**Supplemental Table 1** List of prescription medications used as exclusion criteria for spot urine caffeine and caffeine metabolites in U.S. persons ≥6 y, NHANES 2009–2010

|  |  |
| --- | --- |
| **Prescription medication** | **Participants reporting use in last 30 d[[1]](#footnote-1)** |
|  | *n* |
| Amiodarone | 3 |
| Bupropion | 20 |
| Cimetidine | 2 |
| Ciprofoxacin | 6 |
| Diltiazem | 21 |
| Duloxetine | 15 |
| Efavirenz | 2 |
| Erythromycin | 4 |
| Fluoxetine | 24 |
| Gemfibrozil | 8 |
| Insulin | 16 |
| Isoniazid | 5 |
| Ketoconazole | 1 |
| Omeprazole | 103 |
| Paroxetine | 15 |
| Ritonavir | 2 |
| Sulfamethoxazole | 7 |
| Terbinafine | 1 |
| Verapamil | 18 |

**Supplemental Table 2** Sample sizes for spot urine caffeine and caffeine metabolites by demographic variables and categorical caffeine intake for U.S. persons ≥6 y, NHANES 2009–2010[[2]](#footnote-2)

|  |  |  |
| --- | --- | --- |
| Variable | Spot urine concentration | Spot urine excretion rate |
|  | *n* | |
| All | 2466 | 2261 |
| Demographic |  |  |
| Age (y) |  |  |
| 6–11 | 377 | 324 |
| 12–19 | 385 | 348 |
| 20–39 | 586 | 547 |
| 40–59 | 600 | 557 |
| ≥60 | 518 | 485 |
| Sex |  |  |
| Male | 1215 | 1113 |
| Female | 1251 | 1148 |
| Race-ethnicity |  |  |
| All Hispanic | 826 | 737 |
| Non-Hispanic white | 1042 | 978 |
| Non-Hispanic black | 460 | 418 |
| Caffeine intake[[3]](#footnote-3) |  |  |
| Quartile |  |  |
| 1st | 720 | 655 |
| 2nd | 656 | 582 |
| 3rd | 560 | 527 |
| 4th | 434 | 412 |

**Supplemental Table 3** Limits of detection and detection frequency for spot urine caffeine and caffeine metabolites in U.S. persons ≥6 y, NHANES 2009–2010[[4]](#footnote-4)

|  |  |  |  |
| --- | --- | --- | --- |
| **Analyte** | **LOD** | **Samples <LOD** | **Detection frequency** |
|  | *µmol/L* | *n* | *%* |
| Trimethylxanthines |  |  |  |
| Caffeine (137X) | 0.1 | 251 | 90.8 |
| Trimethyluric acids |  |  |  |
| 137U | 0.05 | 316 | 88.4 |
| Dimethylxanthines |  |  |  |
| Theophylline (13X) | 0.05 | 196 | 92.8 |
| Paraxanthine (17X) | 0.1 | 118 | 95.7 |
| Theobromine (37X) | 0.05 | 27 | 99.0 |
| Dimethyluric acids |  |  |  |
| 13U | 0.05 | 86 | 96.8 |
| 17U | 0.05 | 81 | 97.0 |
| 37U | 0.05 | 171 | 93.7 |
| Methylxanthines |  |  |  |
| 1X | 0.05 | 0 | 100 |
| 3X | 0.05 | 17 | 99.4 |
| 7X | 0.05 | 6 | 99.8 |
| Methyluric acids |  |  |  |
| 1U | 0.05 | 0 | 100 |
| 3U | 0.1 | 538 | 80.2 |
| 7U | 0.1 | 35 | 98.7 |
| Uracils |  |  |  |
| AAMU | 0.1 | 67 | 97.5 |

**Supplemental Table 4** Spot urine caffeine and caffeine metabolite excretion rates in U.S. persons aged ≥6 y, NHANES 2009–2010[[5]](#footnote-5)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Analyte** | **Geometric mean (95% CI)** | **Median (95% CI)** | **95% reference interval** | |
| **2.5th percentile (95% CI)** | **97.5th percentile (95% CI)** |
|  | *nmol/min* | | | |
| Trimethylxanthines | | | | |
| Caffeine (137X) | 1.81 (1.57–2.08) | 2.51 (1.97–2.92) | 0.026 (0.019–0.031) | 49.4 (42.3–60.6) |
| Trimethyluric acids | | | | |
| 137U | 0.763 (0.675–0.863) | 1.07 (0.907–1.26) | 0.014 (0.011–0.016) | 13.9 (11.9–19.8) |
| Dimethylxanthines | | | | |
| Theophylline (13X) | 0.872 (0.796–0.955) | 1.18 (1.05–1.41) | 0.016 (0.014–0.022) | 13.6 (11.4–14.5) |
| Paraxanthine (17X) | 7.47 (6.73–8.29) | 10.6 (9.52–12.4) | 0.048 (0.044–0.068) | 123 (102–141) |
| Theobromine (37X) | 12.4 (11.4–13.5) | 15.9 (14.0–17.8) | 0.178 (0.112–0.281) | 146 (130–171) |
| Dimethyluric acids | | | | |
| 13U | 3.51 (3.17–3.89) | 5.18 (4.75–5.59) | 0.042 (0.030–0.051) | 47.9 (42.7–58.3) |
| 17U | 12.2 (11.0–13.6) | 19.8 (18.2–21.6) | 0.056 (0.045–0.071) | 179 (157–212) |
| 37U | 0.784 (0.714–0.861) | 0.916 (0.842–10.02) | 0.023 (0.018–0.027) | 9.29 (8.31–10.4) |
| Methylxanthines | | | | |
| 1X | 17.1 (15.4–19.0) | 21.7 (19.0–25.3) | 0.512 (0.392–0.653) | 237 (194–336) |
| 3X | 19.2 (17.5–21.0) | 23.7 (21.4–26.5) | 0.330 (0.192–0.487) | 203 (180–225) |
| 7X | 31.4 (28.6–34.3) | 37.6 (33.9–41.9) | 0.590 (0.343–0.830) | 356 (308–400) |
| Methyluric acids | | | | |
| 1U | 39.4 (35.8–43.4) | 46.0 (40.7–50.2) | 2.43 (1.65–3.17) | 455 (365–591) |
| 3U | 0.390 (0.357–0.426) | 0.423 (0.385–0.468) | 0.019 (0.018–0.022) | 4.86 (4.19–5.92) |
| 7U | 9.73 (8.90–10.7) | 11.2 (9.94–12.7) | 0.209 (0.145–0.259) | 124 (111–135) |
| Uracils | | | | |
| AAMU | 27.3 (24.8–30.1) | 40.1 (35.6–44.9) | 0.167 (0.104–0.293) | 428 (389–533) |

**Supplemental Table 5** Spot urine caffeine and caffeine metabolite excretion rates by sex and race-ethnicity for U.S. persons aged ≥6 y, NHANES 2009–2010[[6]](#footnote-6)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Analyte** | **Sex** | | | **Race-ethnicity** | | | |
| **Male** (*n* = 1113) | **Female** (*n* = 1148) | **Wald F *P* value** | **NHW** (*n* = 978) | **NHB** (*n* = 418) | **All Hispanics** (*n* = 737) | **Wald F *P* value** |
|  | *nmol/min* | *nmol/min* |  | *nmol/min* | *nmol/min* | *nmol/min* |  |
| Trimethylxanthines | | | | | | | |
| Caffeine (137X) | 1.96 (1.76–2.19) | 1.67 (1.36–2.06) | 0.082 | 2.33 (1.90–2.86) | 0.764 (0.637–0.917) | 1.21 (1.01–1.47) | <0.0001 |
| Trimethyluric acids | | | | | | | |
| 137U | 0.858 (0.762–0.967) | .682 (.571–0.815) | 0.0159 | 0.981 (0.820–1.17) | 0.370 (0.308–0.443) | 0.500 (0.417–0.598) | <0.0001 |
| Dimethylxanthines | | | | | | | |
| Theophylline (13X) | 0.979 (0.908–1.06) | 0.780 (0.675–0.900) | 0.004 | 1.08 (0.936–1.25) | 0.398 (0.333–0.475) | 0.668 (0.563–0.793) | <0.0001 |
| Paraxanthine (17X) | 9.02 (8.28–9.82) | 6.23 (5.30–7.33) | 0.0001 | 9.18 (7.75–10.9) | 3.45 (2.72–4.37) | 5.58 (4.77–6.53) | <0.0001 |
| Theobromine (37X) | 13.1 (11.9–14.4) | 11.8 (10.0–13.8) | 0.29 | 15.9 (13.9–18.1) | 6.16 (5.07–7.48) | 8.14 (6.77–9.78) | <0.0001 |
| Dimethyluric acids | | | | | | | |
| 13U | 4.20 (3.78–4.66) | 2.96 (2.57–3.40) | <0.0001 | 4.77 (4.14–5.50) | 1.53 (1.23–1.91) | 2.11 (1.81–2.46) | <0.0001 |
| 17U | 13.8 (12.4–15.3) | 10.9 (9.26–12.7) | 0.0065 | 16.7 (14.4–19.3) | 4.94 (3.78–6.46) | 7.45 (6.25–8.88) | <0.0001 |
| 37U | 0.873 (0.799–0.955) | 0.707 (0.609–0.820) | 0.0123 | 1.05 (0.912–1.20) | 0.423 (0.366–0.488) | 0.437 (0.361–0.529) | <0.0001 |
| Methylxanthines | | | | | | | |
| 1X | 21.5 (19.5–23.6) | 13.7 (11.9–15.9) | <0.0001 | 22.3 (19.3–25.8) | 9.37 (7.79–11.3) | 9.90 (8.72–11.2) | <0.0001 |
| 3X | 20.1 (18.1–22.3) | 18.3 (16.0–21.0) | 0.24 | 27.4 (24.4–30.8) | 8.78 (7.20–10.7) | 9.70 (8.28–11.4) | <0.0001 |
| 7X | 35.6 (32.0–39.6) | 27.7 (24.3–31.6) | 0.0035 | 43.5 (38.7–48.8) | 16.5 (13.6–20.1) | 15.6 (13.3–18.2) | <0.0001 |
| Methyluric acids | | | | | | | |
| 1U | 49.1 (44.5–54.3) | 31.9 (28.4–35.8) | <0.0001 | 50.6 (44.3–57.7) | 24.4 (20.9–28.4) | 22.2 (19.9–24.7) | <0.0001 |
| 3U | 0.421 (0.378–0.468) | 0.362 (0.320–0.410) | 0.0478 | 0.562 (0.498–0.634) | 0.188 (0.160–0.220) | 0.189 (0.159–0.224) | <0.0001 |
| 7U | 10.7 (9.63–11.9) | 8.89 (7.84–10.1) | 0.0166 | 13.9 (12.6–15.4) | 4.78 (3.96–5.77) | 4.52 (3.81–5.37) | <0.0001 |
| Uracils | | | | | | | |
| AAMU | 33.9 (30.3–38.0) | 22.2 (19.4–25.3) | <0.0001 | 36.8 (32.3–41.9) | 11.4 (8.53–15.2) | 16.4 (13.9–19.3) | <0.0001 |

**Supplemental Table 6** Spot urine caffeine and caffeine metabolite excretion rates by age for U.S. persons aged ≥6 y, NHANES 2009–2010[[7]](#footnote-7)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Analyte** | **6–11 y** (*n* = 324) | **12–19 y** (*n* = 348) | **20–39 y** (*n* = 547) | **40–59 y** (*n* = 557) | **≥60 y** (*n* = 485) | **Wald F *P* value** |
|  | *nmol/min* | *nmol/min* | *nmol/min* | *nmol/min* | *nmol/min* |  |
| Trimethylxanthines | | | | | | |
| Caffeine (137X) | 0.213 (0.161–0.282) | 0.521 (0.390–0.695) | 2.15 (1.85–2.48) | 4.00 (3.22–4.97) | 2.57 (2.16–3.07) | <0.0001 |
| Trimethyluric acids | | | | | | |
| 137U | 0.107 (0.082–0.138) | 0.283 (0.218–0.367) | 0.928 (0.805–1.07) | 1.51 (1.22–1.85) | 0.964 (0.796–1.17) | <0.0001 |
| Dimethylxanthines | | | | | | |
| Theophylline (13X) | 0.138 (0.111–0.170) | 0.327 (0.265–0.402) | 1.07 (0.919–1.25) | 1.74 (1.50–2.01) | 0.991 (0.860–1.14) | <0.0001 |
| Paraxanthine (17X) | 1.20 (.929–1.55) | 2.98 (2.27–3.89) | 9.25 (7.94–10.8) | 15.1 (12.9–17.7) | 7.75 (6.60–9.10) | <0.0001 |
| Theobromine (37X) | 10.1 (7.89–13.0) | 11.9 (9.66–14.6) | 11.6 (10.1–13.3) | 16.5 (14.2–19.1) | 9.83 (8.51–11.4) | <0.0001 |
| Dimethyluric acids | | | | | | |
| 13U | 0.517 (0.422–0.632) | 1.33 (1.04–1.71) | 4.16 (3.53–4.91) | 6.90 (5.93–8.01) | 4.48 (3.80–5.28) | <0.0001 |
| 17U | 1.45 (1.16–1.83) | 4.42 (3.40–5.76) | 14.0 (11.8–16.6) | 25.7 (21.5–30.8) | 16.8 (14.2–19.8) | <0.0001 |
| 37U | 0.600 (0.488–0.737) | 0.802 (0.640–10.00) | 0.752 (0.646–0.876) | 0.988 (0.844–1.16) | 0.644 (0.565–0.734) | <0.0001 |
| Methylxanthines | | | | | | |
| 1X | 3.85 (3.11–4.77) | 8.11 (6.42–10.3) | 21.3 (18.4–24.6) | 30.8 (27.0–35.2) | 15.9 (13.8–18.4) | <0.0001 |
| 3X | 13.7 (10.9–17.1) | 17.0 (13.8–20.9) | 17.4 (14.9–20.3) | 25.5 (21.7–30.0) | 18.2 (16.1–20.5) | <0.0001 |
| 7X | 28.2 (22.3–35.7) | 32.5 (25.7–41.2) | 29.3 (25.1–34.3) | 39.4 (34.5–45.1) | 24.6 (21.4–28.3) | <0.0001 |
| Methyluric acids | | | | | | |
| 1U | 9.99 (8.26–12.1) | 19.9 (16.0–24.6) | 44.3 (38.7–50.7) | 64.7 (57.6–72.6) | 46.1 (40.7–52.3) | <0.0001 |
| 3U | 0.258 (0.220–0.302) | 0.307 (0.255–0.369) | 0.337 (0.289–0.393) | 0.510 (0.430–0.605) | 0.464 (0.412–0.522) | <0.0001 |
| 7U | 8.55 (7.04–10.4) | 9.19 (7.37–11.5) | 7.65 (6.53–8.97) | 12.7 (11.0–14.7) | 10.5 (9.16–12.0) | <0.0001 |
| Uracils | | | | | | |
| AAMU | 4.07 (3.34–4.95) | 11.0 (8.12–15.0) | 31.4 (26.2–37.7) | 54.7 (47.6–62.9) | 33.6 (28.9–39.1) | <0.0001 |

**Supplemental Table 7** Associations between spot urine caffeine and caffeine metabolite excretion rates and dietary caffeine intake in U.S. persons aged ≥6 y, NHANES 2009–2010[[8]](#footnote-8),[[9]](#footnote-9)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Analyte** | **Spearman correlation[[10]](#footnote-10)** | **Caffeine intake quartile[[11]](#footnote-11)** | | | |
| **Q1[0–8]** (*n* = 655) | **Q2 [9–84]** (*n* = 582) | **Q3 [85–213]**(*n* = 527) | **Q4 [214–3020]**(*n* = 412) |
|  | |*r*| | *nmol/min* | | | |
| Trimethylxanthines | | | | | |
| Caffeine (137X) | 0.59 | 0.323 (0.259–0.404) | 1.12 (.957–1.32) | 3.50 (3.03–4.04) | 7.04 (6.40–7.74) |
| Trimethyluric acids | | | | | |
| 137U | 0.60 | 0.146 (0.123–0.174) | 0.497 (0.415–0.593) | 1.47 (1.27–1.70) | 2.72 (2.41–3.07) |
| Dimethylxanthines | | | | | |
| Theophylline (13X) | 0.64 | 0.171 (0.148–0.199) | 0.601 (0.514–0.702) | 1.63 (1.49–1.77) | 2.94 (2.68–3.22) |
| Paraxanthine (17X) | 0.62 | 1.22 (.996–1.49) | 5.41 (4.58–6.39) | 14.5 (13.1–15.9) | 27.2 (24.1–30.7) |
| Theobromine (37X) | 0.24 | 6.23 (4.99–7.78) | 11.8 (9.97–13.9) | 14.4 (12.5–16.7) | 20.8 (18.9–22.9) |
| Dimethyluric acids | | | | | |
| 13U | 0.68 | 0.612 (0.517–0.725) | 2.48 (2.06–2.99) | 6.75 (6.22–7.34) | 12.6 (11.4–14.0) |
| 17U | 0.66 | 1.71 (1.40–2.08) | 9.14 (7.63–11.0) | 25.1 (22.9–27.5) | 47.7 (42.3–53.8) |
| 37U | 0.24 | 0.450 (0.382–0.531) | 0.710 (0.587–0.858) | 0.877 (0.762–10.01) | 1.28 (1.13–1.45) |
| Methylxanthines | | | | | |
| 1X | 0.65 | 3.84 (3.34–4.40) | 11.9 (10.0–14.1) | 28.4 (25.8–31.2) | 56.7 (48.9–65.7) |
| 3X | 0.30 | 8.84 (7.10–11.0) | 18.0 (15.1–21.5) | 23.1 (20.5–26.0) | 34.7 (31.6–38.0) |
| 7X | 0.27 | 15.6 (12.5–19.5) | 29.3 (24.3–35.3) | 35.8 (31.8–40.3) | 55.5 (49.8–61.8) |
| Methyluric acids | | | | | |
| 1U | 0.65 | 12.0 (11.0–13.2) | 26.7 (22.9–31.3) | 58.9 (54.3–63.9) | 112 (98.1–128) |
| 3U | 0.33 | 0.216 (0.185–0.253) | 0.318 (0.262–0.387) | 0.455 (0.402–0.514) | 0.705 (0.637–0.781) |
| 7U | 0.29 | 4.81 (3.93–5.88) | 9.11 (7.58–10.9) | 10.9 (9.65–12.4) | 17.7 (15.8–19.8) |
| Uracils | | | | | |
| AAMU | 0.67 | 4.20 (3.43–5.13) | 20.4 (16.6–25.2) | 51.6 (47.1–56.5) | 105 (93.3–118) |

**Supplemental Table 8** Pairwise t-test *P* values among geometric mean spot urine caffeine and caffeine metabolite concentrations and excretion rates by caffeine intake quartiles in U.S. persons aged ≥6 y, NHANES 2009–2010[[12]](#footnote-12)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Pairwise t-test comparison of geometric means by caffeine intake quartile** | | | | | |
| **Variable** | **Analyte** | **Q1 vs. Q2** | **Q1 vs. Q3** | **Q1 vs. Q4** | **Q2 vs. Q3** | **Q2 vs Q4** | **Q3 vs. Q4** |
|  |  | *P value* | | | | | |
| Concentration | Caffeine | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  | 137U | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0001 |
|  | Theophylline | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  | Paraxanthine | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  | Theobromine | <0.0001 | 0.0002 | <0.0001 | 0.95 | 0.0009 | 0.0322 |
|  | 13U | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  | 17U | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0001 |
|  | 37U | 0.0001 | 0.0007 | <0.0001 | 0.90 | 0.0100 | 0.0289 |
|  | 1X | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0001 |
|  | 3X | <0.0001 | <0.0001 | <0.0001 | 0.55 | 0.0004 | 0.004 |
|  | 7X | <0.0001 | 0.0001 | <0.0001 | 0.87 | 0.0007 | 0.0036 |
|  | 1U | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0001 |
|  | 3U | 0.0020 | <0.0001 | <0.0001 | 0.09 | 0.0001 | 0.0041 |
|  | 7U | 0.0001 | 0.0001 | <0.0001 | 0.86 | 0.0006 | 0.0064 |
|  | AAMU | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  |  |  |  |  |  |  |  |
| Excretion rate | Caffeine | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  | 137U | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  | Theophylline | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  | Paraxanthine | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  | Theobromine | 0.0001 | <0.0001 | <0.0001 | 0.0411 | <0.0001 | 0.0003 |
|  | 13U | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  | 17U | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  | 37U | 0.0013 | <0.0001 | <0.0001 | 0.0393 | <0.0001 | 0.0001 |
|  | 1X | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  | 3X | 0.0001 | <0.0001 | <0.0001 | 0.0175 | <0.0001 | <0.0001 |
|  | 7X | 0.0002 | <0.0001 | <0.0001 | 0.0490 | <0.0001 | <0.0001 |
|  | 1U | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
|  | 3U | 0.0119 | <0.0001 | <0.0001 | 0.0013 | <0.0001 | <0.0001 |
|  | 7U | 0.0001 | <0.0001 | <0.0001 | 0.08 | <0.0001 | <0.0001 |
|  | AAMU | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

**Supplemental Table 9**  Spearman correlation coefficients describing bivariate associations among spot urine caffeine and caffeine metabolite concentrations for U.S. persons aged ≥6 y, NHANES 2009–2010[[13]](#footnote-13)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 137X | 137U | 13X | 17X | 37X | 13U | 17U | 37U | 1X | 3X | 7X | 1U | 3U | 7U | AAMU |
| 137X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 137U | 0.92 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 13X | 0.90 | 0.90 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 17X | 0.89 | 0.90 | 0.96 |  |  |  |  |  |  |  |  |  |  |  |  |
| 37X | 0.34 | 0.41 | 0.42 | 0.44 |  |  |  |  |  |  |  |  |  |  |  |
| 13U | 0.80 | 0.91 | 0.91 | 0.88 | 0.41 |  |  |  |  |  |  |  |  |  |  |
| 17U | 0.86 | 0.94 | 0.93 | 0.91 | 0.42 | 0.97 |  |  |  |  |  |  |  |  |  |
| 37U | 0.27 | 0.44 | 0.37 | 0.37 | 0.91 | 0.50 | 0.47 |  |  |  |  |  |  |  |  |
| 1X | 0.77 | 0.87 | 0.86 | 0.88 | 0.42 | 0.94 | 0.93 | 0.49 |  |  |  |  |  |  |  |
| 3X | 0.30 | 0.44 | 0.41 | 0.38 | 0.87 | 0.53 | 0.51 | 0.94 | 0.52 |  |  |  |  |  |  |
| 7X | 0.22 | 0.38 | 0.33 | 0.36 | 0.88 | 0.48 | 0.45 | 0.95 | 0.51 | 0.96 |  |  |  |  |  |
| 1U | 0.72 | 0.84 | 0.82 | 0.84 | 0.41 | 0.95 | 0.92 | 0.51 | 0.96 | 0.55 | 0.53 |  |  |  |  |
| 3U | 0.32 | 0.46 | 0.41 | 0.37 | 0.78 | 0.56 | 0.53 | 0.89 | 0.53 | 0.95 | 0.90 | 0.58 |  |  |  |
| 7U | 0.25 | 0.40 | 0.35 | 0.36 | 0.85 | 0.50 | 0.48 | 0.92 | 0.49 | 0.95 | 0.95 | 0.56 | 0.92 |  |  |
| AAMU | 0.73 | 0.83 | 0.84 | 0.84 | 0.39 | 0.94 | 0.92 | 0.47 | 0.88 | 0.51 | 0.49 | 0.90 | 0.53 | 0.51 |  |

**Supplemental Table 10**  Spearman correlation coefficients describing bivariate associations among spot urine caffeine and caffeine metabolite excretion rates for U.S. persons aged ≥6 y, NHANES 2009–2010[[14]](#footnote-14)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 137X | 137U | 13X | 17X | 37X | 13U | 17U | 37U | 1X | 3X | 7X | 1U | 3U | 7U | AAMU |
| 137X |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 137U | 0.94 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 13X | 0.93 | 0.91 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 17X | 0.93 | 0.91 | 0.97 |  |  |  |  |  |  |  |  |  |  |  |  |
| 37X | 0.53 | 0.52 | 0.57 | 0.59 |  |  |  |  |  |  |  |  |  |  |  |
| 13U | 0.86 | 0.92 | 0.93 | 0.91 | 0.52 |  |  |  |  |  |  |  |  |  |  |
| 17U | 0.91 | 0.95 | 0.94 | 0.93 | 0.53 | 0.97 |  |  |  |  |  |  |  |  |  |
| 37U | 0.42 | 0.50 | 0.47 | 0.48 | 0.92 | 0.54 | 0.52 |  |  |  |  |  |  |  |  |
| 1X | 0.84 | 0.89 | 0.89 | 0.91 | 0.53 | 0.95 | 0.94 | 0.54 |  |  |  |  |  |  |  |
| 3X | 0.47 | 0.52 | 0.52 | 0.51 | 0.89 | 0.58 | 0.57 | 0.94 | 0.58 |  |  |  |  |  |  |
| 7X | 0.39 | 0.45 | 0.45 | 0.48 | 0.90 | 0.53 | 0.51 | 0.96 | 0.57 | 0.96 |  |  |  |  |  |
| 1U | 0.82 | 0.87 | 0.88 | 0.89 | 0.53 | 0.96 | 0.94 | 0.55 | 0.97 | 0.60 | 0.58 |  |  |  |  |
| 3U | 0.47 | 0.53 | 0.52 | 0.49 | 0.81 | 0.61 | 0.57 | 0.89 | 0.58 | 0.95 | 0.90 | 0.63 |  |  |  |
| 7U | 0.41 | 0.47 | 0.46 | 0.47 | 0.86 | 0.55 | 0.53 | 0.92 | 0.55 | 0.95 | 0.95 | 0.60 | 0.91 |  |  |
| AAMU | 0.81 | 0.86 | 0.87 | 0.88 | 0.48 | 0.95 | 0.93 | 0.50 | 0.89 | 0.55 | 0.52 | 0.91 | 0.56 | 0.54 |  |

1. A total of 273 instances of a drug identified as either an inducer or inhibitor of any enzyme involved in any stage of caffeine metabolism were identified among a total of 246 individuals. There were also 2 individuals who did not know whether or not they were taking prescription medications who were also excluded from our analyses. [↑](#footnote-ref-1)
2. Individuals who reported using any prescription medications known to inhibit or induce cytochrome P450, N-acetyltransferase 2 or xanthine oxidase activity in the past 30 d were excluded. [↑](#footnote-ref-2)
3. Total 24-h caffeine intake from diet and dietary supplements [↑](#footnote-ref-3)
4. 137U, 1,3,7-trimethyluric acid; 13U, 1,3-dimethyluric acid; 17U, 1,7-dimethyluric acid; 1U, 1-methyluric acid; 1X, 1-methylxanthine; 37U, 3,7-dimethyluric acid; 37X, 3,7-dimethylxanthine; 3U, 3-methyluric acid; 3X, 3-methylxanthine; 7U, 7-methyluric acid; 7X, 7-methylxanthine; AAMU, 5-acetylamino-6-amino-3-methyluracil. [↑](#footnote-ref-4)
5. *n* = 2261. Individuals who reported using any prescription medications known to inhibit or induce cytochrome P450, N-acetyltransferase 2 or xanthine oxidase activity in the past 30 d were excluded. 137U, 1,3,7-trimethyluric acid; 13U, 1,3-dimethyluric acid; 17U, 1,7-dimethyluric acid; 1U, 1-methyluric acid; 1X, 1-methylxanthine; 37U, 3,7-dimethyluric acid; 37X, 3,7-dimethylxanthine; 3U, 3-methyluric acid; 3X, 3-methylxanthine; 7U, 7-methyluric acid; 7X, 7-methylxanthine; AAMU, 5-acetylamino-6-amino-3-methyluracil. [↑](#footnote-ref-5)
6. Values are geometric means (95% CIs). Individuals who reported using any prescription medications known to inhibit or induce cytochrome P450, N-acetyltransferase 2 or xanthine oxidase activity in the past 30 d were excluded. 137U, 1,3,7-trimethyluric acid; 13U, 1,3-dimethyluric acid; 17U, 1,7-dimethyluric acid; 1U, 1-methyluric acid; 1X, 1-methylxanthine; 37U, 3,7-dimethyluric acid; 37X, 3,7-dimethylxanthine; 3U, 3-methyluric acid; 3X, 3-methylxanthine; 7U, 7-methyluric acid; 7X, 7-methylxanthine; AAMU, 5-acetylamino-6-amino-3-methyluracil; NHB, non-Hispanic black; NHW, non-Hispanic white. [↑](#footnote-ref-6)
7. Values are geometric means (95% CIs). Individuals who reported using any prescription medications known to inhibit or induce cytochrome P450, N-acetyltransferase 2 or xanthine oxidase activity in the past 30 d were excluded. 137U, 1,3,7-trimethyluric acid; 13U, 1,3-dimethyluric acid; 17U, 1,7-dimethyluric acid; 1U, 1-methyluric acid; 1X, 1-methylxanthine; 37U, 3,7-dimethyluric acid; 37X, 3,7-dimethylxanthine; 3U, 3-methyluric acid; 3X, 3-methylxanthine; 7U, 7-methyluric acid; 7X, 7-methylxanthine; AAMU, 5-acetylamino-6-amino-3-methyluracil. [↑](#footnote-ref-7)
8. Values are geometric means (95% CIs). Individuals who reported using any prescription medications known to inhibit or induce cytochrome P450, N-acetyltransferase 2 or xanthine oxidase activity in the past 30 d were excluded. 137U, 1,3,7-trimethyluric acid; 13U, 1,3-dimethyluric acid; 17U, 1,7-dimethyluric acid; 1U, 1-methyluric acid; 1X, 1-methylxanthine; 37U, 3,7-dimethyluric acid; 37X, 3,7-dimethylxanthine; 3U, 3-methyluric acid; 3X, 3-methylxanthine; 7U, 7-methyluric acid; 7X, 7-methylxanthine; AAMU, 5-acetylamino-6-amino-3-methyluracil. [↑](#footnote-ref-8)
9. *P* values for pairwise t-tests among intake quartiles appear in Supplemental Table 8 [↑](#footnote-ref-9)
10. *n* = 2176, *P* <0.0001 in all cases. [↑](#footnote-ref-10)
11. Total 24-h caffeine intake from diet and dietary supplements in mg/d. [↑](#footnote-ref-11)
12. Individuals who reported using any prescription medications known to inhibit or induce cytochrome P450, N-acetyltransferase 2 or xanthine oxidase activity in the past 30 d were excluded. Spot urine concentration data and sample sizes appear in Table 4. Excretion rate data and sample sizes appear in Supplemental Table 7. 137U, 1,3,7-trimethyluric acid; 13U, 1,3-dimethyluric acid; 17U, 1,7-dimethyluric acid; 1U, 1-methyluric acid; 1X, 1-methylxanthine; 37U, 3,7-dimethyluric acid; 37X, 3,7-dimethylxanthine; 3U, 3-methyluric acid; 3X, 3-methylxanthine; 7U, 7-methyluric acid; 7X, 7-methylxanthine; AAMU, 5-acetylamino-6-amino-3-methyluracil. [↑](#footnote-ref-12)
13. *n* = 2466, *P* <0.0001 in all cases. 137U, 1,3,7-trimethyluric acid; 137X, caffeine (1,3,7-trimethylxanthine); 13U, 1,3-dimethyluric acid; 13X, theophylline (1,3-dimethylxanthine); 17U, 1,7-dimethyluric acid; 17X, paraxanthine (1,7-dimethylxanthine); 1U, 1-methyluric acid; 1X, 1-methylxanthine; 37U, 3,7-dimethyluric acid; 37X, theobromine (3,7-dimethylxanthine); 3U, 3-methyluric acid; 3X, 3-methylxanthine; 7U, 7-methyluric acid; 7X, 7-methylxanthine; AAMU, 5-acetylamino-6-amino-3-methyluracil. [↑](#footnote-ref-13)
14. *n* = 2261, *P* <0.0001 in all cases. 137U, 1,3,7-trimethyluric acid; 137X, caffeine (1,3,7-trimethylxanthine); 13U, 1,3-dimethyluric acid; 13X, theophylline (1,3-dimethylxanthine); 17U, 1,7-dimethyluric acid; 17X, paraxanthine (1,7-dimethylxanthine); 1U, 1-methyluric acid; 1X, 1-methylxanthine; 37U, 3,7-dimethyluric acid; 37X, theobromine (3,7-dimethylxanthine); 3U, 3-methyluric acid; 3X, 3-methylxanthine; 7U, 7-methyluric acid; 7X, 7-methylxanthine; AAMU, 5-acetylamino-6-amino-3-methyluracil. [↑](#footnote-ref-14)