**Supplementary Material**

Table S1. Definitions of CKM Syndrome Stages

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| --- | --- |
| **CKM Syndrome Stages** | **Definition** |
| Stage 0: No CKM risk factors | Individuals meet all following criteria.   1. Not overweight/obese (body mass index <25 kg/m2, or <23 kg/m2 if Asian ancestry; Waist circumference ≥88/102 cm in women/men (or if Asian ancestry, ≥80/90 cm in women/men) 2. Without metabolic risk factors (hypertension, hypertriglyceridemia [<135 mg/dL], metabolic syndrome, prediabetes, diabetes) or chronic kidney disease (CKD). |
| Stage 1: Excess or dysfunctional adiposity | Individuals with body mass index ≥25 kg/m2 (or ≥ 23 kg/m2 if Asian ancestry), waist circumference ≥88/102 cm in women/men (or if Asian ancestry, ≥80/90 cm in women/men), and/or prediabetes without the presence of other metabolic risk factors or CKD. |
| Stage 2: Metabolic risk factors and CKD | Individuals with metabolic risk factors (hypertriglyceridemia [≥135 mg/dL], hypertension, metabolic syndrome, diabetes), or CKD. |
| Stage 3: Subclinical CVD in CKM | Individuals with very high-risk CKD or high predicted 10-year CVD risk (≥ 20% using PREVENT [Predict Risk of cardiovascular disease EVENTs] base model |
| Stage 4: Clinical CVD in CKM | Individuals with clinical CVD (coronary heart disease, myocardial infarction, stroke or peripheral artery disease) |

CKM, cardiovascular-kidney-metabolic; CKD, chronic kidney disease; CVD, cardiovascular disease.

**Table S2.** Definition of variables involved in this study.

|  |  |
| --- | --- |
| Variables | Description in NHANES |
| Age | Divided into three groups: 20-40 years old, 41-60  years old, >60 years old |
| Sex | Male and Female |
| Race | Mexican American, Non-Hispanic Black, Non-Hispanic White, Other Race |
| Educational level | Below high school, High School or above |
| Marital status | Yes: Married/Living with partner |
| PIR | Poor: <1.3; Not Poor:>=1.3 |
| Obesity | Yes: BMI>=30 |
| Smoking | Smoking status was grouped into never smoker (defined as <100 cigarettes in a lifetime), current smoker (defined as ≥100 cigarettes in a lifetime), and former smoker (defined as ≥100 cigarettes and had quit smoking) |
| Drinking | heavy drinking (≥4 drinks/day for men, ≥3 drinks/day for women, or ≥5 days of drinking in a month),  moderate drinking (≥3 drinks/day for men, ≥2 drinks/day for women, or ≥2 days of drinking in a month),  mild drinking (≤2 drinks/day for men, ≤1 drink/day for women, and ≥12 drinks in a year),  and never-drinking (total number of drinks in a year <12, and dietary alcohol content of 0%) |
| Diabetes | Diabetes was defined as a history of previous diabetes, HbA1c level ≥6.5%, or fasting blood glucose level ≥126 mg/dL |
| Hypertension | The diagnostic criteria consist of self-reported hypertension history, the utilization of antihypertensive medication, a systolic blood pressure (SBP)  ≥ 140mmHg, or a diastolic blood pressure (DBP)  ≥ 90mmHg |
| Hyperlipidemia | (1) Triglyceride (TG) levels ≥150 mg/dl (1.7 mmol/L); (2) Total cholesterol (TC) levels ≥200 mg/dl (5.18 mmol/L); (3) Low-density lipoprotein (LDL) levels ≥130 mg/dl (3.37 mmol/L); (4) High-density lipoprotein (HDL) levels: Men: <40 mg/dl (1.04 mmol/L); Women: <50 mg/dl (1.30 mmol/L); (5) Individuals taking cholesterol-lowering drugs are also considered hyperlipidemia. |

PIR, Ratio of family income to poverty.

**Table S3.** Baseline characteristics of all participants were stratified by CKM stages, weighted.

| **Characteristic** | **Overall**, N = 31,065,216 (100%) | **CKM 0**, N = 3,520,503 (11%) | **CKM 1**, N = 6,952,938 (22%) | **CKM 2**, N = 16,913,617 (55%) | **CKM 3**, N = 1,126,545 (3.6%) | **CKM 4**, N = 2,551,613 (8.4%) | **P Value** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **No. of participants in the sample** | 5,221 | 473 | 1,025 | 2,842 | 315 | 566 | **-** |
| **Age (%)** |  |  |  |  |  |  | **<0.001** |
| *20-40* | 11,690,744 (38%) | 2,319,974 (66%) | 3,751,975 (54%) | 5,471,698 (32%) | 2,876 (0.3%) | 144,220 (5.7%) |  |
| *41-60* | 11,974,829 (39%) | 1,055,033 (30%) | 2,436,672 (35%) | 7,717,698 (46%) | 69,021 (6.1%) | 696,405 (27%) |  |
| *>60* | 7,399,643 (24%) | 145,496 (4.1%) | 764,291 (11%) | 3,724,222 (22%) | 1,054,648 (94%) | 1,710,987 (67%) |  |
| **Sex (%)** |  |  |  |  |  |  | **<0.001** |
| *Female* | 15,410,293 (50%) | 2,247,742 (64%) | 3,631,505 (52%) | 8,047,981 (48%) | 421,380 (37%) | 1,061,685 (42%) |  |
| *Male* | 15,654,923 (50%) | 1,272,761 (36%) | 3,321,433 (48%) | 8,865,637 (52%) | 705,165 (63%) | 1,489,928 (58%) |  |
| **Race (%)** |  |  |  |  |  |  | **<0.001** |
| *Non-Hispanic White* | 20,980,865 (68%) | 2,589,978 (74%) | 4,589,541 (66%) | 11,080,410 (66%) | 833,174 (74%) | 1,887,763 (74%) |  |
| *Other* | 4,042,763 (13%) | 501,463 (14%) | 882,159 (13%) | 2,319,550 (14%) | 110,358 (9.8%) | 229,232 (9.0%) |  |
| *Non-Hispanic Black* | 3,217,873 (10%) | 219,891 (6.2%) | 703,602 (10%) | 1,879,066 (11%) | 115,474 (10%) | 299,841 (12%) |  |
| *Mexican American* | 2,823,714 (9.1%) | 209,171 (5.9%) | 777,636 (11%) | 1,634,592 (9.7%) | 67,539 (6.0%) | 134,776 (5.3%) |  |
| **Married/live with partner (%)** |  |  |  |  |  |  | 0.101 |
| *no* | 10,948,604 (35%) | 1,394,979 (40%) | 2,346,587 (34%) | 5,801,504 (34%) | 477,910 (42%) | 927,624 (36%) |  |
| *yes* | 20,112,208 (65%) | 2,125,524 (60%) | 4,606,351 (66%) | 11,109,127 (66%) | 647,216 (58%) | 1,623,989 (64%) |  |
| **Education level (%)** |  |  |  |  |  |  | **<0.001** |
| *Below high school* | 5,159,568 (17%) | 365,091 (10%) | 830,768 (12%) | 2,980,113 (18%) | 320,223 (29%) | 663,375 (26%) |  |
| *High School or above* | 25,899,476 (83%) | 3,155,412 (90%) | 6,122,170 (88%) | 13,931,799 (82%) | 803,304 (71%) | 1,886,790 (74%) |  |
| **PIR (%)** |  |  |  |  |  |  | **<0.001** |
| *Poor* | 6,033,864 (21%) | 625,952 (19%) | 1,153,623 (18%) | 3,268,172 (21%) | 324,296 (32%) | 661,820 (28%) |  |
| *Not Poor* | 22,987,914 (79%) | 2,661,696 (81%) | 5,386,626 (82%) | 12,532,815 (79%) | 688,315 (68%) | 1,718,462 (72%) |  |
| **Obesity (%)** |  |  |  |  |  |  | **<0.001** |
| *no* | 19,902,198 (64%) | 3,520,503 (100%) | 5,071,480 (73%) | 9,084,340 (54%) | 701,983 (62%) | 1,523,892 (60%) |  |
| *yes* | 11,146,166 (36%) | 0 (0%) | 1,870,889 (27%) | 7,826,155 (46%) | 421,401 (38%) | 1,027,721 (40%) |  |
| **Smoking (%)** |  |  |  |  |  |  | **<0.001** |
| *never* | 16,868,950 (54%) | 2,231,117 (63%) | 4,065,891 (58%) | 9,124,161 (54%) | 476,501 (42%) | 971,280 (38%) |  |
| *former* | 8,002,121 (26%) | 547,848 (16%) | 1,804,589 (26%) | 4,064,443 (24%) | 487,649 (43%) | 1,097,592 (43%) |  |
| *current* | 6,191,046 (20%) | 741,538 (21%) | 1,080,361 (16%) | 3,724,012 (22%) | 162,394 (14%) | 482,741 (19%) |  |
| **Drinking (%)** |  |  |  |  |  |  | **<0.001** |
| *never* | 2,905,745 (10%) | 289,278 (9.1%) | 504,379 (7.8%) | 1,645,920 (11%) | 199,953 (20%) | 266,216 (11%) |  |
| *former* | 3,525,297 (12%) | 184,087 (5.8%) | 580,893 (9.0%) | 1,937,389 (12%) | 258,182 (26%) | 564,746 (24%) |  |
| *mild* | 10,917,403 (38%) | 1,132,637 (36%) | 2,370,689 (37%) | 6,112,409 (39%) | 412,304 (42%) | 889,364 (38%) |  |
| *moderate* | 5,031,520 (18%) | 812,525 (25%) | 1,405,585 (22%) | 2,511,683 (16%) | 29,608 (3.0%) | 272,118 (12%) |  |
| *heavy* | 6,227,108 (22%) | 771,211 (24%) | 1,575,830 (24%) | 3,467,796 (22%) | 87,364 (8.8%) | 324,907 (14%) |  |
| **Hypertension (%)** |  |  |  |  |  |  | **<0.001** |
| *no* | 19,640,523 (63%) | 3,520,503 (100%) | 6,952,938 (100%) | 8,141,731 (48%) | 300,894 (27%) | 724,457 (28%) |  |
| *yes* | 11,424,693 (37%) | 0 (0%) | 0 (0%) | 8,771,887 (52%) | 825,651 (73%) | 1,827,156 (72%) |  |
| **Diabetes (%)** |  |  |  |  |  |  | **<0.001** |
| *no* | 26,119,834 (84%) | 3,520,503 (100%) | 6,952,938 (100%) | 13,521,445 (80%) | 516,992 (46%) | 1,607,956 (63%) |  |
| *yes* | 4,945,382 (16%) | 0 (0%) | 0 (0%) | 3,392,173 (20%) | 609,553 (54%) | 943,657 (37%) |  |
| **Hyperlipidemia (%)** |  |  |  |  |  |  | **<0.001** |
| *no* | 9,369,135 (30%) | 2,158,792 (61%) | 3,426,558 (49%) | 3,258,702 (19%) | 269,870 (24%) | 255,212 (10%) |  |
| *yes* | 21,696,081 (70%) | 1,361,711 (39%) | 3,526,381 (51%) | 13,654,915 (81%) | 856,674 (76%) | 2,296,400 (90%) |  |
| **TyG (mean (SD))** | 8.58 (0.67) | 7.98 (0.39) | 8.20 (0.38) | 8.82 (0.65) | 8.88 (0.72) | 8.77 (0.72) | **<0.001** |
| **WWI (mean (SD))** | 10.94 (0.81) | 10.14 (0.54) | 10.69 (0.73) | 11.08 (0.76) | 11.68 (0.67) | 11.46 (0.76) | **<0.001** |
| **eGFR (mean (SD))** | 95.89 (21.91) | 105.51 (18.53) | 102.23 (18.64) | 96.12 (20.10) | 66.03 (21.14) | 76.95 (23.75) | **<0.001** |

Mean (SD) for continuous variables: the P value was calculated by the weighted One-Way ANOVA.

Percentages (weighted N, %) for categorical variables: the P value was calculated by the weighted chi-square test.

Abbreviation: TyG, Triglyceride-glucose index; WWI, Weight-adjusted waist index; eGFR, estimated glomerular filtration rate; PIR, poverty income ratio; CKM, advanced Cardiovascular-kidney-metabolic syndrome.

**Table S4.** Distribution of metal concentrations among all subjects.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **Percentile** |  |  |  |  |
| **Exposure biomarkers** | **Detection frequency** | **25th** | **50th** | **75th** | **GM** | **Mean** |
| Ba | 99.570% | 0.550 | 1.070 | 2.020 | 1.054 | 1.719 |
| Cd | 98.452% | 0.146 | 0.285 | 0.533 | 0.276 | 0.428 |
| Co | 99.865% | 0.216 | 0.346 | 0.533 | 0.345 | 0.511 |
| Cs | 98.776% | 2.820 | 4.540 | 6.700 | 4.243 | 5.183 |
| Mo | 99.856% | 21.800 | 39.100 | 64.110 | 36.343 | 48.710 |
| Pb | 98.353% | 0.240 | 0.440 | 0.770 | 0.430 | 0.680 |
| Sb | 80.253% | 0.029 | 0.049 | 0.083 | 0.052 | 0.077 |
| Tl | 99.388% | 0.101 | 0.165 | 0.254 | 0.156 | 0.195 |
| W | 90.556% | 0.031 | 0.062 | 0.118 | 0.063 | 0.109 |

Abbreviations: Ba, barium; Cd, cadmium; Co, cobalt; Cs, cesium; Mo, molybdenum; Pb, lead; Sb, antimony; Tl, thallium; W, tungsten; GM, geometric mean.

图表

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**Figure S1.** Pearson's correlation analysis between ln-transformed concentrations of metals

Abbreviations: Ba, barium; Cd, cadmium; Co, cobalt; Cs, cesium; Mo, molybdenum; Pb, lead; Sb, antimony; Tl, thallium; W, tungsten.

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**Figure S2.** Dose-response relationship between metal and CKM were estimated by RCS models. All metals were ln-transformed before analysis. The model was adjusted by age, sex, education level, marital status, PIR, race, obesity, smoking, drinking, hypertension, diabetes, and hyperlipidemia.

图表, 条形图

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**Figure S3.** Weighted values of urinary metals for CKM in WQS models. All metals were ln-transformed before analysis. Models were adjusted for age, sex, education level, marital status, PIR, race, obesity, smoking, drinking, hypertension, diabetes, and hyperlipidemia.

图表

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**Figure S4.** The qgcomp model weights of the urinary metals for CKM. Note: Ba, barium; Cd, cadmium; Co, cobalt; Cs, cesium; Mo, molybdenum; Pb, lead; Sb, antimony; Tl, thallium; W, tungsten. All metals were ln-transformed before analysis. The model was adjusted by age, sex, education level, marital status, PIR, race, obesity, smoking, drinking, hypertension, diabetes, and hyperlipidemia.

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**Figure S5.** Subgroup analysis between urinary metals and CKM. A, Cd - CKM; B, Co - CKM; C, Pb - CKM; D, W - CKM. ORs were calculated each standard deviation increased in metals. All metals were ln-transformed before analysis. Analyses were adjusted for age, sex, education level, marital status, PIR, race, obesity, smoking, drinking, hypertension, diabetes, and hyperlipidemia.