Supplemental Material

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Consensus Clustering Algorithm

Consensus clustering is a method of unsupervised cluster discovery for high-dimensional data, without using outcome information. The procedure of the consensus clustering algorithm is illustrated in **Figure S1.** For a prespecified number of clusters K=2, 3, …, 8, we created a random subset that included 80% of the original data records without replacement and repeated 100 times. For each random subset, we performed K-mean (Euclidean distance based) [1] algorithm and assigned each individual to one of the clusters. After 100 times run, we calculated the frequency that any pair of two individuals, *i* and *j*, were clustered together under each scenario of K and constructed a $N \times N$ matrix of participants' pairwise consensus value, where N is the sample size. The consensus value was measured by the proportion among multiple K-mean clustering runs that two individuals were clustered together. The final cluster membership was determined by applying a hierarchical clustering algorithm using the consensus matrix as a measure of similarity, the result of which can be represented as a consensus heatmap.

The proportion of ambiguously clustered pairs (PAC) [2] is a measure of cluster stability. It is calculated as the proportion of all sample pairs with consensus values falling within the predetermined boundaries. It ranges between 0 and 1. A value closer to zero indicates better cluster stability. We calculated the PAC using two criteria: the *strict criteria* had the predetermined boundary of (0, 1), where a pair of individuals who had consensus value greater than 0 or less than 1 was considered ambiguously clustered, i.e., a pair was unambiguously clustered if the two individuals were either always in the same cluster or always in different clusters across different runs; and the *relaxed criteria* had the predetermined boundary of (0.1, 0.9), where a pair of individuals who had consensus value greater than 0.1 or less than 0.9 was considered ambiguously clustered; i.e., a pair was unambiguously clustered if the two individuals

were clustered in the same cluster for either more than 90% of the time or less than 10% of the time (meaning they were not in the same cluster for more than 90% of the time).

We also calculated the cluster consensus score, defined as the average consensus value for all pairs of individuals belonging to the same cluster [1]. It also ranges between 0 and 1. A value closer to one indicates better cluster stability.

In the spirit of exploratory data analysis, the goal of consensus clustering is to identify maximum number of potential clusters that can exist in the data while maintaining the cluster consensus at a high level. To determine the optimal number of clusters, we synthesized the information from multiple measures, including the consensus matrix heatmap, cluster consensus score and proportion of ambiguously clustered [PAC] pair. As shown in the consensus matrix heatmap (**Figure 1**), the algorithm identified two and three subgroups with clear boundaries, indicating good cluster stability over repeated iterations. The mean cluster consensus score, based on 100 replications, was comparable between the scenario of two and three clusters. However, there was a large decrease in consensus score (from above 90% to below 80%) when increasing the cluster number from three to four (**Figure 2A**). Favorable low PACs were found for three clusters, with a clear elbow point shown using the relaxed PAC criteria (**Figure 2B**). Finally, the distinct cluster profiles shown in **Figure 3** and associated risks of clinical outcomes confirmed the choice of three clusters.

References

1. Monti, Stefano, Pablo Tamayo, Jill Mesirov, and Todd Golub. "Consensus clustering: a resampling-based method for class discovery and visualization of gene expression microarray data." Machine learning 52, no. 1-2 (2003): 91-118.
2. Şenbabaoğlu, Yasin, George Michailidis, and Jun Z. Li. "Critical limitations of consensus clustering in class discovery." Scientific reports 4, no. 1 (2014): 1-13.

Supplemental Tables

Table S1. Baseline characteristics of individuals in the study population (N=2696) and the overall CRIC population (N=3921)

n	Full CRIC 3921	Study Population 2696	SDiff
Age, year	58 (11)	58 (11)	0.064
Female (%)	1771 (45.2)	1186 (44.0)	0.024
Race & Apol1 risks (%)			0.055
White	1507 (38.4)	1107 (41.1)	
Black, low Apol1 risks	1188 (30.3)	776 (28.8)	
Black, high Apol1 risks	284 (7.2)	184 (6.8)	
Hispanic or others	942 (24.0)	629 (23.3)	
Education level (%)			0.054
Less than high school	819 (20.9)	517 (19.2)	
High school graduate	739 (18.9)	515 (19.1)	
Some college	1141 (29.1)	770 (28.6)	
College graduate or higher	1221 (31.2)	894 (33.2)	
Household income (%)			0.055
$20,000 or under	1229 (31.34	788 (29.2)	
$20,001 - $50,000	955 (24.4)	678 (25.2)	
$50,000 - $100,000	732 (18.7)	537 (19.9)	
More than $100,000	392 (10.0)	285 (10.6)	
Don't wish to answer	613 (15.6)	408 (15.1)	
Marital status (%)			0.064
Currently married	2147 (54.8)	1558 (57.8)	
Never married	564 (14.4)	346 (12.8)	
Formerly married	1210 (30.9)	792 (29.4)	
Diabetes (%)	1900 (48.5)	1249 (46.3)	0.043
Hypertension (%)	3376 (86.1)	2316 (85.9)	0.006
Smoke now (%)	512 (13.1)	335 (12.4)	0.019
Alcohol (%)	2464 (62.8)	1720 (63.8)	0.020
Try to lose weight (%)	2739 (69.9)	1906 (70.7)	0.018
Waist circumference, cm	105.5 (16.9)	105.6 (16.1)	0.006
Any Activities with MET score >=6 (%)	919 (23.5)	653 (24.2)	0.017
Weight, kg	90.8 (22.0)	90.9 (21.1)	0.004
BMI, kg/m^2	31.8 (7.2)	31.8 (6.9)	0.001
eGFR, $ml/min/1.73m^2$	44.6 (16.3)	45.4 (15.9)	0.052
UPCR[#], mg/mg	0.15 [0.06, 0.78]	0.14 [0.06, 0.65]	0.089
UACR [#], μg/mg	52.0 [8.7, 455.8]	44.7 [7.8, 382.3]	0.086
Serum urea nitrogen [#], mg/dL	26 [20, 36]	26 [20, 35]	0.024
Uric acid, mg/dL	7.39 (1.90)	7.38 (1.85)	0.008
NGAL[#], ng/mL	14.84 [6.61, 35.39]	13.86 [6.40, 32.33]	0.031
Urinary Sodium, mmol/L	161.1 (77.5)	161.8 (76.4)	0.009
Urinary Potassium, mmol/L	55.0 (26.5)	55.7 (26.5)	0.027
Calcium, mg/dL	9.18 (0.48)	9.20 (0.46)	0.036
FGF23, RU/ml	208.6 (210.1)	193.4 (186.4)	0.076
Phosphate, mg/dL	3.71 (0.64)	3.67 (0.61)	0.068
Chloride, mmol/L	104.8 (3.8)	104.8 (3.7)	0.011
Alkaline Phosphatase[#], U/L	85.0	83.0	0.061

	[70.0, 104.0]	[69.0, 102.0]	
Total Parathyroid Hormone[#], pg/mL	54.0 [35.0, 89.4]	52.0 [34.0, 83.9]	0.054
Aldosterone[#], pg/ml	101.5 [71.6, 151.3]	100.90 [71.8, 151.1]	0.010
Hemoglobin A1C [#], %	6.10 [5.60, 7.30]	6.10 [5.60, 7.10]	0.059
C-Peptide[#], ng/mL	2.90 [1.86, 4.20]	2.95 [1.90, 4.15]	0.002
CBC Hemoglobin, g/dL	12.60 (1.75)	12.67 (1.73)	0.040
Glucose[#], mg/dL	98.0 [87.0, 125.0]	97.0 [86.0, 121.0]	0.060
Fetuin-A[#], mg/mL	0.53 (0.11)	0.53 (0.11)	0.034
Mean cell hemoglobin conc., g/dL	33.54 (1.08)	33.56 (1.07)	0.019
Troponin-I[#], ng/ml	0.00 [0.00, 0.01]	0.00 [0.00, 0.01]	0.004
High-sensitivity Troponin T[#], pg/mL	12.25 [5.74, 23.83]	11.46 [5.65, 21.91]	0.090
High Sensitivity CRP [#], mg/L	2.57 [1.05, 6.51]	2.52 [1.01, 6.20]	0.040
N-terminal pro b-type natriuretic peptide[#], pg/mL	151.6 [63.0, 411.4]	142.5 [61.6, 374.0]	0.055
Bicarbonate, mmol/L	24.42 (3.17)	24.51 (3.10)	0.028
Systolic blood pressure, mmHg	128.0 (21.3)	127.1 (20.6)	0.044
Diastolic blood pressure, mmHg	71.4 (12.5)	70.9 (12.2)	0.044
Interleukin-10[#], pg/mL	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.021
Interleukin-1RA[#], pg/mL	715 [390, 154]	704 [386, 1501]	0.019
Interleukin-6[#], pg/mL	1.88 [1.16, 3.08]	1.82 [1.12, 2.91]	0.059
Interleukin-1 beta[#], pg/mL	0.21 [0.06, 1.28]	0.18 [0.06, 1.23]	0.027
TNF-alpha[#], pg/mL	2.20 [1.50, 3.20]	2.20 [1.50, 3.20]	0.034
TGF-beta[#], ng/mL	10.97 [6.49, 17.88]	10.67 [6.24, 17.60]	0.027
CXCL12, pg/mL	2468 (542)	2449 (532)	0.035
Fibrinogen, g/L	4.15 (1.11)	4.11 (1.08)	0.042
White blood cell, thousand/μL	6.55 (1.94)	6.48 (1.88)	0.037
Total cholesterol, mg/dL	182.4 (42.5)	180.4 (40.3)	0.048
Triglycerides[#], mg/dL	128.0 [89.0, 185.0]	128.0 [89.0, 183.0]	0.016
High-density Lipoprotein, mg/dL	46.8 (13.8)	46.8 (13.7)	0.001
Low-density Lipoprotein, mg/dL	102.0 (34.1)	101.3 (32.6)	0.023
Serum Albumin, g/dL	4.0 (0.5)	4.0 (0.4)	0.050
Family history of kidney disease (%)	607 (15.5)	412 (15.3)	0.006
Diagnosed or treated for any cancer (%)	194 (5.0)	147 (5.5)	0.023
Cardio-Vascular Disease (%)	1308 (33.4)	878 (32.6)	0.017
Congestive Heart Failure (%)	378 (9.6)	242 (9.0)	0.023
History of Chronic Obstructive Pulmonary Disease (%)	122 (3.2)	80 (3.0)	0.011
Acidosis (%)	3224 (82.7)	2251 (83.5)	0.022
NSAID (%)	2007 (51.5)	1422 (52.7)	0.025
Diuretics (%)	2322 (59.6)	1556 (57.7)	0.038
ACE&ARBs (%)	1913 (49.1)	1327 (49.2)	0.003
Betablockers (%)	1921 (49.3)	1312 (48.7)	0.013
Calcium blockers (%)	1581 (40.6)	1081 (40.1)	0.010
Statins (%)	2146 (55.1)	1510 (56.0)	0.019
Steroids (%)	390 (10.0)	261 (9.7)	0.011
Anti-diabetes (%)	1086 (27.9)	783 (29.0)	0.026
Antiplatelet (%)	1793 (46.0)	1271 (47.1)	0.023

* **Abbreviations:** SDiff: standardized difference; FGF-23: fibroblast growth factor 23; PTH: parathyroid hormone; CRP: C-reactive protein; NTproBNP: N-terminal prohormone of brain natriuretic peptide; HbA1C: hemoglobin A1C; CBC: complete blood count; TNF- α: tumor necrosis factor alpha; TGF-β: Transforming Growth Factor Beta; CXCL12: C-X-C Motif Chemokine Ligand 12; HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio; UPCR: urine protein to creatinine ratio; NGAL: neutrophil gelatinase-associated lipocalin; BMI: body mass index; COPD: chronic obstructive pulmonary disease; NSAID: non-steroidal anti-inflammatory drug; ACE: angiotensin-converting-enzyme; ARB: Angiotensin II receptor blockers.
[#] Variables that were summarized as medium [inter quartile range, IQR]

Table S2. Cluster features and standardized difference in the main and sensitivity analyses.

Category	Label	Main analyses	Exclude SES variables	Imputed dataset 1	Imputed dataset 2	Imputed dataset 3
Cluster 1 key features		**Standardized Difference**				
Bone and mineral markers	**Alka. Phosphate**	-0.303	-	-0.301	-0.300	-0.305
	FGF23	-0.346	-0.338	-0.345	-0.350	-0.350
	Phosphate	-0.328	-0.318	-0.348	-0.357	-0.356
	Total PTH	-0.337	-0.336	-0.362	-0.360	-0.357
Cardiac markers	**Systolic BP**	-0.308	-	-0.301	-	-0.302
	HS Troponin T	-0.402	-0.395	-0.389	-0.397	-0.396
Diabetes markers	**CBC Hemoglobin**	0.455	0.436	0.450	0.446	0.451
	Glucose	-0.398	-0.405	-0.395	-0.398	-0.396
	HbA1C	-0.510	-0.523	-0.500	-0.499	-0.506
Health status	**CVD history**	-0.397	-0.402	-0.398	-0.397	-0.397
	BMI	-0.402	-0.399	-0.432	-0.430	-0.430
	Diabetes	-0.686	-0.695	-0.662	-0.671	-0.671
	College grad. or higher	0.313	-	0.314	0.310	0.315
	Hypertension	-0.323	-0.309	-0.320	-0.317	-0.319
	Physical Activities	-	-	0.314	0.309	0.322
	Waist circumference	-0.424	-0.427	-0.446	-0.445	-0.444
	weight	-0.321	-0.324	-0.355	-0.351	-0.350
Inflammation markers	**CXCL12**	-	-	-0.314	-0.310	-0.312
	Fibrinogen	-0.447	-0.440	-0.454	-0.458	-0.457
	Serum Albumin	0.329	0.329	0.364	0.348	0.349
Kidney markers	**eGFR**	0.522	0.508	0.551	0.547	0.549
	Serum urea nitrogen	-0.490	-0.480	-0.498	-0.496	-0.498
	Uric acid	-0.319	-	-0.339	-0.340	-0.334
Medications	**Anti-diabetes medications**	-0.513	-0.516	-0.484	-0.487	-0.491
	Antiplatelet	-	-0.301	-	-	-
	Betablockers	-0.328	-0.318	-0.351	-0.352	-0.353
	Diuretics	-0.401	-	-0.431	-0.427	-0.433
	Statins	-0.356	-	-0.349	-0.358	-0.355
Cluster 2 key features		**Standardized Difference**				
Cardiac markers	**Diastolic BP**	-0.309	-0.323	-	-	-
Diabetes markers	**Glucose**	0.368	0.370	0.306	0.320	0.318
	HbA1C	0.446	0.452	0.389	0.392	0.399
Health status	**Age**	0.368	0.378	0.336	0.345	0.338
	CVD history	0.360	0.374	0.355	0.359	0.356
	BMI	0.489	0.472	0.521	0.516	0.515
	Diabetes	0.632	0.650	0.548	0.564	0.559
	Waist circumference	0.516	0.502	0.541	0.538	0.532
	weight	0.417	0.402	0.458	0.455	0.450
Lipids	**LDL**	-0.333	-0.350	-	-0.306	-
	Total cholesterol	-	-0.323	-	-	-
Medications	**Anti-diabetes medications**	0.538	0.554	0.495	0.509	0.504
	Antiplatelet	0.347	0.381	0.337	0.340	0.339
	Betablockers	-	-	-	0.306	-

	Diuretics	0.365	0.357	0.378	0.373	0.380
	NSAID	0.304	0.326	-	-	-
	Statins	0.398	0.410	0.359	0.377	0.360
Cluster 3 key features		**Standardized Difference**				
Bone and mineral markers	**Alka. Phosphate**	0.598	0.621	0.709	0.687	0.695
	Calcium	-0.618	-0.635	-0.755	-0.723	-0.740
	Chloride	0.667	0.647	0.635	0.632	0.636
	FGF23	0.721	0.783	0.747	0.737	0.739
	Phosphate	0.679	0.711	0.818	0.811	0.819
	Total PTH	0.949	1.015	0.971	1.026	0.996
Cardiac markers	**Bicarbonate**	-0.672	-0.641	-0.694	-0.677	-0.705
	Diastolic BP	0.386	0.413	0.412	0.402	0.404
	HS CRP	0.427	0.422	0.311	0.324	0.320
	NTproBNP	0.800	0.796	0.900	0.859	0.888
	Systolic BP	0.752	0.764	0.802	0.802	0.797
	HS Troponin T	0.954	0.985	1.048	1.027	1.053
Diabetes markers	**CBC Hemoglobin**	-0.659	-0.664	-0.726	-0.731	-0.736
	Fetuin-A	-0.322	-	-0.318		-0.321
	Glucose	-	-	0.328		
	HbA1C	0.314	0.363	0.409	0.397	0.385
Health status	**Acidosis**	-0.735	-0.701	-0.722	-0.701	-0.738
	Diabetes	0.330	0.339	0.445	0.430	0.421
	Less than high school	0.497	0.426	0.532	0.509	0.511
	College grad. or higher	-0.409	-0.364	-0.407	-0.402	-0.405
	Income $20,000 or under	0.554	0.511	0.587	0.561	0.574
	White	-0.521	-0.488	-0.548	-0.564	-0.568
	Hispanic or others	0.460	0.410	0.566	0.552	0.579
	Smoke now	0.329	0.331	0.323	0.311	0.312
Inflammation markers	**CXCL12**	0.567	0.565	0.585	0.571	0.553
	Fibrinogen	0.806	0.848	0.870	0.873	0.878
	Interleukin-1RA	0.301	-	-		
	Interleukin-6	0.551	0.570	0.505	0.482	0.501
	Interleukin-1 beta	0.392	0.388	-		
	Serum Albumin	-0.927	-0.955	-1.068	-1.042	-1.049
	TNF-alpha	0.734	0.707	0.664	0.670	0.667
	White blood cell	0.348	0.383	0.378	0.387	0.398
Kidney markers	**eGFR**	-0.908	-0.942	-0.946	-0.947	-0.949
	NGAL	0.555	0.565	0.722	0.684	0.710
	Serum urea nitrogen	0.743	0.774	0.805	0.782	0.790
	Urinary Potassium	-	-	-0.315	-0.300	-0.311
	UACR	1.328	1.391	1.400	1.371	1.403
	UPCR	1.424	1.483	1.415	1.387	1.444

* **Abbreviations:** FGF-23: fibroblast growth factor 23; PTH: parathyroid hormone; CRP: C-reactive protein; NTproBNP: N-terminal prohormone of brain natriuretic peptide; HbA1C: hemoglobin A1C; CBC: complete blood count; TNF- α: tumor necrosis factor alpha; TGF-β: Transforming Growth Factor Beta; CXCL12: C-X-C Motif Chemokine Ligand 12; HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio; UPCR: urine protein to creatinine ratio; NGAL: neutrophil gelatinase-associated lipocalin; BMI: body mass index; COPD: chronic obstructive pulmonary disease; NSAID: non-steroidal anti-inflammatory drug; ACE: angiotensin-converting-enzyme; ARB: Angiotensin II receptor blockers.

Table S3. The distribution of CKD subgroups revealed by 72 baseline parameters within the CKD classes defined by KDIGO guideline

		UACR >300 mg/g	30≤UACR ≤300 mg/g	UACR<30 mg/g
eGFR <45 mL/min/1.73m^2	**Cluster 1**	97 (16.8)	114 (28.0)	148 (34.7)
	Cluster 2	195 (33.7)	236 (58.0)	264 (62.0)
	Cluster 3	286 (49.5)	57 (14.0)	14 (3.3)
	Total	578	407	426
eGFR ≥45 mL/min/1.73m^2	**Cluster 1**	93 (49.5)	175 (55.4)	576 (73.8)
	Cluster 2	68 (36.2)	135 (42.7)	200 (25.6)
	Cluster 3	27 (14.4)	6 (1.9)	5 (0.6)
	Total	188	316	781

§ Abbreviation: KDIGO: Kidney Disease Improving Global Outcome; eGFR: estimated glomerular filtration rate; UACR: urinary albumin to creatinine ratio

Table S4. The risks of CKD progression, cardiovascular disease and death across overall or stratified periods[†] of follow-up time that were associated with cluster membership, using 72 baseline parameters

		Unadjusted		Adjusted	
	Event n /Total N	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P values**
CKD progression					
Baseline-2 year	201/2696				
Cluster 2		3.39 (2.02, 5.71)	<0.001	1.92 (1.02, 3.58)	0.042
Cluster 3		26.07 (16.09, 42.24)	<0.001	2.47 (1.33, 4.58)	0.004
2-5 years	386/2196				
Cluster 2		2.34 (1.80, 3.04)	<0.001	1.26 (0.88, 1.81)	0.20
Cluster 3		12.40 (9.48, 16.22)	<0.001	1.50 (1.04, 2.17)	0.03
5 year-EOFU	313/1540				
Cluster 2		2.80 (2.20, 3.56)	<0.001	1.28 (0.87, 1.88)	0.21
Cluster 3		6.92 (4.66, 10.28)	<0.001	1.20 (0.74, 1.95)	0.46
Kidney failure requiring RRT					
Baseline-2 year	121/2696				
Cluster 2		4.37 (1.90, 10.04)	<0.001	2.67 (1.03, 6.92)	0.044
Cluster 3		45.14 (20.90, 97.51)	<0.001	3.11 (1.25, 7.69)	0.014
2-5 years	293/2460				
Cluster 2		2.36 (1.71, 3.26)	<0.001	1.05 (0.67, 1.63)	0.84
Cluster 3		14.00 (10.23, 19.17)	<0.001	1.13 (0.73, 1.75)	0.57
5 year-EOFU	275/1987				
Cluster 2		3.00 (2.27, 3.98)	<0.001	1.32 (0.86, 2.01)	0.20
Cluster 3		12.16 (8.58, 17.23)	<0.001	1.35 (0.86, 2.14)	0.19
CHF					
Baseline-2 year	135/2696				
Cluster 2		12.80 (5.55, 29.51)	<0.001	3.41 (1.32, 8.78)	<0.001
Cluster 3		35.24 (15.25, 81.49)	<0.001	7.73 (2.80, 21.33)	<0.001
2-5 years	138/2405				
Cluster 2		5.94 (3.57, 9.88)	<0.001	2.61 (1.37, 4.97)	0.003
Cluster 3		8.31 (4.70, 14.67)	<0.001	3.34 (1.56, 7.18)	0.002
5 year-EOFU	196/2016				
Cluster 2		6.51 (4.42, 9.59)	<0.001	2.30 (1.37, 3.86)	0.002
Cluster 3		6.92 (4.28, 11.19)	<0.001	1.76 (0.94, 3.31)	0.08
CHF, MI, stroke, PAD					
Baseline-1 year[#]	126/2696				
Cluster 2		8.55 (4.27, 17.14)	<0.001	3.40 (1.49, 7.77)	0.004
Cluster 3		17.69 (8.70, 36.01)	<0.001	5.98 (2.41, 14.84)	<0.001
1-5 years	315/2481				
Cluster 2		3.70 (2.77, 4.95)	<0.001	1.40 (0.94, 2.08)	0.09
Cluster 3		5.43 (3.89, 7.60)	<0.001	1.86 (1.16, 3.00)	0.01
5 year-EOFU	279/1887				

Cluster 2	4.26 (3.21, 5.67)	<0.001	1.50 (0.99, 2.26)	0.05
Cluster 3	4.99 (3.44, 7.23)	<0.001	1.71 (1.02, 2.85)	0.04

* Model adjusts for age, gender, black race, education level, diabetes, smoking status, alcohol use, physical activities, BMI levels, eGFR, log transformed UACR, systolic blood pressure, family history of kidney disease, and history of cardiovascular disease.

† Hazard ratios average over full follow-up time 12.3 years were shown if test for Cox model proportion hazard assumption was not violated ($p>=0.05$); Hazard ratios average over 0-2 years, 2-5 years and >5 years were shown if test for Cox model proportion hazard assumption was violated for the overall follow-up time ($p<0.05$).

Due to violate of proportional hazard during the first two year of follow-up for the composite endpoint of CHF, MI, stroke and PAD, the prespecified time intervals for this endpoint was 0-1 year, 1-5 years and > 5 years.

§ Abbreviation: CKD, chronic kidney disease; RRT: renal replacement therapy; CHF: congestive heart failure; MI, myocardial infraction; PAD, peripheral artery disease; PH test: Cox model proportional hazard assumption test for variable of cluster membership.

Table S5. Baseline characteristics of individuals with eGFR<45 ml/min/1.73m^2 (N=1411) across three subgroups revealed by 72 baseline parameters

n	Overall 1411	Cluster 1 580	Cluster 2 601	Cluster 3 230
eGFR, ml/min/1.73m^2	33.2 (7.3)	34.8 (6.7)	33.6 (6.9)	27.9 (7.5)
Age, year	59.6 (10.7)	57.7 (12.4)	62.4 (8.)	57.3 (10.3)
Female (%)	658 (46.6)	279 (48.1)	292 (48.6)	87 (37.8)
Race & Apol1 risks (%)				
White	521 (36.9)	268 (46.2)	223 (37.1)	30 (13.0)
Black, low Apol1 risks	422 (29.9)	149 (25.7)	197 (32.8)	76 (33.0)
Black, high Apol1 risks	93 (6.6)	41 (7.1)	38 (6.3)	14 (6.1)
Hispanic or others	375 (26.6)	122 (21.0)	143 (23.8)	110 (47.8)
Education level (%)				
Less than high school	357 (25.3)	96 (16.6)	166 (27.6)	95 (41.3)
High school graduate	296 (21.0)	115 (19.8)	137 (22.8)	44 (19.1)
Some college	385 (27.3)	163 (28.1)	163 (27.1)	59 (25.7)
College graduate or higher	373 (26.4)	206 (35.5)	135 (22.5)	32 (13.9)
Household income (%)				
$20,000 or under	522 (37.0)	152 (26.2)	239 (39.8)	131 (57.0)
$20,001 - $50,000	363 (25.7)	161 (27.8)	154 (25.6)	48 (20.9)
$50,000 - $100,000	226 (16.0)	131 (22.6)	71 (11.8)	24 (10.4)
More than $100,000	94 (6.7)	50 (8.6)	38 (6.3)	6 (2.6)
Don't wish to answer	206 (14.6)	86 (14.8)	99 (16.5)	21 (9.1)
Marital status (%)				
Currently married	762 (54.0)	326 (56.2)	309 (51.4)	127 (55.2)
Never married	189 (13.4)	91 (15.7)	67 (11.2)	31 (13.5)
Formerly married	460 (32.6)	163 (28.1)	225 (37.4)	72 (31.3)
Diabetes (%)	769 (54.5)	74 (12.8)	524 (87.2)	171 (74.4)
Hypertension (%)	1289 (91.4)	497 (85.7)	568 (94.5)	224 (97.4)
Smoke now (%)	203 (14.4)	92 (15.9)	57 (9.5)	54 (23.5)
Alcohol (%)	823 (58.3)	403 (69.5)	293 (48.8)	127 (55.2)
Try to lose weight (%)	1004 (71.2)	354 (61.0)	505 (84.0)	145 (63.0)
Waist circumference, cm	106.7 (16.5)	98.2 (13.7)	116.3 (14.7)	103.4 (14.3)
Any Activities with MET score >=6 (%)	263 (18.6)	162 (27.9)	66 (11.0)	35 (15.2)
Weight, kg	91.0 (21.6)	81.2 (16.8)	102.3 (20.8)	86.3 (20.3)
BMI, kg/m^2	32.3 (7.1)	28.8 (5.4)	36.2 (6.9)	30.6 (6.4)
UPCR[#], mg/mg	0.32 [0.08, 1.27]	0.18 [0.06, 0.66]	0.24 [0.07, 0.80]	3.44 [1.61, 5.78]
UACR [#], μg/mg	150.5 [19.9, 798.3]	63.7 [12.3, 389.2]	92.7 [19.4, 470.7]	2159.5 [928.6, 3961.4]
Serum urea nitrogen [#], mg/dL	34.0 [26.0, 43.0]	30.0 [23.0, 37.0]	37.0 [29.0, 46.0]	40.0 [31.0, 48.8]
Uric acid, mg/dL	7.93 (1.80)	7.55 (1.73)	8.36 (1.79)	7.74 (1.74)
NGAL[#], ng/mL	19.77 [9.15, 46.12]	15.75 [8.10, 35.47]	16.90 [7.92, 32.80]	67.54 [33.75, 131.73]
Urinary Sodium, mmol/L	155.3 (74.3)	146.3 (67.3)	165.7 (80.1)	151.0 (71.9)
Urinary Potassium, mmol/L	52.8 (26.9)	49.8 (23.1)	57.6 (31.3)	47.8 (21.0)
Calcium, mg/dL	9.18 (0.50)	9.29 (0.47)	9.20 (0.47)	8.83 (0.48)

FGF23, RU/ml	247.9 (210.7)	202.2 (170.2)	249.5 (193.1)	359.1 (291.2)
Phosphate, mg/dL	3.86 (0.62)	3.66 (0.57)	3.92 (0.59)	4.20 (0.66)
Chloride, mmol/L	105.6 (3.8)	105.4 (3.7)	105.0 (3.7)	107.4 (3.8)
Alkaline Phosphatase[#], U/L	89.0 [74.0, 108.0]	86.0 [71.8, 105.0]	88.0 [73.0, 106.0]	102.0 [86.0, 126.8]
Total Parathyroid Hormone[#], pg/mL	69.6 [45.0, 116.6]	61.2 [40.9, 99.1]	68.0 [44.9, 109.0]	109.0 [68.3, 171.8]
Aldosterone[#], pg/ml	108.9 [78.9, 159.0]	114.5 [80.9, 168.8]	104.3 [75.8, 148.2]	107.7 [79.4, 158.4]
Hemoglobin A1C [#], %	6.2 [5.7, 7.3]	5.7 [5.4, 6.1]	7.0 [6.2, 8.0]	6.6 [5.8, 8.2]
C-Peptide[#], ng/mL	3.25 [2.14, 4.55]	3.05 [2.21, 4.11]	3.50 [2.15, 5.10]	3.19 [1.80, 4.57]
CBC Hemoglobin, g/dL	12.14 (1.64)	12.71 (1.58)	11.95 (1.51)	11.17 (1.55)
Glucose[#], mg/dL	98.0 [86.0, 126.0]	90.0 [84.0, 99.0]	116.0 [93.0, 148.0]	108.0 [88.0, 148.0]
Fetuin-A[#], mg/mL	0.52 (0.11)	0.53 (0.11)	0.52 (0.10)	0.49 (0.10)
Mean cell hemoglobin conc., g/dL	33.42 (1.07)	33.62 (1.05)	33.19 (1.06)	33.48 (1.06)
Troponin-I[#], ng/ml	0.00 [0.00, 0.01]	0.00 [0.00, 0.00]	0.00 [0.00, 0.01]	0.01 [0.00, 0.02]
High-sensitivity Troponin T[#], pg/mL	16.69 [8.89, 29.62]	10.48 [6.07, 18.20]	20.26 [11.48, 32.00]	33.09 [18.23, 54.82]
High Sensitivity CRP [#], mg/L	2.92 [1.09, 7.11]	2.36 [0.93, 5.43]	3.65 [1.36, 8.03]	3.39 [1.10, 8.55]
N-terminal pro b-type natriuretic peptide[#], pg/mL	228.00 [99.13, 581.50]	152.30 [75.39, 332.85]	244.30 [104.70, 566.70]	742.75 [284.78, 1736.50]
Bicarbonate, mmol/L	23.71 (3.14)	23.75 (3.10)	24.21 (3.02)	22.32 (3.16)
Systolic blood pressure, mmHg	129.7 (21.3)	124.3 (18.9)	128.2 (20.2)	147.0 (21.4)
Diastolic blood pressure, mmHg	70.0 (12.6)	72.2 (11.9)	65.7 (11.8)	75.5 (13.0)
Interleukin-10[#], pg/mL	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
Interleukin-1RA[#], pg/mL	807.5 [442.7, 1617.0]	694.3 [395.0, 1381.8]	897.8 [505.3, 1637.8]	1045.3 [423.6, 1941.5]
Interleukin-6[#], pg/mL	2.22 [1.40, 3.46]	1.73 [1.08, 2.74]	2.45 [1.68, 3.57]	2.76 [1.87, 4.73]
Interleukin-1 beta[#], pg/mL	0.35 [0.06, 1.50]	0.27 [0.06, 1.34]	0.27 [0.06, 1.29]	0.91 [0.06, 2.44]
TNF-alpha[#], pg/mL	2.60 [1.90, 3.70]	2.40 [1.70, 3.40]	2.60 [1.90, 3.50]	3.45 [2.70, 4.78]
TGF-beta[#], ng/mL	10.87 [6.58, 17.67]	11.00 [6.54, 18.54]	10.51 [6.67, 16.28]	11.20 [6.54, 19.12]
CXCL12, pg/mL	2615 (534)	2543 (509)	26178 (529)	2790 (569)
Fibrinogen, g/L	4.37 (1.12)	3.94 (0.99)	4.49 (1.04)	5.15 (1.16)
White blood cell, thousand/μL	6.76 (1.90)	6.49 (1.85)	6.92 (1.88)	7.07 (1.95)
Total cholesterol, mg/dL	179.4 (41.5)	189.6 (40.1)	166.0 (36.4)	188.6 (47.3)
Triglycerides[#], mg/dL	138.0 [98.5, 197.5]	128.0 [92.0, 183.0]	143.0 [106.0, 203.0]	143.5 [106.0, 215.8]
High-density Lipoprotein, mg/dL	45.4 (13.3)	49.5 (14.1)	42.0 (11.1)	43.7 (13.3)
Low-density Lipoprotein, mg/dL	98.3 (33.1)	106.9 (32.7)	87.8 (29.5)	104.2 (35.2)
Serum Albumin, g/dL	3.9 (0.4)	4.0 (0.4)	3.9 (0.4)	3.5 (0.4)

Family history of kidney disease (%)	235 (16.7)	84 (14.5)	103 (17.1)	48 (20.9)
Diagnosed or treated for any cancer (%)	73 (5.2)	36 (6.2)	32 (5.3)	5 (2.2)
Cardio-Vascular Disease (%)	557 (39.5)	113 (19.5)	327 (54.4)	117 (50.9)
Congestive Heart Failure (%)	173 (12.3)	16 (2.8)	111 (18.5)	46 (20.0)
History of Chronic Obstructive Pulmonary Disease (%)	46 (3.3)	13 (2.2)	29 (4.8)	4 (1.7)
Acidosis (%)	1068 (75.7)	447 (77.1)	491 (81.7)	130 (56.5)
NSAID (%)	716 (50.7)	206 (35.5)	406 (67.6)	104 (45.2)
Diuretics (%)	940 (66.6)	278 (47.9)	496 (82.5)	166 (72.2)
ACE&ARBs (%)	719 (51.0)	259 (44.7)	348 (57.9)	112 (48.7)
Betablockers (%)	789 (55.9)	240 (41.4)	401 (66.7)	148 (64.4)
Calcium blockers (%)	671 (47.6)	224 (38.6)	321 (53.4)	126 (54.8)
Statins (%)	845 (59.9)	243 (41.9)	456 (75.9)	146 (63.5)
Steroids (%)	137 (9.7)	64 (11.0)	61 (10.2)	12 (5.2)
Anti-diabetes (%)	466 (33.0)	36 (6.2)	343 (57.1)	87 (37.8)
Antiplatelet (%)	691 (49.0)	182 (31.4)	400 (66.6)	109 (47.4)

* **Abbreviations:** FGF-23: fibroblast growth factor 23; PTH: parathyroid hormone; CRP: C-reactive protein; NTproBNP: N-terminal prohormone of brain natriuretic peptide; HbA1C: hemoglobin A1C; CBC: complete blood count; TNF- α: tumor necrosis factor alpha; TGF-β: Transforming Growth Factor Beta; CXCL12: C-X-C Motif Chemokine Ligand 12; HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio; UPCR: urine protein to creatinine ratio; NGAL: neutrophil gelatinase-associated lipocalin; BMI: body mass index; COPD: chronic obstructive pulmonary disease; NSAID: non-steroidal anti-inflammatory drug; ACE: angiotensin-converting-enzyme; ARB: Angiotensin II receptor blockers.

[#] Variables that were summarized as medium [inter quartile range, IQR]

Table S6. The adjusted risks of CKD progression, cardiovascular disease and death associated with CKD subgroups among patients with eGFR<45 ml/min/1.73m^2 (N=1411)

Outcome	Model	Cluster 1	Cluster 2		Cluster 3	
			HR (95% CI)	p value	HR (95% CI)	p value
CKD progression	**Unadjusted**	Ref	1.33 (1.11, 1.58)	0.002	6.98 (5.68, 8.57)	<0.001
	Adjusted		1.30 (0.98, 1.73)	0.066	1.62 (1.17, 2.24)	0.004
Kidney failure requiring RRT	**Unadjusted**	Ref	1.33 (1.09, 1.61)	0.005	7.06 (5.69, 8.77)	<0.001
	Adjusted		1.34 (0.98, 1.83)	0.062	1.78 (1.27, 2.48)	0.001
CHF	**Unadjusted**	Ref	3.23 (2.45, 4.25)	<0.001	4.90 (3.56, 4.74)	<0.001
	Adjusted		1.32 (0.88, 1.97)	0.174	1.70 (1.06, 2.73)	0.029
MI, stroke, PAD	**Unadjusted**	Ref	2.13 (1.64, 2.78)	<0.001	3.10 (2.56, 4.26)	<0.001
	Adjusted		1.17 (0.78, 1.74)	0.454	1.97 (1.21, 3.21)	0.006
CHF, MI, stroke, PAD	**Unadjusted**	Ref	2.46 (1.98, 3.04)	<0.001	3.71 (2.86, 4.79)	<0.001
	Adjusted		1.03 (0.75, 1.43)	0.838	1.58 (1.07, 2.34)	0.021
Death	**Unadjusted**	Ref	2.11 (1.72, 2.58)	<0.001	3.11 (2.45, 3.95)	<0.001
	Adjusted		1.54 (1.14, 2.08)	0.005	2.42 (1.68, 3.49)	<0.001

* Model adjusts for age, gender, race&Apol1 risks, education level, diabetes, smoking status, alcohol use, physical activities, BMI, eGFR, UACR, systolic blood pressure, family history of kidney disease, history of cardiovascular disease

Abbreviation: CKD, chronic kidney disease; RRT: renal replacement therapy; MI, myocardial infraction; PAD, peripheral artery disease.

Table S7. Baseline characteristics of individuals with eGFR≥45 ml/min/1.73m^2 (N=1285) across two subgroups revealed by 72 baseline parameters

n	Overall 1285	Cluster 1 677	Cluster 2 608
eGFR, ml/min/1.73m^2	58.9 (11.3)	62.7 (12.4)	54.6 (8.0)
Age, year	57.0 (10.6)	54.3 (11.1)	60.1 (8.9)
Female (%)	528 (41.1)	302 (44.6)	226 (37.2)
Race & Apol1 risks (%)			
White	586 (45.6)	372 (55.0)	214 (35.2)
Black, low Apol1 risks	354 (27.6)	132 (19.5)	222 (36.5)
Black, high Apol1 risks	91 (7.2)	41 (6.1)	50 (8.2)
Hispanic or others	254 (19.8)	132 (19.5)	122 (20.1)
Education level (%)			
Less than high school	160 (12.5)	47 (6.9)	113 (18.6)
High school graduate	219 (17.0)	82 (12.1)	137 (22.5)
Some college	385 (30.0)	185 (27.3)	200 (32.9)
College graduate or higher	521 (40.5)	363 (53.6)	158 (26.0)
Household income (%)			
$20,000 or under	266 (20.7)	91 (13.4)	175 (28.8)
$20,001 - $50,000	315 (24.5)	142 (22.0)	173 (28.5)
$50,000 - $100,000	311 (24.2)	199 (29.4)	112 (18.4)
More than $100,000	191 (14.9)	140 (20.7)	51 (8.4)
Don't wish to answer	202 (15.7)	105 (15.5)	97 (16.0)
Marital status (%)			
Currently married	796 (62.0)	445 (65.7)	351 (57.7)
Never married	157 (12.2)	79 (11.7)	78 (12.8)
Formerly married	332 (25.8)	153 (22.6)	179 (29.4)
Diabetes (%)	480 (37.4)	54 (8.0)	426 (70.2)
Hypertension (%)	1027 (79.9)	453 (66.9)	574 (94.4)
Smoke now (%)	132 (10.3)	66 (9.8)	66 (10.9)
Alcohol (%)	897 (69.8)	545 (80.5)	352 (57.9)
Try to lose weight (%)	902 (70.2)	411 (60.7)	491 (80.8)
Waist circumference, cm	104.8 (15.8)	98.6 (13.9)	110.7 (15.3)
Any Activities with MET score >=6 (%)	390 (30.4)	263 (38.9)	127 (20.9)
Weight, kg	90.8 (20.7)	84.6 (18.9)	97.6 (20.5)
BMI, kg/m^2	31.3 (6.6)	29.1 (5.6)	33.7 (6.8)
UPCR[#], mg/mg	0.08 [0.05, 0.23]	0.06 [0.04, 0.14]	0.12 [0.05, 0.35]
UACR [#], μg/mg	14.5 [4.9, 101.9]	9.0 [4.2, 42.2]	30.4 [6.5, 190.2]
Serum urea nitrogen [#], mg/dL	21.0 [17.0, 25.0]	19.0 [16.0, 23.0]	23.0 [19.0, 27.0]
Uric acid, mg/dL	6.77 (1.72)	6.42 (1.69)	7.17 (1.67)
NGAL[#], ng/mL	9.50 [5.00, 19.53]	9.30 [5.00, 18.60]	10.00 [5.00, 20.97]
Urinary Sodium, mmol/L	168.9 (78.1)	156.6 (75.3)	182.5 (79.0)
Urinary Potassium, mmol/L	59.0 (25.8)	59.3 (25.7)	58.6 (25.8)
Calcium, mg/dL	9.22 (0.42)	9.26 (0.38)	9.18 (0.46)
FGF23, RU/ml	133.5 (131.4)	108.4 (72.2)	161.5 (171.0)
Phosphate, mg/dL	3.47 (0.52)	3.41 (0.50)	3.53 (0.55)

Chloride, mmol/L	104.0 (3.4)	103.8 (3.3)	104.1 (3.6)
Alkaline Phosphatase[#], U/L	78.0 [65.0, 94.0]	73.0 [63.0, 87.0]	83.0 [70.0, 102.3]
Total Parathyroid Hormone[#], pg/mL	40.0 [29.0, 58.0]	37.0 [28.0, 49.6]	45.6 [31.2, 70.0]
Aldosterone[#], pg/ml	91.6 [66.5, 137.1]	91.0 [66.5, 141.0]	91.9 [66.5, 134.2]
Hemoglobin A1C [#], %	6.0 [5.5, 6.7]	5.6 [5.3, 6.0]	6.7 [6.0, 7.7]
C-Peptide[#], ng/mL	2.61 [1.80, 3.70]	2.35 [1.75, 3.30]	3.05 [2.00, 4.20]
CBC Hemoglobin, g/dL	13.25 (1.63)	13.78 (1.45)	12.67 (1.62)
Glucose[#], mg/dL	96.0 [86.0, 114.0]	90.00 [83.0, 97.0]	112.0 [95.0, 144.0]
Fetuin-A[#], mg/mL	0.54 (0.11)	0.55 (0.10)	0.53 (0.11)
Mean cell hemoglobin conc., g/dL	33.72 (1.04)	33.94 (0.92)	33.47 (1.11)
Troponin-I[#], ng/ml	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.01]
High-sensitivity Troponin T[#], pg/mL	7.68 [3.48, 14.30]	5.10 [1.50, 9.16]	12.36 [7.00, 20.34]
High Sensitivity CRP [#], mg/L	2.06 [0.95, 5.03]	1.59 [0.82, 3.84]	2.85 [1.21, 6.71]
N-terminal pro b-type natriuretic peptide[#], pg/mL	85.4 [38.2, 194.7]	62.2 [28.7, 137.9]	123.9 [59.4, 268.4]
Bicarbonate, mmol/L	25.39 (2.82)	25.59 (2.64)	25.16 (2.99)
Systolic blood pressure, mmHg	124.2 (19.3)	118.6 (16.2)	130.5 (20.7)
Diastolic blood pressure, mmHg	71.9 (11.7)	72.8 (10.9)	70.8 (12.4)
Interleukin-10[#], pg/mL	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
Interleukin-1RA[#], pg/mL	612.0 [335.7, 1338.7]	546.0 [314.7, 1267.7]	671.9 [369.3, 1450.7]
Interleukin-6[#], pg/mL	1.46 [0.90, 2.34]	1.12 [0.71, 1.72]	1.93 [1.28, 2.87]
Interleukin-1 beta[#], pg/mL	0.06 [0.06, 0.86]	0.06 [0.06, 0.81]	0.06 [0.06, 0.92]
TNF-alpha[#], pg/mL	1.70 [1.20, 2.40]	1.50 [1.00, 2.20]	1.90 [1.40, 2.70]
TGF-beta[#], ng/mL	10.41 [5.86, 17.49]	9.85 [5.45, 17.25]	11.07 [6.37, 17.88]
CXCL12, pg/mL	2266.69 (466.49)	2197.69 (456.33)	2343.53 (466.03)
Fibrinogen, g/L	3.82 (0.94)	3.53 (0.82)	4.14 (0.97)
White blood cell, thousand/μL	6.16 (1.81)	5.85 (1.67)	6.50 (1.90)
Total cholesterol, mg/dL	181.6 (39.0)	190.6 (37.8)	171.5 (37.8)
Triglycerides[#], mg/dL	116.0 [81.0, 168.0]	109.0 [78.0, 154.0]	124.0 [87.8, 183.0]
High-density Lipoprotein, mg/dL	48.3 (14.0)	51.2 (14.9)	45.2 (12.1)
Low-density Lipoprotein, mg/dL	104.5 (31.8)	112.5 (31.1)	95.7 (30.3)
Serum Albumin, g/dL	4.0 (0.4)	4.1 (0.4)	4.0 (0.4)
Family history of kidney disease (%)	177 (13.8)	72 (10.6)	105 (17.3)
Diagnosed or treated for any cancer (%)	74 (5.8)	42 (6.2)	32 (5.3)
Cardio-Vascular Disease (%)	321 (25.0)	72 (10.6)	249 (41.0)
Congestive Heart Failure (%)	69 (5.4)	9 (1.3)	60 (9.9)
History of Chronic Obstructive Pulmonary Disease (%)	34 (2.7)	17 (2.5)	17 (2.8)
Acidosis (%)	1183 (92.1)	643 (95.0)	540 (88.8)
NSAID (%)	706 (54.9)	302 (44.6)	404 (66.5)
Diuretics (%)	616 (47.9)	215 (31.8)	401 (66.0)
ACE&ARBs (%)	608 (47.3)	248 (36.6)	360 (59.2)
Betablockers (%)	523 (40.7)	181 (26.7)	342 (56.3)
Calcium blockers (%)	410 (31.9)	139 (20.5)	271 (44.6)

Statins (%)	665 (51.8)	228 (33.7)	437 (71.9)
Steroids (%)	124 (9.7)	71 (10.5)	53 (8.7)
Anti-diabetes (%)	317 (24.8)	29 (4.3)	288 (47.4)
Antiplatelet (%)	580 (45.1)	204 (30.1)	376 (61.8)

* **Abbreviations:** FGF-23: fibroblast growth factor 23; PTH: parathyroid hormone; CRP: C-reactive protein; NTproBNP: N-terminal prohormone of brain natriuretic peptide; HbA1C: hemoglobin A1C; CBC: complete blood count; TNF- α: tumor necrosis factor alpha; TGF-β: Transforming Growth Factor Beta; CXCL12: C-X-C Motif Chemokine Ligand 12; HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio; UPCR: urine protein to creatinine ratio; NGAL: neutrophil gelatinase-associated lipocalin; BMI: body mass index; COPD: chronic obstructive pulmonary disease; NSAID: non-steroidal anti-inflammatory drug; ACE: angiotensin-converting-enzyme; ARB: Angiotensin II receptor blockers.
[#] Variables that were summarized as medium [inter quartile range, IQR]

Table S8. The adjusted risks of CKD progression, cardiovascular disease and death associated with CKD subgroups among patients with eGFR≥45 ml/min/1.73m^2 (N=1285)

Outcome	Model	Cluster 1	Cluster 2	
			HR (95% CI)	p value
CKD progression	**Unadjusted**	Ref	4.22 (3.11, 5.73)	<0.001
	Adjusted		1.70 (1.09, 2.64)	0.018
Kidney failure requiring RRT	**Unadjusted**	Ref	4.92 (3.11, 7.81)	<0.001
	Adjusted		2.01 (1.05, 3.84)	0.036
CHF	**Unadjusted**	Ref	9.56 (5.57, 16.38)	<0.001
	Adjusted		3.96 (2.02, 7.76)	<0.001
MI, stroke, PAD	**Unadjusted**	Ref	4.50 (3.04, 6.66)	<0.001
	Adjusted		2.40 (1.39, 4.13)	0.002
CHF, MI, stroke, PAD	**Unadjusted**	Ref	5.48 (3.95, 7.62)	<0.001
	Adjusted		2.58 (1.65, 4.02)	<0.001
Death	**Unadjusted**	Ref	3.70 (2.65, 5.16)	<0.001
	Adjusted		1.88 (1.18, 2.98)	0.008

* Model adjusts for age, gender, race&Apol1 risks, education level, diabetes, smoking status, alcohol use, physical activities, BMI, eGFR, UACR, systolic blood pressure, family history of kidney disease, history of cardiovascular disease

Abbreviation: CKD, chronic kidney disease; RRT: renal replacement therapy; MI, myocardial infraction; PAD, peripheral artery disease.

Table S9. Baseline characteristics of individuals with UACR<30mg/g (N=1207) across two subgroups revealed by 72 baseline parameters

n	Overall 1207	Cluster 1 678	Cluster 2 529
UACR [#], μg/mg	6.64 [3.99, 13.91]	5.84 [3.59, 10.71]	8.60 [4.70, 17.15]
eGFR, ml/min/1.73m^2	52.0 (16.1)	59.1 (15.0)	42.8 (12.2)
Age, year	60.1 (9.4)	57.9 (9.8)	63.0 (8.0)
Female (%)	625 (51.8)	307 (45.3)	318 (60.1)
Race & Apol1 risks (%)			
White	599 (49.6)	395 (58.3)	204 (38.6)
Black, low Apol1 risks	334 (27.7)	144 (21.2)	190 (35.9)
Black, high Apol1 risks	56 (4.6)	30 (4.4)	26 (4.9)
Hispanic or others	218 (18.1)	109 (16.1)	109 (20.6)
Education level (%)			
Less than high school	172 (14.3)	43 (6.34)	129 (24.39)
High school graduate	220 (18.2)	85 (12.54)	135 (25.52)
Some college	350 (29.0)	190 (28.02)	160 (30.25)
College graduate or higher	465 (38.5)	360 (53.10)	105 (19.85)
Household income (%)			
$20,000 or under	284 (23.5)	86 (12.7)	198 (37.4)
$20,001 - $50,000	293 (24.3)	145 (21.4)	148 (28.0)
$50,000 - $100,000	268 (22.2)	197 (29.1)	71 (13.4)
More than $100,000	165 (13.7)	140 (20.7)	25 (4.7)
Don't wish to answer	197 (16.3)	110 (16.2)	87 (16.5)
Marital status (%)			
Currently married	702 (58.2)	446 (65.8)	256 (48.4)
Never married	122 (10.1)	60 (8.9)	62 (11.7)
Formerly married	383 (31.7)	172 (25.37)	211 (39.9)
Diabetes (%)	421 (34.9)	89 (13.1)	332 (62.76)
Hypertension (%)	981 (81.3)	483 (71.2)	498 (94.1)
Smoke now (%)	123 (10.2)	61 (9.0)	62 (11.7)
Alcohol (%)	814 (67.4)	534 (78.8)	280 (52.9)
Try to lose weight (%)	876 (72.6)	448 (66.1)	428 (80.9)
Waist circumference, cm	105.6 (16.0)	100.0 (13.8)	112.7 (15.7)
Any Activities with MET score >=6 (%)	297 (24.6)	234 (34.5)	63 (11.9)
Weight, kg	90.6 (20.5)	85.4 (18.3)	97.3 (21.3)
BMI, kg/m^2	31.9 (7.0)	29.3 (5.4)	35.2 (7.3)
UPCR[#], mg/mg	0.05 [0.04, 0.08]	0.05 [0.03, 0.07]	0.06 [0.04, 0.08]
Serum urea nitrogen [#], mg/dL	22.0 [18.0, 30.0]	19.0 [16.0, 24.0]	27.0 [22.0, 36.0]
Uric acid, mg/dL	7.03 (1.84)	6.44 (1.65)	7.78 (1.80)
NGAL[#], ng/mL	10.42 [5.02, 21.20]	8.80 [5.00, 16.26]	13.90 [6.38, 25.63]
Urinary Sodium, mmol/L	155.9 (73.4)	156.4 (77.9)	155.3 (67.2)
Urinary Potassium, mmol/L	56.5 (25.9)	60.2 (26.5)	51.7 (24.1)
Calcium, mg/dL	9.29 (0.44)	9.30 (0.42)	9.27 (0.47)
FGF23, RU/ml	157.4 (152.8)	111.5 (67.7)	216.2 (203.2)
Phosphate, mg/dL	3.55 (0.56)	3.43 (0.51)	3.70 (0.58)

Chloride, mmol/L	104.0 (3.6)	103.6 (3.4)	104.5 (3.7)
Alkaline Phosphatase[#], U/L	79.0 [66.0, 97.0]	74.0 [64.0, 88.0]	88.0 [73.0, 106.0]
Total Parathyroid Hormone[#], pg/mL	42.0 [30.2, 63.0]	36.3 [27.0, 49.5]	55.5 [38.0, 84.0]
Aldosterone[#], pg/ml	97.0 [70.0, 149.1]	93.4 [68.3, 146.6]	99.3 [71.2, 156.7]
Hemoglobin A1C [#], %	6.0 [5.5, 6.6]	5.7 [5.4, 6.1]	6.4 [5.8, 7.3]
C-Peptide[#], ng/mL	2.85 [1.90, 3.90]	2.45 [1.76, 3.40]	3.40 [2.40, 4.60]
CBC Hemoglobin, g/dL	12.95 (1.61)	13.59 (1.45)	12.13 (1.42)
Glucose[#], mg/dL	94.0 [86.0, 110.0]	91.0 [85.0, 99.0]	104.0 [90.0, 130.0]
Fetuin-A[#], mg/mL	0.53 (0.11)	0.54 (0.10)	0.52 (0.11)
Mean cell hemoglobin conc., g/dL	33.58 (1.05)	33.90 (0.93)	33.18 (1.06)
Troponin-I[#], ng/ml	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
High-sensitivity Troponin T[#], pg/mL	8.59 [4.01, 14.39]	6.29 [1.50, 10.83]	11.96 [6.73, 19.44]
High Sensitivity CRP [#], mg/L	2.26 [1.00, 5.89]	1.69 [0.85, 3.86]	3.49 [1.47, 8.12]
N-terminal pro b-type natriuretic peptide[#], pg/mL	99.5 [47.1, 224.4]	77.3 [33.6, 163.1]	153.9 [73.6, 376.9]
Bicarbonate, mmol/L	25.15 (2.88)	25.78 (2.65)	24.35 (2.96)
Systolic blood pressure, mmHg	120.3 (17.6)	119.2 (16.6)	121.7 (18.7)
Diastolic blood pressure, mmHg	68.5 (11.5)	71.2 (10.6)	65.1 (11.6)
Interleukin-10[#], pg/mL	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]
Interleukin-1RA[#], pg/mL	646.4 [362.7, 1338.4]	537.2 [312.2 1124.1]	829.6 [455.8, 1617.7]
Interleukin-6[#], pg/mL	1.55 [0.94, 2.55]	1.15 [0.75, 1.81]	2.24 [1.46, 3.29]
Interleukin-1 beta[#], pg/mL	0.06 [0.06, 0.81]	0.06 [0.06, 0.68]	0.19 [0.06, 1.13]
TNF-alpha[#], pg/mL	1.80 [1.20, 2.60]	1.50 [1.10, 2.20]	2.30 [1.60, 3.20]
TGF-beta[#], ng/mL	10.40 [5.75, 17.23]	9.73 [5.18, 17.77]	11.00 [6.56, 16.56]
CXCL12, pg/mL	2328 (509)	2213 (458.)	2476 (533)
Fibrinogen, g/L	3.86 (0.98)	3.54 (0.83)	4.27 (1.01)
White blood cell, thousand/μL	6.19 (1.81)	5.79 (1.56)	6.70 (1.97)
Total cholesterol, mg/dL	180.2 (39.1)	186.6 (37.4)	171.9 (39.6)
Triglycerides[#], mg/dL	120.0 [85.0, 168.0]	111.0 [81.0, 154.0]	133.0 [93.0, 188.0]
High-density Lipoprotein, mg/dL	48.5 (13.9)	51.4 (14.8)	44.8 (11.8)
Low-density Lipoprotein, mg/dL	102.4 (31.4)	108.6 (30.6)	94.4 (30.6)
Serum Albumin, g/dL	4.1 (0.4)	4.2 (0.4)	4.0 (0.4)
Family history of kidney disease (%)	162 (13.4)	82 (12.1)	80 (15.1)
Diagnosed or treated for any cancer (%)	71 (5.9)	42 (6.2)	29 (5.5)
Cardio-Vascular Disease (%)	332 (27.5)	88 (13.0)	244 (46.1)
Congestive Heart Failure (%)	87 (7.2)	7 (1.0)	80 (15.1)
History of Chronic Obstructive Pulmonary Disease (%)	36 (3.0)	17 (2.5)	19 (3.6)
Acidosis (%)	1086 (90.0)	649 (95.7)	437 (82.6)
NSAID (%)	698 (57.8)	354 (52.2)	344 (65.0)
Diuretics (%)	686 (56.8)	268 (39.5)	418 (79.0)
ACE&ARBs (%)	551 (45.7)	245 (36.1)	306 (57.8)
Betablockers (%)	534 (44.2)	221 (32.6)	313 (59.2)

Calcium blockers (%)	369 (30.6)	166 (24.5)	203 (38.4)
Statins (%)	651 (53.9)	265 (39.1)	386 (73.0)
Steroids (%)	141 (11.7)	82 (12.1)	59 (11.2)
Anti-diabetes (%)	299 (24.8)	56 (8.3)	243 (45.9)
Antiplatelet (%)	583 (48.3)	264 (38.9)	319 (60.3)

* **Abbreviations:** FGF-23: fibroblast growth factor 23; PTH: parathyroid hormone; CRP: C-reactive protein; NTproBNP: N-terminal prohormone of brain natriuretic peptide; HbA1C: hemoglobin A1C; CBC: complete blood count; TNF- α: tumor necrosis factor alpha; TGF-β: Transforming Growth Factor Beta; CXCL12: C-X-C Motif Chemokine Ligand 12; HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio; UPCR: urine protein to creatinine ratio; NGAL: neutrophil gelatinase-associated lipocalin; BMI: body mass index; COPD: chronic obstructive pulmonary disease; NSAID: non-steroidal anti-inflammatory drug; ACE: angiotensin-converting-enzyme; ARB: Angiotensin II receptor blockers.
[#] Variables that were summarized as medium [inter quartile range, IQR]

Table S10. The adjusted risks of CKD progression, cardiovascular disease and death associated with CKD subgroups among patients UACR<30mg/g (N=1207)

Outcome	Model	Cluster 1	Cluster 2	
			HR (95% CI)	p value
CKD progression	**Unadjusted**	Ref	5.04 (3.23, 7.85)	<0.001
	Adjusted		2.06 (1.12, 3.81)	0.021
Kidney failure requiring RRT	**Unadjusted**	Ref	10.48 (4.73, 23.2)	<0.001
	Adjusted		3.02 (1.14, 7.97)	0.026
CHF	**Unadjusted**	Ref	7.99 (4.88, 13.07)	<0.001
	Adjusted		2.60 (1.36, 4.96)	0.004
MI, stroke, PAD	**Unadjusted**	Ref	3.28 (2.33, 4.61)	<0.001
	Adjusted		1.24 (0.76, 2.03)	0.391
CHF, MI, stroke, PAD	**Unadjusted**	Ref	4.43 (3.30, 5.94)	<0.001
	Adjusted		1.71 (1.12, 2.59)	0.012
Death	**Unadjusted**	Ref	4.02 (3.00, 5.38)	<0.001
	Adjusted		1.58 (1.04, 2.39)	0.030

* Model adjusts for age, gender, race&Apol1 risks, education level, diabetes, smoking status, alcohol use, physical activities, BMI, eGFR, UACR, systolic blood pressure, family history of kidney disease, history of cardiovascular disease

Abbreviation: CKD, chronic kidney disease; RRT: renal replacement therapy; CHF: congestive heart failure; MI, myocardial infraction; PAD, peripheral artery disease.

Supplemental Figures

Figure S1. The Consensus Clustering Algorithm Flow Chart

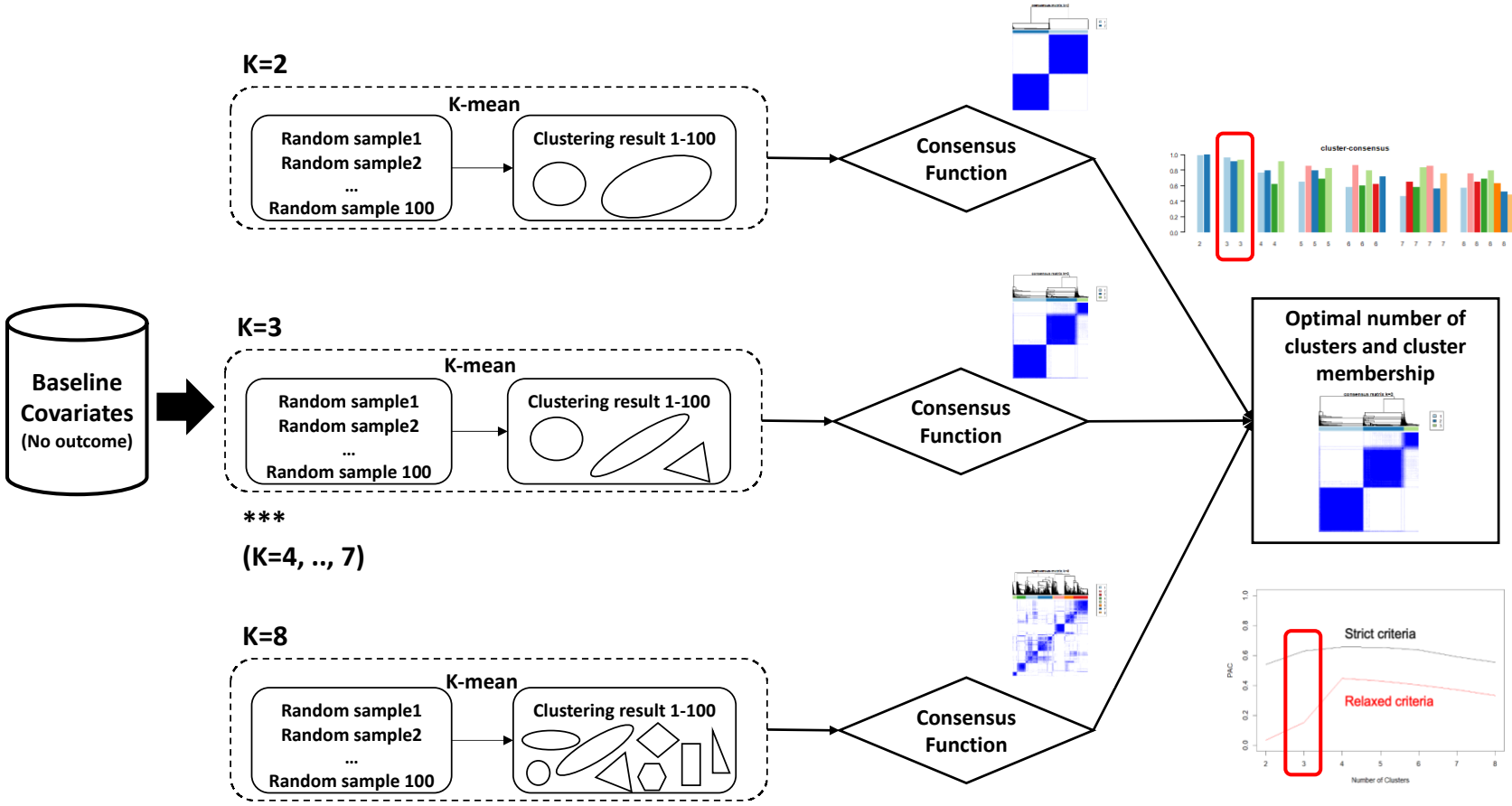
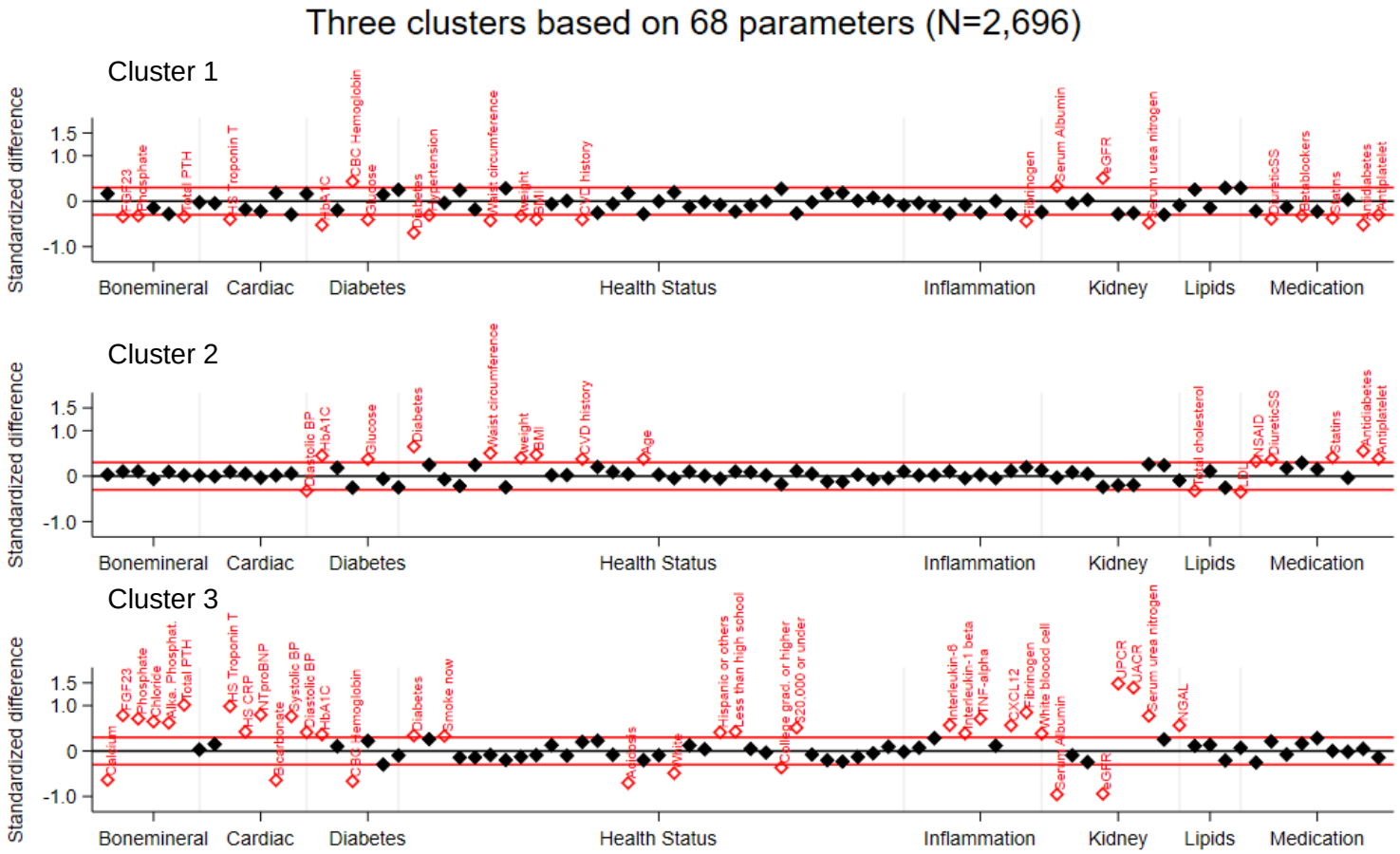
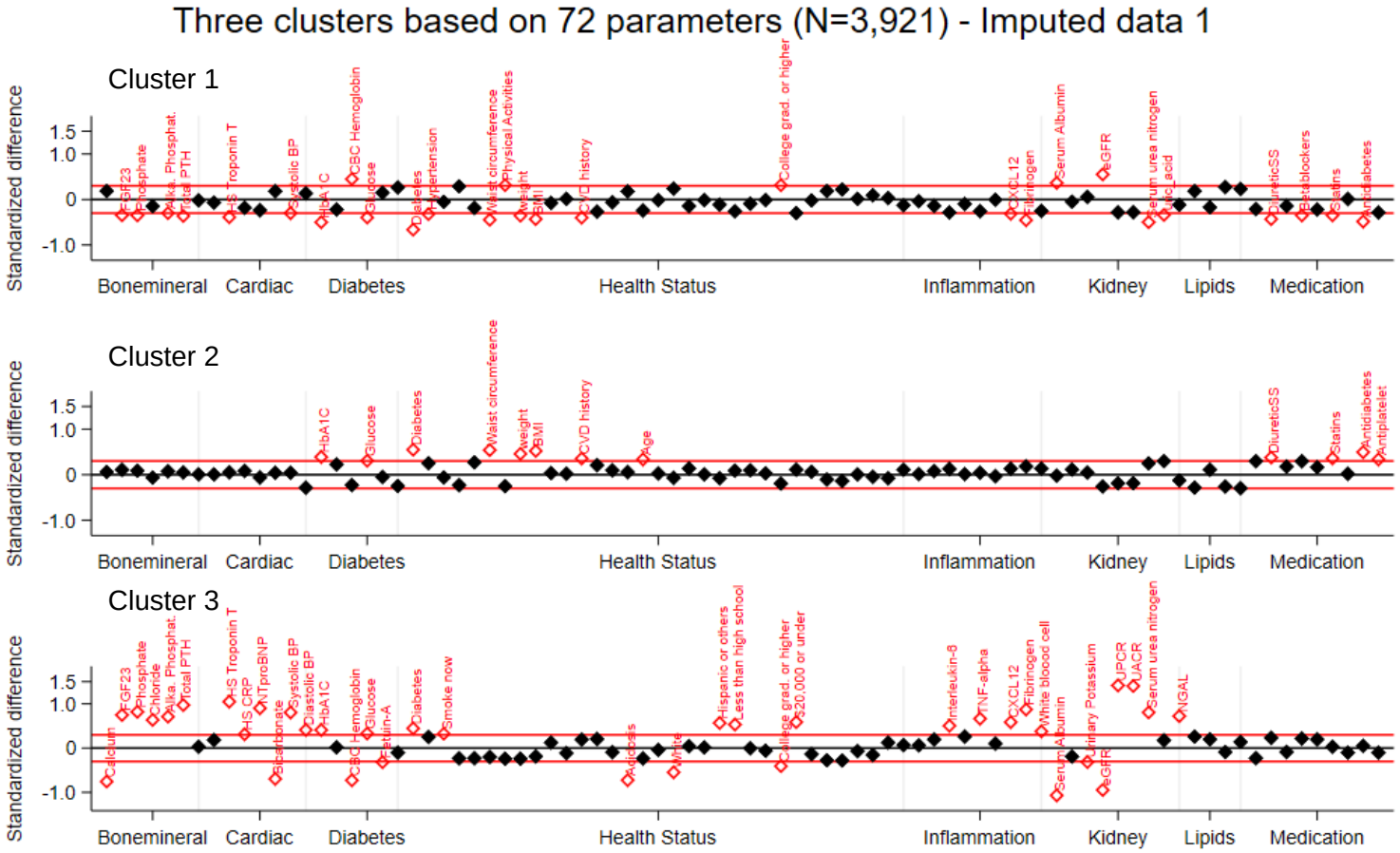


Figure S2. The Manhattan plot of the standardized differences across three subgroups based on 68 non-SES baseline parameters in the main analysis population (N=2,696)



* The red horizontal lines represent the standardized differences cut-offs of >0.3 or <-0.3;
§ The gray vertical lines layout the category each marker belongs, including bone and mineral markers, cardiac markers, diabetes markers, factors of health status, inflammation markers, kidney markers, lipids markers, and use of medications.

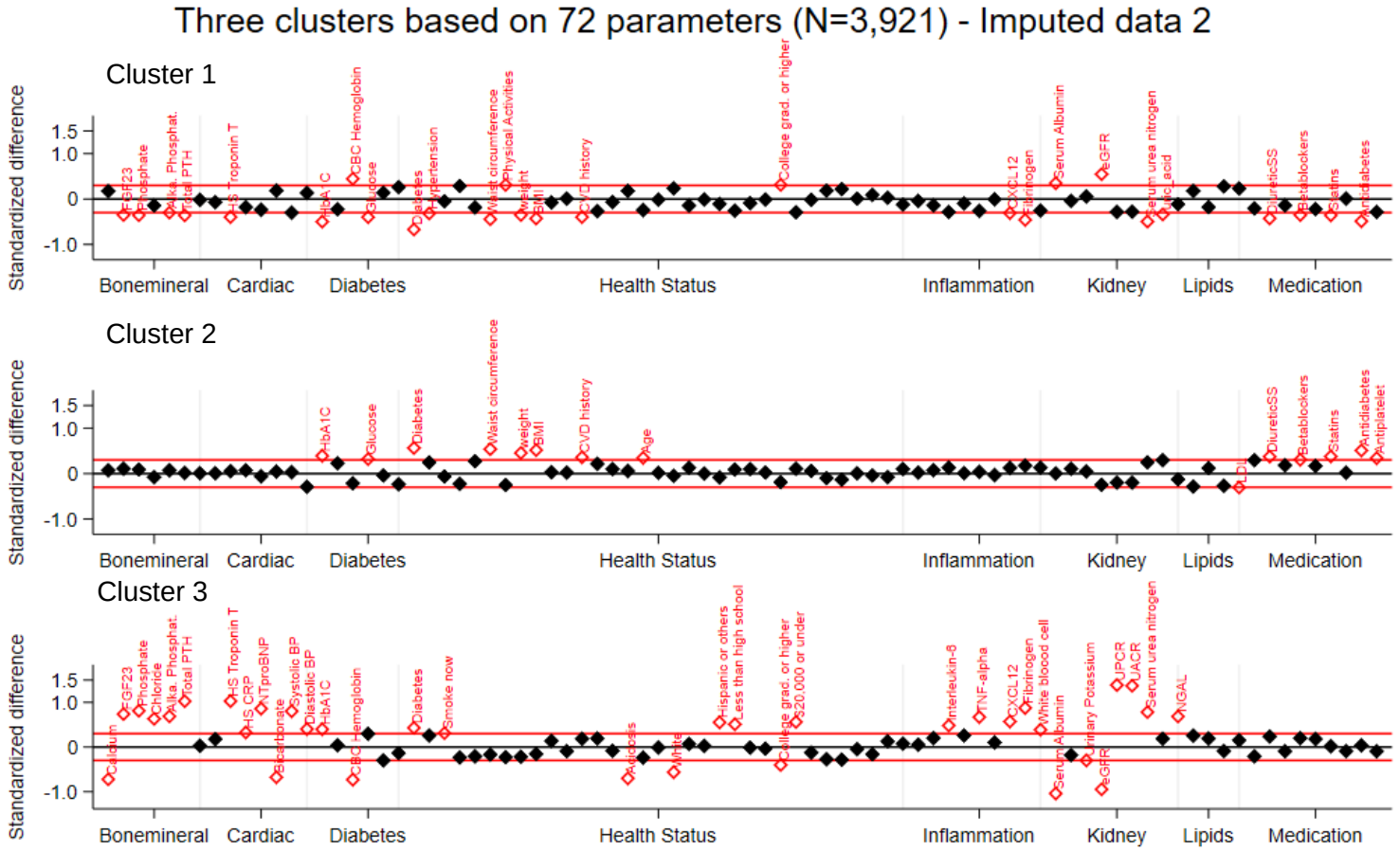
Figure S3. The Manhattan plot of the standardized differences across three subgroups based on 72 baseline parameters in imputed dataset 1 (N=3,921)



* The red horizontal lines represent the standardized differences cut-offs of >0.3 or <-0.3;

§ The gray vertical lines layout the category each marker belongs, including bone and mineral markers, cardiac markers, diabetes markers, factors of health status, inflammation markers, kidney markers, lipids markers, and use of medications.

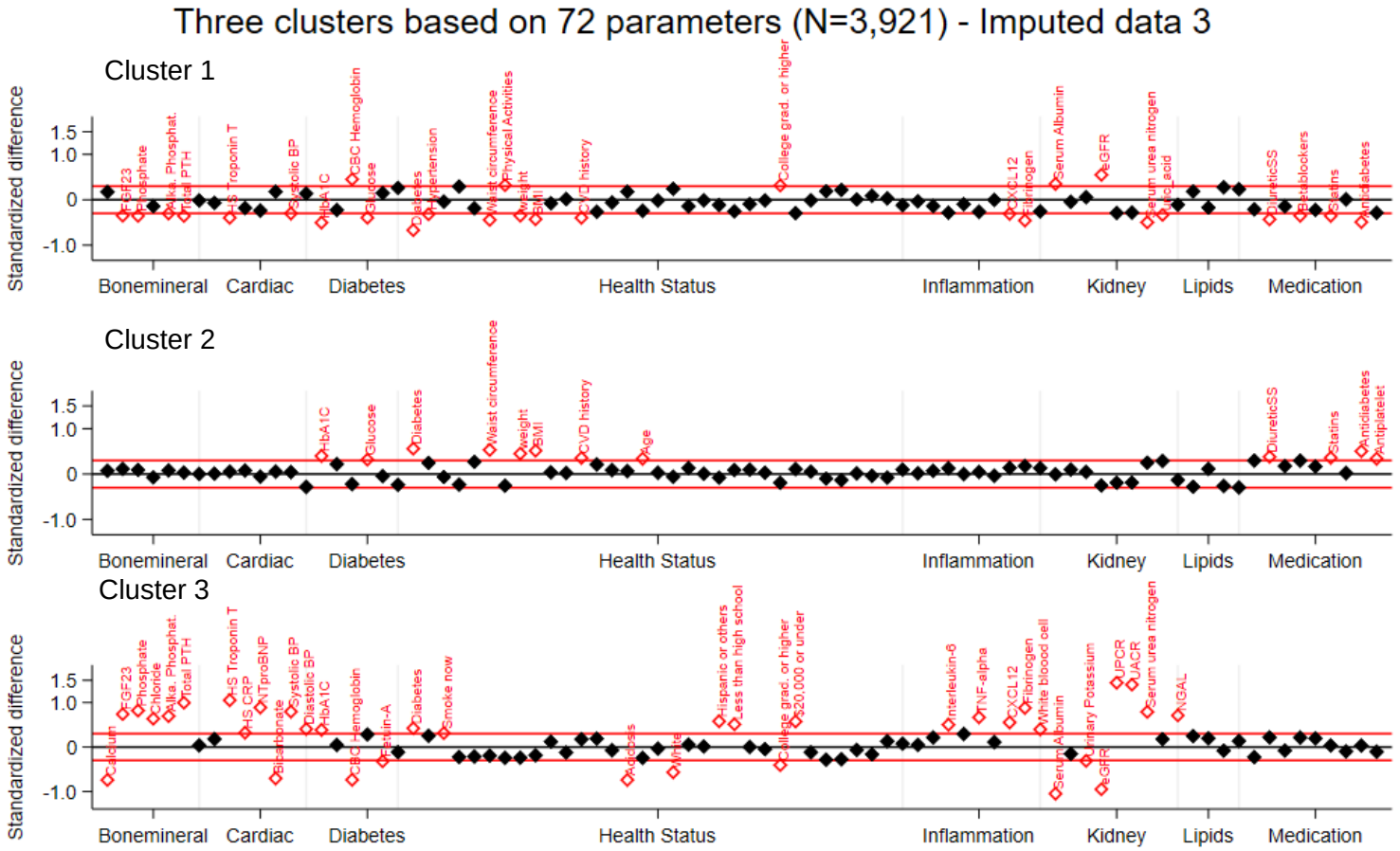
Figure S4. The Manhattan plot of the standardized differences across three subgroups based on 72 baseline parameters in imputed dataset 2 (N=3,921)



* The red horizontal lines represent the standardized differences cut-offs of >0.3 or <-0.3;

§ The gray vertical lines layout the category each marker belongs, including bone and mineral markers, cardiac markers, diabetes markers, factors of health status, inflammation markers, kidney markers, lipids markers, and use of medications.

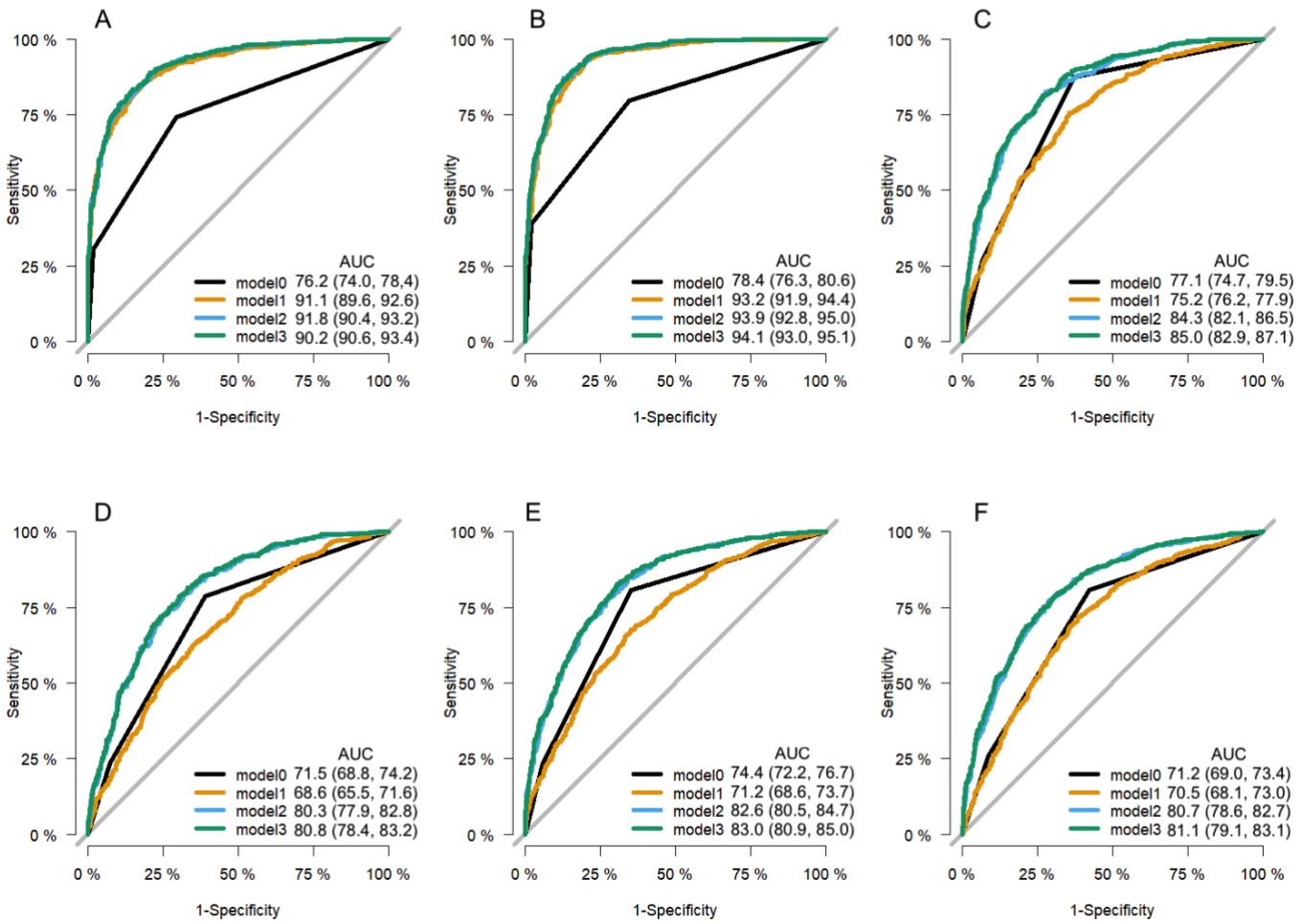
Figure S5. The Manhattan plot of the standardized differences across three subgroups based on 72 baseline parameters in imputed dataset 3 (N=3,921)



* The red horizontal lines represent the standardized differences cut-offs of >0.3 or <-0.3;

§ The gray vertical lines layout the category each marker belongs, including bone and mineral markers, cardiac markers, diabetes markers, factors of health status, inflammation markers, kidney markers, lipids markers, and use of medications.

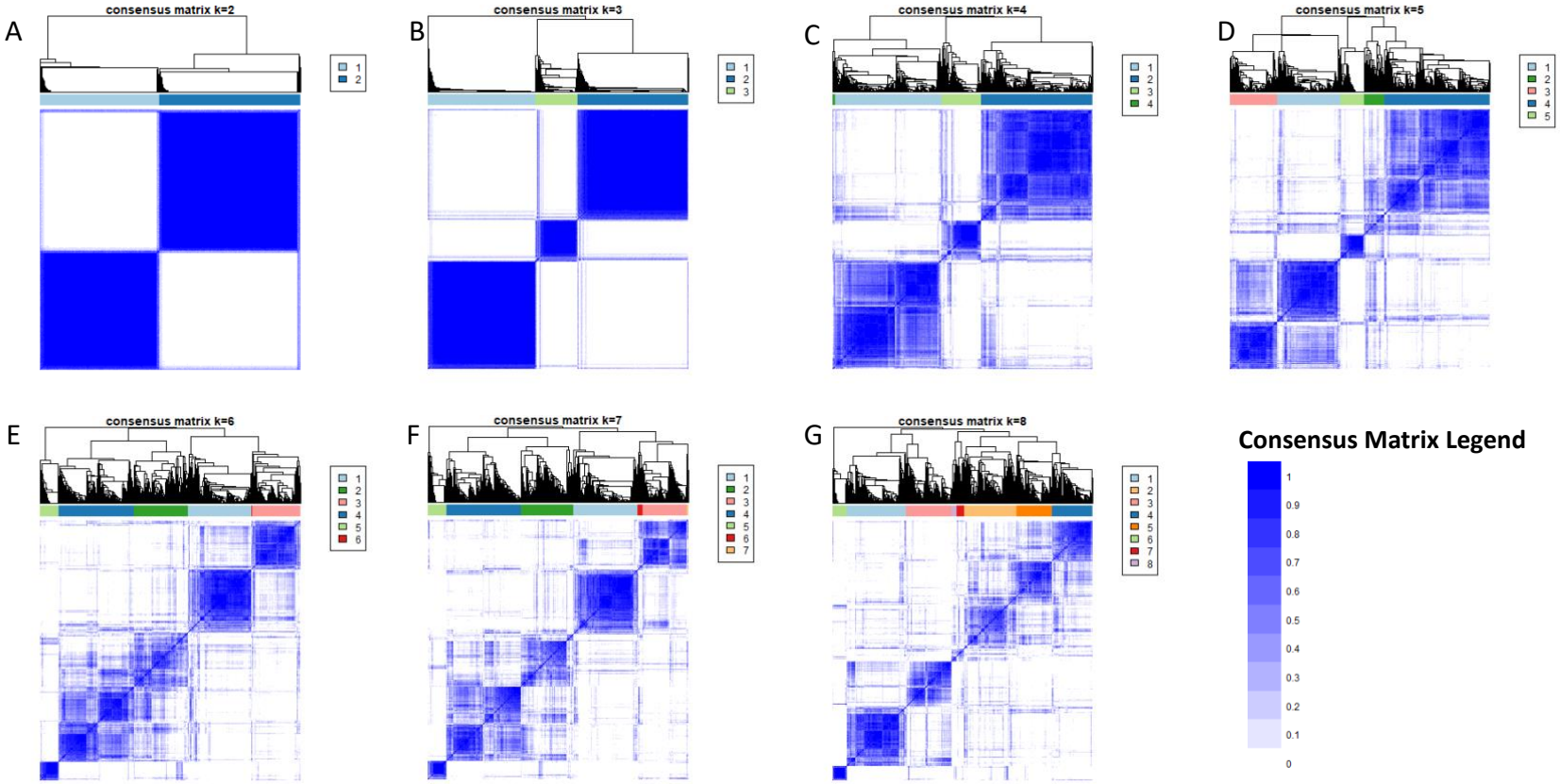
Figure S6. Time-dependent ROC curves of Cox regression for six clinical endpoints at year 10 (A. CKD progression; B. kidney failure requiring RRT; C. CHF; D. MI, stoke, PAD; E. CHF, MI, stoke, PAD; F. death)



* Model 0 includes CKD cluster membership; Model 1 includes eGFR and log transformed UACR; Model 2 includes age, gender, race&Apol1 risks, education level, diabetes, smoking status, alcohol use, physical activities, BMI, eGFR, UACR, systolic blood pressure, family history of kidney disease, history of cardiovascular disease and income level; and Model 3 includes variables in Model 2 and CKD cluster membership

Abbreviation: ROC: receiver operating characteristic; CKD, chronic kidney disease; RRT: renal replacement therapy; CHF: congestive heart failure; MI, myocardial infraction; PAD, peripheral artery disease.

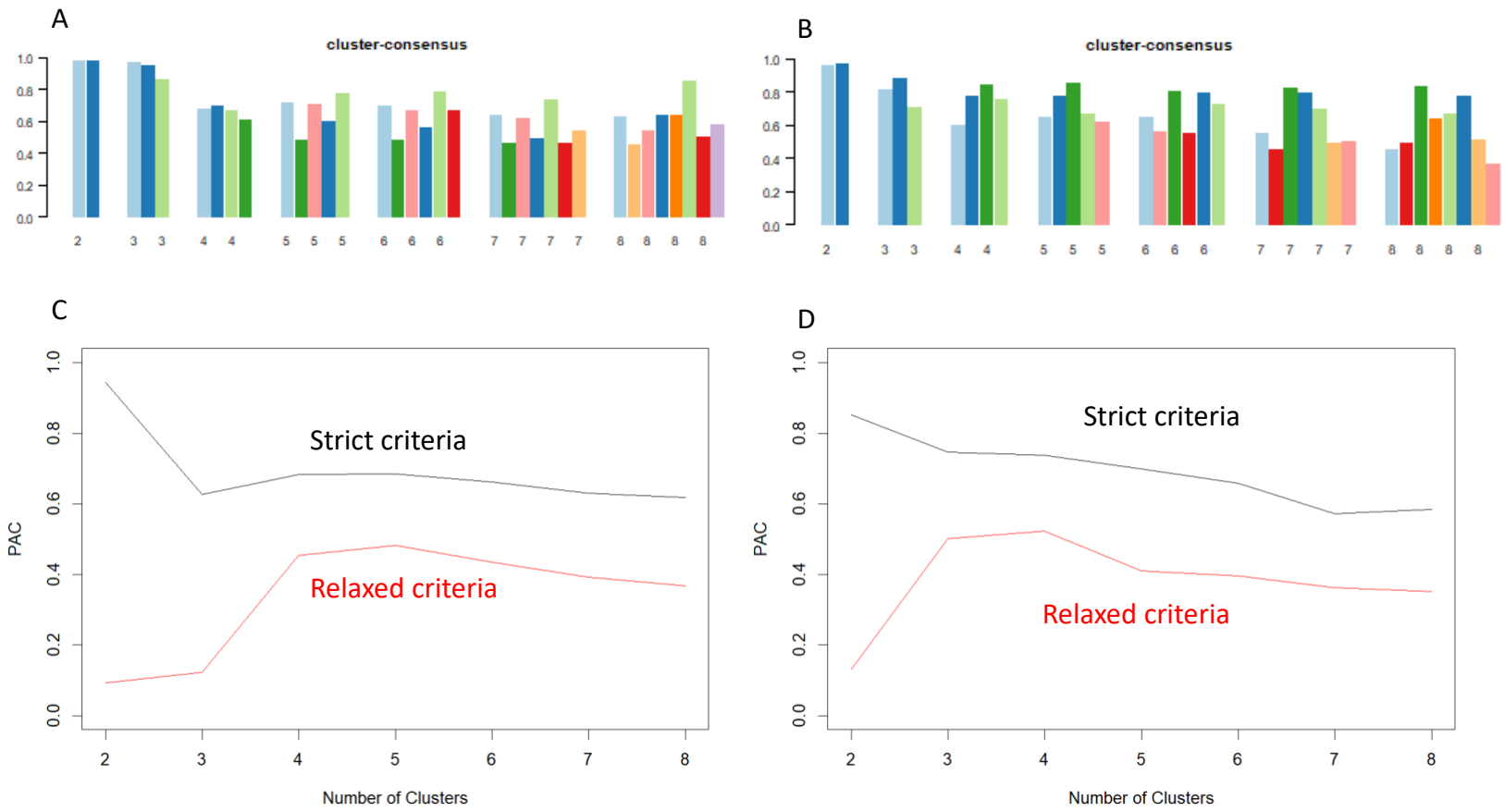
Figure S7. The consensus matrix heatmaps of K=2 to K=8 among individuals with eGFR<45 ml/min/1.73m^2 (N=1411), using the 72 baseline parameters



* The darkest blue color represents perfect consensus where two individuals always group together; the white color represents perfect consensus where two individuals always group separately; and the blue color scales in between represent ambiguous consensus, where two individuals are grouped together in some runs but separately in others.

§ Panel A, K=2; Panel B, K=3; Panel C, K=4; Panel D, K=5; Panel E, K=6; Panel F, K=7; Panel G, K=8.

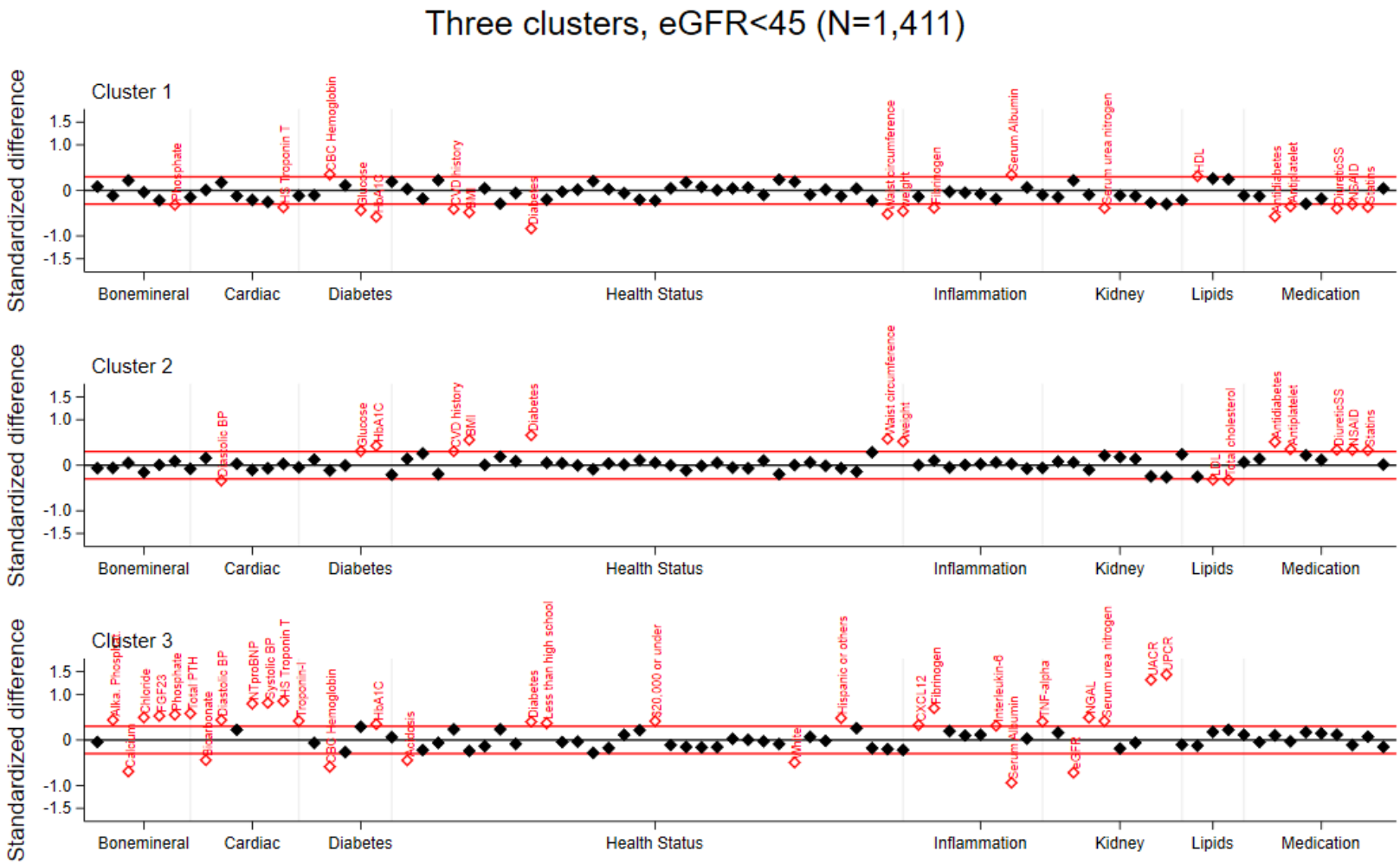
Figure S8. Cluster consensus score and proportion of ambiguously clustered (PAC) pair for consensus clustering using all parameters among individuals with baseline eGFR<45 ml/min/1.73m^2 (N=1411, Panel A and C) and among individuals with baseline eGFR≥ 45 ml/min/1.73m^2 (N=1285, Panel B and D)



* The bar plots shown in panel A and C represent the mean cluster consensus score under each scenario of number of clusters K=2 to K=8, based on 100 replicates of 80% resampling of the CRIC participants with baseline eGFR<45 ml/min/1.73m^2 or ≥ 45 ml/min/1.73m^2 .

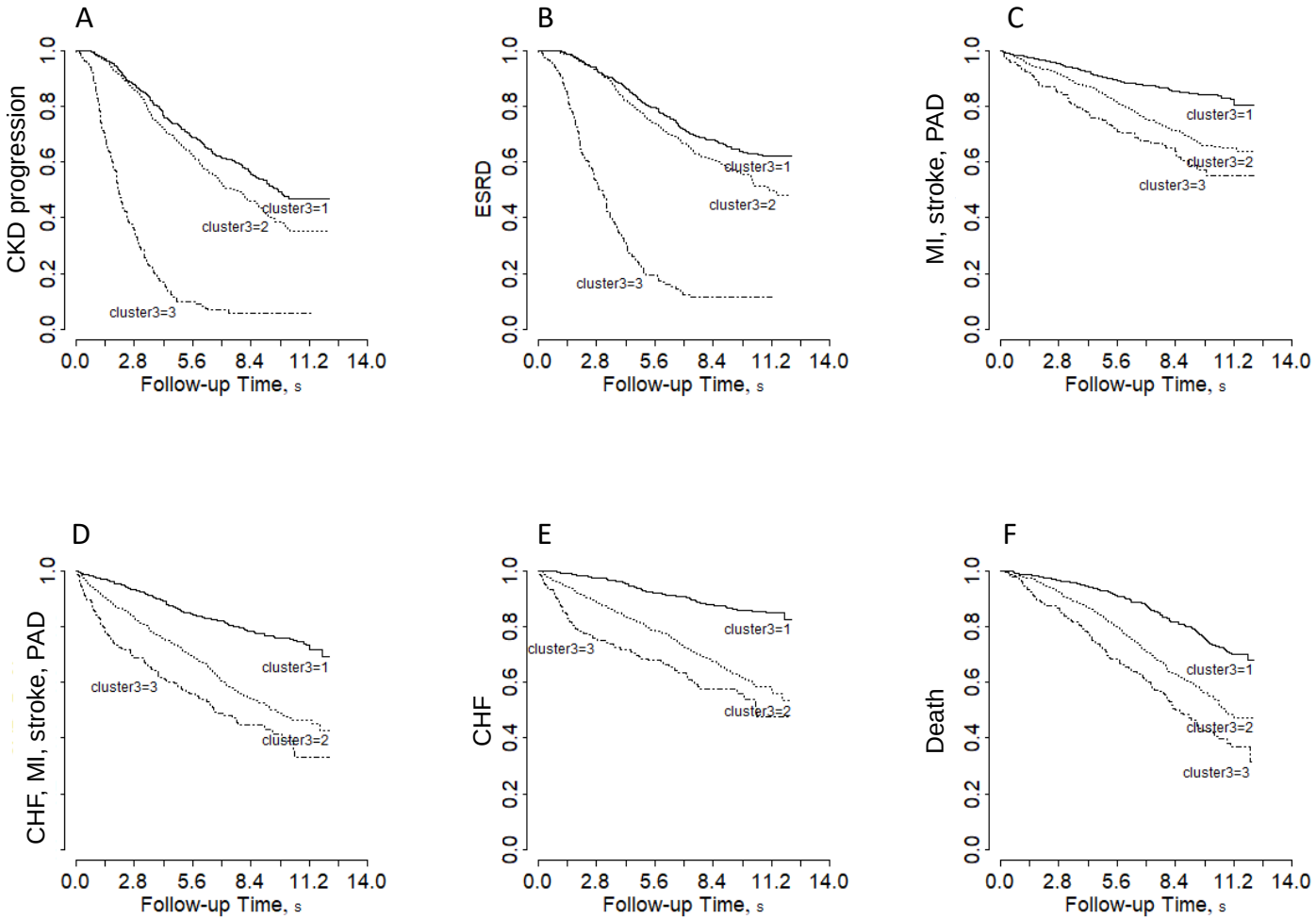
§ The black line in Figure 2B shows the PAC values using the strict criteria with predetermined boundary of [0, 1] as definition for ambiguously clustered pair; and the red line in Figure 2B represents the PAC values using the relaxed criteria with predetermined boundary of [0.1, 0.9] as definition for ambiguously clustered pair.

Figure S9. The Manhattan plot of the standardized differences across three subgroups among individuals with eGFR< 45 ml/min/1.73m^2 (N=1411) for each of the 72 baseline parameters



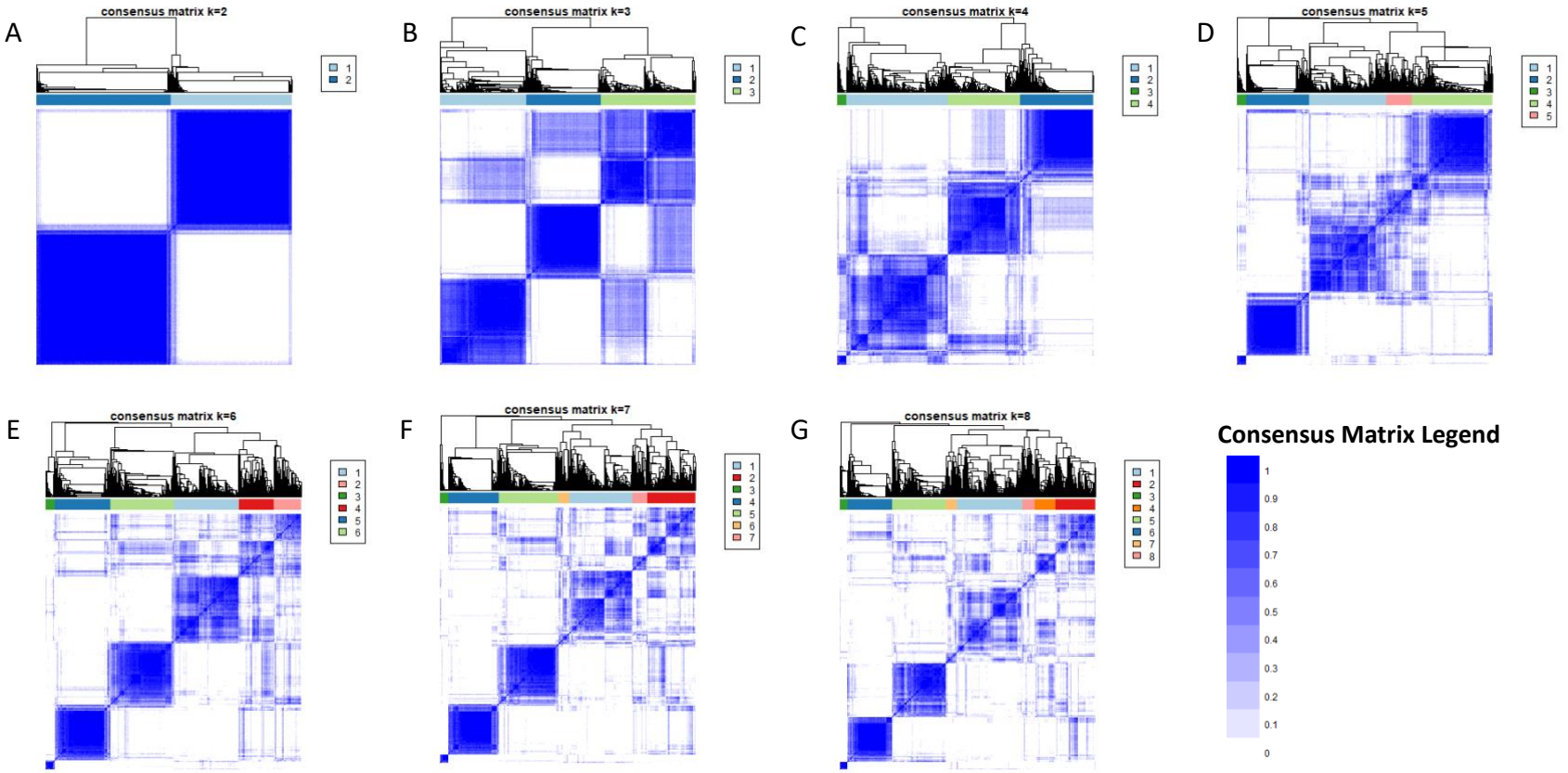
* The y-axis is the standardized differences value and the x-axis shows the 8 categories of the baseline parameters.
# The red horizontal lines represent the standardized differences cut-offs of >0.3 or <-0.3.
§ The gray vertical lines layout the category each marker belongs, including bone and mineral markers, cardiac markers, diabetes markers, factors of health status, inflammation markers, kidney markers, lipids markers, and use of medications.

Figure S10. Kaplan-Meier survival plots of the three subgroups defined by 72 baseline parameters among individuals with baseline eGFR< 45 ml/min/1.73m^2 (N=1411) and the outcomes of CKD progression (A), kidney failure requiring RRT (B), composite outcome of MI, stroke, and PAD (C), composite outcome of CHF, MI, stroke, and PAD (D), CHF (E), and death (F)



Abbreviation: CKD, chronic kidney disease; RRT: renal replacement therapy; MI, myocardial infraction; PAD, peripheral artery disease.

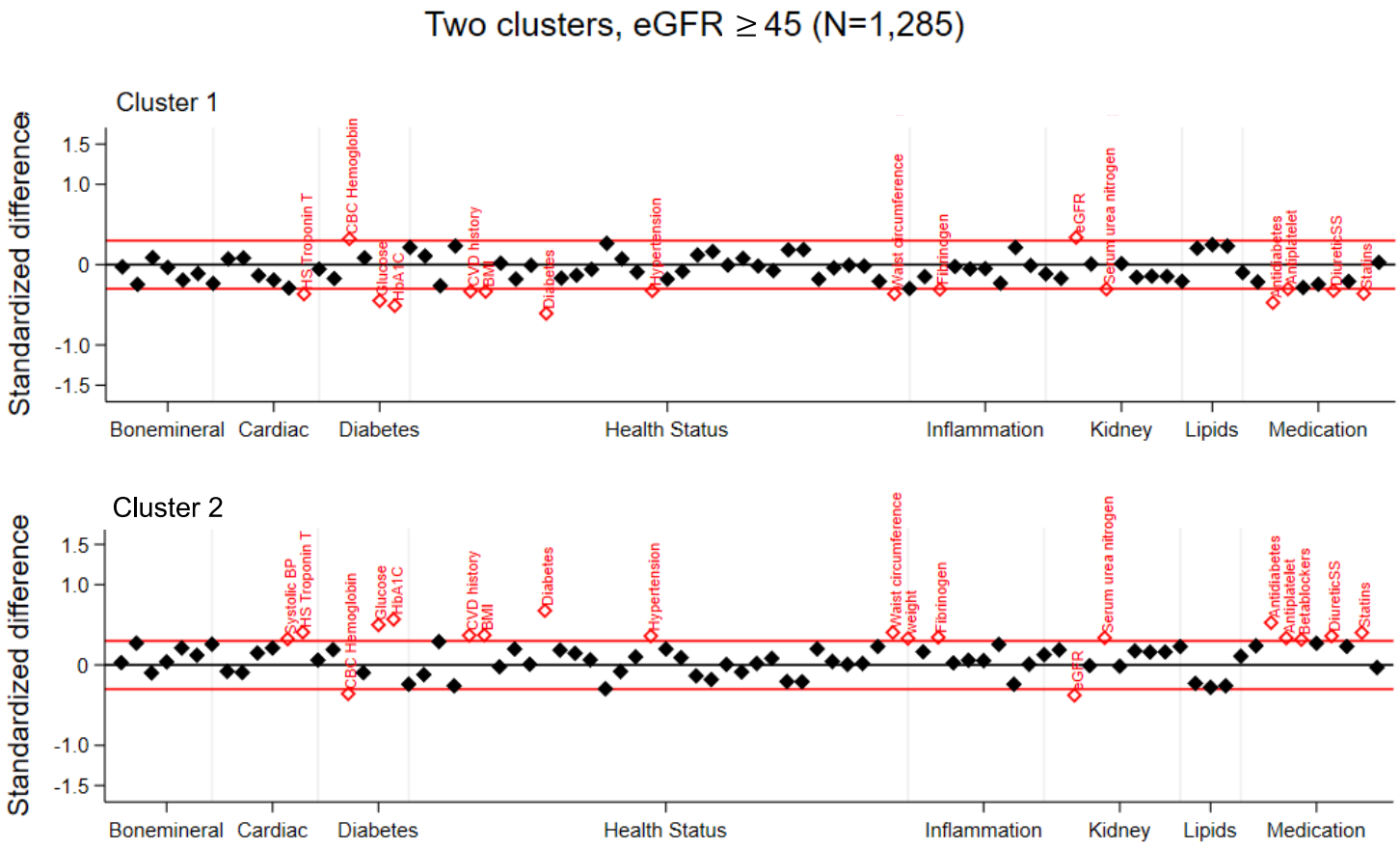
Figure S11. The consensus matrix heatmaps of K=2 to K=8 among individuals with eGFR≥45 ml/min/1.73m^2 (N=1285), using the 72 baseline parameters



* The darkest blue color represents perfect consensus where two individuals always group together; the white color represents perfect consensus where two individuals always group separately; and the blue color scales in between represent ambiguous consensus, where two individuals are grouped together in some runs but separately in others.

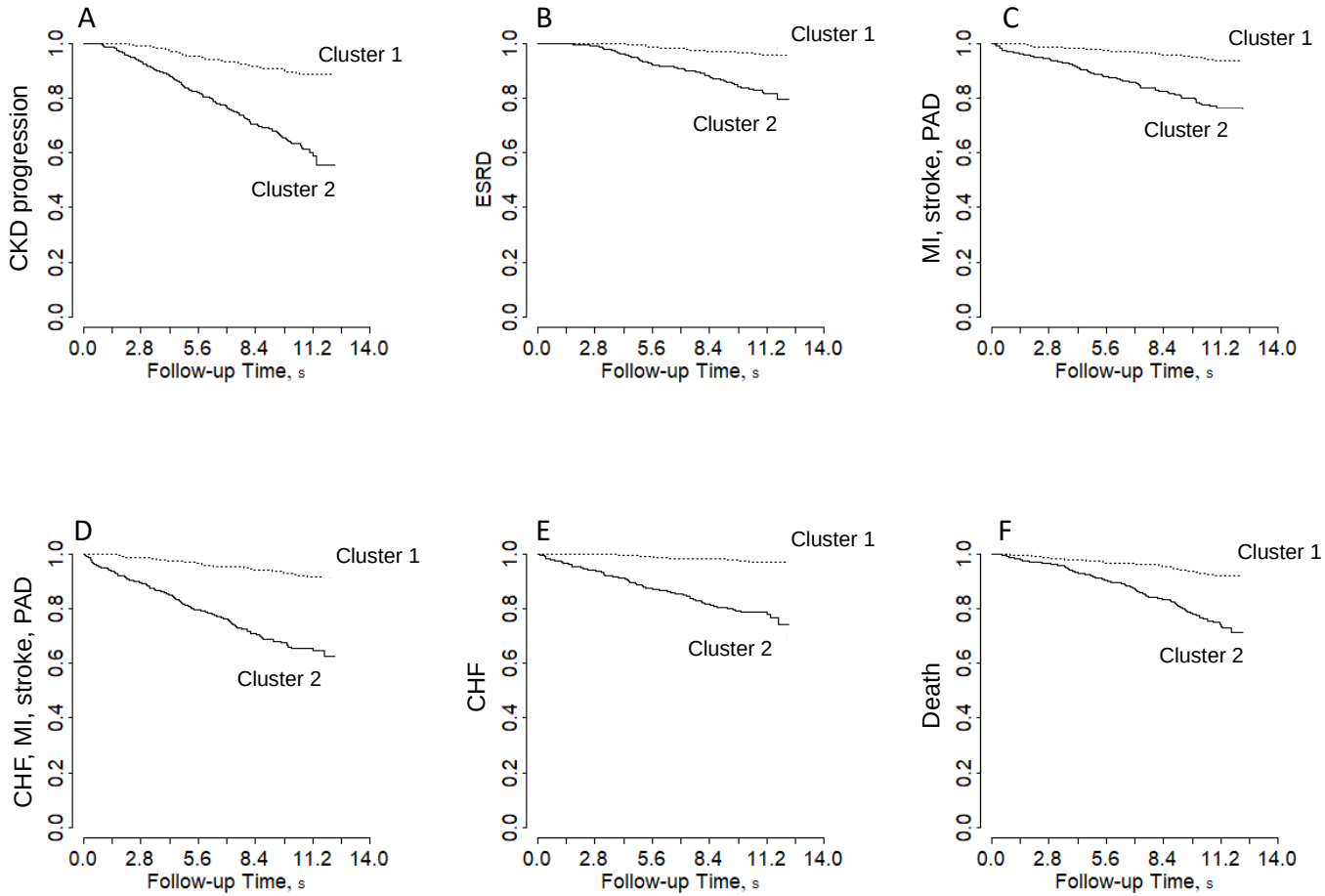
§ Panel A, K=2; Panel B, K=3; Panel C, K=4; Panel D, K=5; Panel E, K=6; Panel F, K=7; Panel G, K=8.

Figure S12. The Manhattan plot of the standardized differences across two subgroups among individuals with eGFR≥ 45 ml/min/1.73m^2 (N=1285) for each of the 72 baseline parameters



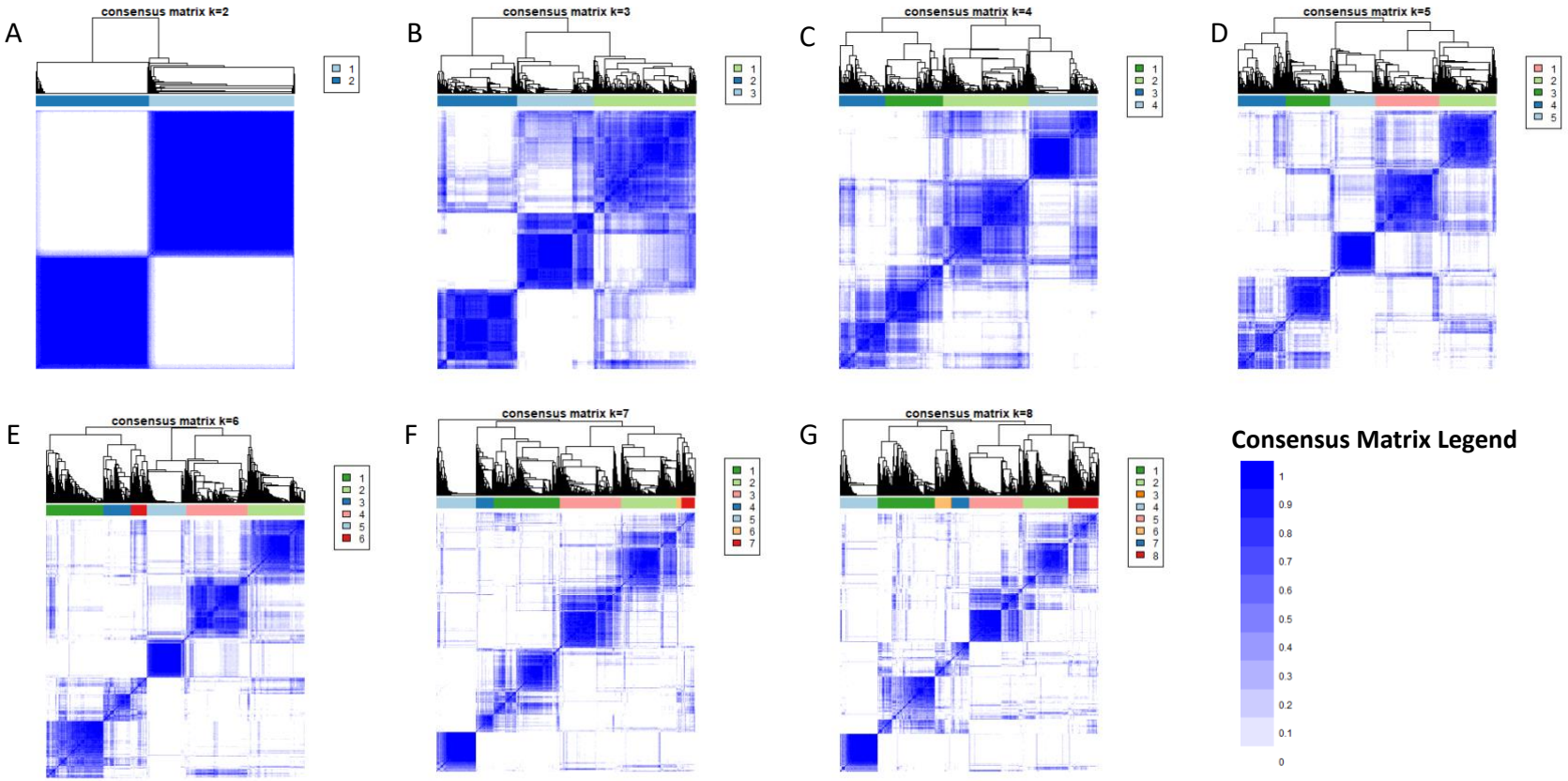
The y-axis is the standardized differences value and the x-axis shows the 8 categories of the baseline parameters.
* The red horizontal lines represent the standardized differences cut-offs of >0.3 or <-0.3;
§ The gray vertical lines layout the category each marker belongs, including bone and mineral markers, cardiac markers, diabetes markers, factors of health status, inflammation markers, kidney markers, lipids markers, and use of medications.

Figure S13. Kaplan-Meier survival plots of the two subgroups defined by 72 baseline parameters among individuals with baseline eGFR≥45 ml/min/1.73m^2 (N=1285) and the outcomes of CKD progression (A), kidney failure requiring RRT (B), composite outcome of MI, stroke, and PAD (C), composite outcome of CHF, MI, stroke, and PAD (D), CHF (E), and death (F)



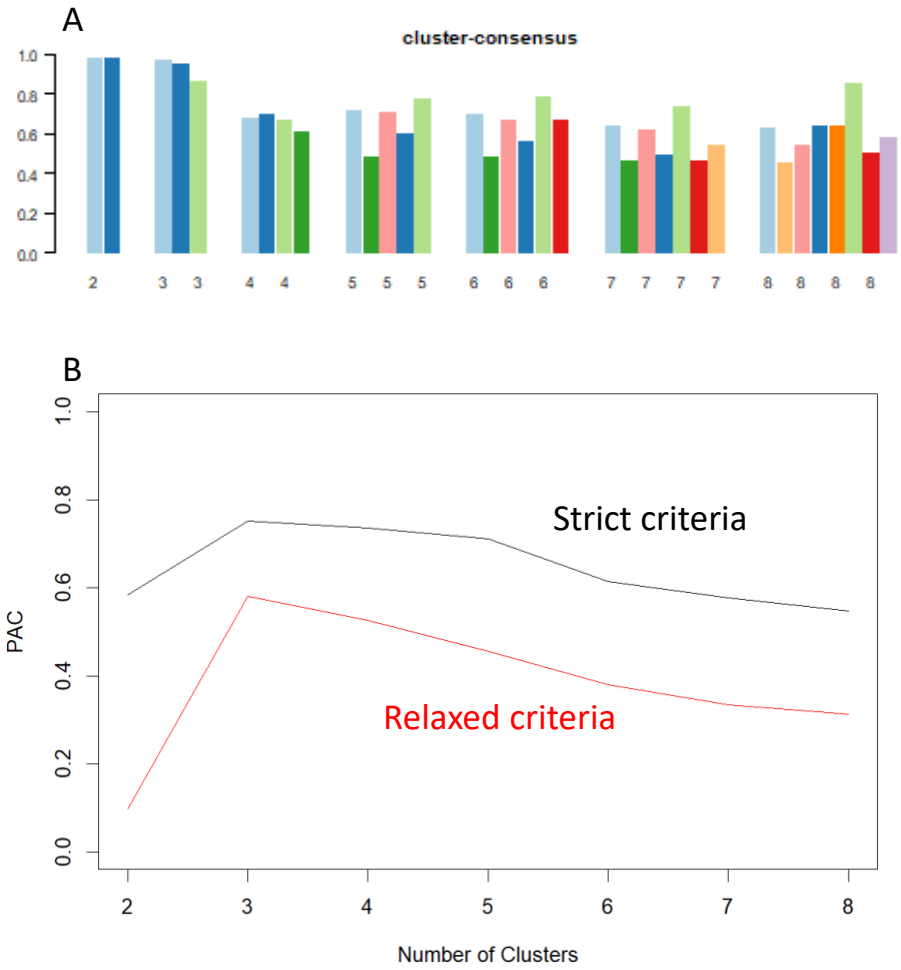
Abbreviation: CKD, chronic kidney disease; RRT: renal replacement therapy; MI, myocardial infraction; PAD, peripheral artery disease.

Figure S14. The consensus matrix heatmaps of K=2 to K=8 among individuals with UACR < 30mg/g (N=1207), using the 72 baseline parameters



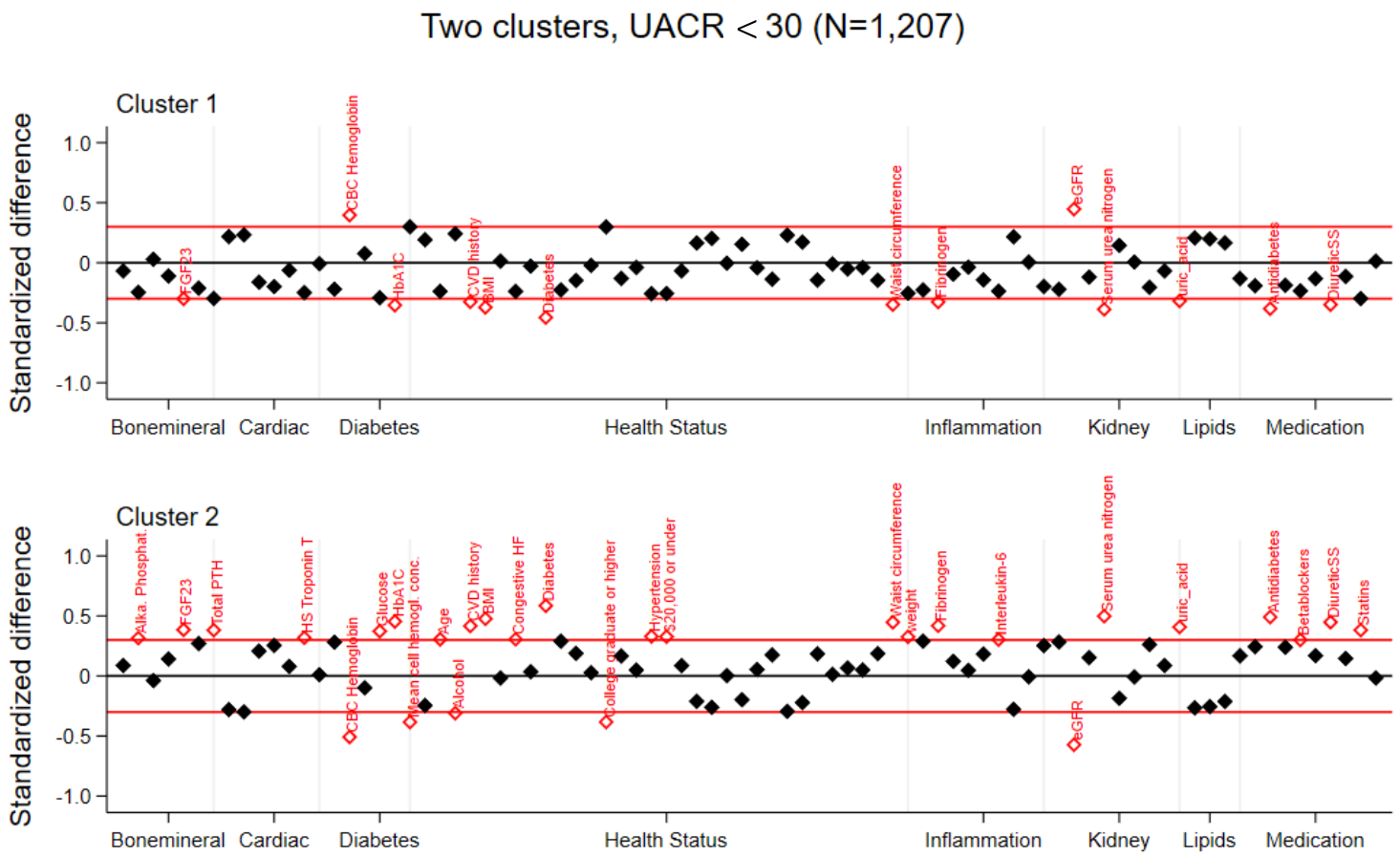
* The darkest blue color represents perfect consensus where two individuals always group together; the white color represents perfect consensus where two individuals always group separately; and the blue color scales in between represent ambiguous consensus, where two individuals are grouped together in some runs but separately in others.
§ Panel A, K=2; Panel B, K=3; Panel C, K=4; Panel D, K=5; Panel E, K=6; Panel F, K=7; Panel G, K=8.

Figure S15. Cluster consensus score and proportion of ambiguously clustered (PAC) pair for consensus clustering using all parameters among individuals with baseline UACR < 30mg/g (N=1207, Panel A and B)



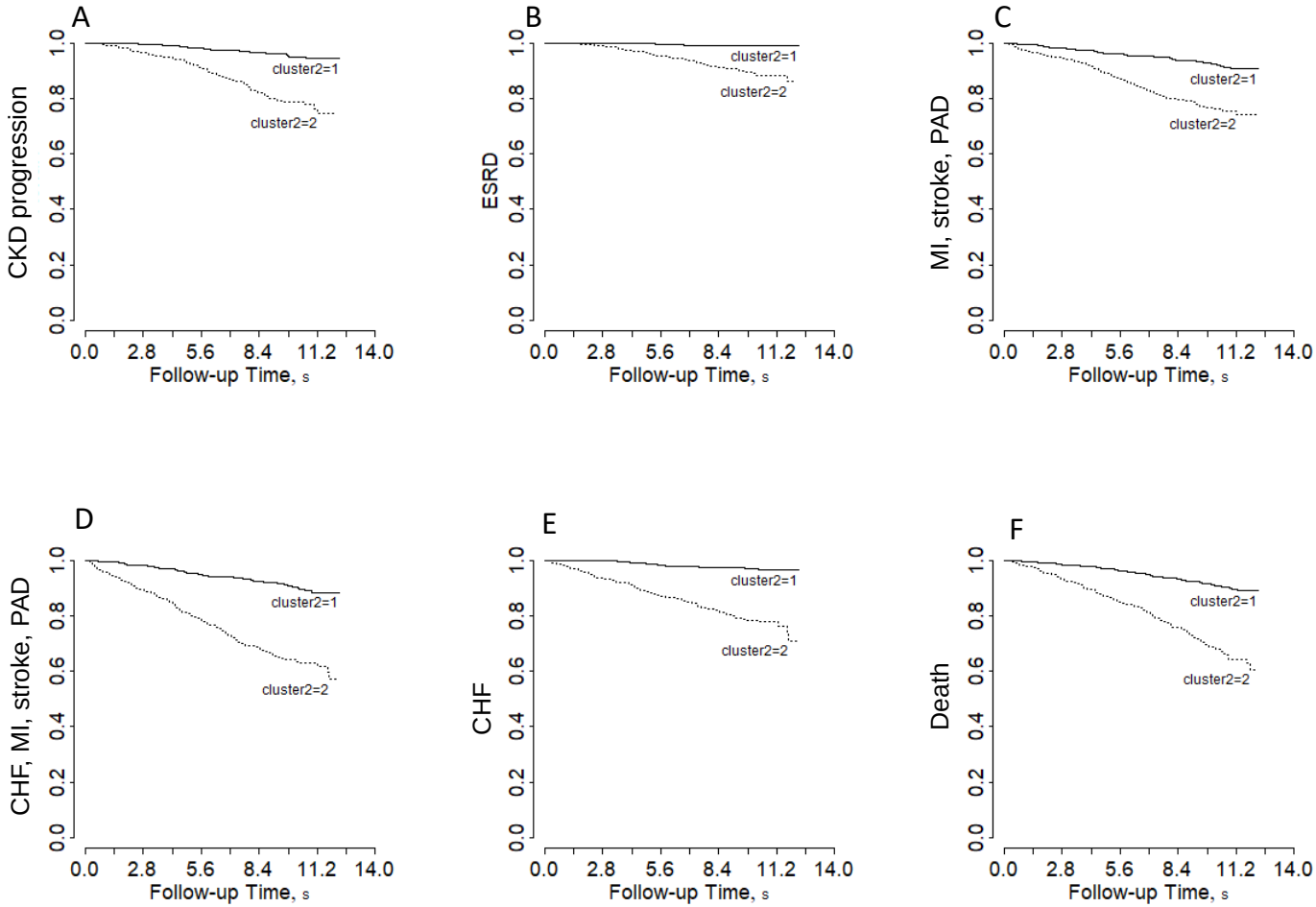
* The bar plots shown in panel A represent the mean cluster consensus score under each scenario of number of clusters K=2 to K=8, based on 100 replicates of 80% resampling of the CRIC participants with baseline UACR<30mg/g.
§ The black line in Figure 2B shows the PAC values using the strict criteria with predetermined boundary of [0, 1] as definition for ambiguously clustered pair; and the red line in Figure 2B represents the PAC values using the relaxed criteria with predetermined boundary of [0.1, 0.9] as definition for ambiguously clustered pair.

Figure S16. The Manhattan plot of the standardized differences across two subgroups among individuals with UACR<30 mg/g (N=1207) for each of the 72 baseline parameters



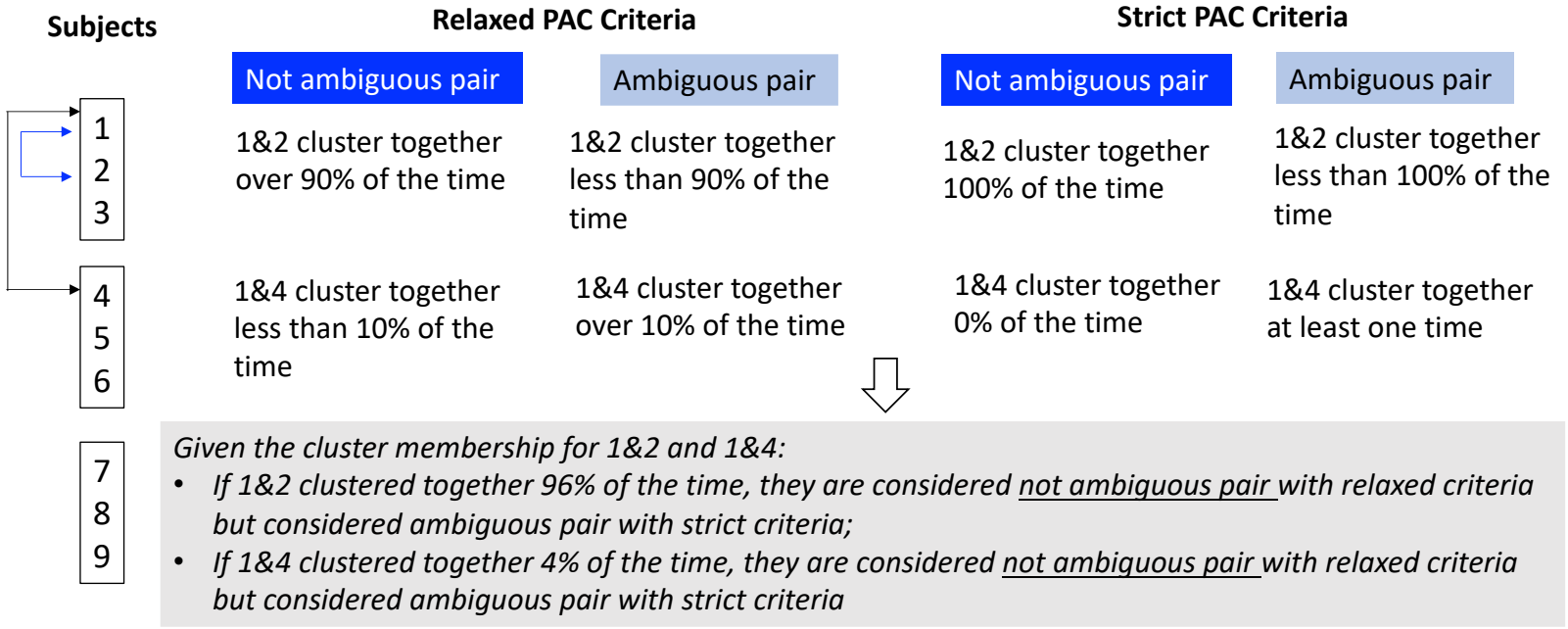
The y-axis is the standardized differences value and the x-axis shows the 8 categories of the baseline parameters.
* The red horizontal lines represent the standardized differences cut-offs of >0.3 or <-0.3.
§ The gray vertical lines layout the category each marker belongs, including bone and mineral markers, cardiac markers, diabetes markers, factors of health status, inflammation markers, kidney markers, lipids markers, and use of medications.

Figure S17. Kaplan-Meier survival plots of the two subgroups defined by 72 baseline parameters among individuals with baseline UACR< 30mg/g (N=1207) and the outcomes of CKD progression (A), kidney failure requiring RRT (B), composite outcome of MI, stroke, and PAD (C), composite outcome of CHF, MI, stroke, and PAD (D), CHF (E), and death (F)



Abbreviation: CKD, chronic kidney disease; RRT: renal replacement therapy; MI, myocardial infraction; PAD, peripheral artery disease.

Figure S18. An illustration of PAC relaxed criteria versus strict criteria



Number of pairs: 8 × 9/2 = 36; In this case of 9 subjects and 3 clusters: **PAC = # ambiguous pair/36**
Using the pairs of subjects 1&2 (from same cluster) and subjects 1&4 (from different clusters) as examples

Abbreviation: PAC: Proportion of ambiguously clustered pairs