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| Supplemental Table 1. Additional characteristics of the study population according to sex specific fasting plasma total homocysteine (tHcy) tertiles (µmol/L).  |
|  | **Women** | **Men** |
|  |  |  | *tHcy (µmol/L) tertiles* |  |  |  | *tHcy (µmol/L) tertiles* |  |
|  |  | 1 (<7.7) |  | 2(7.7-9.6)  |  | 3(>9.6) |  | 1(<9.3) |  | 2(9.3-11.1) |  | 3(>11.1) |
|  | *N* |  | *N* |  | *N* |  | *N* |  | *N* |  | *N* |  |
| (from BMI, Table 1) | 125 |  | 123 |  | 120 |  | 116 |  | 116 |  | 116 |  |
| Overweight§ | 41 | 32.8 (25.2, 41.4) | 43 | 35.0 (27.1, 43.7) | 28 | 23.3 (16.7, 31.7) | 48 | 41.0 (32.8, 50.5) | 53 | 45.7 (36.9, 54.7) | 48 | 41.4 (32.5, 50.1) |
| Obesity§ | 23 | 18.4 (12.6, 26.1) | 26 | 21.1 (14.9, 29.2) | 35 | 30.2 (22.6, 29.1) | 28 | 24.1 (17.3, 32.7) | 33 | 28.4 (21.0, 37.2) | 30 | 25.9 (18.6, 34.2) |
| Plasma folate <7 nmol/L§ |  | 7.2 ( 3.8, 13.1) |  | 19.2 (13.3, 27.0) |  | 24.0 (17.2, 32.3)\*\* |  | 9.4 (5.3, 16.1) |  | 18.6 (12.6, 26.2) |  | 31.6 (23.9, 40.5)\*\*\* |
| Plasma cobalamin <220 mol/L§ | 8 | 6.5 (3.3, 12.2) | 10 | 8.0 (4.4, 14.1) | 19 | 15.7 (10.3, 23.2)**\*\*** | 4 | 3.4 (1.3, 8.5) | 10 | 8.5 (4.7, 14.9) | 14 | 12.0 (7.3, 19.1) |
| Riboflavin deficiency§,ǁ | 56 | 45.5 (37.0, 54.3) | 42 | 33.6 (25.9, 42.3) | 37 | 30.6 (23.1, 39.3) | 48 | 41.4 (32.8, 50.5) | 30 | 25.6 (18.6, 34.2) | 34 | 29.8 (22.2, 38.8) |
| Suboptimal riboflavin status§,ǂ | 67 | 54.5 (45.7, 63.0) | 83 | 66.4 (57.7, 74.1) | 84 | 69.4 (60.7, 76.9)\* | 68 | 58.6 (49.5, 67.2) | 87 | 74.4 (65.8, 81.4) | 80 | 70.2 (61.2, 77.8)\* |
| *MTHFR* CC*+ SLC19A1* GG§ | 11 | 8.8 (5.0, 15.1) | 4 | 3.3 (1.3, 8.2) | 13 | 10.8 (6.4, 17.7) | 15 | 12.8 (7.9, 20.1) | 13 | 11.1 (6.6, 18.1) | 10 | 8.7 (4.8, 15.3) |
| *MTHFR* CC*+ SLC19A1* GA/AA§ | 39 | 31.2 (23.7, 39.8) | 32 | 26.2 (19.2, 34.7) | 31 | 25.8 (18.8, 34.2) | 38 | 32.5 (24.7, 41.4) | 29 | 24.8 (17.8, 33.3) | 20 | 17.4 (11.6, 25.3) |
| *MTHFR* CT*+ SLC19A1* GG§ | 14 | 11.2 (6.8, 17.9) | 11 | 9.0 (5.1, 15.4) | 7 | 5.8 (2.9, 11.6) | 16 | 13.7 (8.6, 21.1) | 13 | 11.1 (6.6, 18.1) | 13 | 11.3 (6.7, 18.4) |
| *MTHFR* CT*+ SLC19A1* GA/AA§ | 50 | 40.0 (31.8, 48.8) | 52 | 42.6 (34.2, 51.5) | 41 | 34.2 (26.3, 43.0) | 39 | 33.3 (25.4, 42.3) | 46 | 39.3 (30.9, 48.4) | 33 | 28.7 (21.2, 37.6) |
| *MTHFR* TT*+ SLC19A1* GG§ | 5 | 4.0 (1.7, 9.0) | 7 | 5.7 (2.8, 11.4) | 8 | 6.7 (3.4, 12.6) | 2 | 1.7 (0.5, 6.0) | 9 | 7.7 (4.1, 14.0) | 12 | 10.4 (6.1, 17.4) |
| *MTHFR* TT*+ SLC19A1* GA/AA§ | 6 | 4.8 (2.2, 10.1) | 16 | 13.1 (8.2, 20.2) | 20 | 16.7 (11.1, 24.4)**\*** | 7 | 6.0 (2.9, 11.8) | 7 | 6.0 (2.9, 11.8) | 27 | 23.5 (16.7, 32.0)**\*\*\*** |
| Abbreviations: BMI, Body Mass Index; EGRAC, Erythrocyte Glutathione Reductase Activation Coefficient; *MTHFR*, Methylene Tetrahydrofolate Reductase 677C>T polymorphism; *SLC19A1,* Solute Carrier family 19A member 1 80G>A polymorphism. 24 participants were excluded after the medical checkup due to declared B vitamin supplement use. A further 59 participants were excluded from all analyses involving tHcy because their blood samples were not processed within 2 h of collection and 5 participants because they had suspected altered renal function (plasma creatinine >97 mmol/L for women and >124 mmol/L for men).†median (P25, P75), ‡arithmetic mean (95% CI), §% (95% CI), ¶category of habitual alcohol intake (moderate <16 g/d in women and <24 g/d in men), high (≥16 g/d in women and ≥24 g/d in men); ǀgeometric mean (95% CI), ǁEGRAC ≥1.4; ǂEGRAC ≥1.2 - <1.4.Chi-square test comparing categorical variables and ANOVA comparing continuous variables between tHcy tertiles, \*\*\**P*<0.001, \*\**P*<0.01, \**P*<0.05.Supplemental Table 2. Participant characteristics by age group and sex.

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|  | **50 years or younger** | **Over 50 years** |
|  | Women | Men | Women | Men |
|  | *N* |  | *N* |  | *N* |  | *N* |  |
| Age (years) | 254 | 34.0 (32.9, 35.0) | 240 | 34.5 (33.4, 35.6) | 118 | 61.7 (60.3, 63.0) | 113 | 60.9 (59.6, 62.2) |
| BMI (kg/m2)‡ | 250 | 25.0 (24.3, 25.6) | 237 | 26.5 (26.0, 27.0)\*\*\* | 115 | 30.4 (29.4, 31.3) | 112 | 29.2 (28.4, 30.0) |
| Smokers§ | 254 | 42.9 (37.9, 49.1) | 240 | 44.6 (38.4, 50.9) | 116 | 5.2 (2.4, 10.8) | 113 | 26.5 (19.3, 35.4)\*\*\* |
| Alcohol consumption§,¶ | 254 |  | 240 |  | 118 |  | 113 |  |
|  Low to moderate |  | 14.6 (10.8, 19.4) |  | 37.9 (32.0, 44.2)\*\*\* |  | 14.4 (9.2, 21.9) |  | 29.2 (21.6, 38.2)\*\* |
|  High |  | 3.9 (2.2, 7.1) |  | 25.0(19.9, 30.8)\*\*\* |  | 6.8 (3.5, 12.8) |  | 32.7 (24.8, 41.8)\*\*\* |
| Diagnosed hypertension§ | 254 | 3.5 (1.9, 6.6) | 240 | 6.3 (3.8, 10.1) | 118 | 37.3 (29.1, 46.3) | 113 | 24.8 (17.7, 33.5)\* |
| Low socioeconomic status§ | 254 | 31.1 (25.7, 37.0) | 240 | 10.8 (7.5, 15.4)\*\*\* | 118 | 82.2 (74.3, 88.1) | 113 | 55 8 (46.6, 64.6)\*\*\* |
| Plasma folate (nmol/L)ǀ | 254 | 10.5 (9.9, 11.2) | 239 | 9.6 (9.0, 10.2)\* | 118 | 16.8 (15.1, 18.6) | 113 | 14.4 (13.1, 15.7)\* |
| Red cell folate (nmol/L)ǀ | 254 | 735 (702, 770) | 239 | 776 (742, 812) | 118 | 966 (905, 1031) | 113 | 980 (918, 1045) |
| Plasma cobalamin (pmol/L)ǀ | 254 | 333 (317, 349) | 239 | 349 (335, 364) | 117 | 385 (359, 413) | 113 | 343 (321, 367)\* |
| EGRACǀ | 250 | 1.41 (1.38, 1.44) | 235 | 1.38 (1.36, 1.41) | 116 | 1.28 (1.24, 1.31) | 111 | 1.30 (1.27, 1.33) |
| tHcy (µmol/L)ǀ | 254 | 8.4 (8.1, 8.7) | 239 | 10.1 (9.8, 10.5)\*\*\* | 118 | 9.4 (8.9, 9.9) | 113 | 10.6 (10.2, 11.1)\*\*\* |
| Plasma creatinine (µmol/L)‡ | 254 | 67.9 (61.9, 73.8) | 240 | 81.3 (80.0, 82.7)\*\*\* | 118 | 66.4 (64.7, 68.1) | 113 | 82.2 (79.9, 84.6)\*\*\* |
| Plasma total cholesterol (mmol/L)‡ | 254 | 4.9 (4.8, 5.1) | 239 | 5.2 (5.1, 5.4)\*\* | 117 | 5.9 (5.7, 6.1) | 113 | 5.6 (5.4, 5.8) |
| *MTHFR* CC§ | 254 | 32.7 (27.2, 38.7) | 239 | 35.6 (29.8, 41.8) | 118 | 41.5 (33.0, 50.6) | 113 | 36.3 (28.0, 45.5) |
| *MTHFR* CT§ |  | 49.6 (43.5, 55.7) |  | 47.8 (41.5, 54.0) |  | 42.4 (33.8, 51.4) |  | 42.5 (33.8, 51.7) |
| *MTHFR* TT§ |  | 17.7 (13.5, 22.99 |  | 16.7 (14.8, 24.7) |  | 16.1 (10.6, 23.8) |  | 21.2 (14.7, 29.7) |
| *SLC19A1* GG§ | 250 | 20.8 (16.2, 26.3) | 239 | 29.7 (24.3, 35.8)\* | 116 | 23.3 (16.5, 31.8) | 111 | 28.8 (21.2, 37.9) |
| *SLC19A1* GA§ |  | 52.8 (46.6, 58.9) |  | 51.1 (44.7, 57.3) |  | 50.9 (41.9, 59.8) |  | 43.2 (34.3, 52.5) |
| *SLC19A1* AA§ |  | 26.4 (21.3, 32.2) |  | 19.3 (14.8, 24.7) |  | 25.9 (18.8, 34.5) |  | 27.9 (20.4, 36.9) |

Abbreviations: BMI, Body Mass Index; EGRAC, Erythrocyte Glutathione Reductase Activation Coefficient; *MTHF36.3 (28.0, 45.5)* Methylene Tetrahydrofolate Reductase 677C>T polymorphism; *SLC19A1,* Solute Carrier family 19A member 1 80G>A polymorphism. 24 participants were excluded after the medical checkup due to declared B vitamin supplement use. A further 59 participants were excluded from all analyses involving tHcy because their blood samples were not processed within 2 h of collection and 5 participants because they had suspected altered renal function (plasma creatinine >97 mmol/L for women and >124 mmol/L for men).†median (P25, P75), ‡arithmetic mean (95% CI), §% (95% CI), ¶category of habitual alcohol intake (moderate <16 g/d in women and <24 g/d in men), high (≥16 g/d in women and ≥24 g/d in men); ǀgeometric mean (95% CI), ǁEGRAC ≥1.4; ǂEGRAC ≥1.2 - <1.4.Chi-square test comparing categorical variables and ANOVA comparing continuous variables between tHcy tertiles, \*\*\**P*<0.001, \*\**P*<0.01, \**P*<0.05. |