

Supplementary Table 1: Characteristics of participants by quartiles of IL-18 standardized to UCr

	IL18 standardized to UCr (pg/mg)				p-value	All
	Q1	Q2	Q3	Q4		
Range	3 – 18	19 – 31	32 – 55	56 – 84,848		
N	754	752	750	754		3010
Age (years)	73.5 (2.8)	73.7 (2.8)	73.6 (2.9)	73.7 (3.0)	0.624	73.6 (2.9)
Male	517 (69)	447 (59)	317 (42)	186 (25)	<0.001	1467 (49)
Race/Ethnicity						
White	391 (52)	447 (59)	458 (61)	468 (62)	<0.001	1764 (59)
Black	363 (48)	305 (41)	292 (39)	286 (38)		1246 (41)
Site						
Memphis	359 (48)	357 (48)	373 (50)	415 (55)	0.003	1504 (50)
Pittsburgh	395 (52)	395 (53)	377 (50)	339 (45)		1506 (50)
Education						
< HS	209 (28)	190 (25)	172 (23)	185 (25)	0.919	756 (25)
HS Grad	222 (30)	227 (30)	266 (36)	264 (35)		979 (33)
Postsecondary	322 (43)	334 (45)	307 (41)	304 (40)		1267 (42)
Diabetes	184 (25)	169 (23)	170 (24)	178 (25)	0.905	701 (24)
Hypertension	510 (68)	484 (64)	499 (67)	499 (66)	0.774	1992 (66)
SBP mm Hg	135 (21)	135 (21)	137 (20)	136 (22)	0.174	136 (21)
Smoking						
Never	289 (38)	282 (38)	352 (47)	387 (51)	<0.001	1310 (44)
Former	85 (11)	71 (10)	75 (10)	79 (11)		310 (10)
Current	380 (50)	397 (53)	321 (43)	287 (38)		1385 (46)
Prevalent HF	26 (4)	25 (3)	22 (3)	20 (3)	0.321	93 (3)
Prevalent CHD	182 (25)	171 (23)	145 (20)	145 (20)	0.005	643 (22)
CRP*	1.54 [0.92,2.87]	1.58 [0.97,2.92]	1.79 [1.03,3.44]	1.89 [1.09,3.40]	<0.001	1.68 [0.99, 3.13]
Albumin (g/dl)	3.98 (0.32)	3.99 (0.32)	3.99 (0.31)	3.96 (0.32)	0.225	3.98 (0.31)
LDL (mg/dl)	122 (34)	123 (33)	120 (34)	121 (37)	0.377	122 (35)
HDL (mg/dl)	52 (16)	52 (16)	55 (17)	57 (18)	<0.001	54 (17)
eGFR _{cys} (ml/min/1.73 m ²)	77 (20)	78 (21)	78 (20)	82 (23)	<0.001	79 (21)
eGFR _{cys} < 60 ml/min/1.73 m ²	158 (21)	130 (17)	110 (15)	111 (15)	<0.001	509 (17%)
UACR* mg/g	6.58 [3.50,17.00]	7.58 [4.30,17.72]	8.52 [4.74, 20.33]	10.57 [6.03,26.64]	<0.001	8.26 [4.55,20.31]
UACR >30 mg/g	124 (16)	122 (16)	134 (18)	178 (24)	<0.001	558 (19)

Data are presented as mean (SD), n (%) or *median [IQR]. HF=heart failure. SBP=systolic blood pressure. CRP=C-reactive protein. LDL=low density lipoprotein cholesterol. HDL=high density lipoprotein cholesterol. HS=high school

Supplementary Table 2: Characteristics of participants by quartiles of ACR (mg/g)

	ACR				p-value	All
	Q1	Q2	Q3	Q4		
Range	0.5 – 4.6 mg/g	4.7 – 8.3 mg/g	8.4 – 20.3 mg/g	20.4 – 38,720 mg/g		
N	754	752	754	750		3010
Age (years)	73.3 (2.7)	73.5 (2.8)	73.8 (3.0)	73.9 (3.0)	<0.001	73.6 (2.9)
Male	396 (53)	340 (45)	329 (44)	402 (54)	0.846	1467 (49)
Race/Ethnicity						
White	457 (61)	470 (63)	459 (61)	378 (50)	<0.001	1764 (59)
Black	297 (39)	282 (38)	295 (39)	372 (50)		1246 (41)
Site						
Memphis	385 (51)	384 (51)	358 (48)	377 (50)	0.463	1504 (50)
Pittsburgh	369 (49)	368 (49)	396 (53)	373 (50)		1506 (50)
Education						
< HS	180 (24)	193 (26)	173 (23)	210 (28)	0.175	756 (25)
HS Grad	233 (31)	260 (35)	257 (34)	229 (31)		979 (33)
Postsecondary	338 (45)	298 (40)	323 (43)	308 (41)		1267 (42)
Diabetes	126 (17)	134 (18)	159 (22)	282 (39)	<0.001	701 (24)
Hypertension	412 (55)	464 (62)	521 (69)	595 (79)	<0.001	1992 (66)
SBP mm Hg	131 (18)	133 (19)	137 (21)	142 (23)	<0.001	136 (21)
Smoking						
Never	319 (42)	341 (45)	336 (45)	314 (42)	0.612	1310 (44)
Former	73 (10)	61 (8)	79 (11)	97 (13)		310 (10)
Current	360 (48)	350 (47)	337 (45)	338 (45)		1385 (46)
Prevalent HF	11 (2)	14 (2)	19 (3)	49 (7)	<0.001	93 (3)
Prevalent CHD	136 (18)	144 (20)	153 (21)	210 (29)	<0.001	643 (22)
CRP*	1.59 [0.94,2.83]	1.67 [1.01,3.05]	1.64 [1.01,3.09]	1.85 [1.04,3.72]	0.001	1.68 [0.99, 3.13]
Albumin (g/dl)	3.93 (0.31)	3.99 (0.31)	4.01 (0.31)	3.99 (0.33)	<0.001	3.98 (0.31)
LDL (mg/dl)	121 (33)	125 (34)	123 (36)	118 (36)	0.070	122 (35)
HDL (mg/dl)	54 (16)	55 (17)	56 (18)	52 (17)	0.156	54 (17)
eGFR _{cys} (ml/min/1.73 m ²)	81 (19)	81 (19)	81 (20)	73 (25)	<0.001	79 (21)
eGFR _{cys} < 60 ml/min/1.73 m ²	81 (11)	97 (13)	107 (14)	224 (30)	<0.001	509 (17)
UACR* mg/g	3.05 [2.22,3.76]	6.13 [5.34,7.08]	12.3 [9.86,15.21]	49.70 [29.43,118.70]	<0.001	8.26 [4.55,20.31]
UACR >30 mg/g	0 (0)	0 (0)	0 (0)	558 (19)	<0.001	558 (19)

Data are presented as mean (SD), n (%) or *median [IQR]. HF=heart failure. SBP=systolic blood pressure. CRP=C-reactive protein. LDL=low density lipoprotein cholesterol. HDL=high density lipoprotein cholesterol. HS=high school

Supplementary Table 3. Association of KIM-1, IL-18 and UACR with progression of kidney disease defined as $\Delta eGFR-CysC$ (continuous using linear mixed models)

	Unadjusted	Demographic adjusted*	Risk factor adjusted**	Adjusted for ACR
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
KIM 1 standardized to UCr (ng/mg)				
Continuous (per doubling)	0.03 (-0.04, 0.11)	0.03 (-0.04,0.11)	0.04 (-0.04, 0.12)	0.09 (0.01, 0.18)
Quartiles				
< 497	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
497 – 814	0.08 (-0.18, 0.33)	0.06 (-0.20, 0.32)	0.04 (-0.21, 0.28)	0.04 (-0.21, 0.29)
815 – 1239	0.10 (-0.14, 0.35)	0.08 (-0.17, 0.34)	0.11 (-0.15, 0.36)	0.13 (-0.13, 0.38)
≥ 1240	-0.10 (-0.34, 0.15)	-0.12 (-0.38, 0.14)	-0.07 (-0.33, 0.19)	-0.02 (-0.29, 0.25)
IL-18 standardized to UCr pg/mg				
Continuous (per doubling)	-0.001 (-0.07,0.07)	-0.02 (-0.09,0.06)	0.005 (-0.07, 0.08)	0.05 (-0.04,0.13)
Quartiles				
< 19	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
19 – 31	0.10 (-0.15,0.34)	0.08 (-0.17,0.33)	0.12 (-0.12,0.36)	0.14 (-0.10,0.38)
32 – 55	-0.08 (-0.39,0.17)	-0.12 (-0.39,0.14)	-0.08 (-0.33,0.18)	-0.05 (-0.30,0.21)
≥ 56	-0.05(-0.30,0.21)	-0.12 (-0.40,0.16)	0.01 (-0.26,0.28)	0.08 (-0.20,0.35)
ACR (mg/g)				
Continuous (per doubling)	-0.10 (-0.17,-0.39)	-0.10 (-0.17,-0.38)	-0.08 (-0.14,-0.02)	--
>30 vs <30 mg/g	-0.60 (-0.87,-0.34)	-0.60 (-0.86,-0.34)	-0.51 (-0.78,-0.25)	--
Quartiles				
< 4.6	1.00 (ref)	1.00 (ref)	1.00 (ref)	--
4.6 – 8.3	-0.23 (-0.47,0.003)	-0.23 (-0.47,0.002)	-0.20 (-0.43,0.03)	--
8.4 – 20.3	-0.27 (-0.50,-0.04)	-0.28 (-0.51,-0.05)	-0.16 (-0.39,0.06)	--
>20.3	-0.54 (-0.81,-0.27)	-0.54 (-0.81,-0.27)	-0.44 (-0.70,-0.17)	--

*Adjusted for age, sex, race, site and education

**further adjusted for diabetes, hypertension, SBP, smoking, prevalent HF, prevalent CHD, albumin and CRP

Supplementary Table 4. Association of KIM-1, IL-18 and UACR with progression of kidney disease defined as $\Delta eGFR-CysC > 3$ ml/min/1.73 m²

	Unadjusted	Demographic adjusted*	Risk factor adjusted**	Adjusted for ACR
KIM 1 standardized to UCr (ng/mg)				
Continuous (per doubling)	0.98 (0.92, 1.07)	1.04 (0.96, 1.13)	1.00 (0.91, 1.08)	0.92 (0.84, 1.01)
Quartiles				
< 497	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
497 – 814	1.05 (0.82, 1.35)	1.12 (0.87, 1.44)	1.07 (0.83, 1.39)	1.04 (0.80, 1.35)
815 – 1239	0.98 (0.76, 1.26)	1.14 (0.88, 1.49)	1.04 (0.80, 1.37)	0.98 (0.75, 1.28)
≥ 1240	1.07 (0.83, 1.37)	1.29 (0.98, 1.69)	1.10 (0.83, 1.45)	0.95 (0.71, 1.26)
IL-18 standardized to UCr pg/mg				
Continuous (per doubling)	1.00 (0.93, 1.07)	1.03 (0.96, 1.10)	1.02 (0.95, 1.10)	0.97 (0.90, 1.05)
Quartiles				
< 19	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
19 – 31	0.93 (0.72, 1.20)	0.96 (0.75, 1.25)	0.97 (0.75, 1.26)	0.94 (0.72, 1.22)
32 – 55	1.01 (0.79, 1.31)	1.12 (0.86, 1.45)	1.10 (0.85, 1.44)	1.06 (0.81, 1.38)
≥ 56	1.05 (0.82, 1.35)	1.18 (0.90, 1.55)	1.16 (0.88, 1.52)	1.04 (0.79, 1.38)
ACR (mg/g)				
Continuous (per doubling)	1.16 (1.11, 1.22)	1.15 (1.10, 1.20)	1.13 (1.08, 1.19)	--
>30 vs <30 mg/g	1.90 (1.52, 2.37)	1.80 (1.43, 2.25)	1.66 (1.31, 2.10)	--
Quartiles				
< 4.6	1.00 (ref)	1.00 (ref)	1.00 (ref)	--
4.6 – 8.3	1.30 (1.00, 1.68)	1.31 (1.01, 1.71)	1.32 (1.01, 1.72)	--
8.4 – 20.3	1.31 (1.01, 1.70)	1.33 (1.03, 1.74)	1.33 (1.02, 1.74)	--
>20.3	2.01 (1.55, 2.59)	1.92 (1.48, 2.48)	1.76 (1.34, 2.30)	--

*Adjusted for age, sex, race, site and education

**further adjusted for diabetes, hypertension, SBP, smoking, prevalent HF, prevalent CHD, albumin and CRP

Supplementary Table 5. Association of KIM-1/cr with mortality in models adjusted for serum bicarbonate, parathyroid hormone, phosphorus and hemoglobin

	Demo & Risk factor adjusted*	Further adjusted for ACR and eGFR	Further adjusted for HCO₃, PTH, phos and Hgb
KIM 1 standardized to UCr (ng/mg)			
Quartiles			
< 497	1.00 (ref)	1.00 (ref)	1.00 (ref)
497 – 814	1.08 (0.89, 1.31)	1.07 (0.88, 1.30)	1.08 (0.89, 1.32)
815 – 1239	1.12 (0.91, 1.37)	1.08 (0.88, 1.32)	1.08 (0.89, 1.37)
≥ 1240	1.33 (1.09, 1.62)	1.20 (0.98, 1.47)	1.18 (0.96, 1.54)

*Adjusted for age, sex, race, site and education, diabetes, hypertension, SBP, smoking, prevalent HF, prevalent CHD, albumin and CRP

Supplementary Table 6. Association of KIM-1/cr with mortality in additional analyses adjusted for hemoglobin A1C and time dependent changes in systolic blood pressure.

	Demo, Risk factor and kidney function adjusted*	Additional adjustment for HbA1c	Additional adjustment for time dependent SBP
KIM 1 standardized to UCr (ng/mg)			
Quartiles			
< 497	1.00 (ref)	1.00 (ref)	1.00 (ref)
497 – 814	1.19 (1.01, 1.39)	1.19 (1.01, 1.40)	1.24 (1.06, 1.45)
815 – 1239	1.12 (0.95, 1.33)	1.12 (0.95, 1.33)	1.13 (0.96, 1.33)
≥ 1240	1.28 (1.08, 1.47)	1.28 (1.08, 1.51)	1.35 (1.14, 1.60)

*Adjusted for age, sex, race, site and education, diabetes, hypertension, SBP, smoking, prevalent HF, prevalent CHD, albumin and CRP