**Supplementary Data**

**Supplementary Table S1.** Baseline characteristics of FACT participants with vs. without PTHM measures

|  |  |  |  |
| --- | --- | --- | --- |
|  | PTHMs Measured (*n* = 324) | PTHMs Not Measured (*n* = 285) |  |
| Characteristic | Median (IQR) | Median (IQR) | *P*a |
| Age (years) | 39 (34-44) | 37 (30-45) | 0.05 |
| BMI (kg/m2)b | 19.2 (17.7-21.3) | 19.5 (18.0-21.4) | 0.44 |
| Blood Arsenic (µg/L) | 8.7 (6.0-12.4) | 8.8 (6.3-12.6) | 0.38 |
| bSe (µg/L) | 134 (122-149) | 137 (123-155) | 0.10 |
| RBC Folate (nmol/L)c | 451 (363-603) | 435 (364-562) | 0.55 |
| Plasma Folate (nmol/L) | 12 (9-17) | 15 (11-22) | <0.01 |
| Plasma Vitamin B12 (pmol/L) | 215 (153-319) | 216 (153-298) | 0.58 |
| Plasma Choline (µmol/L) | 11.0 (9.8-13.1) | 11.9 (10.1-13.6) | 0.01 |
| Plasma Betaine (µmol/L) | 43 (34-52) | 45 (34-61) | 0.05 |
| Plasma Hcys (µmol/L) | 11 (9-16) | 11 (8-15) | 0.42 |
| Folate Deficientd (%) | 23.1 | 15.8 | 0.03 |
| Vitamin B12 Deficiente (%) | 24.4 | 23.5 | 0.88 |
| HHcysf (%) | 40.7 | 36.1 | 0.28 |
| Ever Smoker (%) | 28.8 | 25.3 | 0.38 |
| Education > 5 years (%) | 22.5 | 21.4 | 0.12 |
| Own TV (%) | 38.3 | 50.9 | <0.01 |

a*P* was from by Wilcoxon rank-sum test and Chi Square test for difference between those with vs. without PTHM measures for continuous and categorical variables, respectively

b*n* = 315 in those with PTHMs measured, *n* = 284 in those without PTHMs measured

c*n* = 250 in those with PTHMs measured, *n* = 146 in those without PTHMs measured

dPlasma folate < 9 nmol/L

ePlasma vitamin B12 < 151 pmol/L

fPlasma Hcys > 13 µmol/L

**Supplementary Table S2.** Baseline characteristics of FACT participants with vs. without RBC folate measures

|  |  |  |  |
| --- | --- | --- | --- |
|  | RBC Folate Measured (*n* = 250) | RBC Folate Not Measured (*n* = 74) |  |
| Characteristic | Median (IQR) | Median (IQR) | *P*a |
| Age (years) | 39 (33-45) | 38 (34-44) | 0.52 |
| BMI (kg/m2)b | 19.1 (17.7-21.3) | 19.7 (17.8-21.4) | 0.73 |
| Plasma Folate (nmol/L) | 13 (9-17) | 12 (9-17) | 0.81 |
| Plasma Vitamin B12 (pmol/L) | 209 (149-301) | 247 (178-343) | 0.04 |
| Plasma Choline (µmol/L) | 11.0 (9.8-13.0) | 11.3 (9.7-13.2) | 0.64 |
| Plasma Betaine (µmol/L) | 43.2 (34.5-53.0) | 40.5 (33.8-50.8) | 0.49 |
| Plasma Hcys (µmol/L) | 12 (9-16) | 11 (9-14) | 0.21 |
| Blood Arsenic (µg/L) | 8.8 (6.1-12.5) | 8.2 (5.6-11.9) | 0.53 |
| bSe (µg/L) | 134 (122-150) | 134 (117-147) | 0.39 |
| uCr (mg/dL) | 46 (28-72) | 59 (32-98) | 0.04 |
| H3K36me2c, relative % of total H3 | 1.46 (1.26-1.73) | 1.39 (1.26-1.66) | 0.41 |
| H3K36me3d, relative % of total H3 | 1.61 (1.26-1.88) | 1.61 (1.39-1.91) | 0.45 |
| H3K79me2e, relative % of total H3 | 1.25 (1.03-1.75) | 1.32 (1.05-1.86) | 0.52 |
| Folate Deficient (%)f | 23.6 | 21.6 | 0.72 |
| Vitamin B12 Deficient (%)g | 26.0 | 18.9 | 0.21 |
| HHcys (%)h | 41.6 | 37.8 | 0.56 |
| Male (%) | 50.0 | 50.0 | 0.99 |
| Ever Smoker (%) | 26.9 | 35.1 | 0.17 |
| Education > 5 years (%) | 22.8 | 21.6 | 0.83 |
| Own TV (%) | 41.6 | 27.0 | 0.02 |

a*P* was from Wilcoxon rank-sum test and Chi Square test for difference between those with vs. without RBC folate measures for continuous and categorical variables, respectively

b*n* = 245 for those with RBC folate measures, *n* = 70 for those without RBC folate measures

c*n* = 245 for those with RBC folate measures, *n* = 73 for those without RBC folate measures

d*n* = 239 for those with RBC folate measures, *n* = 67 for those without RBC folate measures

e*n* = 249 for those with RBC folate measures, *n* = 72 for those without RBC folate measures

fPlasma folate < 9 nmol/L

gPlasma vitamin B12 < 151 pmol/L

hPlasma Hcys > 13 µmol/L

**Supplementary Table S3**. Associations (β (95% CI)) between OCM indices and PTHMs by sex in FACT participants, comparing models additionally adjusting for BMI

|  |  |  |  |
| --- | --- | --- | --- |
|  | **H3K36me2** | **H3K36me3** | **H3K79me2** |
|  | Malese | Femalesf | Malesg | Femalesh | Malesi | Femalesj |
| Plasma Folatea | -0.02 (-0.12, 0.07) | -0.01 (-0.13, 0.11) | -0.04 (-0.13, 0.05) | -0.02 (-0.15, 0.11) | -0.02 (-0.13, 0.10) | -0.10 (-0.27, 0.06) |
| Plasma Folateb | -0.04 (-0.14, 0.05) | 0.00 (-0.11, 0.12) | -0.05 (-0.14, 0.04) | 0.00 (0.13, 0.14) | -0.01 (-0.12, 0.11) | -0.11 (-0.28, 0.05) |
| Plasma Folatec | -0.05 (-0.14, 0.05) | 0.00 (-0.12, 0.12) | -0.05 (-0.14, 0.04) | -0.01 (-0.14, 0.13) | -0.01 (-0.13, 0.11) | -0.12 (-0.29, 0.04) |
| Plasma Folated | -0.04 (-0.14, 0.05) | 0.00 (-0.12, 0.12) | -0.05 (-0.13, 0.04) | -0.01 (-0.14, 0.13) | -0.02 (-0.13, 0.10) | -0.12 (-0.29, 0.04) |
|  |  |  |  |  |  |  |
| RBC Folatea | -0.30 (-0.49, -0.10)\* | -0.08 (-0.21, 0.05) | -0.13 (-0.31, 0.05) | 0.03 (-0.14, 0.19) | -0.08 (-0.34, 0.17) | -0.18 (-0.38, 0.02) |
| RBC Folateb | -0.23 (-0.41, -0.05) | -0.08 (-0.21, 0.04) | -0.19 (-0.38, 0.01) | 0.03 (-0.13, 0.20) | -0.17 (-0.43, 0.08) | -0.18 (-0.38, 0.02) |
| RBC Folatec | -0.23 (-0.41, -0.05) | -0.07 (-0.20, 0.06) | -0.19 (-0.38, 0.01) | 0.04 (-0.13 0.20) | -0.17 (-0.43, 0.08) | -0.16 (-0.35, 0.04) |
| RBC Folated | -0.24 (-0.42, -0.05) | -0.07 (-0.20, 0.06) | -0.22 (-0.41, -0.02) | 0.04 (-0.13, 0.20) | -0.15 (-0.41, 0.11) | -0.15 (-0.35, 0.04) |
|  |  |  |  |  |  |  |
| Vitamin B12a | 0.00 (-0.11, 0.11) | -0.01 (-0.13, 0.11) | -0.01 (-0.12, 0.10) | 0.12 (0.01, 0.23) | -0.03 (-0.17, 0.11) | 0.25 (0.11, 0.39)\*\* |
| Vitamin B12b | -0.02 (-0.13, 0.09) | -0.01 (-0.11, 0.12) | -0.01 (-0.12, 0.10) | 0.11 (0.00, 0.22) | 0.01 (-0.14, 0.15) | 0.23 (0.09, 0.37)\*\* |
| Vitamin B12c | -0.01 (-0.12, 0.10) | -0.02 (-0.12, 0.08) | 0.00 (-0.11, 0.11) | 0.12 (0.01, 0.24) | 0.00 (-0.14, 0.15) | 0.23 (0.09, 0.37)\* |
| Vitamin B12d | -0.01 (-0.13, 0.10) | -0.02 (-0.12, 0.08) | -0.01 (-0.12, 0.10) | 0.13 (0.01, 0.24) | 0.02 (-0.13, 0.16) | 0.23 (0.09, 0.37)\*\* |
|  |  |  |  |  |  |  |
| Cholinea | 0.30 (0.01, 0.60) | -0.08 (-0.33, 0.18) | 0.18 (-0.08, 0.43) | 0.37 (0.10, 0.64)\* | 0.06 (-0.27, 0.39) | 0.29 (-0.05, 0.63) |
| Cholineb | 0.39 (0.11, 0.66)\* | -0.11 (-0.36, 0.14) | 0.17 (-0.09, 0.43) | 0.35 (0.08, 0.62)\* | 0.00 (-0.34, 0.33) | 0.28 (-0.06, 0.62) |
| Cholinec | 0.42 (0.14, 0.70)\* | -0.13 (-0.38, 0.13) | 0.21 (-0.04, 0.47) | 0.36 (0.09, 0.64)\* | 0.00 (-0.34, 0.34) | 0.20 (-0.14, 0.55) |
| Cholined | 0.42 (0.14, 0.70)\* | -0.16 (-0.43, 0.10) | 0.17 (-0.09, 0.43) | 0.33 (0.04, 0.62) | 0.03 (-0.31, 0.37) | 0.16 (-0.20, 0.51) |
|  |  |  |  |  |  |  |
| Hcysa | -0.18 (-0.29, -0.06)\* | -0.02 (-0.17, 0.13) | -0.15 (-0.28, -0.02) | -0.14 (-0.31, 0.03) | 0.08 (-0.10, 0.25) | 0.18 (-0.03, 0.39) |
| Hcysb | -0.19 (-0.30, -0.07)\* | 0.00 (-0.16, 0.15) | -0.15 (-0.29, -0.02) | -0.12 (-0.30, 0.05) | 0.06 (-0.12, 0.23) | 0.16 (-0.06, 0.38) |
| Hcysc | -0.19 (-0.31, -0.07)\* | 0.00 (-0.16, 0.16) | -0.15 (-0.28, -0.02) | -0.15 (-0.32, 0.03) | 0.06 (-0.12, 0.24) | 0.17 (-0.05, 0.39) |
| Hcysd | -0.19 (-0.31, -0.07)\* | 0.00 (-0.15, 0.16) | -0.15 (-0.28, -0.02) | -0.14 (-0.32, 0.04) | 0.06 (-0.12, 0.24) | 0.18 (-0.04, 0.40) |

False discovery rate-adjusted \**P* < 0.05, \*\**P* < 0.01

Models include all nutritional indices (except for RBC folate) simultaneously; RBC folate models were run separately but included plasma vitamin B12, choline, and Hcys in models

Models b-d are adjusted for age, education, TV ownership, and bSe; for H3K36me3 and H3K79me2 in men, these models were additionally adjusted for cigarette smoking status

aUnadjusted Model, bMain Model, cMain Model (Excluding those without BMI measures), dMain Model (additionally adjusted for BMI)

e*n* = 159 for models a and b, *n* = 157 for models c and d; *n* = 122 for all RBC folate models

f*n* = 159 for models a and b, *n* = 152 for models c and d; *n* = 123 for all RBC folate models

g*n* = 154 for models a and b, *n* = 152 for models c and d; *n* = 121 for all RBC folate models

h*n* = 152 for models a and b, *n* = 146 for models c and d; *n* = 118 for RBC folate models a and b, *n* = 114 for RBC folate models c and d

i*n* = 162 for models a and b, *n* = 160 for models c and d; *n* = 125 for all RBC folate models

j*n* = 159 for models a and b, *n* = 153 for models c and d; *n* = 124 for RBC folate models a and b, *n* = 120 for RBC folate models c and d

**Supplementary Table S4.** Associations (β (95% CI)) between OCM indices and PTHMs by sex in FACT participants, comparing models additionally adjusting for blood arsenic

|  |  |  |  |
| --- | --- | --- | --- |
|  | **H3K36me2** | **H3K36me3** | **H3K79me2** |
|  | Malesc | Femalesd | Malese | Femalesf | Malesg | Femalesh |
| Plasma Folatea | -0.04 (-0.14, 0.05) | 0.00 (-0.11, 0.12) | -0.05 (-0.14, 0.04) | 0.00 (-0.13, 0.14) | -0.01 (-0.13, 0.11) | -0.11 (-0.28, 0.05) |
| Plasma Folateb | -0.05 (-0.14, 0.05) | -0.01 (-0.13, 0.11) | -0.05 (-0.14, 0.04) | -0.01 (-0.14, 0.13) | -0.01 (-0.13, 0.11) | -0.11 (-0.28, 0.06) |
|  |  |  |  |  |  |  |
| RBC Folatea | -0.23 (-0.41, -0.05) | -0.08 (-0.21, 0.04) | -0.19 (-0.38, 0.01) | 0.03 (-0.13, 0.20) | -0.17 (-0.43, 0.08) | -0.18 (-0.38, 0.02) |
| RBC Folateb | -0.24 (-0.42, -0.06) | -0.11 (-0.24, 0.02) | -0.18 (-0.38, 0.01) | 0.02 (-0.14, 0.19) | -0.16 (-0.42, 0.10) | -0.19 (-0.39, 0.01) |
|  |  |  |  |  |  |  |
| Vitamin B12a | -0.02 (-0.13, 0.09) | -0.01 (-0.11, 0.08) | -0.01 (-0.12, 0.10) | 0.11 (0.00, 0.22) | 0.01 (-0.14, 0.15) | 0.23 (0.09, 0.37)\*\* |
| Vitamin B12b | -0.02 (-0.13, 0.09) | -0.02 (-0.11, 0.08) | -0.01 (-0.12, 0.10) | 0.11 (-0.01, 0.22) | 0.01 (-0.13, 0.15) | 0.23 (0.09, 0.38)\*\* |
|  |  |  |  |  |  |  |
| Cholinea | 0.39 (0.11, 0.66)\* | -0.11 (-0.36, 0.14) | 0.17 (-0.09, 0.43) | 0.35 (0.08, 0.62)\* | 0.00 (-0.34, 0.33) | 0.28 (-0.06, 0.62) |
| Cholineb | 0.36 (0.08, 0.64)\* | -0.09 (-0.34, 0.16) | 0.15 (-0.11, 0.41) | 0.36 (0.09, 0.64)\* | -0.03 (-0.37, 0.30) | 0.28 (-0.06, 0.63) |
|  |  |  |  |  |  |  |
| Betainea | 0.04 (-0.20, 0.27) | 0.01 (-0.16, 0.18) | -0.08 (-0.31, 0.15) | 0.05 (-0.15, 0.25) | 0.12 (-0.17, 0.42) | -0.02 (-0.26, 0.22) |
| Betaineb | 0.02 (-0.22, 0.25) | 0.02 (-0.15, 0.19) | -0.10 (-0.33, 0.13) | 0.05 (-0.15, 0.25) | 0.10 (-0.20, 0.39) | -0.02 (-0.26, 0.22) |
|  |  |  |  |  |  |  |
| Hcysa | -0.19 (-0.30, -0.07)\* | 0.00 (-0.16, 0.15) | -0.15 (-0.29, -0.02) | -0.12 (-0.30, 0.05) | 0.06 (-0.12, 0.23) | 0.16 (-0.06, 0.38) |
| Hcysb | -0.19 (-0.31, -0.07)\*\* | 0.00 (-0.15, 0.16) | -0.15 (-0.29, -0.02) | -0.11 (-0.29, 0.07) | 0.05 (-0.12, 0.23) | 0.16 (-0.06, 0.38) |

*P*-values adjusted for false discovery rate \*\*<0.01, \*<0.05

aAdjusted for age, education, and TV ownership, and blood selenium. Models for H3K36me3 and H3K79me2 in men were additionally adjusted for cigarette smoking status.

bAdjusted for all variables included in model a and additionally adjusted for blood arsenic

c*n* = 159, *n* = 122 for RBC folate analyses

d*n* = 159, *n* = 123 for RBC folate analyses

e*n* = 154, *n* = 121 for RBC folate analyses

f*n* = 152, *n* = 118 for RBC folate analyses

g*n* = 162, *n* = 125 for RBC folate analyses

h*n* = 159, *n* = 124 for RBC folate analyses

**Supplementary Table S5**. Associations (β (95% CI))a between OCM indices and PTHMs by sex in FACT participants, comparing nutrients in model alone vs. included simultaneously

|  |  |  |  |
| --- | --- | --- | --- |
|  | **H3K36me2** | **H3K36me3** | **H3K79me2** |
|  | Malesd | Femalese | Malesf | Femalesg | Malesh | Femalesi |
| Plasma Folateb | -0.04 (-0.14, 0.05) | 0.00 (-0.11, 0.12) | -0.05 (-0.14, 0.04) | 0.00 (0.13, 0.14) | -0.01 (-0.13, 0.11) | -0.11 (-0.28, 0.05) |
| Plasma Folatec | -0.01 (-0.11, 0.09) | 0.00 (-0.11, 0.11) | -0.02 (-0.11, 0.07) | 0.05 (-0.07, 0.18) | -0.01 (-0.12, 0.10) | -0.13 (-0.29, 0.04) |
|  |  |  |  |  |  |  |
| RBC Folateb | -0.23 (-0.41, -0.05) | -0.08 (-0.21, 0.04) | -0.19 (-0.38, 0.01) | 0.03 (-0.13, 0.20) | -0.17 (-0.43, 0.08) | -0.18 (-0.38, 0.02) |
| RBC Folatec | -0.11 (-0.30, 0.08) | -0.08 (-0.21, 0.03) | -0.08 (-0.26, 0.10) | 0.05 (-0.11, 0.21) | -0.15 (-0.38, 0.08) | -0.16 (-0.36, 0.04) |
|  |  |  |  |  |  |  |
| Vitamin B12b | -0.02 (-0.13, 0.09) | -0.01 (-0.11, 0.12) | -0.01 (-0.12, 0.10) | 0.11 (0.00, 0.22) | 0.01 (-0.14, 0.15) | 0.23 (0.09, 0.37)\*\* |
| Vitamin B12c | 0.01 (-0.11, 0.13) | 0.00 (-0.10, 0.09) | 0.00 (-0.11, 0.11) | 0.10 (-0.01, 0.21) | 0.00 (-0.14, 0.14) | 0.19 (0.05, 0.33)\* |
|  |  |  |  |  |  |  |
| Cholineb | 0.39 (0.11, 0.66)\* | -0.11 (-0.36, 0.14) | 0.17 (-0.09, 0.43) | 0.35 (0.08, 0.62)\* | 0.01 (-0.34, 0.33) | 0.28 (-0.06, 0.62) |
| Cholinec | 0.37 (0.08, 0.66) | -0.10 (-0.34, 0.14) | 0.17 (-0.09, 0.43) | 0.28 (0.01, 0.54) | 0.00 (-0.33, 0.33) | 0.22 (-0.12, 0.56) |
|  |  |  |  |  |  |  |
| Betaineb | 0.04 (-0.20, 0.27) | 0.01 (-0.16, 0.18) | -0.08 (-0.31, 0.15) | 0.05 (-0.15, 0.25) | 0.12 (-0.17, 0.42) | -0.02 (-0.26, 0.22) |
| Betainec | 0.17 (-0.05, 0.40) | -0.02 (-0.17, 0.14) | 0.06 (-0.14, 0.26) | 0.17 (-0.01, 0.35) | 0.07 (-0.18, 0.32) | 0.08 (-0.14, 0.31) |
|  |  |  |  |  |  |  |
| Hcysb | -0.19 (-0.30, -0.07)\* | 0.00 (-0.16, 0.15) | -0.15 (-0.29, -0.02) | -0.12 (-0.30, 0.05) | 0.06 (-0.12, 0.23) | 0.16 (-0.06, 0.38) |
| Hcysc | -0.17 (-0.29, -0.05)\* | -0.01 (-0.15, 0.13) | -0.14 (-0.27, -0.01) | -0.12 (-0.28, 0.05) | 0.06 (-0.11, 0.23) | 0.18 (-0.02, 0.39) |

*P*-values were adjusted for multiple tests by controlling for the false discovery rate \**P* < 0.05, \*\**P* < 0.01

aEstimated regression coefficients and corresponding 95% confidence intervals for associations between natural log (ln)-transformed OCM indices and PTHMs. All models were adjusted for age, education (dichotomized at 5 years), TV ownership, and ln-bSe; for H3K36me3 and H3K79me2 in men, these models were additionally adjusted for cigarette smoking status. H3K36me2 was inverse-transformed and an inverse link function was used. H3K36me3 and H3K79me2 were ln-transformed.

bAll nutrients included simultaneously (RBC folate or plasma folate and vitamin B12, choline, and Hcys); models for RBC folate included vitamin B12, choline, and Hcys; models for plasma betaine included plasma folate, vitamin B12, choline, and Hcys

cNutrient examined individually in models

d*n* = 159, *n* = 122 for RBC folate models

e*n* = 159, *n* = 123 for RBC folate models

f*n* = 154, *n* = 121 for RBC folate models

g*n* = 152, *n* = 118 for RBC folate models

h*n* = 162, *n* = 124 for RBC folate models

i*n* = 159, *n* = 124 for RBC folate models

**Supplementary Table S6**. Associationsa between plasma OCM indices and PTHMs stratified by age and sex

|  |  |  |  |
| --- | --- | --- | --- |
|  | Age > 38 y | Age ≤ 38 y |  |
|  | β (95% CI) | *P*FDRb | β (95% CI) | *P*FDRb | *P*diffc |
| H3K36me2 |  |  |  |  |  |
| **Men**d |  |  |  |  |  |
| Folate | -0.04 (-0.15, 0.08) | 0.91 | -0.15 (-0.32, 0.02) | 0.48 |  |
| B12 | 0.02 (-0.13, 0.17) | 0.99 | -0.06 (-0.25, 0.13) | 0.36 |  |
| Choline | 0.43 (0.06, 0.81) | 0.12 | 0.35 (-0.08, 0.77) | 0.26 |  |
| Hcys | -0.16 (-0.31, -0.01) | 0.16 | -0.31 (-0.53, -0.09) | 0.04 | 0.29 |
| **Women**e |  |  |  |  |  |
| Folate | 0.27 (0.01, 0.53) | 0.48 | -0.06 (-0.19, 0.07) | 0.91 |  |
| B12 | -0.13 (-0.31, 0.04) | 0.36 | 0.00 (-0.12, 0.12) | 0.99 |  |
| Choline | -0.21 (-0.61, 0.18) | 0.50 | -0.09 (-0.39, 0.21) | 0.61 |  |
| Hcys | 0.10 (-0.12, 0.32) | 0.44 | -0.01 (-0.22, 0.20) | 0.94 |  |
| H3K36me3 |  |  |  |  |  |
| **Men**f |  |  |  |  |  |
| Folate | -0.05 (-0.16, 0.06) | 0.91 | 0.03 (-0.14, 0.19) | 0.91 |  |
| B12 | -0.01 (-0.16, 0.15) | 0.99 | -0.14 (-0.32, 0.05) | 0.36 |  |
| Choline | 0.06 (-0.31, 0.43) | 0.73 | 0.35 (-0.04, 0.75) | 0.24 |  |
| Hcys | -0.28 (-0.46, -0.10) | 0.03 | 0.11 (-0.12, 0.34) | 0.44 | <0.01 |
| **Women**g |  |  |  |  |  |
| Folate | -0.03 (-0.25, 0.20) | 0.91 | 0.01 (-0.17, 0.19) | 0.91 |  |
| B12 | 0.11 (-0.06, 0.27) | 0.38 | 0.13 (-0.03, 0.30) | 0.36 |  |
| Choline | 0.59 (0.18, 0.99) | 0.07 | 0.26 (-0.13, 0.64) | 0.38 |  |
| Hcys | -0.11 (-0.34, 0.13) | 0.44 | -0.16 (-0.46, 0.13) | 0.44 |  |
| H3K79me2 |  |  |  |  |  |
| **Men**h |  |  |  |  |  |
| Folate | 0.02 (-0.13, 0.17) | 0.91 | -0.05 (-0.25, 0.15) | 0.91 |  |
| B12 | -0.06 (-0.26, 0.13) | 0.80 | 0.01 (-0.23, 0.24) | 0.99 |  |
| Choline | -0.14 (-0.61, 0.33) | 0.61 | 0.16 (-0.34, 0.66) | 0.61 |  |
| Hcys | -0.02 (-0.25, 0.21) | 0.94 | -0.18 (-0.12, 0.47) | 0.44 |  |
| **Women**i |  |  |  |  |  |
| Folate | 0.03 (-0.32, 0.38) | 0.91 | -0.15 (-0.34, 0.04) | 0.52 |  |
| B12 | 0.10 (-0.17, 0.36) | 0.80 | 0.31 (0.14, 0.48) | <0.01 | 0.18 |
| Choline | 0.20 (-0.44, 0.85) | 0.61 | 0.39 (-0.03, 0.81) | 0.24 |  |
| Hcys | 0.19 (-0.17, 0.55) | 0.44 | 0.18 (-0.12, 0.49) | 0.44 |  |

aEstimated regression coefficients and corresponding 95% confidence intervals for associations between natural log (ln)-transformed

OCM indices and PTHMs were determined using generalized linear models, which were adjusted for age, education (dichotomized at

5 years), TV ownership, ln-blood selenium, and cigarette smoking status for analyses of H3K36me3 and H3K79me2 among men.

H3K36me2 was inverse-transformed and an inverse-link function was used for corresponding models. H3K36me3 and H3K79me2

were ln-transformed.

bFalse discovery rate-adjusted *P*-values

cWald test for difference between groups was calculated if there was a significant association in one of the strata after adjusting for the

false discovery rate

d *n* = 101 for age > 38, *n* = 58 for age ≤ 38

e *n* = 60 for age > 38 y, *n* = 99 for age ≤ 38

f *n* = 96 for age > 38 y, *n* = 58 for age ≤ 38

g *n* = 57 for age > 38 y, *n* = 95 for age ≤ 38

h *n* = 102 for age > 38 y, *n* = 60 for age ≤ 38

i *n* = 60 for age > 38 y, *n* = 99 for age ≤ 38

**Supplementary Table S7**. Associationsa between plasma OCM indices and PTHMs stratified by blood arsenic and sex

|  |  |  |  |
| --- | --- | --- | --- |
|  | Blood arsenic > 8.79 µg/L | Blood arsenic ≤ 8.79 µg/L |  |
|  | B (95% CI) | *P*FDRb | B (95% CI) | *P*FDRb | *P*diffc |
| H3K36me2 |  |  |  |  |  |
| **Men**d |  |  |  |  |  |
| Folate | -0.07 (-0.18, 0.05) | 0.84 | -0.04 (-0.18, 0.10) | 0.87 |  |
| B12 | -0.13 (-0.28, 0.02) | 0.27 | 0.08 (-0.07, 0.24) | 0.51 |  |
| Choline | 0.24 (-0.19, 0.66) | 0.56 | 0.38 (0.04, 0.71) | 0.18 |  |
| Hcys | -0.18 (-0.32, -0.04) | 0.06 | -0.20 (-0.40, 0.01) | 0.18 |  |
| **Women**e |  |  |  |  |  |
| Folate | -0.06 (-0.27, 0.15) | 0.87 | 0.00 (-0.14, 0.14) | 0.99 |  |
| B12 | -0.03 (-0.19, 0.12) | 0.83 | -0.02 (-0.14, 0.10) | 0.83 |  |
| Choline | -0.23 (-0.61, 0.14) | 0.53 | 0.05 (-0.28, 0.38) | 0.87 |  |
| Hcys | -0.01 (-0.22, 0.20) | 0.92 | 0.02 (-0.21, 0.25) | 0.92 |  |
| H3K36me3 |  |  |  |  |  |
| **Men**f |  |  |  |  |  |
| Folate | -0.06 (-0.18, 0.07) | 0.84 | -0.08 (-0.23, 0.07) | 0.84 |  |
| B12 | -0.03 (-0.20, 0.15) | 0.83 | 0.02 (-0.13, 0.17) | 0.83 |  |
| Choline | -0.03 (-0.45, 0.38) | 0.87 | 0.31 (-0.04, 0.66) | 0.30 |  |
| Hcys | -0.25 (-0.44, -0.06) | 0.06 | -0.01 (-0.23, 0.20) | 0.92 |  |
| **Women**g |  |  |  |  |  |
| Folate | -0.10 (-0.35, 0.15) | 0.87 | -0.05 (-0.14, 0.04) | 0.84 |  |
| B12 | 0.10 (-0.10, 0.30) | 0.51 | -0.01 (-0.12, 0.10) | 0.83 |  |
| Choline | 0.61 (0.16, 1.06) | 0.10 | 0.12 (-0.23, 0.47) | 0.87 |  |
| Hcys | -0.20 (-0.46, 0.06) | 0.29 | -0.15 (-0.29, -0.02) | 0.12 |  |
| H3K79me2 |  |  |  |  |  |
| **Men**h |  |  |  |  |  |
| Folate | -0.03 (-0.18, 0.12) | 0.96 | 0.01 (-0.19, 0.22) | 0.98 |  |
| B12 | -0.16 (-0.37, 0.05) | 0.31 | 0.18 (-0.03, 0.39) | 0.27 |  |
| Choline | 0.06 (-0.44, 0.56) | 0.87 | -0.11 (-0.59, 0.36) | 0.87 |  |
| Hcys | 0.03 (-0.21, 0.26) | 0.92 | 0.10 (-0.21, 0.40) | 0.80 |  |
| **Women**i |  |  |  |  |  |
| Folate | -0.26 (-0.58, 0.07) | 0.84 | 0.01 (-0.18, 0.21) | 0.98 |  |
| B12 | 0.39 (0.14, 0.64) | 0.04 | 0.15 (-0.02, 0.32) | 0.27 | 0.12 |
| Choline | 0.48 (-0.10, 1.06) | 0.30 | 0.06 (-0.38, 0.49) | 0.87 |  |
| Hcys | 0.14 (-0.18, 0.47) | 0.78 | 0.10 (-0.22, 0.42) | 0.80 |  |

aEstimated regression coefficients and corresponding 95% confidence intervals for associations between natural log (ln)-transformed

OCM indices and PTHMs were determined using generalized linear models, which were adjusted for age, education (dichotomized at

5 years), TV ownership, ln-blood selenium, and cigarette smoking status for analyses of H3K36me3 and H3K79me2 among men.

H3K36me2 was inverse-transformed and an inverse-link function was used for corresponding models. H3K36me3 and H3K79me2

were ln-transformed.

bFalse discovery rate-adjusted *P*-values

cWald test for difference between groups was calculated if there was a significant association in one of the strata after adjusting for the

false discovery rate

d *n* = 85 for blood arsenic > 8.79 µg/L, *n* = 74 for blood arsenic ≤ 8.79 µg/L

e *n* = 71 for blood arsenic > 8.79 µg/L, *n* = 88 for blood arsenic ≤ 8.79 µg/L

f *n* = 84 for blood arsenic > 8.79 µg/L, *n* = 70 for blood arsenic ≤ 8.79 µg/L

g *n* = 70 for blood arsenic > 8.79 µg/L, *n* = 82 for blood arsenic ≤ 8.79 µg/L

h *n* = 88 for blood arsenic > 8.79 µg/L, *n* = 74 for blood arsenic ≤ 8.79 µg/L

i *n* = 72 for blood arsenic > 8.79 µg/L, *n* = 87 for blood arsenic ≤ 8.79 µg/L

**Supplementary Table S8.** Associationsa between changes in OCM indices and changes in PTHMs from baseline to week 12

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Men |  | Women |  |
| H3K36me2a | β (95% CI) | *PFDR*b | β (95% CI) | P*FDR*b |
| RBC Folate | 0.02 (-0.14, 0.17) | 0.86 | 0.11 (-0.03, 0.26) | 0.27 |
| Plasma Folate | -0.05 (-0.15, 0.05) | 0.59 | 0.09 (0.00, 0.18) | 0.16 |
| Vitamin B12 | 0.26 (0.04, 0.48) | 0.13 | -0.08 (-0.26, 0.08) | 0.65 |
| Choline | 0.26 (-0.17, 0.69) | 0.41 | 0.08 (-0.21, 0.38) | 0.68 |
| Hcys | -0.14 (-0.39, 0.12) | 0.52 | 0.05 (-0.20, 0.31) | 0.68 |
| H3K36me3c |  |  |  |  |
| RBC Folate | -0.04 (-0.19, 0.11) | 0.86 | 0.16 (-0.05, 0.38) | 0.27 |
| Plasma Folate | -0.03 (-0.12, 0.05) | 0.59 | -0.05 (-0.19, 0.09) | 0.59 |
| Vitamin B12 | 0.19 (-0.02, 0.39) | 0.19 | -0.08 (-0.43, 0.27) | 0.78 |
| Choline | -0.22 (-0.59, 0.15) | 0.41 | -0.08 (-0.54, 0.38) | 0.73 |
| Hcys | 0.11 (-0.12, 0.34) | 0.52 | -0.29 (-0.70, 0.11) | 0.44 |
| H3K79me2d |  |  |  |  |
| RBC Folate | -0.02 (-0.29, 0.24) | 0.86 | -0.11 (-0.25, 0.03) | 0.27 |
| Plasma Folate | 0.03 (-0.12, 0.17) | 0.73 | -0.10 (-0.18, -0.01) | 0.14 |
| Vitamin B12 | 0.29 (-0.05, 0.63) | 0.19 | 0.02 (-0.22, 0.26) | 0.87 |
| Choline | 0.34 (-0.28, 0.96) | 0.41 | 0.22 (-0.09, 0.53) | 0.41 |
| Hcys | 0.16 (-0.24, 0.57) | 0.52 | 0.20 (-0.06, 0.45) | 0.44 |

aEstimated regression coefficients and corresponding 95% confidence intervals for associations between natural log (ln)-transformed changes in OCM indices and ln-transformed changes in PTHMs were determined using linear regression models. Changes in OCM indices were included simultaneously in models, which were additionally adjusted for baseline age, BMI, education (dichotomized at 5 years), TV ownership, and ln-blood selenium

b *n* = 78 for men, *n* = 81 for women; for RBC folate analyses, *n* = 74 for men, *n* = 78 for women

cAdjusted for multiple tests by controlling for the false discovery rate

d *n* = 78 for men, *n* = 74 for women; for RBC folate analyses, *n* = 74 for men, *n* = 72 for women

e *n* = 80 for men, *n* = 74 for women; for RBC folate analyses, *n* = 76 for men, *n* = 72 for women

**Supplementary Figure S1**

**A** **H3K36me2**

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**B H3K36me3**

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**C H3K79me2**

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**Supplementary Figure S1**. Sex-Specific Associations between OCM Indices and PTHMs in FACT Participants with RBC Folate Measures

Estimated regression coefficients and 95% confidence intervals for associations between each OCM index and (**A**) H3K36me2, (**B**) H3K36me3, and (**C**) H3K79me2 are shown separately by sex. The dashed line represents the null (β = 0). Associations with confidence intervals that do not cross the null are statistically significant (*P* < 0.05). Asterisks (\*\**P* < 0.01, \*\*\**P* < 0.001) indicate sex differences with p-values calculated from the Wald test. OCM indices were natural log-transformed and were included simultaneously in models. Models were adjusted for age, education, TV ownership, and ln-bSe. Analyses for H3K36me3 and H3K79me2 in men were additionally adjusted for cigarette smoking status. H3K36me2 was inverse-transformed and was modeled using a generalized linear model with an inverse-link function. H3K36me3 and H3K79me2 were natural log-transformed and were modeled using linear models. Sample sizes were as follows: H3K36me2: *n* = 122 for men, *n* = 123 for women; H3K36me3: *n* = 121 for men, *n* = 118 for women; H3K79me2: *n* = 125 for men, *n* = 124 for women.