Figure S1. Participant flow diagram
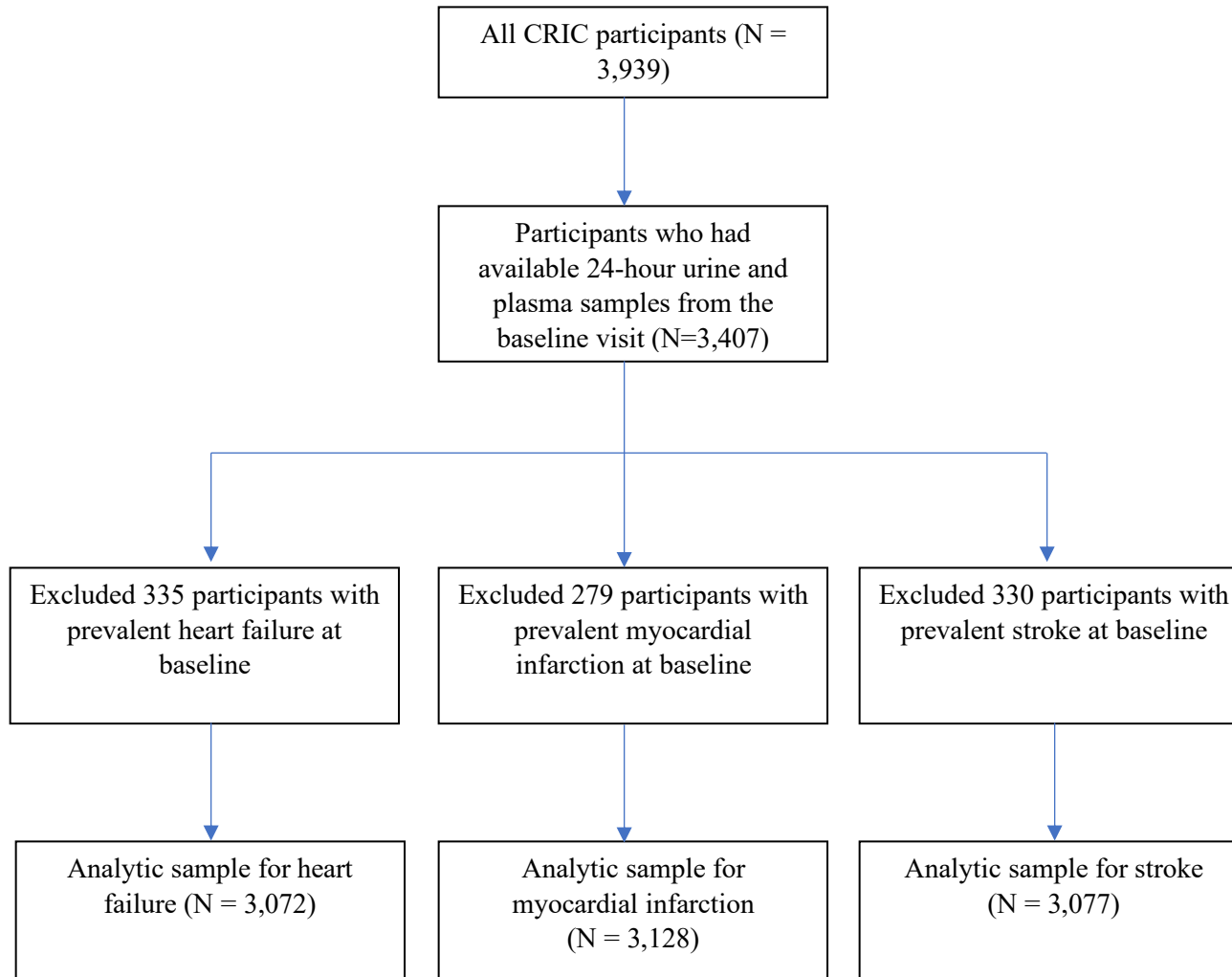
```
                    ┌─────────────────────────────┐
                    │  All CRIC participants (N =  │
                    │          3,939)             │
                    └──────────────┬──────────────┘
                                   │
                    ┌──────────────▼──────────────┐
                    │   Participants who had      │
                    │  available 24-hour urine and│
                    │    plasma samples from the  │
                    │   baseline visit (N=3,407)  │
                    └──────────────┬──────────────┘
                                   │
      ┌────────────────────────────┼────────────────────────────┐
      │                            │                            │
┌─────▼──────────────┐   ┌─────────▼──────────┐   ┌────────────▼─────────┐
│ Excluded 335       │   │ Excluded 279       │   │ Excluded 330         │
│ participants with  │   │ participants with  │   │ participants with    │
│ prevalent heart    │   │ prevalent          │   │ prevalent stroke at  │
│ failure at baseline│   │ myocardial         │   │ baseline             │
│                    │   │ infarction at      │   │                      │
│                    │   │ baseline           │   │                      │
└─────┬──────────────┘   └─────────┬──────────┘   └────────────┬─────────┘
      │                            │                            │
┌─────▼──────────────┐   ┌─────────▼──────────┐   ┌────────────▼─────────┐
│ Analytic sample    │   │ Analytic sample    │   │ Analytic sample for  │
│ for heart failure  │   │ for myocardial     │   │ stroke (N = 3,077)   │
│ (N = 3,072)        │   │ infarction         │   │                      │
│                    │   │ (N = 3,128)        │   │                      │
└────────────────────┘   └────────────────────┘   └──────────────────────┘
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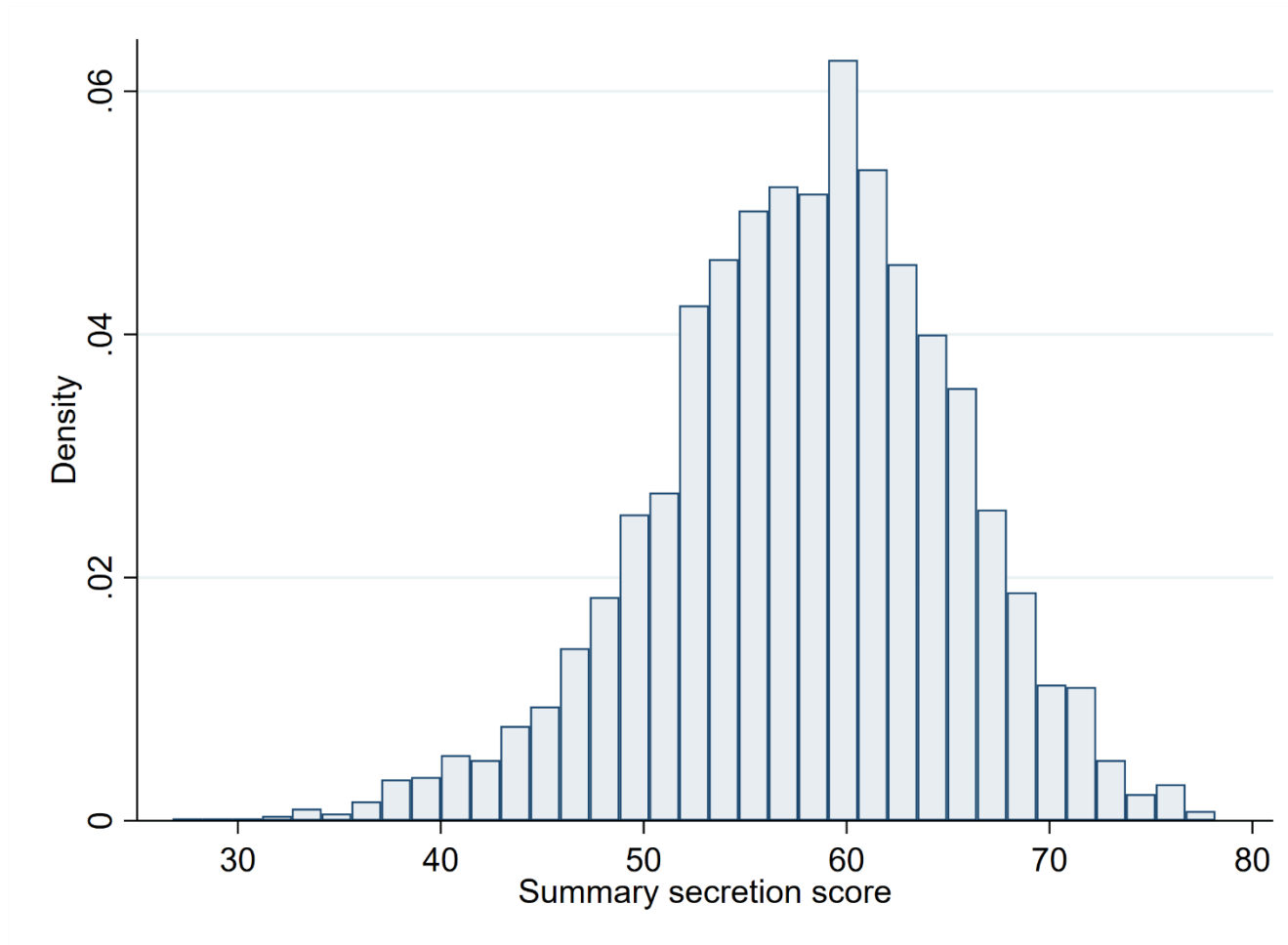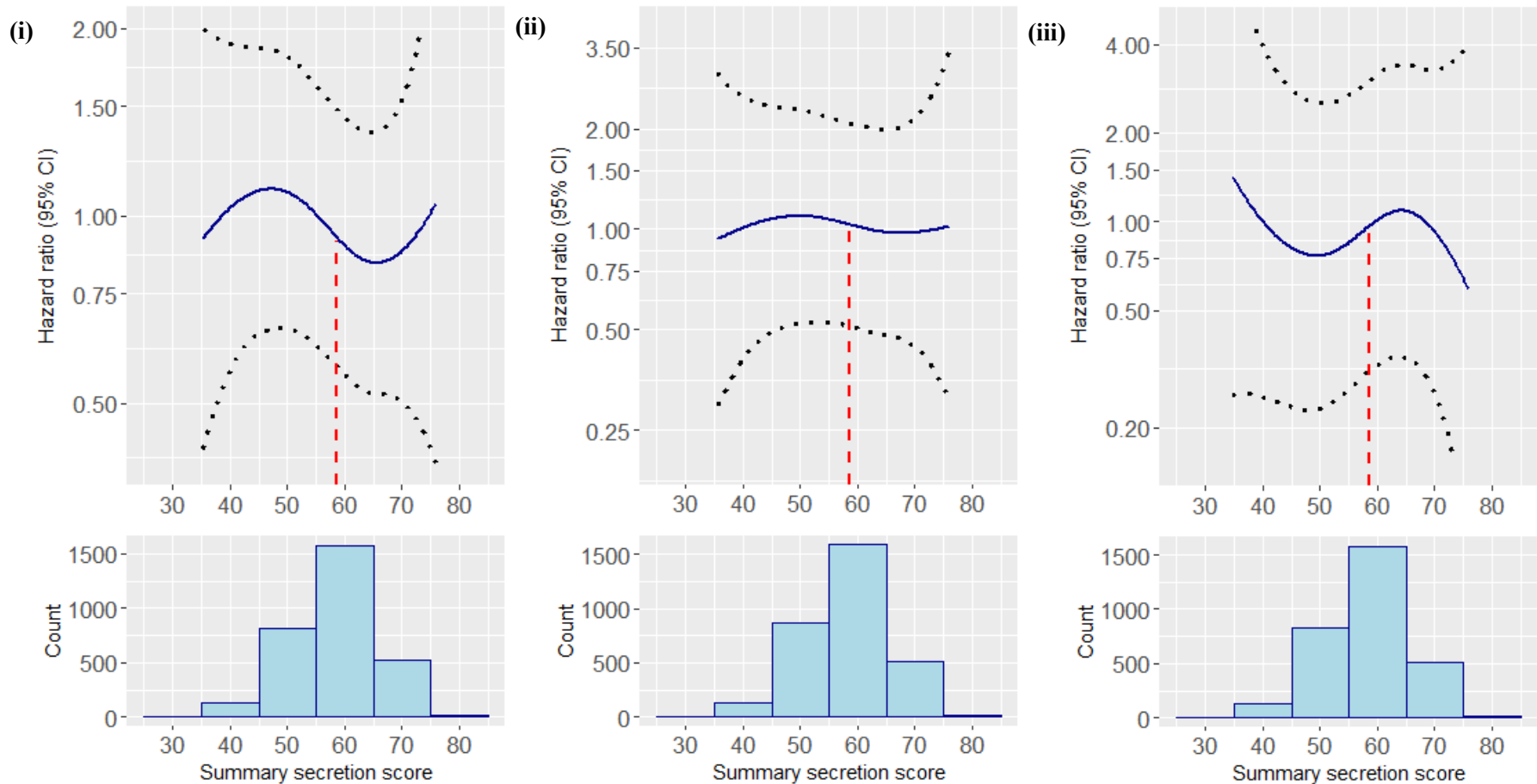**Figure S2. Distribution of the summary secretion score.**

Figure S3. Association of summary secretion score with incident heart failure (i), myocardial infarction (ii), and stroke (iii) [a, b, c]

[a] Hazard ratio adjusted for age, race, sex, clinical sites, educational attainment, smoking status, history of cardiovascular disease, diabetes, body mass index, systolic blood pressure, triglyceride, 24-hour urinary albumin excretion, ACEi/ARB, loop diuretics, beta blockers, and estimated GFR.

[b] Hazard ratio predicted using restricted cubic splines with two knots placed at the 20th and the 80th percentiles of the summary secretion score. P-values for non-linearity at two knots were 0.2 and 0.3 for heart failure; 0.6 and 0.7 for myocardial infarction; and 0.2 and 0.2 for stroke.

[c] Vertical dashed lines represent the median of the summary secretion score.

Item S1. Supplemental Methods

Chemicals
Formic acid was purchased from Fisher or EMD, LC-MS grade water, methanol, and ammonium hydroxide from Fisher, DMSO from Pierce, d_6-DMSO from EMD, and D_2O from Cambridge Isotopes.

Table a of Item S1: Analyte and internal standard vendors and solid phase extraction used for urine

Compound (endogenous)	Vendor	Compound (IS)	Vendor	SPE for urine
3-Hydroxy hippurate	Toronto Research Chemicals PN: H943125			MCX
Adipic acid	Sigma PN: 09582-50G	Adipic acid (13C6)	Cambridge Isotopes PN: CLM-4723-0.1	MCX
Cinnamoylglycine	Sigma PN: S658200-25MG	Cinnamoylglycine (2H2)	Medical Isotopes PN: D32615	MCX
Dimethyluric acid	Toronto Research Chemicals PN: D479695	Dimethyluric acid (13C4,15N3)	Sigma PN: 705640	MCX
Hippurate	Sigma PN: 112003-5G	Hippuric acid (2H5)	Toronto Research Chemicals PN: H356702	MCX
Indoxyl sulfate	Sigma PN: I3875-250MG	Indoxyl sulfate (13C6)	Sigma PN: 809780-1MG	MCX
Isovalerylglycine	Toronto Research Chemicals PN: I917600	Isovarylglycine (2H2)	CDN Isotopes PN: D-6230	MCX
Kynurenic acid	Sigma PN: K3375-250MG	Kynurenic acid (2H5)	Toronto Research Chemicals PN: K660502	HLB
Pantothenic acid	Sigma PN: 21210-5G-F			HLB
p-cresol-sulfate	Collaborator Provided	p-Cresol sulfate (2H7)	Collaborator Provided	MCX
Pyridoxic acid	Sigma PN: P9630-25MG	Pyridoxic acid (2H3)	Toronto Research Chemicals PN: P991877	MCX
Suberic acid	Sigma PN: 60930-100G			MCX
Succinic acid	Sigma PN: S3674-100G	Succinic acid (13C4)	Toronto Research Chemicals PN: S688767	HLB
Tiglylglycine	Toronto Research Chemicals PN: T440100	Tirlylglycine (13C2,15N)	Toronto Research Chemicals PN: H-T440102	MCX
Trimethyluric acid	Toronto Research Chemicals PN: T797995	Trimethyluric acid (13C4,15N3)	Sigma PN: 705667-5MG	MCX
Xanthosine	Toronto Research Chemicals PN: X742100			MCX

Internal standard mix

All internal standards were combined in a single tube and the volume brought to 20 mL with methanol. The concentration of each analyte in the internal standard mix is listed in Table b.

Table b of Item S1:

Internal Standard	IS Stock Solvent	Working Concentration (ug/mL)
Adipic acid ($^{13}C_6$)	MeOH	25
Cinnamoylglycine ($^2H_2$)	MeOH	0.025
Dimethyluric acid ($^{13}C_4, ^{15}N_3$)	MeOH	10
Hippuric acid ($^2H_5$)	DMSO	1
Indoxyl sulfate ($^{13}C_6$)	DMSO	5
Isovarylglycine ($^2H_2$)	DMSO	0.25
Kynurenic acid ($^2H_5$)	DMSO	0.5
p-Cresol sulfate ($^2H_7$)	75%ACN/25%MeOH	2.5
Pyridoxic acid ($^2H_3$)	DMSO	0.5
Succinic acid ($^{13}C_4$)	MeOH	100
Tirlylglycine ($^{13}C_2, ^{15}N$)	MeOH	1
Trimethyluric acid ($^{13}C_4, ^{15}N_3$)	DMSO	10

Extraction from plasma and serum

Analytes were extracted from plasma or serum by protein precipitation in organic solvent. In a 96-well Acroprep Advance filter plate (Pall PN: 8148), 100 µL of sample, 10 µL of internal standard mix, and 300 µL acetonitrile (ACN)/1% formic acid were combined. The plate was sealed (Pall Cap Mat PN: 5230) and vigorously agitated with a multitube vortexer (10 min on maximum speed). The plate was then spun down for 10 min at 1,509x*g* and the filtrate collected in a new 96-well collection plate (Grainger PN: 786201). The filtrate was then passed through a phospholipid removal plate (Phenomenex PN: 8E-S133-TGB) using a positive pressure manifold (Biotage, Pressure+96). The resulting sample was captured in

a 2mL 96-well plate (Grainger PN: 4780270) and dried down in a centrifugal vacuum evaporator overnight.

Extraction from urine

Analytes were extracted from urine by two different solid phase extractions (*see* **Table a** for which analytes were extracted by each solid phase). In a 96-well plate (Grainger PN: 780270), 20 μL sample, 10 μL internal standard, and 870 μL formic acid diluent were mixed and then added to either a mixed cation exchange extraction plate or a hydrophilic-lipophilic binding extraction plate (Waters MCX PN: 186000248 with 2% formic acid in water as the diluent and HLB PN: WAT058951 with 0.2% formic acid in water as the diluent). Using the positive pressure manifold (Biotage, Pressure+96), the plates were washed with 1 mL diluent and the analytes were eluted (HLB elution: 1 mL of 60% acetonitrile, 40% methanol, MCX elution: twice with 600 μL of 60% acetonitrile, 40% methanol + 5% ammonium hydroxide) into a new 96-well plate (Grainger PN: 780270). The eluent was dried down in a centrifugal vacuum overnight.

Liquid chromatography-tandem mass spectrometry

Dried extracts were reconstituted in 80 μL of 5% acetonitrile/0.2% formic acid in water and filtered through a large-pore filter plate (Millipore, MSBVN1210) to remove particulates. A volume of 20 μL or 5 μL (for plasma/serum and urine, respectively) was injected onto a Restek PFPP chromatographic column (50 mm x 2.1 mm Pinnacle DB PFPP 1.9 μm Restek PN: 9419252), which was developed using a gradient (Shimadzu Nexera XR 20A, **Tables c and d**). The column eluate was introduced into a triple quadrupole tandem mass spectrometer (Sciex 6500, **Tables e-g**). Data was collected by a combination of scheduled (53 sec window around the retention times listed in **Tables e-g**) and unscheduled MRMs (**Tables e-g**). Endogenous peak areas (determined in Skyline, **Figures a and b**) were normalized to internal standard peak areas (peak area ratio). To reduce run-to-run variability, all peak area ratios for study samples were normalized to the average peak area ratio observed in 5 replicates of a matrix-matched single point calibrator processed in each batch and for each study sample the resulting ratio was multiplied by the concentration of each analyte in the single point calibrator. To monitor process quality, two matrix-matched quality control samples were processed in parallel in each batch.

Table c of Item S1. Chromatographic parameters.

Mobile Phase A	Water + 0.2% Formic Acid
Mobile Phase B	80% ACN/20%MeOH + 0.2% Formic acid
Flow Rate	0.4 mL/min
Autosampler Temperature	7 °C
Column Oven Temperature	40 °C

Table d of Item S1. Chromatographic program.

Time (min)	Action
0.00	Divert to Waste
0.00	2% B
0.25	2% B
0.50	Divert to Instrument
4.85	25% B
4.95	85% B
6.25	85% B
6.35	2% B
7.00	Divert to Waste
10.70	End Run

Table e of Item S1. Mass Spectrometric Parameters (Part 1).

Compound	Mass (Da)	Pos/Neg Mode	Internal Standard	Internal standard in urine (if different)	Retention Time (min)	Un/scheduled
3-Hydroxy hippurate	194.9	Neg	Hippuric acid ($^2H_5$)		2.1	Scheduled
Adipic acid	145.9	Neg	Adipic acid ($^{13}C_6$)		1.6	Scheduled
Cinnamoylglycine	205.1	Pos	Cinnamoylglycine ($^2H_2$)		4.4	Scheduled
Dimethyluric acid	196.1	Neg	Dimethyluric acid ($^{13}C_4, ^{15}N_3$)		2.1	Scheduled
Hippurate	179.1	Pos	Hippuric acid ($^2H_5$)		2.5	Scheduled
Indoxyl sulfate	213	Neg	Indoxyl sulfate ($^{13}C_6$)		1.8	Unscheduled
Isovalerylglycine	159.1	Neg	Isovarylglycine ($^2H_2$)		1.7	Scheduled
Kynurenic acid	189.1	Pos	Kynurenic acid ($^2H_5$)		3.1	Unscheduled
Pantothenic acid	219	Pos	Pyridoxic acid ($^2H_3$)	Kynurenic acid ($^2H_5$)	1.3	Scheduled
p-cresol-sulfate	188.01	Neg	p-Cresol sulfate ($^2H_7$)		2.2	Unscheduled
Pyridoxic acid	183.05	Pos	Pyridoxic acid ($^2H_3$)		1.6	Scheduled
Suberic acid	174.1	Pos	None		3.6	Scheduled
Succinic acid	118	Neg	Succinic acid ($^{13}C_4$)		0.6	Scheduled
Tiglylglycine	157	Neg	Tirlylglycine ($^{13}C_2, ^{15}N$)		1.6	Scheduled
Trimethyluric acid	210.1	Pos	Trimethyluric acid ($^{13}C_4, ^{15}N_3$)		2.6	Scheduled
Xanthosine	284.2	Pos	Pyridoxic acid ($^2H_3$)		1.1	Scheduled

Table f of Item S1. Mass Spectrometric Parameters (Part 2).

Compound	DP	EP	CXP	MS1	MS1 (detuned in urine)	MS3	CE
3-Hydroxy hippurate	-46	-10	-13	193.9		149.9, 92.9	-19, -23
Adipic acid	-36	-10	-13	144.9		126.8, 83	-13, -16
Cinnamoylglycine	30	10	13	206.1		131.2, 103	16, 37
Dimethyluric acid	-45	-10	-13	195.1		180, 109.7, 136.9	-24, -29, -34
Hippurate	14	10	13	180.1	181.1	105, 51.1, 77, 50	19, 77, 43, 115
Indoxyl sulfate	-31	-10	-13	212		132, 79.9, 80.8, 77	-26, -24, -21, -43
Isovalerylglycine	-25	-10	-13	158.1		113.9, 73.9	-17, -19
Kynurenic acid	42	10	13	190.1	191.1	144.1, 89, 116.1	26, 52, 42
Pantothenic acid	51	10	13	220		202.1, 124.1, 184.1, 90	28, 16, 20, 18
p-cresol-sulfate	-29	-10	-13	188.01	188.01	107, 79.9, 104.9, 77	-28, -21, -44, -45
Pyridoxic acid	31	10	13	184.05		166.1, 92.1, 148.1, 65.2	17, 38, 28, 43
Suberic acid	30	10	13	175.1		157.2, 83.1, 111.1, 55	11, 15, 23, 33
Succinic acid	-21	-10	-13	117		98.9	-16
Tiglylglycine	-22	-10	-13	156		111.9, 95.8, 109.9	-16, -21, -18
Trimethyluric acid	94	10	13	211.1		196.1, 126, 154	31, 25, 25
Xanthosine	38	10	13	285.2		153.1, 133, 136.1	15, 15, 45

Table g of Item S1. Mass Spectrometric Parameters (Part 3).

Internal Standard	Retention Time (min)	DP	EP	CXP	MS1	MS3	CE
Adipic acid ($^{13}C_6$)	1.6	-24	-10	-13	151	133, 106.1, 88, 86.1	-17, -14, -18, -26
Cinnamoylglycine ($^2H_2$)	4.4	40	10	13	208.1	131.1, 103, 77.1, 51.1	17, 39, 58, 87
Dimethyluric acid ($^{13}C_4, ^{15}N_3$)	2.1	-62	-10	-13	201.1	186, 141.1, 112.9	-25, -34, -30
Hippuric acid ($^2H_5$)	2.4	26	10	13	185.1	110.2, 82.1, 54.1	19, 43, 73
Indoxyl sulfate ($^{13}C_6$)	1.8	-30	-10	-13	218	138, 110, 83.1, 80.9	-27, -33, -41, -21
Isovarylglycine ($^2H_2$)	1.7	-20	-10	-13	160.1	116.1, 100.1, 76	-18, -25, -17
Kynurenic acid ($^2H_5$)	3.1	38	10	13	195.1	149.2, 121.1, 94.1	28, 43, 53
p-Cresol sulfate ($^2H_7$)	2.1	-30	-10	-13	194.1	114, 112.1, 110, 79.9	-28, -47, -50, -24
Pyridoxic acid ($^2H_3$)	1.6	34	10	13	187.2	150.1, 141.1, 94, 67	30, 31, 40, 45
Succinic acid ($^{13}C_4$)	0.6	-15	-10	-13	120.9	103, 76.1, 57.9	-15, -16, -19
Tirlylglycine ($^{13}C_2, ^{15}N$)	1.6	-18	-10	-13	159.1	114, 112, 98, 77	-16, -18, -21, -15
Trimethyluric acid ($^{13}C_4, ^{15}N_3$)	2.6	18	10	13	218.2	203.2, 130.1	28, 28

Assignment of single point calibrator concentrations using quantitative NMR and standard addition
Quantitative NMR. Non-isotopically labeled analytes were dissolved in D_2O (p-cresol sulfate) or d_6-DMSO (all others) and analyzed by proton (^1H) NMR on a AV-300 (Bruker). The instrument was calibrated against a Bruker certified pamoic acid standard (100 mg/ml pamoic acid in d_6-DMSO + 1% TMS, Part no. Z10298). Samples were auto-tuned and matched and shimmed with a software script to ensure consistent measurement conditions. ^1H NMR peaks of pamoic acid that were integrated and assigned to stoichiometric counts of ^1H are shown in **Table h**.

Table h of Item S1. Pamoic acid internal NMR standard integrals and assignments.

Proton chemical shift range	Integrated Area	Number of protons
8.698 to 8.344	2.0	2
8.344 to 8.002	2.044	2
8.002 to 7.741	1.9882	2
7.493 to 7.110	3.9668	4

[1]H NMR data were collected under identical conditions. Clean peaks that did not exhibit overlap with adjacent peaks and that did not have interference from solvent and other buffer peaks were chosen for assignment. These peaks were unambiguously assigned to respective [1]H atoms of the molecule using established protocol of small molecule resonance assignment by multiplet and chemical shift analysis as well as ab-initio simulation of [1]H spectra from the known structures of the molecules. Both the above steps were carried out using Topspin 3.5 (Bruker) and MestReNova 12.0.1 (Mestrelab Research S.L.) software. The integrated areas of the assigned peaks were then computed and compared with the pamoic acid standard integrals as internal references and the effective concentration was determined using the ERETIC2 protocol from within the Topspin 3.5 software [PMID: 25215441]. Cinnamoylglycine required the higher resolution of an AV700 system. The same stocks measured by NMR were then spiked into the plasma and urine single point calibrators and used by standard addition to assign the concentration of each analyte in the single point calibrators.

Standard addition: Concentration of analytes was initially estimated by comparing peak areas of internal standards of known concentration, to peak areas of unknown endogenous analytes. Each matrix-matched single point calibrator (**SPC**) was spiked with 3% (serum) or 5% (urine) analyte stock solution (in DMSO) to a final concentration of approximately 30-fold (serum) or 10-fold (urine) higher than the estimated concentration of endogenous analyte in each SPC. Analyte mixes and spiked SPC were prepared in singlicate and extracted in triplicate on three independent days. Endogenous analyte concentration was calculated by multiplying the peak area ratio of the SPC (with 3% or 5% blank DMSO for serum or urine, respectively) by the slope of the linear regression of concentration vs. peak area ratio (2-4 data points for each curve, spanning the linear portion of the spike-recovery experiment).

Limits of quantification and linearity
Upper limit of quantification (**ULOQ**) was defined as the highest concentration in the standard addition experiment that demonstrated a linear response across the three days. Lower limit of quantitation (**LLOQ**) was determined by diluting single point calibrator into negative matrix and extracting in triplicate. LLOQ was determined to be the lowest concentration at which the recovery was between 80-120% and the within-day CV% of the measurement was <20%. Plasma samples were diluted into either MSG3000 (Golden West Diagnostics), 30% bovine serum albumin (Sigma) in phosphate buffered saline, or saline [data shown is for the most relevant matrix that lacked isobaric interference]. Urine samples were diluted into water.

Table i of Item S1. Limits of quantification for each analyte.

Compound (endogenous)	Serum LLOQ (ng/mL)	Urine LLOQ (ng/mL)	Serum ULOQ	Average r^2 (serum)[d]	Urine ULOQ	Average r^2 (urine)[d]
3-Hydroxy hippurate[a]	0.96	116	415	0.9892	284639	0.9951
Adipic acid[a]	ND	730	3428	0.9898	29056	0.9899
Cinnamoylglycine[a]	0.22	0.67	156	0.9905	1088	0.9958
Dimethyluric acid[a]	0.23	26	336	0.9945	144413	0.9887
Hippurate[a]	9.5	380	2559	0.9844	1169664	0.9938
Indoxyl sulfate[a]	9.1	330	10517	0.9897	969097	0.9913
Isovalerylglycine[b]	0.55	16	75	0.9967	20049	0.9849
Kynurenic acid[a]	0.70	6.7	309	0.9986	124985	0.9938
Pantothenic acid[a]	6.3	114	2191	0.9976	13288	0.9842
p-cresol-sulfate[a]	29	49	38217	0.9896	104148	0.8875
Pyridoxic acid[a]	1.5	21	480	0.9951	50291	0.9359
Suberic acid[a]	ND	631	3172	0.9798	55909	0.9807
Succinic acid[a]	ND	2397	107158	0.9988	22247	0.9521
Tiglylglycine[c]	0.55	15	169	0.9984	58664	0.9980
Trimethyluric acid[a]	0.22	8.0	123	0.9979	18647	0.9791
Xanthosine[a]	0.31	2.4	329	0.9975	5009	0.9783

[a] Plasma diluted with MSG3000.

[b] Plasma diluted with 30% bovine serum albumin.

[c] Plasma diluted with saline.

d Pearson correlation coefficient of the standard addition experiment in each single point calibrator.

ND: Not determined due to isobaric interference in dilution matrices.
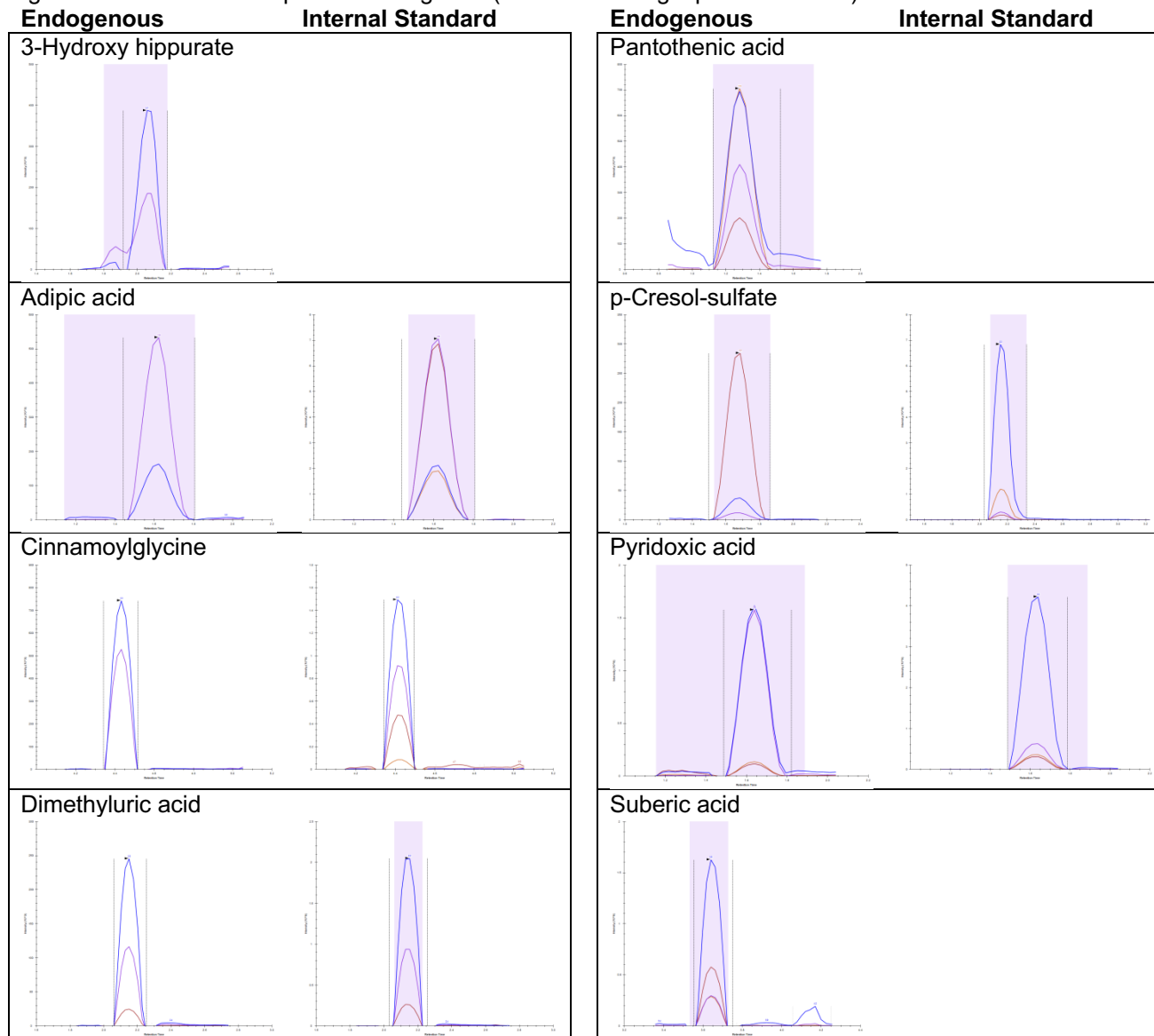
Interference

SPC, hemolyzed, lipemic, high-protein (7 g/dL), and low-protein samples (<3 g/dL) were each spiked to a final concentration 3-fold higher than the approximate endogenous concentration of each analyte and percent recoveries were calculated (SPC was assumed to be 100% recovery for each). Interference was defined by a recovery outside the range of 75-125% of expected. Hemolysis interfered with trimethyluric acid recovery. High total protein interfered with the recovery of 3-hydroxy hippurate and isovalerylglycine. Lipemia and low total protein did not interfere with any

analyte recoveries.

Table j of Item S1. Recoveries in different matrices.

	Lipemic	Hemolysis	Low total protein	High total protein
3-Hydroxy hippurate	116%	102%	93%	72%
Adipic acid	96%	124%	102%	119%
Cinnamoylglycine	112%	118%	112%	118%
Dimethyluric acid	104%	108%	109%	101%
Hippurate	116%	117%	104%	98%
Indoxyl sulfate	109%	118%	106%	94%
Isovalerylglycine	111%	123%	114%	130%
Kynurenic acid	112%	122%	109%	117%
Pantothenic acid	106%	112%	108%	126%
p-cresol-sulfate	109%	114%	104%	94%
Pyridoxic acid	108%	112%	106%	116%
Suberic acid	98%	117%	110%	96%
Succinic acid	109%	116%	108%	123%
Tiglylglycine	111%	118%	115%	124%
Trimethyluric acid	88%	55%	92%	108%
Xanthosine	99%	120%	113%	100%

Figure a of Item S1. Example chromatograms (from serum single point calibrator).

Endogenous   Internal Standard   Endogenous   Internal Standard

3-Hydroxy hippurate		Pantothenic acid	
Adipic acid		p-Cresol-sulfate	
Cinnamoylglycine		Pyridoxic acid	
Dimethyluric acid		Suberic acid	

Hippurate

Succinic acid

Indoxyl sulfate

Tiglylglycine

Isovalerylglycine

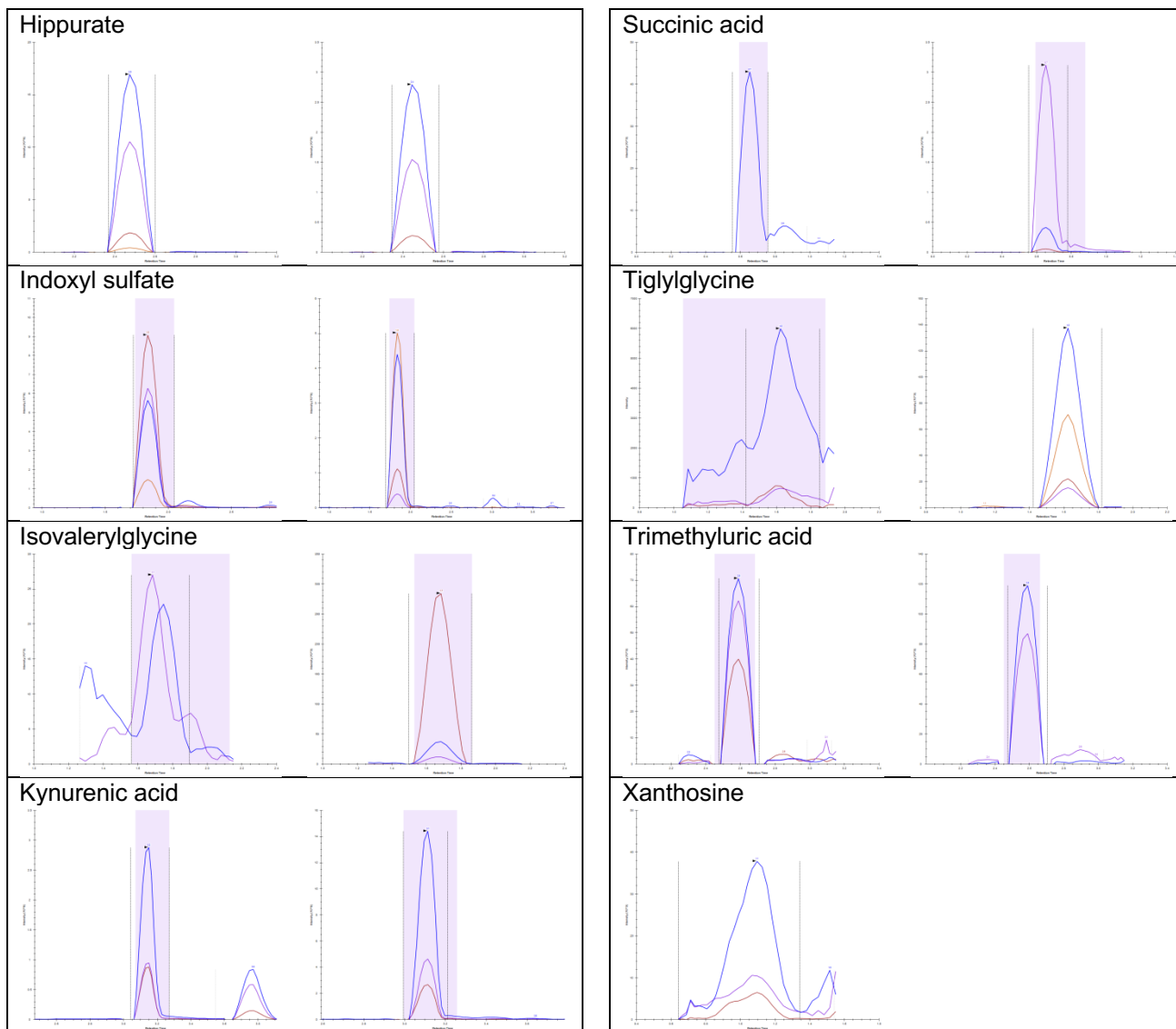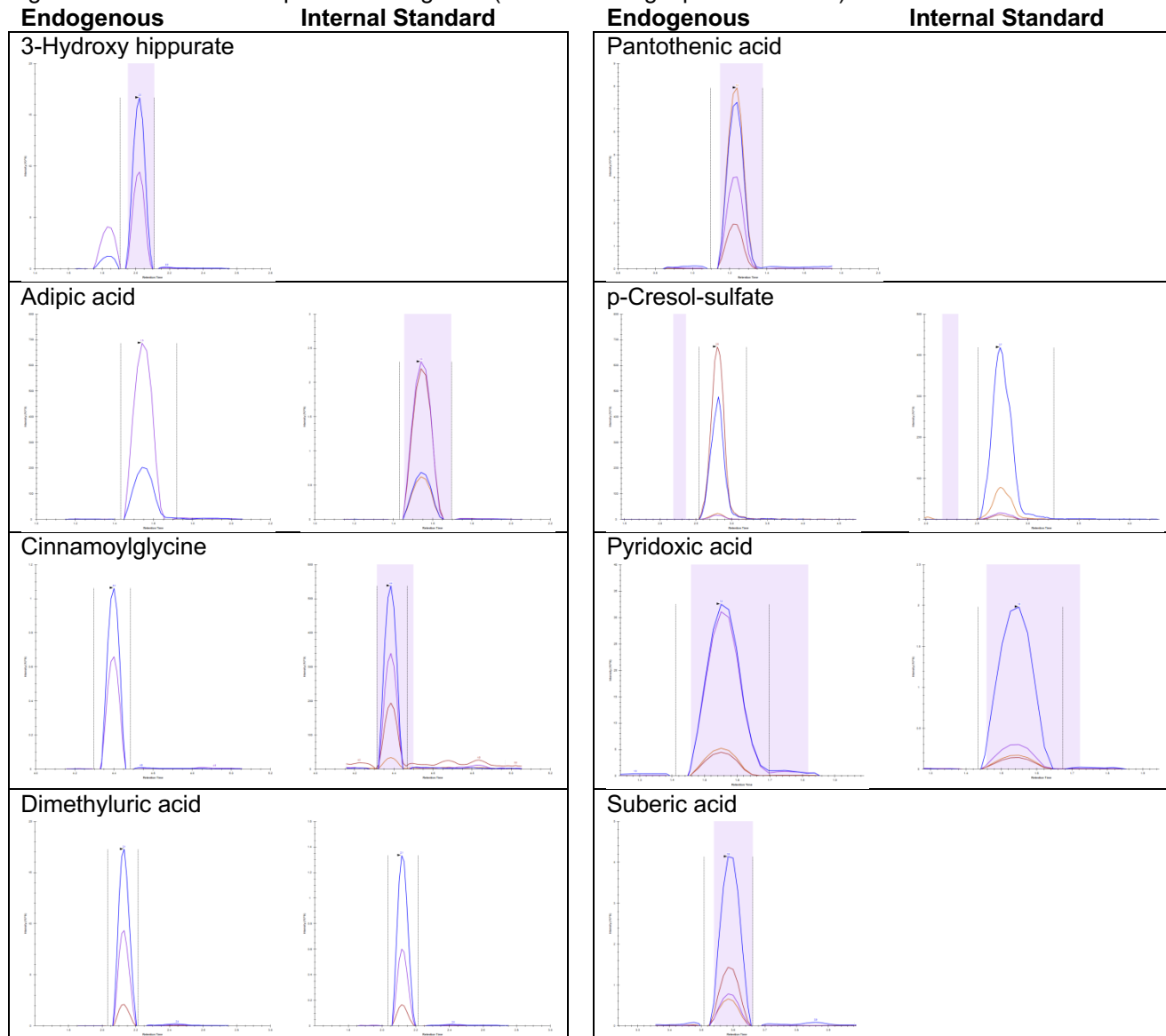### Trimethyluric acid

Kynurenic acid

Xanthosine

Figure b of Item S1. Example chromatograms (from urine single point calibrator).
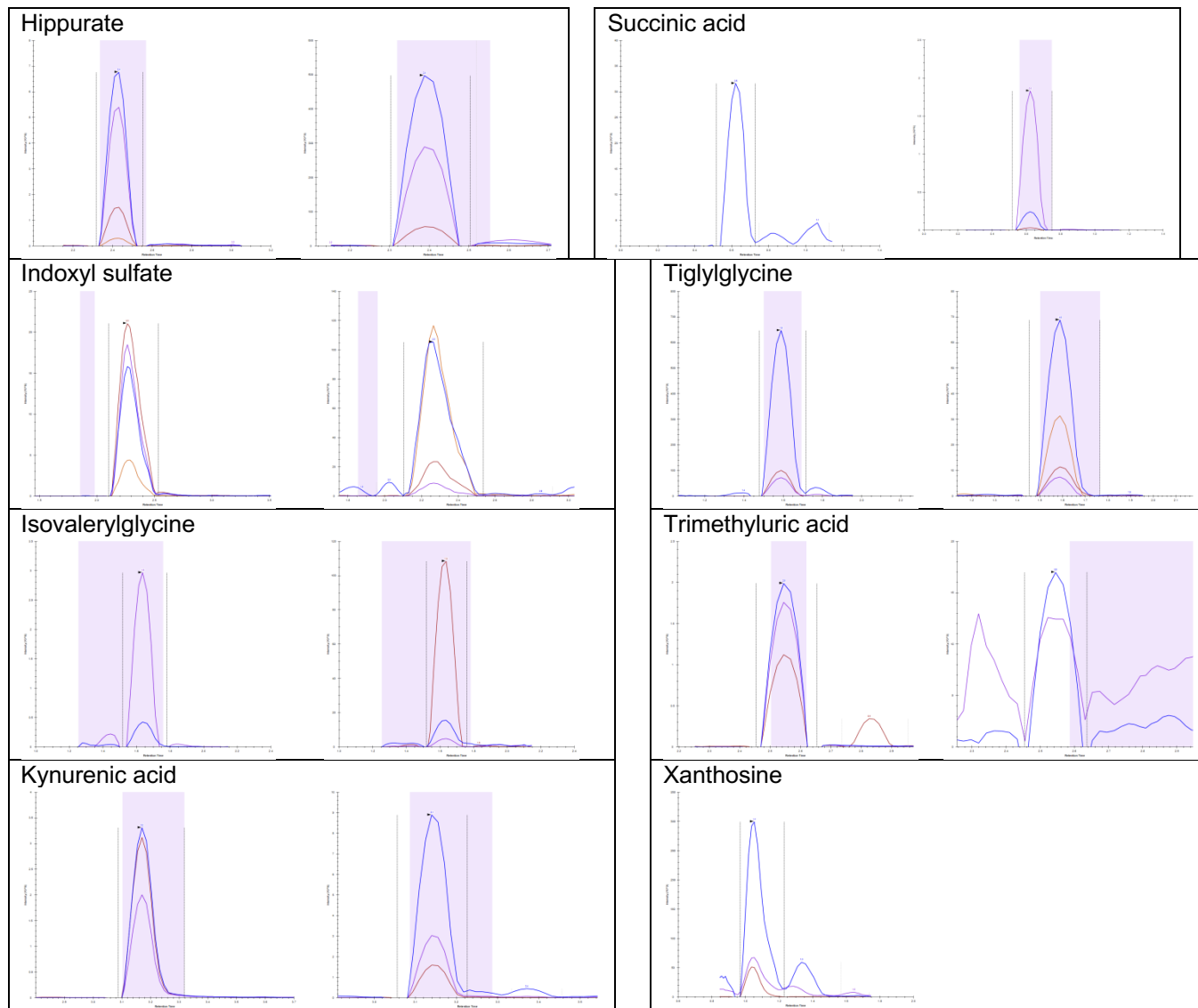
Table S1. Variability of secretory solutes and their respective urinary clearances.

Solute	Diurnal coefficient of variation in plasma concentration over 24-hours[a], % (N = 46)	Visit-to-visit coefficient of variation in plasma concentration[b], % (N = 27)	Visit-to-visit coefficient of variation in 24-hour urinary clearance[b,c], % (N = 23)
Cinnamoylglycine	42.9	36.3	32.9
Indoxyl sulfate	20.9	24.1	20.8
Isovalerylglycine	26.9	24.6	23.7
Kynurenic acid	17.5	18.2	41.0
P-cresol sulfate	20.2	36.5	21.8
Pyridoxic acid	26.7	31.9	23.2
Tiglylglycine	29.3	22.7	24.1
Xanthosine	26.9	15.8	18.1
Summary clearance	-	-	6.7

[a] Diurnal variation determined from five serial plasma measurements at 0, 1, 3-5, 8, and 24 hours.

[b] Visit-to-visit variation determined from measurements at two study visits median 65 days apart (IQR 44 -84 days).

[c] Visit-to-visit variation in urinary clearances based on time-averaged plasma concentrations at each visit.

Table S2. Kidney clearances and protein binding of secretory solutes.[a]

	Median kidney clearance (mL/min, IQR)	Correlation with eGFR[b]	Protein binding in healthy individuals, %[c]	Protein binding in non-dialyzed patients with estimated GFR <20 mL/min/1.73m^2, %[c]
Pyridoxic acid	456 (282, 715)	0.57	83 $\pm$ 4	87 $\pm$ 1
Isovalerylglycine	225 (142, 348)	0.50	6 $\pm$ 13	4 $\pm$ 7
Tiglylglycine	182 (111, 286)	0.56	33 $\pm$ 20	24 $\pm$ 15
Kynurenic acid	92 (63, 136)	0.61	97 $\pm$ 1	96 $\pm$ 2
Xanthosine	77 (46, 121)	0.44	11 $\pm$ 14	15 $\pm$ 13
Cinnamoylglycine	57 (33, 101)	0.40	91 $\pm$ 12	95 $\pm$ 3
Indoxyl sulfate	34 (22, 51)	0.56	97 $\pm$ 1	93 $\pm$ 2
p-cresol sulfate	10 (6, 15)	0.52	97 $\pm$ 1	96 $\pm$ 2

[a] IQR: inter-quartile range; eGFR: estimated GFR.

[b] Pearson correlations between log-transformed secretory solute clearances and log-transformed eGFR, each standardized to 1.73 m^2 body surface area.

[c] Plasma filtration experiments performed in 14 healthy individuals with normal kidney function and 14 patients with advanced chronic kidney disease not receiving dialysis. Plasma was filtered using a centrifugal filter (Amicon Ultra, 3kD MWCO) at 11,200xg for 30 minutes at room temperature. Preliminary experiments were performed to confirm that observed differences between the filtrate and unfiltered plasma could not be attributed to adsorption to the Amicon Ultra filtration units.

Table S3. Associations between secretory solute clearances and subdistribution hazard ratio of cardiovascular events [a,b]

	Heart failure			Myocardial infarction			Stroke		
	HR [c]	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Pyridoxic acid	1.06	0.94-1.19	0.4	1.00	0.88-1.14	0.9	1.14	0.91-1.42	0.3
Isovalerylglycine	1.09	0.97-1.23	0.1	1.00	0.86-1.15	0.9	1.02	0.84-1.24	0.8
Tiglylglycine	1.08	0.96-1.21	0.2	1.02	0.89-1.17	0.8	1.01	0.83-1.22	0.9
Kynurenic acid	1.01	0.87-1.17	0.9	0.99	0.83-1.17	0.9	0.90	0.68-1.18	0.4
Xanthosine	1.06	0.97-1.15	0.2	1.09	1.00-1.19	0.04[d]	0.97	0.83-1.13	0.7
Cinnamoylglycine	1.01	0.92-1.09	0.9	0.94	0.85-1.04	0.2	0.97	0.84-1.11	0.6
Indoxyl sulfate	1.04	0.91-1.19	0.5	0.86	0.73-1.01	0.07	0.77	0.58-1.01	0.06
p-cresol sulfate	0.97	0.88-1.08	0.6	0.94	0.83-1.08	0.4	0.88	0.73-1.08	0.2
Summary score	1.05	0.89-1.25	0.6	1.00	0.81-1.25	0.9	0.90	0.64-1.26	0.5

[a] Results from subdistribution proportional hazard regression with death as the competing event.

[b] Model adjusted for age, race, sex, clinical sites, educational attainment, smoking status, history of cardiovascular disease, diabetes, body mass index, systolic blood pressure, triglyceride, 24-hour urinary albumin excretion, ACEi/ARB, loop diuretics, beta blockers, and estimated GFR.

[c] Subdistribution hazard ratio expressed per 50% lower secretory solute clearance or per 10 units lower summary secretion score

[d] Not statistically significant after correction for multiple comparisons using the Hommel method.

Table S4. Associations between secretory solute clearances and all heart failure events (incident and recurrent) [a, b, c, d]

	Model 1			Model 2			Model 3		
	IRR[e]	95% CI	P-value	IRR	95% CI	P-value	IRR	95% CI	P-value
Pyridoxic acid	1.36	1.26-1.47	< 0.001*	1.19	1.08-1.32	< 0.001*	1.10	0.96-1.24	0.2
Isovalerylglycine	1.32	1.19-1.46	< 0.001*	1.08	0.95-1.21	0.2	0.99	0.86-1.13	0.9
Tiglylglycine	1.34	1.23-1.46	< 0.001*	1.16	1.05-1.28	0.004*	1.07	0.95-1.20	0.3
Kynurenic acid	1.43	1.28-1.60	< 0.001*	1.18	1.04-1.35	0.01	1.04	0.89-1.21	0.6
Xanthosine	1.22	1.13-1.33	< 0.001*	1.10	1.02-1.19	0.01	1.05	0.96-1.13	0.3
Cinnamoylglycine	1.16	1.07-1.25	< 0.001*	1.09	1.01-1.18	0.03	1.04	0.95-1.14	0.4
Indoxyl sulfate	1.33	1.21-1.46	< 0.001*	1.10	0.98-1.23	0.1	0.95	0.83-1.09	0.5
p-cresol sulfate	1.23	1.14-1.34	< 0.001*	1.07	0.96-1.19	0.2	0.95	0.85-1.08	0.4
Summary score	1.60	1.43-1.79	< 0.001*	1.25	1.09-1.44	< 0.001*	1.07	0.90-1.28	0.4

[a] Results from Poisson regression.

[b] Model 1 adjusted for age, race, and sex. Model 2 additionally adjusted for clinical sites, educational attainment, smoking status, history of cardiovascular disease, diabetes, body mass index, systolic blood pressure, triglyceride, 24-hour urinary albumin excretion, ACEi/ARB, loop diuretics, and beta blockers. Model 3 additionally adjusted for estimated GFR.

[c] Overall event rate: 5.8 events per 100 person-years (95% CI: 5.3 – 6.5).

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

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

Table S5. Associations of secretory solute clearances with ischemic stroke and hemorrhagic stroke [a,b]

	Ischemic stroke[c]			Hemorrhagic stroke[d]		
	HR[e]	95% CI	P-value	HR	95% CI	P-value
Pyridoxic acid	1.18	0.91-1.53	0.2	1.08	0.67-1.75	0.7
Isovalerylglycine	1.06	0.82-1.36	0.7	0.84	0.52-1.37	0.5
Tiglylglycine	0.94	0.73-1.22	0.7	1.15	0.72-1.84	0.6
Kynurenic acid	0.84	0.60-1.18	0.3	0.80	0.42-1.53	0.5
Xanthosine	0.93	0.77-1.14	0.5	1.08	0.75-1.56	0.7
Cinnamoylglycine	0.96	0.80-1.14	0.6	0.99	0.71-1.36	0.9
Indoxyl sulfate	0.67	0.49-0.90	0.009[f]	0.88	0.50-1.54	0.7
p-cresol sulfate	0.83	0.65-1.06	0.1	0.88	0.56-1.37	0.6
Summary score	0.84	0.56-1.28	0.4	0.95	0.43-2.09	0.9

[a] Results from Cox proportional hazard regression.

[b] Model adjusted for age, race, sex, clinical sites, educational attainment, smoking status, history of cardiovascular disease, diabetes, body mass index, systolic blood pressure, triglyceride, 24-hour urinary albumin excretion, ACEi/ARB, loop diuretics, and beta blockers, and estimated GFR.

[c] Incidence rate of ischemic stroke: 0.4 events per 100 person-years (95% CI: 0.3 – 0.5). Median follow up time: 8.2 years.

[d] Incidence rate of hemorrhagic stroke: 0.10 events per 100 person-years (95% CI: 0.07 – 0.15). Median follow up time: 9.4 years.

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

[f] Not statistically significant after correction for multiple comparisons using the Hommel method.

Table S6. Associations of plasma concentrations of secretory solutes with incident heart failure, myocardial infarction, and stroke[a,b,c]

	Heart failure						Myocardial infarction						Stroke					
	Model 2			Model 3			Model 2			Model 3			Model 2			Model 3		
	HR[d]	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Pyridoxic acid	1.11	1.04-1.19	0.002*	1.07	1.00-1.15	0.06	1.07	0.99-1.16	0.1	1.04	0.96-1.13	0.4	1.03	0.90-1.18	0.6	1.02	0.88-1.17	0.8
Isovalerylglycine	1.18	1.04-1.34	0.01	1.05	0.92-1.21	0.5	1.19	1.01-1.39	0.04	1.09	0.92-1.29	0.3	0.94	0.74-1.21	0.7	0.89	0.68-1.17	0.4
Tiglylglycine	1.15	1.03-1.28	0.01*	1.03	0.92-1.16	0.6	1.17	1.03-1.34	0.02	1.09	0.95-1.26	0.2	1.07	0.88-1.30	0.5	1.04	0.84-1.29	0.7
Kynurenic acid	1.17	1.02-1.34	0.02	0.95	0.80-1.11	0.5	1.12	0.96-1.32	0.2	0.96	0.80-1.17	0.7	0.84	0.64-1.09	0.2	0.71	0.52-0.97	0.03
Xanthosine	1.10	1.03-1.18	0.006*	1.07	0.99-1.15	0.08	1.10	1.02-1.19	0.01*	1.08	1.00-1.17	0.06	0.99	0.86-1.14	0.9	0.98	0.85-1.13	0.8
Cinnamoylglycine	1.04	0.98-1.10	0.2	1.00	0.94-1.06	0.9	1.00	0.93-1.07	0.9	0.97	0.91-1.04	0.5	1.04	0.93-1.15	0.5	1.03	0.93-1.15	0.6
Indoxyl sulfate	1.04	0.93-1.16	0.5	0.91	0.82-1.02	0.1	0.98	0.86-1.12	0.8	0.89	0.78-1.02	0.09	1.05	0.86-1.28	0.6	1.02	0.83-1.26	0.8
p-cresol sulfate	1.08	1.00-1.17	0.04	1.02	0.94-1.10	0.7	1.10	1.01-1.20	0.03	1.06	0.97-1.16	0.2	1.11	0.97-1.27	0.1	1.10	0.95-1.27	0.2

[a] Results from Cox proportional hazard regression.

[b] Model 2 adjusted for age, race, sex, clinical sites, educational attainment, smoking status, history of cardiovascular disease, diabetes, body mass index, systolic blood pressure, triglyceride, 24-hour urinary albumin excretion, ACEi/ARB, loop diuretics, and beta blockers. Model 3 additionally adjusted for estimated GFR.

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

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

Table S7. Associations of model covariates with incident heart failure, myocardial infarction, and stroke[a,b]

	Incident heart failure		Incident myocardial infarction		Incident stroke	
	Hazard ratio	P-value	Hazard ratio	P-value	Hazard ratio	P-value
Age, years	1.03	< 0.001	1.03	< 0.001	1.04	0.002
Female	0.92	0.4	0.78	0.04	1.00	0.9
Black	1.01	0.9	1.05	0.7	1.12	0.6
Hispanic	1.03	0.9	1.27	0.4	2.43	0.01
Body mass index*	1.02	0.002	0.99	0.2	0.98	0.2
Education categories						
Less than high school	Ref.	/	Ref.	/	Ref.	/
High school graduate	0.76	0.06	1.13	0.5	0.93	0.8
Some college	0.64	0.001	0.93	0.7	1.00	0.9
College graduate or higher	0.60	0.001	0.56	0.005	0.55	0.06
Current smoker	1.27	0.1	1.38	0.06	2.43	< 0.001
Diabetes	1.67	< 0.001	1.49	0.003	1.21	0.4
Prior cardiovascular disease	1.44	0.001	2.11	< 0.001	1.24	0.3
Systolic blood pressure*	1.07	0.007	1.01	0.8	1.11	0.02
Urine albumin*	1.10	< 0.001	1.04	0.06	1.09	0.006
Triglyceride*	1.00	0.4	1.01	0.08	1.00	0.9
ACEi / ARB use	1.30	0.03	1.21	0.2	1.11	0.6
Beta blocker use	1.44	0.001	1.59	< 0.001	1.33	0.2
Loop diuretic use	1.55	< 0.001	1.17	0.2	1.21	0.4
Estimated GFR*	1.22	< 0.001	1.16	0.02	1.07	0.4

Body mass index per one kg/m² greater; Systolic blood pressure per 10 mmHg greater; Urine albumin per 50% greater; Triglycerides per 10 mg/dL greater; Estimated GFR per 10 mL/min/1.73m² lower

[a] Results from Cox proportional hazard regression.

[b] Models included the summary secretion score as the exposure and adjusted for age, race, sex, clinical sites, educational attainment, smoking status, history of cardiovascular disease, diabetes, body mass index, systolic blood pressure, triglyceride, 24-hour urinary albumin excretion, ACEi/ARB, loop diuretics, beta blockers, and estimated GFR.