384, 1072)	560 (342, 960)	512 (285, 866)
Pyridoxic acid				
Clearance	266 (187, 388)	393 (273, 546)	548 (389, 757)	760 (517, 1048)
Plasma concentration	16 (10, 30)	11 (7, 21)	9 (6, 17)	8 (5, 16)
Dimethyluric acid				
Clearance	273 (170, 517)	396 (241, 663)	510 (312, 846)	687 (422, 1134)
Plasma concentration	26 (5, 63)	20 (5, 47)	18 (5, 40)	16 (5, 34)
Trimethyluric acid				
Clearance	152 (84, 267)	230 (126, 411)	300 (170, 526)	432 (235, 769)
Plasma concentration	1.5 (0.4, 3.8)	1.0 (0.3, 2.6)	1.0 (0.3, 2.2)	0.8 (0.3, 1.8)
Isovalerylglycine				
Clearance	145 (99, 220)	195 (134, 276)	259 (170, 384)	347 (229, 487)
Plasma concentration	8 (6, 12)	6 (5, 9)	6 (4, 7)	5 (4, 7)
Tiglylglycine				
Clearance	109 (74, 161)	157 (103, 231)	214 (143, 308)	292 (198, 428)
Plasma concentration	10 (7, 15)	8 (5, 11)	6 (4, 9)	5 (3, 7)

Kynurenic acid				
Clearance	58 (42, 80)	83 (60, 112)	105 (79, 141)	145 (105, 195)
Plasma concentration	24 (18, 32)	17 (13, 22)	14 (10, 18)	10 (8, 13)
Xanthosine				
Clearance	47 (29, 71)	67 (43, 104)	90 (58, 130)	115 (77, 169)
Plasma concentration	14 (10, 19)	11 (9, 16)	10 (8, 13)	9 (7, 11)
Cinnamoylglycine				
Clearance	36 (22, 59)	51 (32, 85)	67 (41, 110)	88 (52, 157)
Plasma concentration	28 (11, 54)	18 (7, 36)	15 (6, 30)	12 (5, 24)
Indoxyl sulfate				
Clearance	21 (15, 30)	30 (22, 43)	40 (29, 54)	52 (38, 73)
Plasma concentration	2693 (1978, 3523)	1900 (1293, 2576)	1551 (1077, 2122)	1164 (778, 1660)
p-cresol sulfate				
Clearance	6 (4, 8)	9 (6, 12)	12 (8, 17)	15 (10, 23)
Plasma concentration	14567 (8871, 21457)	9585 (5413, 14138)	7438 (3920, 11590)	4957 (2792, 7894)

[a] Data shown as median (interquartile range). Kidney clearance and plasma concentration of secretory solutes shown in mL/min and ng/mL, respectively.

Table S3. Correlations among the individual secretory solutes clearances.[a]

	Hippurate	Pyridoxic acid	Dimethyluric acid	Trimethyluric acid	Isovalerylglycine	Tiglylglycine	Kynurenic acid	Xanthosine	Cinnamoylglycine	Indoxyl sulfate	p-cresol sulfate
Hippurate	1.00										
Pyridoxic acid	0.41	1.00									
Dimethyluric acid	0.33	0.40	1.00								
Trimethyluric acid	0.35	0.43	0.74	1.00							
Isovalerylglycine	0.38	0.57	0.40	0.41	1.00						
Tiglylglycine	0.46	0.56	0.37	0.40	0.74	1.00					
Kynurenic acid	0.46	0.69	0.44	0.47	0.70	0.70	1.00				
Xanthosine	0.34	0.45	0.31	0.32	0.44	0.46	0.48	1.00			
Cinnamoylglycine	0.48	0.39	0.30	0.30	0.42	0.54	0.48	0.34	1.00		
Indoxyl sulfate	0.44	0.62	0.42	0.43	0.62	0.61	0.71	0.42	0.47	1.00	
p-cresol sulfate	0.38	0.53	0.36	0.36	0.53	0.55	0.62	0.40	0.45	0.75	1.00

[a] Pearson correlation between ln-transformed solute clearances.

Table S4. Associations of baseline participant characteristics with the summary secretion score.[a, b]

Characteristics	Adjusted difference in summary secretion score (95% CI)[c]	P-value[d]
Age, per 10 years	0.25 (0.06, 0.44)	0.009
Female	-1.71 (-2.11, -1.32)	< 0.001*
Black	-0.80 (-1.20, -0.39)	< 0.001*
Hispanic	-0.34 (-0.96, 0.28)	0.28
Body mass index, kg/m^2	0.13 (0.10. 0.15)	< 0.001*
College graduate or higher	0.85 (0.41, 1.29)	< 0.001*
Current smoker	0.74 (0.15, 1.34)	0.01
History of diabetes	1.09 (0.68, 1.49)	< 0.001*
History of cardiovascular disease	-0.48 (-0.91, -0.05)	0.03
History of peripheral vascular disease	0.10 (-0.68, 0.88)	0.81
Systolic blood pressure, per 10 mmHg	-0.18 (-0.28, -0.09)	< 0.001*
Lab measurements		
Serum albumin, g/dL	-0.32 (-0.75, 0.12)	0.16
24-hour urine albumin, g/24h	0.29 (0.17, 0.42)	< 0.001*

Phosphate, mg/dL	-0.12 (-0.45, 0.21)	0.46
HDL, mg/dL	0.00 (-0.01, 0.01)	0.89
CO2, mEq/L	0.06 (0.00, 0.13)	0.05
Hemoglobin, per 10 g/dL	-0.01 (-0.14, 0.12)	0.88
Medications		
Insulin	0.93 (0.47, 1.39)	< 0.001*
Statin	0.74 (0.34, 1.14)	< 0.001*
ACEi / ARB	1.38 (0.96, 1.80)	< 0.001*
Loop diuretic	-0.44 (-0.88, -0.01)	0.05
Thiazide diuretic	0.66 (0.22, 1.09)	0.003*

[a] HDL: high-density lipoprotein; ACEi: angiotensin-converting-enzyme inhibitor; ARB: angiotensin II receptor blocker.

[b] Conversion factors for units: albumin in g/dL to g/L, × 10; phosphate in mg/dL to mmol/L, × 0.3229; HDL in mg/dL to mmol/L, × 0.02586; bicarbonate in mEq/L to mmol/L, × 1; hemoglobin in g/dL to g/L, × 10.

[c] From regressing the summary secretion score on each characteristic. Positive values indicate an association with higher summary secretion score after adjustment and negative values indicate an association with lower summary secretion score. Associations for age, sex, race, and BMI adjusted for eGFR; other associations adjusted for eGFR plus age, race, sex, and BMI.

[d] * denotes statistical significance after correction for multiple comparisons using the Hommel method.

Table S5. Secretory solute clearances by self-reported etiologies of chronic kidney disease. [a]

	All participants with self-reported cause of CKD (N = 1,991)	Hypertensive (N = 940)	Diabetic (N = 779)	Glomerular (N = 98)	Obstructive (N = 174)	P-value[b]
Hippurate	453 (264, 795)	414 (244, 714)	496 (278, 854)	546 (330, 849)	453 (263, 833)	0.003*
Pyridoxic acid	410 (259, 641)	383 (246, 594)	425 (271, 658)	511 (301, 809)	467 (259, 723)	< 0.001*
Dimethyluric acid	438 (243, 759)	425 (233, 736)	441 (256, 804)	459 (254, 813)	468 (274, 746)	0.08
Trimethyluric acid	234 (126, 450)	220 (118, 404)	242 (138, 493)	277 (151, 533)	248 (141, 515)	0.005*
Isovalerylglycine	208 (132, 317)	197 (132, 296)	221 (130, 327)	268 (173, 442)	212 (140, 344)	< 0.001*
Tiglylglycine	170 (104, 260)	162 (102, 243)	172 (105, 261)	229 (145, 356)	189 (103, 275)	< 0.001*
Kynurenic acid	86 (59, 126)	82 (56, 120)	88 (61, 129)	108 (70, 154)	87 (55, 129)	< 0.001*
Xanthosine	71 (42, 113)	68 (40, 107)	76 (44, 121)	79 (50, 142)	73 (43, 112)	0.003*
Cinnamoylglycine	54 (32, 96)	50 (33, 90)	57 (32, 98)	69 (39, 117)	57 (28, 101)	0.06
Indoxyl sulfate	32 (21, 47)	31 (20, 46)	33 (22, 48)	28 (22, 48)	34 (20, 49)	0.21
p-cresol sulfate	9 (6, 14)	9 (6, 13)	9 (6, 13)	9 (6, 15)	6 (6, 14)	0.92

[a] Secretory solutes clearance shown as median (interquartile range)

[b] p-value from analysis of variance (ANOVA) on ln-transformed secretory solutes clearances. * denotes statistical significance after correction for multiple comparisons using the Hommel method.

Table S6. Adjusted incidence rates of CKD progression by quartiles of the summary secretion score and categories of baseline eGFR and 24-hour urinary albumin excretion[a, b, c]

		All participants	eGFR, ml/min/1.73m^2 [d]			24-hour urinary albumin excretion, g/24h [e]		
			< 30	30 – 60	> 60	< 0.03	0.03 – 1	> 1
Summary secretion score	Q1	7.4 (6.7-8.2)	12.3 (10.8-14.1)	5.6 (4.7-6.5)	3.1 (1.3-8.6)	2.5 (1.7-3.7)	7.3 (6.1-8.6)	20.7 (17.0-25.3)
	Q2	5.1 (4.6-5.7)	10.0 (8.4-11.8)	4.5 (3.9-5.1)	2.7 (1.6-4.7)	1.7 (1.2-2.3)	6.1 (5.2-7.1)	17.9 (14.8-21.7)
	Q3	3.5 (3.1-4.0)	8.9 (6.7-11.9)	3.3 (2.9-3.8)	2.7 (1.8-4.2)	1.3 (0.9-1.8)	5.1 (4.3-6.0)	16.1 (13.5-19.1)
	Q4	2.4 (2.1-2.8)	4.7 (2.8-7.8)	3.0 (2.6-3.6)	1.2 (0.8-1.8)	1.1 (0.7-1.8)	4.8 (3.9 – 5.9)	14.3 (11.5-17.9)

[a] CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

[b] Incidence rates presented as the number of events per 100 person-years (95% confidence interval).

[c] Poisson models adjusted for age, black race, female sex, diabetes, eGFR (in the model for all participants and models stratified by 24-hour urinary albumin excretion categories), and log-transformed 24-hour urinary albumin excretion (in the model for all participants and models stratified by eGFR categories). In order to predict the adjusted rates of CKD progression, model covariates were set as either their mean (for continuous variables) or their proportion (for binary variables) in the analytic population.

[d] P-for interaction by categories of eGFR: 0.06

[e] P-for interaction by categories of 24-hour urinary albumin excretion: 0.002

Table S7. Number of CRIC participants who completed follow-up visits for analyses of slope[a]

Visit	Baseline	1	2	3	4	5	6	7	8	9	10	11	12
N	3,075	2,972	2,641	2,408	2,124	1,920	1,750	1,575	1,372	1,148	770	381	42

[a] Participants could miss one visit and show up at later visits

Table S8. Associations between secretory solute clearances and the composite outcome of CKD progression and all-cause mortality.[a, b, c]

	HR[d]	95% CI	P-value[e]
Hippurate	1.03	0.99-1.06	0.11
Pyridoxic acid	1.12	1.06-1.19	< 0.001*
Dimethyluric acid	1.02	0.99-1.06	0.24
Trimethyluric acid	1.03	1.00-1.07	0.04
Isovalerylglycine	1.14	1.07-1.20	< 0.001*
Tiglylglycine	1.09	1.04-1.15	0.001*
Kynurenic acid	1.11	1.03-1.20	0.004*
Xanthosine	1.10	1.06-1.15	< 0.001*
Cinnamoylglycine	1.09	1.05-1.13	< 0.001*
Indoxyl sulfate	1.10	1.03-1.18	0.004*
p-cresol sulfate	1.04	0.98-1.10	0.16
Summary score	1.23	1.13-1.34	< 0.001*

[a] CKD: chronic kidney disease; HR: hazard ratio; CI: confidence interval.

[b] CKD progression defined as 50% decline in $eGFR_{CRIC}$ from baseline, initiation of chronic dialysis, or kidney transplantation over follow-up. Results from the Cox proportional hazard model.

[c] Model adjusted for age, race, sex, $eGFR_{CRIC}$, log-transformed 24-hour urinary albumin excretion, clinical site, BMI, diabetes, smoking status. SBP, any CVD, and ACEi/ARB.

[d] Hazard ratio expressed per 50% lower secretory solute clearance or per 10 units lower summary secretion score.

[e] * denotes statistical significance after correction for multiple comparisons using the Hommel method.

Table S9. Adjusted incidence rates of all-cause mortality by quartiles of the summary secretion score and categories of baseline eGFR and 24-hour urinary albumin excretion[a, b, c]

		All participants	eGFR, ml/min/1.73m^2 [d]			24-hour urinary albumin excretion, g/24h [e]		
			< 30	30 – 60	> 60	< 0.03	0.03 – 1	> 1
Summary secretion score	Q1	4.4 (3.9-4.9)	5.9 (5.0-6.8)	3.7 (3.1-4.4)	1.7 (0.6-5.2)	3.3 (2.5-4.3)	3.4 (2.8-4.2)	4.6 (3.3-6.3)
	Q2	3.5 (3.1-3.9)	5.0 (4.0-6.2)	3.3 (2.8-3.8)	1.8 (0.9-3.6)	2.9 (2.3-3.6)	3.1 (2.6-3.7)	4.2 (3.1-5.6)
	Q3	2.3 (2.0-2.6)	3.5 (2.3-5.3)	2.3 (1.9-2.6)	1.2 (0.7-2.1)	1.8 (1.4-2.3)	2.5 (2.1-3.0)	4.1 (3.1-5.4)
	Q4	1.6 (1.4-1.9)	7.9 (3.9-15.9)[f]	1.7 (1.4-2.1)	1.0 (0.7-1.5)	1.7 (1.2-2.3)	2.1 (1.6-2.7)	3.6 (2.6-5.0)

[a] eGFR: estimated glomerular filtration rate.

[b] Incidence rates presented as the number of events per 100 person-years (95% confidence interval).

[c] Poisson models adjusted for age, black race, female sex, diabetes, eGFR (in the model for all participants and models stratified by 24-hour urinary albumin excretion categories), and log-transformed 24-hour urinary albumin excretion (in the model for all participants and models stratified by eGFR categories). In order to predict the adjusted rates of all-cause mortality, model covariates were set as either their mean (for continuous variables) or their proportion (for binary variables) in the analytic population.

[d] P-for interaction by categories of eGFR: 0.14

[e] P-for interaction by categories of 24-hour urinary albumin excretion: 0.001

[f] There were only 10 participants in this category

Table S10. Associations between secretory solute clearances and CKD progression in the iGFR subcohort.[a, b, c]

	Complete cohort adjusted for eGFR and model 2 covariates[d]			Iothalamate GFR cohort adjusted for eGFR and model 2 covariates			Iothalamate GFR cohort adjusted for eGFR, iGFR, and model 2 covariates		
	N = 3,207			N= 1,187			N= 1,187		
	HR[e]	95% CI	P-value[f]	HR	95% CI	P-value	HR	95% CI	P-value
Hippurate	1.01	0.97-1.05	0.74	1.07	1.00-1.14	0.05	1.06	0.99-1.13	0.10
Pyridoxic acid	1.18	1.10-1.26	< 0.001*	1.36	1.20-1.54	< 0.001*	1.33	1.17-1.51	< 0.001*
Dimethyluric acid	1.03	0.99-1.07	0.21	1.01	0.94-1.08	0.80	0.99	0.93-1.06	0.86
Trimethyluric acid	1.03	0.99-1.07	0.12	0.99	0.92-1.06	0.70	0.98	0.91-1.04	0.47
Isovalerylglycine	1.13	1.05-1.21	0.001*	1.15	1.02-1.30	0.02	1.13	1.00-1.27	0.05
Tiglylglycine	1.06	1.00-1.13	0.05	1.09	0.97-1.24	0.15	1.06	0.94-1.20	0.34
Kynurenic acid	1.21	1.10-1.32	< 0.001*	1.28	1.10-1.51	0.002*	1.23	1.05-1.45	0.01
Xanthosine	1.13	1.08-1.19	< 0.001*	1.16	1.07-1.26	< 0.001*	1.15	1.06-1.24	0.001*
Cinnamoylglycine	1.11	1.06-1.17	< 0.001*	1.15	1.06-1.25	0.001*	1.13	1.04-1.24	0.004*
Indoxyl sulfate	1.15	1.06-1.24	< 0.001*	1.22	1.05-1.42	0.008	1.18	1.02-1.38	0.03
p-cresol sulfate	1.08	1.01-1.16	0.02	1.02	0.90-1.16	0.74	0.99	0.87-1.13	0.89
Summary score	1.28	1.16-1.41	< 0.001*	1.39	1.16-1.67	< 0.001*	1.32	1.09-1.59	0.004*

[a] CKD: chronic kidney disease; iGFR: iothalamate-measured glomerular filtration rate; eGFR: estimated glomerular filtration rate; HR: hazard ratio; CI: confidence interval.

[b] Results from a subcohort of participants with iGFR measurements. In this subcohort, there were 457 cases of CKD progression.

[c] CKD progression defined as 50% decline in $eGFR_{CRIC}$ from baseline, initiation of chronic dialysis, or kidney transplantation over follow-up. Results from the Cox proportional hazard model.

[d] Model adjusted for age, race, sex, clinical site, $eGFR_{CRIC}$, log-transformed 24hr urinary albumin excretion, BMI, diabetes, smoking status, systolic blood pressure, any CVD and ACEi/ARB.

[e] Hazard ratio expressed per 50% lower secretory solute clearance or per 10 units lower summary secretion score.

[f] * denotes statistical significance after correction for multiple comparisons using the Hommel method.

Table S11. Associations between secretory solute clearances and all-cause mortality in the iGFR subcohort.[a, b, c]

	Complete cohort adjusted for eGFR and model 2 covariates[d]			Iothalamate GFR cohort adjusted for eGFR and model 2 covariates			Iothalamate GFR cohort adjusted for eGFR, iGFR, and model 2 covariates		
	N = 3,416			N= 1,239			N= 1,239		
	HR[e]	95% CI	P-value[f]	HR	95% CI	P-value	HR	95% CI	P-value
Hippurate	1.07	1.02-1.11	0.002*	1.07	0.97-1.18	0.15	1.07	0.98-1.18	0.15
Pyridoxic acid	1.10	1.02-1.19	0.01	0.97	0.83-1.14	0.74	0.98	0.83-1.15	0.76
Dimethyluric acid	1.02	0.97-1.06	0.47	0.96	0.88-1.05	0.42	0.97	0.88-1.06	0.47
Trimethyluric acid	1.06	1.02-1.11	0.004*	1.01	0.93-1.10	0.84	1.01	0.93-1.10	0.83
Isovalerylglycine	1.23	1.14-1.32	< 0.001*	1.19	1.03-1.37	0.02	1.19	1.03-1.38	0.02
Tiglylglycine	1.19	1.11-1.28	< 0.001*	1.26	1.08-1.47	0.004*	1.26	1.08-1.47	0.003*
Kynurenic acid	1.13	1.03-1.24	0.01	1.03	0.95-1.24	0.79	1.03	0.85-1.25	0.76
Xanthosine	1.06	1.01-1.12	0.03	1.08	0.98-1.18	0.12	1.08	0.98-1.19	0.11
Cinnamoylglycine	1.06	1.01-1.12	0.02	1.08	0.97-1.19	0.15	1.08	0.98-1.19	0.14
Indoxyl sulfate	1.06	0.97-1.15	0.22	0.92	0.77-1.10	0.36	0.92	0.76-1.11	0.37
p-cresol sulfate	1.01	0.93-1.08	0.87	0.97	0.83-1.11	0.59	0.96	0.83-1.11	0.62
Summary score	1.27	1.14-1.41	< 0.001*	1.15	0.91-1.45	0.24	1.16	0.92-1.47	0.21

[a] iGFR: iothalamate-measured glomerular filtration rate; eGFR: estimated glomerular filtration rate; HR: hazard ratio; CI: confidence interval.

[b] Results from a subcohort of participants with iGFR measurements. In this subcohort, there were 279 cases of all-cause death.

[c] Results from the Cox proportional hazard model.

[d] Model adjusted for age, race, sex, clinical site, $eGFR_{CRIC}$, log-transformed 24hr urinary albumin excretion, BMI, diabetes, smoking status, systolic blood pressure, any CVD and ACEi/ARB.

[e] Hazard ratio expressed per 50% lower secretory solute clearance or per 10 units lower summary secretion score.

[f] * denotes statistical significance after correction for multiple comparisons using the Hommel method.

Table S12. Associations between secretory solute clearances and CKD progression with additional adjustment for insulin, statins, and diuretics.[a, b, c]

	HR[d]	95% CI	P-value[e]
Hippurate	1.01	0.97-1.05	0.58
Pyridoxic acid	1.18	1.10-1.26	< 0.001*
Dimethyluric acid	1.03	0.99-1.07	0.19
Trimethyluric acid	1.03	1.00-1.08	0.09
Isovalerylglycine	1.13	1.06-1.21	< 0.001*
Tiglylglycine	1.07	1.00-1.14	0.04
Kynurenic acid	1.22	1.11-1.33	< 0.001*
Xanthosine	1.14	1.08-1.20	< 0.001*
Cinnamoylglycine	1.12	1.06-1.17	< 0.001*
Indoxyl sulfate	1.15	1.07-1.25	< 0.001*
p-cresol sulfate	1.09	1.02-1.16	0.02
Summary score	1.29	1.17-1.43	< 0.001*

[a] CKD: chronic kidney disease; HR: hazard ratio; CI: confidence interval.

[b] CKD progression defined as 50% decline in $eGFR_{CRIC}$ from baseline, initiation of chronic dialysis, or kidney transplantation over follow-up. Results from the Cox proportional hazard model.

[c] Model adjusted for all covariates in Model 2, with additional adjustment for insulin, statins, loop diuretics, and thiazide diuretics.

[d] Hazard ratio expressed per 50% lower secretory solute clearance or per 10 units lower summary secretion score.

[e] * denotes statistical significance after correction for multiple comparisons using the Hommel method.

Table S13. Associations between secretory solute clearances and CKD progression defined using eGFR from CKD-EPI equation.[a, b, c]

	HR[d]	95% CI	P-value[e]
Hippurate	1.01	0.98-1.05	0.50
Pyridoxic acid	1.22	1.15-1.30	< 0.001*
Dimethyluric acid	1.04	1.00-1.08	0.05
Trimethyluric acid	1.05	1.01-1.09	0.02
Isovalerylglycine	1.19	1.11-1.28	< 0.001*
Tiglylglycine	1.10	1.03-1.16	0.003*
Kynurenic acid	1.28	1.17-1.40	< 0.001*
Xanthosine	1.17	1.11-1.23	< 0.001*
Cinnamoylglycine	1.14	1.09-1.20	< 0.001*
Indoxyl sulfate	1.21	1.12-1.31	< 0.001*
p-cresol sulfate	1.11	1.04-1.8	0.002*
Summary score	1.39	1.26-1.53	< 0.001*

[a] CKD: chronic kidney disease; HR: hazard ratio; CI: confidence interval.

[b] CKD progression defined as 50% decline in $eGFR_{CKD\text{-}EPI}$ from baseline, initiation of chronic dialysis, or kidney transplantation over follow-up. Results from the Cox proportional hazard model.

[c] Model adjusted for age, race, sex, $eGFR_{CKD\text{-}EPI}$, log-transformed 24-hour urinary albumin excretion, BMI, diabetes, smoking status, SBP, any CVD, and ACEi/ARB.

[d] Hazard ratio expressed per 50% lower secretory solute clearance or per 10 units lower summary secretion score.

[e] * denotes statistical significance after correction for multiple comparisons using the Hommel method.

Table S14. Associations between secretory solute plasma concentration and CKD progression.[a, b, c]

	HR[d]	95% CI	P-value[e]
Hippurate	0.99	0.94-1.05	0.85
Pyridoxic acid	1.07	1.02-1.11	0.004*
Dimethyluric acid	0.98	0.96-1.00	0.06
Trimethyluric acid	0.97	0.95-1.00	0.07
Isovalerylglycine	1.05	0.96-1.14	0.28
Tiglylglycine	1.04	0.97-1.12	0.25
Kynurenic acid	1.01	0.92-1.12	0.77
Xanthosine	1.05	1.00-1.09	0.04
Cinnamoylglycine	1.00	0.97-1.04	0.85
Indoxyl sulfate	1.07	0.99-1.15	0.10
p-cresol sulfate	0.99	0.95-1.03	0.53

[a] CKD: chronic kidney disease; HR: hazard ratio; CI: confidence interval.

[b] CKD progression defined as 50% decline in $eGFR_{CRIC}$ from baseline, initiation of chronic dialysis, or kidney transplantation over follow-up. Results from the Cox proportional hazard model.

[c] Model adjusted for age, race, sex, $eGFR_{CRIC}$, log-transformed 24-hour urinary albumin excretion, clinical site, BMI, diabetes, smoking status. SBP, any CVD, and ACEi/ARB.

[d] Hazard ratio expressed per 50% higher plasma secretory solute concentration.

[e] * denotes statistical significance after correction for multiple comparisons using the Hommel method.

Figure S1. Participant flow diagram

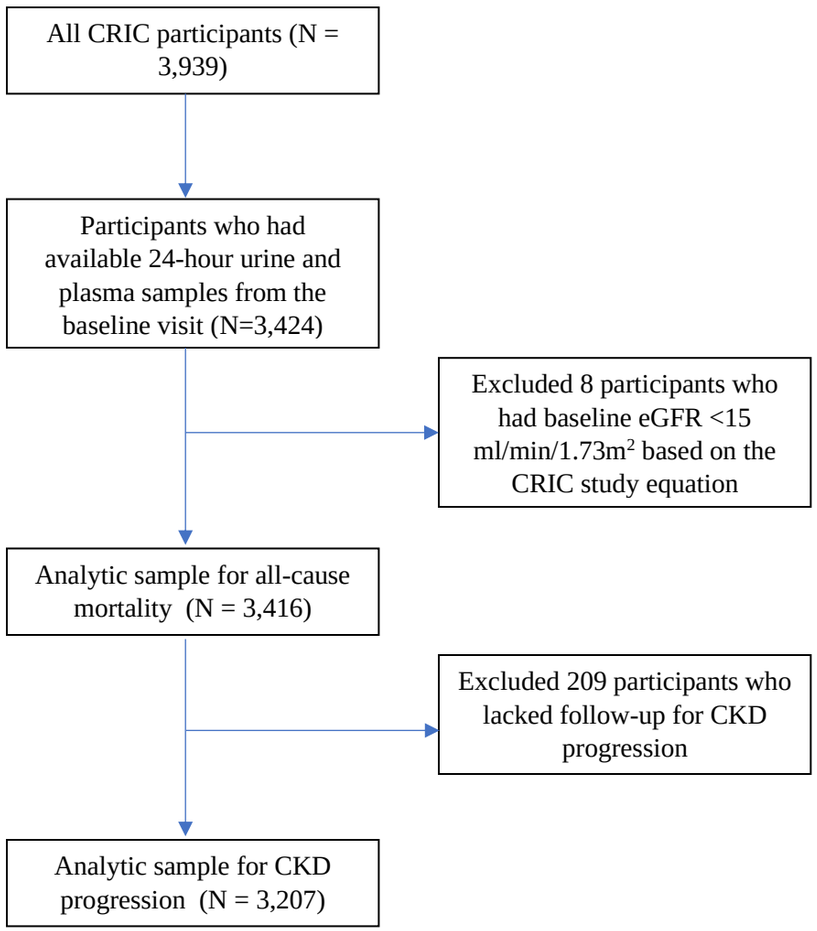

Figure S2. Distribution of the summary secretion score