

Table S1. Characteristics of missing participants compared with total population.

Characteristics	Total Population (n=2253)	Missing (n=261)
Age, years	73.2 (9.0)	73.3 (10.0)
Male Sex	1349 (60)	155 (59)
Black Race	564 (25)	97 (37)
Some College or Greater	1597 (71)	176 (67)
Body mass index, kg/m ²	29.5 (4.9)	29.6 (6.1)
Current Smoking	198 (16.2)	22(14)
Depression Score	3.0 (4.0)	2.6 (3.4)
eGFR, mL/min/1.73m ²	45.9 (10.4)	42.9 (11.7)
Urine creatinine	124.2 (73.9)	118.8 (75.0)
SBP, mmHg	139.7 (16.3)	139.5 (17.3)
DBP, mmHg	74.4 (12.2)	73.9 (13.7)
Treated by diuretic	1211 (54)	157 (60.2)
Treated by ARB or ACEi	1404 (62)	155 (59.4)
LDL Cholesterol	105.9 (34.6)	103.7 (31.0)
Biomarkers		Median (IQR)
IL-18, pg/mL	30.9 (16.5, 56.9)	29.3 (14.1, 58.6)
NGAL, ng/mL	27.9 (14.9, 8.8)	23.7 (11.6, 60.1)
YKL-40, pg/mL	551.1 (218.6, 1268.6)	506.4 (162.3, 1273.1)
KIM-1, pg/mL	855.1 (390.5, 1593.4)	763.2 (367.0, 1619.8)
MCP-1, pg/mL	180 (90.2, 322.6)	187.5 (84.8, 363.8)
α1M, mg/g	13.5 (7.3, 25.1)	11.8 (5.2, 23.2)
β2M, ng/mL	102.6 (38.9, 324.5)	189.4 (33.9, 597.7)
Umod, ng/mL	6.6 (4.4, 10.0)	5.5 (3.1, 9.0)
Urine Albumin, mg/L	16.0 (7, 49)	28.0 (8, 86)

Note. Values for continuous variables are given as mean ± standard deviation; those for categorical variables, as count (percentage).

Abbreviations: eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; LDL, low-density lipoprotein; IL-18, interleukin-18; KIM-1, kidney injury molecule 1; NGAL, neutrophil gelatinase-associated lipocalin; MCP-1, monocyte chemoattractant protein 1; β2M, β-2 microglobulin; α1M, α-1 microglobulin; Umod, uromodulin.

Table S2. Correlation Matrix

Biomarker	IL-18	NGAL	YKL-40	KIM-1	MCP-1	α 1M	β 2M	Umod	Albumin	eGFRcr-cys
Log ₂ IL-18, pg/mL	1.00									
Log ₂ NGAL, ng/mL	0.48	1.00								
Log ₂ YKL-40, pg/mL	0.49	0.61	1.00							
Log ₂ KIM-1, pg/mL	0.64	0.37	0.41	1.00						
Log ₂ MCP-1, pg/mL	0.62	0.39	0.41	0.81	1.00					
Log ₂ α 1M, mg/g	0.38	0.17	0.18	0.41	0.41	1.00				
Log ₂ β 2M, ng/mL	0.02	0.14	0.21	0.09	0.08	0.48	1.00			
Log ₂ Umod, ng/mL	0.30	0.21	0.16	0.43	0.45	0.10	-0.0007	1.00		
Log ₂ Urine Albumin, mg/L	0.34	0.26	0.24	0.37	0.33	0.51	0.25	-0.02	1.00	
eGFRcr-cys	0.08	-0.05	0.07	0.00	0.07	-0.25	-0.19	0.38	-0.28	1.00

Note. IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; MCP, monocyte chemoattractant protein-1; β 2M, β 2-microglobulin; α 1M, α 1-microglobulin; Umod, uromodulin.

Table S3. Cross-sectional Association between Urine Biomarkers of Kidney Tubule Injury and Dysfunction and Frailty in 2253 SPRINT Participants with CKD using the less fit group as the referent

Biomarker	Fit (FI < 10)	Frailty Index	
		Less fit (10 > FI ≤ 21)	Frail (FI > 21)
		OR (95% CI)	
Log₂ IL-18, pg/mL			
Unadjusted	0.95 (0.85, 1.07)	-	1.11 (1.03, 1.20)**
Adjusted ^a	9.93 (0.75, 1.16)	-	1.06 (0.94, 1.20)
Adjusted + eGFR & albumin ^b	0.99 (0.78, 1.27)	-	1.06 (0.93, 1.20)
Log₂ NGAL, ng/mL			
Unadjusted	0.96 (0.87, 1.04)	-	1.08 (1.02, 1.14)
Adjusted ^a	0.82 (0.69, 0.99)	-	1.02 (0.93, 1.12)
Adjusted + eGFR & albumin	0.87 (0.73, 1.04)	-	0.98 (0.89, 1.08)
Log₂ YKL-40, pg/mL			
Unadjusted	1.03 (0.97, 1.10)	-	1.04 (0.99, 1.08)
Adjusted ^a	1.00 (0.88, 1.13)	-	1.00 (0.93, 1.07)
Adjusted + eGFR & albumin	1.00 (0.87, 1.15)	-	1.00 (0.93, 1.08)
Log₂ KIM-1, pg/mL			
Unadjusted	0.91 (0.84, 0.99)*	-	1.09 (1.02, 1.16)*
Adjusted ^a	0.85 (0.73, 0.99)*	-	1.17 (1.06, 1.30)**
Adjusted + eGFR & albumin ^b	0.91 (0.77, 1.09)	-	1.12 (1.00, 1.25)
Log₂ MCP-1, pg/mL			
Unadjusted	0.90 (0.81, 1.01)	-	1.12 (1.04, 1.20)**
Adjusted ^a	0.87 (0.72, 1.06)	-	1.22 (1.08, 1.38)**
Adjusted + eGFR & albumin ^b	0.92 (0.85, 1.14)	-	1.22 (1.08, 1.38)**
Log₂ α1M, mg/g			
Unadjusted	0.94 (0.84, 1.06)	-	1.18 (1.09, 1.28)***
Adjusted ^a	0.67 (0.54, 0.84)**	-	1.36 (1.20, 1.55)***
Adjusted + eGFR & albumin ^b	0.81 (0.62, 1.05)	-	1.25 (1.08, 1.45)**
Log₂ β2M, ng/mL			
Unadjusted	1.02 (0.96, 1.07)	-	1.02 (0.98, 1.06)
Adjusted ^a	0.92 (0.84, 1.01)	-	1.03 (0.97, 1.08)

Adjusted + eGFR & albumin ^b 0.97 (0.87, 1.07) - 0.99 (0.94, 1.05)

Log₂ Umod, ng/mL

Unadjusted 1.01 (0.87, 1.18) - 0.81 (0.73, 0.89)***
 Adjusted^a 0.99 (0.74, 1.31) - 0.87 (0.74, 1.02)
 Adjusted + eGFR & albumin ^b 0.80 (0.58, 1.10) - 1.02 (0.87, 1.21)

Log₂ albumin, mg/L

Unadjusted 0.95 (0.88, 1.02) - 1.10 (1.06, 1.15)***
 Adjusted^a 0.82 (0.72, 0.94) - 1.10 (1.03, 1.18)**
 Adjusted + eGFR 0.88 (0.77, 1.01) - 1.03 (0.96, 1.11)

Note. IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; MCP, monocyte chemoattractant protein-1; β2M, β2-microglobulin; α1M, α1-microglobulin; Umod, uromodulin.

a Adjusted for age, race, sex, body mass index, alcohol use, years of education, insurance status, baseline systolic and diastolic blood pressure, smoking status, and urine creatinine.

B Adjusted for all variables listed above and estimated glomerular filtration rate (eGFR) and Log₂ albumin.

*P<0.05; **P<0.01; ***P<0.001

Table S4. Regression coefficients for full model evaluating β 2M with MoCA score (range 0-30) among 2253 SPRINT Participants with CKD.

	β coefficient	95% CI	p-value
β 2M	-0.09	-0.17, -0.01	0.032
Urine creatinine	-0.001	-0.004, 0.002	0.345
eGFR	0.01	-0.01, 0.03	0.557
Urine albumin	0.00	-0.10, 0.11	0.949
Age (years)	-0.11	-0.14, -0.08	<0.001
Male Sex	-0.98	-1.45, -0.50	<0.001
Black Race	-2.18	-2.70, -1.67	<0.001
Education			
Less than High School Diploma	-4.45	-5.10, -3.79	<0.001
High School Diploma	-1.72	-2.68, -1.64	<0.001
Some College or Greater (reference)	-	-	-
Insurance			
Medicare (reference)	-	-	-
Uninsured	-0.71	-1.74, 0.31	0.171
Medicaid	0.44	-0.45, 1.32	0.332
VA	-0.11	-0.68, 0.47	0.714
Private	0.55	0.06, 1.03	0.028
Depression Score	-0.03	-0.08, 0.02	0.217
Currently Smoking	0.26	-0.34, 0.86	0.395
Body Mass Index	0.02	-0.02, 0.06	0.256
Any alcohol use in the last 12 months	1.20	0.27, 2.13	0.011
Use of diuretic	-0.21	-0.62, 0.20	0.312
Use of an ARB	0.60	0.07, 1.14	0.028
Use of Ace inhibitor	-0.21	-0.64, 0.23	0.35
SBP	-0.01	-0.22, 0.01	0.31
DBP	0.03	0.01, 0.05	0.008

Abbreviations: β 2M, β -2 microglobuline; GFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor

Table S5. Odds Ratio for the full model evaluating α 1M with being in the frail category compared with fit group (less fit group omitted) among 2253 SPRINT Participants with CKD.

	Odds Ratio	95% CI	p-value
α 1M	1.48	1.11, 1.96	0.007
Urine creatinine	1.00	1.00, 1.00	0.854
eGFR	0.92	0.95	<0.001
Urine albumin	1.05	0.89, 1.24	0.56
Age (years)	1.030	0.99, 1.07	0.189
Male Sex	0.65	0.33, 1.27	0.208
Black Race	0.860	0.43, 1.70	0.664
Education			
Less than High School Diploma	2.24	0.92, 5.48	0.076
High School Diploma	1.480	0.73, 2.99	0.275
Some College or Greater (reference)	-	-	-
Insurance			
Medicare (reference)	-	-	-
Uninsured	1.93	0.20, 18.24	0.565
Medicaid	1.070	0.30, 3.89	0.916
VA	2.17	1.02, 4.61	0.045
Private	0.96	0.52, 1.75	0.889
Depression Score	2.14	1.77, 2.59	<0.001
Currently Smoking	3.77	1.31, 10.89	0.014
Body Mass Index	1.150	1.08, 1.22	<0.001
Any alcohol use in the last 12 months	0.54	0.16, 1.82	0.322
Use of diuretic	2.29	1.33, 3.96	0.003
Use of an ARB	1.14	0.54, 2.41	0.729
Use of Ace inhibitor	1.210	0.69, 2.11	0.51
SBP	1.0200	1.003, 1.04	0.026
DBP	0.98	0.96, 1.01	0.216

Abbreviations: α 1M, α -1 microglobulin; GFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor