39156 in the NHANES 2011-2018

Excluded n= 15664

Age<18 years: n= 15331

Being Pregnant: n= 247

Under dialysis: n= 86

Excluded n= 4735

Missing eGFR: n= 2456

Missing urine albumin-to-creatinine ratio: n= 284

Missing folate forms: n= 1995

23492 included in the analysis

18757 included in the analysis

**Supplement Figure 1. Flow chart of the participants in the current analysis**

**Supplementary Table 1.** Concentrations of serum folate forms in the US adult population ≥18 y by survey period, NHANES 2011–2018

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Analyte** | **NHANES survey period** | | | |
| **2011**–**2012** | **2013**–**2014** | **2015**–**2016** | **2017-2018\*** |
| **5-mTHF** |  |  |  |  |
| Sample size, *n* | 5134 | 5657 | 5408 | 3268 |
| Response rates, % | 91.4 | 95.5 | 94.3 | 94.5 |
| Range, nmol/L | 1.88-295.00 | 3.03-331.00 | 3.16-1370.00 | 2.28-331.00 |
| Median (Q1, Q3), nmol/L | 34.10 (23.10-50.30) | 36.40 (24.80-52.60) | 33.60 (23.10-48.70) | 31.80 (21.90-48.12) |
| **UMFA** |  |  |  |  |
| Sample size, *n* | 5134 | 5657 | 5400 | 3268 |
| Response rates | 91.4 | 95.5 | 94.2 | 94.5 |
| Range, nmol/L | 0.06-195 | 0.14-1010.00 | 0.10-418.00 | 0.10-368.00 |
| Median (Q1, Q3), nmol/L | 0.72（0.53-1.03） | 0.76（0.55-1.17） | 0.62（0.45-0.94） | 0.61（0.46-0.90） |
| **MeFox** |  |  |  |  |
| Sample size, *n* | 5136 | 5657 | 5408 | 3268 |
| Response rates | 91.5 | 95.5 | 94.3 | 94.5 |
| Range, nmol/L | 0.24-20.40 | 0.16-56.30 | 0.07-59.70 | 0.11-48.50 |
| Median (Q1, Q3), nmol/L | 1.48（0.92-2.46） | 1.51（0.97-2.55） | 1.38（0.83-2.37） | 1.22（0.76-48.5） |

**\***In NHANES 2017-2018, folate forms were measured in all examined female participants aged 12-49 years, and in a one-half subsample of other examined participants one year and older.

**Supplementary Table 2. Supplement stratified analysis for 5-methyltetrahydrofolate (5-mTHF).\***

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Reduced eGFR** | | | | **Macroalbuminuria** | | | |
| **Subgroup** | **Q1-2**  **Prevalence (%)** | **Q3-4**  **Prevalence (%)** | **Q3-4 vs Q1-2**  **OR (95%CI)** | ***P*-interaction** | **Q1-2**  **Prevalence (%)** | **Q3-4**  **Prevalence (%)** | **Q3-4 vs Q1-2**  **OR (95%CI)** | ***P-*interaction** |
| Vitamin B12, pmol/L**†** |  |  |  | 0.216 |  |  |  | 0.219 |
| <248 | 64(4.7) | 62(9.9) | 1.18(0.63,2.20) |  | 13(1.0) | 12(1.9) | 1.23(0.39,3.87) |  |
| ≥248 | 251(5.7) | 454(8.3) | 0.73(0.55,0.95) |  | 95(1.9) | 83(1.2) | 0.54(0.34,0.85) |  |
| Use of folic acid-containing supplements |  |  |  | 0.667 |  |  |  | 0.146 |
| No | 500(5.3) | 383(5.9) | 0.73(0.56,0.95) |  | 174(1.6) | 105(1.2) | 0.66(0.46,0.95) |  |
| Yes | 40(6.0) | 374(9.4) | 0.63(0.34,1.18) |  | 16(4.0) | 55(1.2) | 0.31(0.12,0.82) |  |
| Fasting |  |  |  | 0.477 |  |  |  | 0.703 |
| No | 328(5.9) | 460(8.1) | 0.75(0.59,0.96) |  | 107(2.0) | 90(1.3) | 0.69(0.39,1.19) |  |
| Yes | 275(5.0) | 375(6.8) | 0.66(0.49,0.89) |  | 108(1.7) | 93(1.3) | 0.61(0.43,0.86) |  |
| Reduced eGFR |  |  |  | **-** |  |  |  | 0.794 |
| No | - | - | - |  | 118(1.2) | 101(0.8) | 0.66(0.40,1.07) |  |
| Yes | - | - | - |  | 97(14.0) | 82(8.9) | 0.71(0.45,1.14) |  |
| Urinary albumin-to-creatinine ratio, mg/g |  |  |  | 0.606 |  |  |  | - |
| <30 | 380(4.2) | 536(5.9) | 0.70(0.56,0.87) |  | - | - | - |  |
| ≥30 | 223(17.4) | 299(21.7) | 0.78(0.51,1.18) |  | - | - | - |  |

**\***All estimates accounted for complex survey designs. Binomial regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), and maximum likelihood ratio was used to calculate *P* value for interaction. Analysis was adjusted for age (continuous), sex, BMI (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), education level (less than high school, high school or equivalent, and college or above), smoking status (never, past, and current), history of diabetes (no and yes) and hypertension (no and yes), total cholesterol (continuous), high-density lipoprotein cholesterol (continuous), and hemoglobin A1c (continuous). Kidney outcomes were binary variable (no and yes) and folate forms were defined as binary variable according to the results of Table 2-3.

**†**Vitamin B12 was only available for NHANES 2011-2014, and the analysis was limited to NHANES 2011-2014.

**Supplementary Table 3. Supplement stratified analysis for unmetabolized folic acid (UMFA).\***

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Subgroup** | **Reduced eGFR** | | | | **Macroalbuminuria** | | | |
| Q1  Prevalence (%) | Q2-4  Prevalence (%) | Q2-4 vs Q1  OR (95%CI) | *P*-interaction | Q1-3  Prevalence (%) | Q2  Prevalence (%) | Q4 vs Q1-3  OR (95%CI) | *P*-interaction |
| Vitamin B12, pmol/L |  |  |  | 0.255 |  |  |  | 0.820 |
| <248 | 12(3.1) | 114(7.8) | 1.33(0.46,3.82) |  | 3(1.4) | 22(1.4) | 0.93(0.55,1.59) |  |
| ≥248 | 31(1.8) | 674(8.2) | 2.34(1.26,4.37) |  | 27(1.1) | 151(1.5) | 0.98(0.81,1.18) |  |
| Use of folic acid-containing supplements |  |  |  | 0.004 |  |  |  | 0.260 |
| No | 92(2.2) | 791(7.0) | 2.30(1.49,3.55) |  | 193(1.2) | 86(2.4) | 1.71(1.18,2.47) |  |
| Yes | 4(0.5) | 410(9.5) | 10.26(3.43,30.63) |  | 25(1.6) | 46(1.7) | 0.94(0.38,2.29) |  |
| Fasting |  |  |  | 0.373 |  |  |  | 0.780 |
| No | 39(2.2) | 749(8.4) | 2.48(1.40,4.39) |  | 113(1.3) | 84(2.1) | 1.54(0.91,2.60) |  |
| Yes | 73(2.1) | 577(7.4) | 1.85(1.19,2.87) |  | 132(1.3) | 69(2.3) | 1.42(1.02,1.96) |  |

**\***All estimates accounted for complex survey designs. Binomial regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), and maximum likelihood ratio was used to calculate *P* value for interaction. Analysis was adjusted for age (continuous), sex, BMI (continuous), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others), education level (less than high school, high school or equivalent, and college or above), smoking status (never, past, and current), history of diabetes (no and yes) and hypertension (no and yes), total cholesterol (continuous), high-density lipoprotein cholesterol (continuous), and hemoglobin A1c (continuous). Kidney outcomes were binary variable (no and yes) and folate forms were defined as binary variable according to the results of Table 2-3.

**†**Vitamin B12 was only available for NHANES 2011-2014, and the analysis was limited to NHANES 2011-2014.