**Supplementary Table 1. Additional sample characteristics, by vitamin B12 and folate groups**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | Vitamin B12 ≥258 pmol/L | | Vitamin B12 <258pmol/L | | *P* for comparison across all groups |
|  |  | Folate ≤45.3 nmol/L | Folate >45.3 nmol/L | Folate ≤45.3 nmol/L | Folate >45.3 nmol/L |
|  |  | *'Normal* B12*/*  *Normal Folate'* | *'Normal* B12*/*  *High Folate'* | *'Low* B12*/*  *High Folate'* | *'Low* B12*/*  *Normal Folate'* |
| *n (%)* | *3,871* | (*n* 2,433) | (*n* 306) | (*n* 51) | (*n* 1,081) |
| Educational Attainment | 3,871 |  |  |  |  |  |
| None/Primary | 846 | 502 (20.6) | 54 (17.7) | 14 (27.5) | 276 (25.5) | 0.002 |
| *P* |  | Reference | 0.2005 | 0.2841 | 0.0017\* |  |
| Secondary | 1,727 | 1108 (45.5) | 131 (42.8) | 22 (43.1) | 466 (43.1) | 0.515 |
| *P* |  | Reference | 0.3641 | 0.7342 | 0.1801 |  |
| Tertiary/Higher | 1,298 | 823 (33.8) | 121 (39.5) | 15 (29.4) | 339 (31.4) | 0.052 |
| *P* |  | Reference | 0.0535 | 0.4980 | 0.1485 |  |
| Household Wealth – above average [n (%)] | 1,897 / 3,712 | 1,184 (50.6) | 179 (61.9) | 32 (65.3) | 502 (48.6) | 0.000 |
| *P* |  | Reference | 0.0010\* | 0.0417\* | 0.2227 |  |
| Living Alone [n (%)] | 629 / 3,871 | 381 (15.7) | 56 (18.3) | 7 (13.7) | 185 (17.1) | 0.4940 |
| *P* |  | Reference | 0.2578 | 0.6944 | 0.2859 |  |
| Physical Activity Level (IPAQ) [n (%)] | 3,871 |  |  |  |  |  |
| Low | 1,051 | 647 (26.6) | 83 (27.1) | 12 (23.5) | 309 (28.6) | 0.6050 |
| *P* |  | Reference | 0.8439 | 0.6136 | 0.2249 |  |
| Moderate | 1,376 | 870 (35.8) | 123 (40.2) | 19 (37.3) | 363 (33.6) | 0.1850 |
| *P* |  | Reference | 0.1353 | 0.8285 | 0.2093 |  |
| High | 1,445 | 916 (37.7) | 100 (32.7) | 20 (39.2) | 409 (37.8) | 0.3720 |
| *P* |  | Reference | 0.0824 | 0.8223 | 0.9163 |  |
| Smokers [*n* (%)] | 568 / 3,871 | 344 (14.1) | 33 (10.8) | 9 (17.7) | 182 (16.8) | 0.0340 |
| *P* |  | Reference | 0.0793 | 0.5188 | 0.0442\* |  |
| Alcohol Consumers [n (%)] | 2,889 /3,601 | 1,825 (80.1) | 233 (80.9) | 36 (73.5) | 795 (80.7) | 0.6400 |
| *P* |  | Reference | 0.7384 | 0.3038 | 0.6759 |  |
| BMI (kg/m2) | 3,866/3,871 | 27.9 (25.2, 31.0) | 27.3 (24.2, 29.8) | 29.7 (26.8, 31.7) | 28.5 (25.6, 31.8) | 0.0001 |
| *P* |  | Reference | 0.0006\* | 0.0759 | 0.0006\* |  |
| Grip Strength | 3,813 | 24.8 (19.3, 33.5) | 22.3 (17.5, 30. 8) | 26.0 (18.0, 34.0) | 25.8 (19.3, 33.3) | 0.0008 |
| *P* |  | Reference | 0.0003\* | 0.9916 | 0.4080 |  |
| Hypertension [n (%)] | 1,573/3,854 | 927 (38.2) | 135 (44.3) | 29 (56.9) | 482 (44.9) | 0.0000 |
| *P* |  | Reference | 0.0454\* | 0.0085\* | 0.0002\* |  |
| Diabetes [n (%)] | 250/3,832 | 131 (5.5) | 20 (6.6) | 9 (17.7) | 90 (8.4) | 0.000 |
| *P* |  | Reference | 0.4498 | 0.0242\* | 0.0023\* |  |
| CES-D (Depressive Symptoms) | 3,821/3,871 | 3.0 (1.0, 7.0) | 3.0 (1.0, 7.0) | 4.0 (0.0, 7.0) | 3.0 (1.0, 7.0) | 0.9961 |
| *P* |  | Reference | 0.6359 | 0.9264 | 0.7284 |  |
| Creatinine (umol/L) | 3,871 | 77.0 (66.0, 89.0) | 75.5(64.0, 85.0) | 76 (66.0, 91.0) | 77 (67.0, 88.0) | 0.0217 |
| *P* |  | Reference | 0.0093\* | 0.4537 | 0.2719 |  |
| Statin Use [n (%)] | 1,125/3,871 | 703 (28.9) | 89 (29.1) | 21 (41.2) | 312 (28.8) | 0.2970 |
| *P* |  | Reference | 0.8786 | 0.0803 | 0.9845 |  |
| Thyroid Medication Use [n (%)] | 253/3,871 | 159 (6.5) | 26 (8.5) | 4 (7.8) | 64 (5.9) | 0.396 |
| *P* |  | Reference | 0.2465 | 0.7331 | 0.4828 |  |
| Proton Pump Inhibitors [n (%)] | 440/3,871 | 280 (11.5) | 32 (10.4) | 11 (21.8) | 117 (10.8) | 0.117 |
| *P* |  | Reference | 0.5737 | 0.0857 | 0.5499 |  |
| Metformin [n (%)] | 139/3,871 | 66 (2.7) | 10 (3.3) | 5 (9.8) | 58 (5.4) | 0.000 |
| *P* |  | Reference | 0.6098 | 0.0928 | 0.0005\* |  |
| History of Stroke | 43/3,871 | 27 (1.1) | 3 (1.0) | 0 (0) | 13 (1.2) | 0.983 |
| *P* |  | Reference | 0.8301 | 0.0000 | 0.8137 |  |

1 Non-normally distributed continuous variables were described as medians and interquartile ranges (IQR) (all such values), and compared using Kruskal-Wallis test as appropriate, and Mann–Whitney U test for pairwise comparisons with the reference category. Categorical variables were compared using the chi-square tests of Fisher’s exact test, as appropriate

\*Statistically significant after adjustment for multiple comparisons (*q* value <0.013).

**Supplementary Table 2. Selected sample characteristics, by vitamin B12 and folate groups – stratified by age**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  | |  | | *P* for comparison across groups1 |
|  |  | *'Normal* B12*/*  *Normal Folate'* | *'Normal* B12*/*  *High Folate'* | *'Low* B12*/*  *High Folate'* | *'Low* B12*/*  *Normal Folate'* |
| *n (%)* | *3,871* | (*n* 2,433) | (*n* 306) | (*n* 51) | (*n* 1,081) |
| **Age < 50 years (*n* 3,871)** | | | | | | |
| Age, mean (SD) | 3,871 | 60 (55, 67)1 | 62 (56, 68) | 66 (57, 73) | 61 (55, 68) | 0.0001 |
| *P* |  | Reference | 0.0016\* | 0.0011\* | 0.0033\* |  |
| Female [*n* (%)] | 2,045/3,871 | 1,292 (53.1) | 199 (64.8) | 23 (45.1) | 531 (49.1) | 0.0000 |
| *P* |  | Reference | 0.0001\* | 0.2602 | 0.0294 |  |
| Vitamin B12 (pmol/L) | 3,871 | 361.3 (308.7, 435.2) | 420.9 (344.6, 514.0) | 214.2 (160.1, 241.3) | 205.9 (170.3, 235.4) | 0.0001 |
| *P* |  | Reference | 0.0000\* | 0.0000\* | 0.0000\* |  |
| Folate (nmol/L) | 3,871 | 18.8 (13.1, 26.9) | 56.5 (50.0, 65.7) | 55.4 (49.1, 61.5) | 14.7 (10.7, 22.0) | 0.0001 |
| *P* |  | Reference | 0.0000\* | 0.0000\* | 0.0000\* |  |
| Creatinine (umol/L) | 3,871 | 77.0 (66.0, 89.0) | 76.0 (64.0, 85.0) | 76 (66.0, 91.0) | 77 (67.0, 88.0) | 0.0217 |
| *P* |  | Reference | 0.0130 | 0.4399 | 0.2356 |  |
| Folic Acid Supplement Use [n (%)] | 123/3,871 | 68 (2.8) | 22 (7.2) | 7 (13.7) | 26 (2.4) | 0.0000 |
| *P* |  | Reference | 0.0039\* | 0.0251 | 0.4969 |  |
| MMSE | 3,871 | 29 (28.0, 30.0) | 29 (29.0, 30.0) | 29 (28.0, 30.0) | 29 (28.0, 30.0) | 0.0219 |
| *P* |  | Reference | 0.0128\* | 0.6987 | 0.1751 |  |
| MoCA | 3,871 | 26 (24.0, 28.0) | 26 (25.0, 28.0) | 26 (24.0, 27.0) | 26 (24.0, 28.0) | 0.0054 |
| *P* |  | Reference | 0.0503 | 0.4997 | 0.0131 |  |
| **Age < 60 years (*n* 1,801)** | | | | | | |
| *n (%)* | *1801* | (*n* 1,187) | (*n* 125) | (*n* 15) | (*n* 474) |  |
| Female [*n* (%)] | 975/1,801 | 633 (53.3) | 82 (65.6) | 8 (53.3) | 252 (53.2) | 0.068 |
| *P* |  | Reference | 0.0065\* | 0.9997 | 0.9521 |  |
| Vitamin B12 (pmol/L) | 1,801 | 361.4 (308.4, 438.4) | 413.9 (336.5, 501.3) | 198.6 (148.2, 230.5) | 205.9 (171.3, 234.7) | 0.0001 |
| *P* |  | Reference | 0.0000\* | 0.0000\* | 0.0000\* |  |
| Folate (nmol/L) | 1,801 | 18.1 (12.7, 25.2) | 55.4 (49.7, 62.4) | 55.9 (52.7, 63.2) | 14.9 (11.2, 22.3) | 0.0001 |
| *P* |  | Reference | 0.0000\* | 0.0000\* | 0.0000\* |  |
| Creatinine (umol/L) | 1,801 | 75 (65, 86) | 70 (61, 81) | 69 (62, 84) | 74 (65, 84) | 0.0221 |
| *P* |  | Reference | 0.0041\* | 0.2433 | 0.7001 |  |
| Folic Acid Supplement Use [n (%)] | 58/1,801 | 38 (3.2) | 8 (6.4) | 1 (6.7) | 11 (2.3) | 0.086 |
| *P* |  | Reference | 0.1565 | 0.6043 | 0.3063 |  |
| MMSE | 1,801 | 29 (29, 30) | 30 (29, 30) | 30 (29, 30) | 29 (29, 30) | 0.1640 |
| *P* |  | Reference | 0.0643 | 0.1827 | 0.8986 |  |
| MoCA | 1,801 | 27 (25, 28) | 27 (25, 28) | 27 (26, 28) | 26 (25, 28) | 0.2391 |
| *P* |  | Reference | 0.3307 | 0.6915 | 0.1195 |  |
| **Age 60 - 69 years (*n* 1,359)** | | | | | | |
| *n (%)* | *1,359* | (*n* 845) | (*n* 115) | (*n* 17) | (*n* 382) |  |
| Female [*n* (%)] | 718/1,359 | 446 (52.8) | 78 (67.8) | 7 (41.2) | 187 (49.0) | 0.003 |
| *P* |  | Reference | 0.0014\* | 0.3504 | 0.2147 |  |
| Vitamin B12 (pmol/L) | 1,359 | 367.4 (413.4, 439.2) | 431.2 (357.1, 521.5) | 216.0 (187.3, 251.5) | 210.7 (173.9, 237.6) | 0.0001 |
| *P* |  | Reference | 0.0001\* | 0.0000\* | 0.0000\* |  |
| Folate (nmol/L) | 1,359 | 19.6 9 (13.5, 27.9) | 56.8 (50.7, 65.7) | 51.1 (48.1, 56.4) | 14.6 (10.3, 22.2) | 0.0001 |
| *P* |  | Reference | 0.0000\* | 0.0000\* | 0.0000\* |  |
| Creatinine (umol/L) | 1,359 | 78 (66.5, 89.5) | 76 (65, 85) | 78 (71, 91) | 79 (68, 88) | 0.3360 |
| *P* |  | Reference | 0.1464 | 0.5650 | 0.5129 |  |
| Folic Acid Supplement Use [n (%)] | 43/1,359 | 22 (2.6) | 9 (7.8) | 3 (17.7) | 9 (2.4) | 0.001 |
| *P* |  | Reference | 0.0427 | 0.1153 | 0.7947 |  |
| MMSE | 1,359 | 29 (28, 30) | 29 (29, 30) | 29 (28, 30) | 29 (28, 30) | 0.0755 |
| *P* |  | Reference | 0.6832 | 0.6832 | 0.8383 |  |
| MoCA | 1,359 | 26 (24, 28) | 27 (25, 28) | 27 (26, 28) | 26 (25, 28) | 0.2391 |
| *P* |  | Reference | 0.0074\* | 0.4045 | 0.3567 |  |
| **Age 70 - 79 years (*n* 616)** | | | | | | |
| *n (%)* | *616* | (*n* 349) | (*n* 61) | (*n*15) | (*n* 191) |  |
| Female [*n* (%)] | 300/616 | 182 (52.2) | 34 (55.7) | 7 (46.7) | 77 (40.3) | 0.041 |
| *P* |  | Reference | 0.6057 | 0.6870 | 0.0081**\*** |  |
| Vitamin B12 (pmol/L) | 616 | 352.4 (305.9, 422.6) | 401.5 (341.9, 522.8) | 216.4 (156.5, 241.3) | 205.0 (169.6, 236.0) | 0.0001 |
| *P* |  | Reference | 0.0001\* | 0.0000\* | 0.000\* |  |
| Folate (nmol/L) | 616 | 20.1 (13.6, 29.6) | 59.9 (50.2, 69.0) | 55.6 (47.0, 64.6) | 14.8 (11.3, 22.3) | 0.0001 |
| *P* |  | Reference | 0.0000\* | 0.0000\* | 0.0000\* |  |
| Creatinine (umol/L) | 616 | 80 (69, 93) | 81 (68, 95) | 83 (72, 99) | 82 (72, 97) | 0.6782 |
| *P* |  | Reference | 0.8518 | 0.5813 | 0.2852 |  |
| Folic Acid Supplement Use [n (%)] | 19/616 | 8 (2.3) | 3 (4.90 | 3 (20.0) | 5 (2.6) | 0.013 |
| *P* |  | Reference | 0.3664 | 0.0991 | 0.8174 |  |
| MMSE | 616 | 29 (28, 30) | 29 (28, 30) | 29 (28, 29) | 29 (27, 30) | 0.1310 |
| *P* |  | Reference | 0.3820 | 0.8018 | 0.0540 |  |
| MoCA | 616 | 25 (24, 27) | 26 (24, 27) | 24 (24, 26) | 25 (23, 27) | 0.3896 |
| *P* |  | Reference | 0.4702 | 0.4152 | 0.2614 |  |
| **Age ≥ 80 years (*n* 95)** | | | | | | |
| *n (%)* | 95 | (*n* 52) | (*n* 5) | (*n* 4) | (*n* 34) |  |
| Female [*n* (%)] | 52/95 | 31 (59.6) | 5 (100) | 1 (25.0) | 15 (44.1) | 0.153 |
| *P* |  | Reference | 0.1915 | 0.1850 | 0.1637 |  |
| Vitamin B12 (pmol/L) | 95 | 329.9 (292.6, 399.7) | 386.2 (304.8, 608.4) | 216.0 (162.5, 244.0) | 176.2 (149.6, 222.9) | 0.0001 |
| *P* |  | Reference | 0.2952 | 0.0009\* | 0.0000\* |  |
| Folate (nmol/L) | 95 | 18.5 (12.4, 28.4) | 52.2 (47.7, 57.3) | 61.4 (53.4, 63.8) | 11.7 (9.2, 16.4) | 0.0001 |
| *P* |  | Reference | 0.0001\* | 0.0009\* | 0.0001\* |  |
| Creatinine (umol/L) | 95 | 87.5 (71.5, 104.5) | 80.5 (70, 87) | 92 (77, 104) | 89.5 (75, 109) | 0.7626 |
| *P* |  | Reference | 0.4588 | 0.8113 | 0.6333 |  |
| Folic Acid Supplement Use [n (%)] | 3/95 | 0 (0) | 2 (40.0) | 0 (0) | 1 (2.9) | 0.008 |
| *P* |  | Reference | 0.1172 | . | 0.3199 |  |
| MMSE | 95 | 28 (27, 29) | 27 (27, 29) | 27 (25.5, 28) | 28 (27, 30) | 0.4271 |
| *P* |  | Reference | 0.3375 | 0.1907 | 0.6680 |  |
| MoCA | 95 | 23.5 (21, 26) | 22.5 (20, 27) | 24 (21.5, 26) | 25 (21, 27) | 0.4840 |
| *P* |  | Reference | 0.4840 | 0.7607 | 0.1240 |  |

1 Non-normally distributed continuous variables were described as medians and interquartile ranges (IQR) (all such values), and compared using Kruskal-Wallis test as appropriate, and Mann–Whitney U test for pairwise comparisons with the reference category. Categorical variables were compared using the chi-square tests of Fisher’s exact test, as appropriate

\*Statistically significant after adjustment for multiple comparisons (*q* value <0.013).

**Supplementary Table 3. Associations of concentrations of vitamin B12 and folate status with global cognition (MMSE & MoCA): (incidence rate ratios; IRR, standard errors; SE and 95% Confidence Intervals; 95% CIs)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Model 0** | | | | | **Model 1** | | | | | **Model 2** | | | | |
|  | **IRR** | **SE** | **95% CIs** | | ***P*** | **IRR** | **SE** | **95% CIs** | | ***P*** | **IRR** | **SE** | **95% CIs** | | ***P*** |
| **≥ 50 years** | ***n* 3,871** | | | | | ***n* 3,712** | | | | | ***n* 3,299** | | | | |
| **MMSE** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ‘normal B12/high folate’ | 0.83 | 0.07 | 0.70 | 0.98 | 0.030 | 0.85 | 0.07 | 0.72 | 1.00 | 0.050 | 0.84 | 0.07 | 0.71 | 1.00 | 0.047 |
| ‘low B12/high folate’ | 1.24 | 0.25 | 0.84 | 1.83 | 0.274 | 0.90 | 0.14 | 0.66 | 1.22 | 0.501 | 0.88 | 0.14 | 0.64 | 1.21 | 0.438 |
| 'low B12/normal folate’ | 1.07 | 0.05 | 0.98 | 1.17 | 0.131 | 0.99 | 0.04 | 0.91 | 1.08 | 0.852 | 0.95 | 0.04 | 0.87 | 1.04 | 0.270 |
| **MoCA** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ‘normal B12/high folate’ | 0.91 | 0.04 | 0.83 | 0.99 | 0.031 | 0.92 | 0.04 | 0.86 | 1.00 | 0.041 | 0.92 | 0.03 | 0.85 | 1.00 | 0.043 |
| ‘low B12/high folate’ | 1.08 | 0.08 | 0.93 | 1.25 | 0.303 | 0.93 | 0.06 | 0.82 | 1.04 | 0.200 | 0.90 | 0.06 | 0.79 | 1.02 | 0.101 |
| 'low B12/normal folate’ | 1.06 | 0.03 | 1.01 | 1.12 | 0.011 | 1.03 | 0.02 | 0.98 | 1.07 | 0.262 | 1.00 | 0.02 | 0.95 | 1.04 | 0.948 |
| **≥ 60 years** | ***n* 2,070** | | | | | ***n* 1,972** | | | | | ***n* 1,761** | | | | |
| **MMSE** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ‘normal B12/high folate’ | 0.82 | 0.08 | 0.67 | 0.99 | 0.042 | 0.84 | 0.08 | 0.70 | 1.01 | 0.068 | 0.82 | 0.08 | 0.68 | 0.99 | 0.043 |
| ‘low B12/high folate’ | 1.23 | 0.27 | 0.81 | 1.89 | 0.319 | 0.99 | 0.18 | 0.68 | 1.43 | 0.949 | 0.99 | 0.17 | 0.70 | 1.39 | 0.946 |
| ‘low B12/normal folate’ | 1.08 | 0.05 | 0.98 | 1.20 | 0.119 | 0.99 | 0.05 | 0.90 | 1.09 | 0.874 | 0.96 | 0.05 | 0.86 | 1.06 | 0.416 |
| **MoCA** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ‘normal B12/high folate’ | 0.87 | 0.05 | 0.78 | 0.97 | 0.014 | 0.91 | 0.04 | 0.83 | 1.00 | 0.043 | 0.89 | 0.05 | 0.80 | 0.99 | 0.025 |
| ‘low B12/high folate’ | 1.01 | 0.09 | 0.86 | 1.20 | 0.877 | 0.91 | 0.07 | 0.79 | 1.05 | 0.20 | 0.90 | 0.07 | 0.78 | 1.04 | 0.165 |
| ‘low B12/normal folate’ | 1.04 | 0.03 | 0.98 | 1.11 | 0.150 | 1.00 | 0.03 | 0.95 | 1.06 | 0.99 | 0.98 | 0.03 | 0.92 | 1.03 | 0.413 |

Reference group = ‘normal B-12/normal folate', IRR =1.00

**Supplementary Table 4. Multivariate associations of concentrations of vitamin B12 and folate status with measures of global cognition (MMSE and MoCA), aged ≥ 50 years: (incidence rate ratios; IRR and 95% Confidence Intervals; 95% CIs)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Multivariate models:** | **MMSE** | | **MoCA** | |
|  | **Model 1** | **Model 2** | **Model 1** | **Model 2** |
| *n* | 3,712 | 3,299 | 3,712 | 3,299 |
| **Concentrations of vitamin B12 and folate status** |  |  |  |  |
| **‘normal B12/high folate’** | 0.85\* | 0.84\* | 0.92\* | 0.92\* |
|  | [0.72,1.00] | [0.71,1.00] | [0.86,1.00] | [0.85,1.00] |
| **‘low B12/high folate’** | 0.90 | 0.88 | 0.92 | 0.9 |
|  | [0.66,1.22] | [0.64,1.21] | [0.82,1.04] | [0.79,1.02] |
| **'low B12/normal folate’** | 0.99 | 0.95 | 1.03 | 1.00 |
|  | [0.91,1.08] | [0.87,1.04] | [0.98,1.07] | [0.95,1.04] |
| **Age (y)** |  |  |  |  |
| 50-59 | 1.00 | 1.00 | 1.00 | 1.00 |
|  | [1.00,1.00] | [1.00,1.00] | [1.00,1.00] | [1.00,1.00] |
| 60-69 | 1.11\* | 1.16\*\* | 1.12\*\*\* | 1.11\*\*\* |
|  | [1.02,1.21] | [1.05,1.27] | [1.07,1.16] | [1.06,1.16] |
| 70-79 | 1.41\*\*\* | 1.44\*\*\* | 1.27\*\*\* | 1.23\*\*\* |
|  | [1.28,1.56] | [1.28,1.62] | [1.21,1.35] | [1.15,1.31] |
| 80+ | 1.86\*\*\* | 1.88\*\*\* | 1.62\*\*\* | 1.54\*\*\* |
|  | [1.58,2.18] | [1.60,2.21] | [1.47,1.78] | [1.38,1.72] |
| **Sex** |  |  |  |  |
| Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  | [1.00,1.00] | [1.00,1.00] | [1.00,1.00] | [1.00,1.00] |
| Female | 0.89\*\* | 0.82\*\*\* | 0.99 | 0.90\*\* |
|  | [0.83,0.96] | [0.73,0.92] | [0.95,1.02] | [0.85,0.96] |
| **Educational Attainment** |  |  |  |  |
| None/Primary | 1.00 | 1.00 | 1.00 | 1.00 |
|  | [1.00,1.00] | [1.00,1.00] | [1.00,1.00] | [1.00,1.00] |
| Secondary | 0.60\*\*\* | 0.60\*\*\* | 0.80\*\*\* | 0.81\*\*\* |
|  | [0.56,0.65] | [0.55,0.66] | [0.76,0.83] | [0.77,0.85] |
| Tertiary/Higher | 0.34\*\*\* | 0.36\*\*\* | 0.48\*\*\* | 0.50\*\*\* |
|  | [0.30,0.38] | [0.32,0.40] | [0.46,0.51] | [0.47,0.53] |
| **Above Average Asset Wealth** | 0.91\* | 0.92 | 0.94\*\* | 0.94\*\* |
|  | [0.85,0.99] | [0.85,1.00] | [0.91,0.98] | [0.90,0.98] |
| **Living Alone** |  | 0.99 |  | 1.00 |
|  |  | [0.89,1.11] |  | [0.95,1.06] |
| **Physical Activity Level (IPAQ) [n (%)]** |  |  |  |  |
| Low |  | 1.00 |  | 1.00 |
|  |  | [1.00,1.00] |  | [1.00,1.00] |
| Moderate |  | 0.95 |  | 1.00 |
|  |  | [0.86,1.04] |  | [0.94,1.05] |
| High |  | 0.97 |  | 1.00 |
|  |  | [0.88,1.06] |  | [0.95,1.05] |
| **Smokers** |  | 1.10 |  | 1.04 |
|  |  | [0.98,1.23] |  | [0.98,1.11] |
| **Alcohol Consumers** |  | 1.02 |  | 0.98 |
|  |  | [0.93,1.12] |  | [0.93,1.02] |
| **BMI (kg/m2)** |  |  |  |  |
| Normal |  | 1.00 |  | 1.00 |
|  |  | [1.00,1.00] |  | [1.00,1.00] |
| Overweight |  | 1.08 |  | 1.04 |
|  |  | [0.97,1.19] |  | [0.99,1.10] |
| Obese [n (%)] |  | 1.10 |  | 1.10\*\* |
|  |  | [0.99,1.23] |  | [1.03,1.16] |
| **Mean grip strength** |  | 0.99 |  | 0.99\*\*\* |
|  |  | [0.99,1.00] |  | [0.99,1.00] |
| **Hypertension** |  | 1.02 |  | 1.02 |
|  |  | [0.95,1.10] |  | [0.98,1.06] |
| **Diabetes** |  | 1.07 |  | 1.08\* |
|  |  | [0.92,1.23] |  | [1.00,1.16] |
| **CES-D (Depressive Symptoms)** |  | 1.00 |  | 1.00 |
|  |  | [1.00,1.01] |  | [1.00,1.01] |
| **Folic Acid Supplement Use** |  | 1.21 |  | 1.08 |
|  |  | [0.75,1.96] |  | [0.81,1.43] |
| **Proton Pump Inhibitors** |  | 1.00 |  | 0.98 |
|  |  | [0.89,1.12] |  | [0.92,1.04] |
| **Statin Use** |  | 0.96 |  | 1.01 |
|  |  | [0.87,1.05] |  | [0.96,1.06] |
| **Thyroid Medication Use** |  | 1.06 |  | 1.01 |
|  |  | [0.92,1.23] |  | [0.93,1.09] |
| **Previous Stroke** |  | 1.19 |  | 1.07 |
|  |  | [0.84,1.67] |  | [0.89,1.29] |

Reference group = ‘normal B12/normal folate', IRR =1.00,  \*P<0•05, \*\*P<0•01, \*\*\*P<0•001

**Supplementary Table 5. Multivariate associations vitamin B12 and folate groups with measures of global cognition (MMSE and MoCA), aged ≥ 60 years: (incidence rate ratios; IRR and 95% Confidence Intervals; 95% CIs)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Multivariate models:** | **MMSE** | | **MoCA** | |
|  |  | |  | |
|  | **Model 1** | **Model 2** | **Model 1** | **Model 2** |
| *n* | **1,972** | 1,761 | 1,972 | 1,761 |
| **Concentrations of vitamin B12 and folate status** |  |  |  |  |
| **‘normal B12/high folate’** | 0.84 | 0.82\* | 0.91\* | 0.89\* |
|  | [0.70,1.01] | [0.68,0.99] | [0.83,1.00] | [0.80,0.99] |
| **‘low B12/high folate’** | 0.99 | 0.99 | 0.91 | 0.9 |
|  | [0.68,1.43] | [0.70,1.39] | [0.79,1.04] | [0.78,1.04] |
| **'low B12/normal folate’** | 0.99 | 0.96 | 1.00 | 0.98 |
|  | [0.90,1.09] | [0.86,1.06] | [0.95,1.06] | [0.92,1.03] |
| **Age (y)** |  |  |  |  |
| 60-69 | 1.00 | 1.00 | 1.00 | 1.00 |
|  | [1.00,1.00] | [1.00,1.00] | [1.00,1.00] | [1.00,1.00] |
| 70-79 | 1.29\*\*\* | 1.25\*\*\* | 1.15\*\*\* | 1.11\*\*\* |
|  | [1.17,1.42] | [1.13,1.39] | [1.08,1.21] | [1.05,1.18] |
| 80+ | 1.68\*\*\* | 1.63\*\*\* | 1.45\*\*\* | 1.40\*\*\* |
|  | [1.44,1.96] | [1.39,1.91] | [1.32,1.61] | [1.25,1.57] |
| **Sex** |  |  |  |  |
| Male | 1.00 | 1.00 | 1.00 | 1.00 |
|  | [1.00,1.00] | [1.00,1.00] | [1.00,1.00] | [1.00,1.00] |
| Female | 0.89\* | 0.82\*\* | 0.96 | 0.88\*\* |
|  | [0.81,0.98] | [0.71,0.94] | [0.91,1.01] | [0.81,0.96] |
| **Educational Attainment** |  |  |  |  |
| None/Primary | 1.00 | 1.00 | 1.00 | 1.00 |
|  | [1.00,1.00] | [1.00,1.00] | [1.00,1.00] | [1.00,1.00] |
| Secondary | 0.66\*\*\* | 0.63\*\*\* | 0.80\*\*\* | 0.80\*\*\* |
|  | [0.60,0.73] | [0.57,0.70] | [0.76,0.85] | [0.75,0.85] |
| Tertiary/Higher | 0.41\*\*\* | 0.40\*\*\* | 0.50\*\*\* | 0.52\*\*\* |
|  | [0.36,0.46] | [0.35,0.46] | [0.47,0.54] | [0.48,0.55] |
| **Above Average Asset Wealth** | 0.87\*\* | 0.88\* | 0.93\*\* | 0.92\*\* |
|  | [0.79,0.96] | [0.80,0.98] | [0.88,0.98] | [0.87,0.97] |
| **Living Alone** |  | 1.08 |  | 1.01 |
|  |  | [0.95,1.23] |  | [0.95,1.09] |
| **Physical Activity Level (IPAQ) [n (%)]** |  |  |  |  |
| Low |  | 1.00 |  | 1.00 |
|  |  | [1.00,1.00] |  | [1.00,1.00] |
| Moderate |  | 0.95 |  | 1.00 |
|  |  | [0.85,1.07] |  | [0.93,1.07] |
| High |  | 0.98 |  | 0.99 |
|  |  | [0.87,1.10] |  | [0.92,1.06] |
| **Smokers** |  |  |  |  |
|  |  | 1.07 |  | 1.03 |
| **Alcohol Consumers** |  | [0.92,1.25] |  | [0.94,1.13] |
|  |  | 1.04 |  | 0.97 |
| **BMI (kg/m2)** |  | [0.94,1.16] |  | [0.91,1.02] |
| Normal |  | 1.00 |  | 1.00 |
|  |  | [1.00,1.00] |  | [1.00,1.00] |
| Overweight |  | 0.97 |  | 1.02 |
|  |  | [0.86,1.10] |  | [0.95,1.09] |
| Obese [n (%)] |  | 0.99 |  | 1.07 |
|  |  | [0.87,1.13] |  | [0.99,1.15] |
| **Mean grip strength** |  | 0.99 |  | 0.99\*\* |
|  |  | [0.99,1.00] |  | [0.99,1.00] |
| **Hypertension** |  | 0.99 |  | 1.00 |
|  |  | [0.90,1.10] |  | [0.95,1.05] |
| **Diabetes** |  | 1.11 |  | 1.04 |
|  |  | [0.95,1.30] |  | [0.94,1.14] |
| **CES-D (Depressive Symptoms)** |  | 1.01 |  | 1.00 |
|  |  | [1.00,1.01] |  | [1.00,1.01] |
| **Folic Acid Supplement Use** |  | 1.14 |  | 1.08 |
|  |  | [0.72,1.80] |  | [0.80,1.46] |
| **Proton Pump Inhibitors** |  | 0.98 |  | 0.97 |
|  |  | [0.86,1.12] |  | [0.90,1.05] |
| **Statin Use** |  | 0.97 |  | 1.01 |
|  |  | [0.87,1.08] |  | [0.96,1.08] |
| **Thyroid Medication Use** |  | 1.06 |  | 1.01 |
|  |  | [0.89,1.26] |  | [0.91,1.12] |
| **Previous Stroke** |  | 0.94 |  | 1.03 |
|  |  | [0.65,1.35] |  | [0.83,1.27] |

Reference group = ‘normal B12/normal folate', IRR =1.00,  \*P<0•05, \*\*P<0•01, \*\*\*P<0•001

**Supplementary Table 6. Sensitivity Analysis : Associations of vitamin B12 and folate groups with global cognition (MMSE & MoCA); (incidence rate ratios; IRR, standard errors; SE and 95% Confidence Intervals; 95% CIs)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Model 0** | | | | | **Model 1** | | | | | **Model 2** |  |  |  |  |
|  | **IRR** | **SE** | **95% CIs** | | ***P*** | **IRR** | **SE** | **95% CIs** | | ***P*** | **IRR** | **SE** | **95% CIs** | | ***P*** |
| **≥ 50 years** | ***n* 4,463** | | | | | ***n* 4,263** | | | | | ***n* 3,765** | | | | |
| **MMSE** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ‘normal B12/high folate’ | 0.85 | 0.08 | 0.70 | 1.03 | 0.088 | 0.88 | 0.08 | 0.74 | 1.05 | 0.157 | 0.88 | 0.08 | 0.74 | 1.05 | 0.145 |
| ‘low B12/high folate’ | 1.17 | 0.22 | 0.82 | 1.68 | 0.379 | 0.85 | 0.14 | 0.63 | 1.17 | 0.319 | 0.83 | 0.14 | 0.61 | 1.15 | 0.267 |
| 'low B12/normal folate’ | 1.15 | 0.06 | 1.04 | 1.26 | 0.004 | 1.06 | 0.46 | 0.98 | 1.16 | 0.162 | 1.02 | 0.05 | 0.93 | 1.12 | 0.656 |
| **MoCA** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ‘normal B12/high folate’ | 0.89 | 0.04 | 0.81 | 0.98 | 0.021 | 0.90 | 0.04 | 0.83 | 0.98 | 0.020 | 0.92 | 0.40 | 0.84 | 1.00 | 0.042 |
| ‘low B12/high folate’ | 1.01 | 0.08 | 0.86 | 1.19 | 0.873 | 0.86 | 0.06 | 0.74 | 1.00 | 0.043 | 0.86 | 0.07 | 0.73 | 1.01 | 0.069 |
| 'low B12/normal folate’ | 1.07 | 0.03 | 1.03 | 1.13 | 0.004 | 1.03 | 0.02 | 0.99 | 1.08 | 0.152 | 1.01 | 0.03 | 0.97 | 1.07 | 0.517 |
| **≥ 60 years** | ***n* 2,426** | | | | | ***n* 2,298** | | | | | ***n* 2,040** | | | | |
| **MMSE** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ‘normal B12/high folate’ | 0.81 | 0.84 | 0.66 | 0.99 | 0.044 | 0.85 | 0.08 | 0.71 | 1.03 | 0.101 | 0.84 | 0.08 | 0.69 | 1.02 | 0.084 |
| ‘low B12/high folate’ | 1.16 | 0.23 | 0.78 | 1.17 | 0.457 | 0.97 | 1.18 | 0.67 | 1.40 | 0.870 | 1.00 | 0.19 | 0.69 | 1.45 | 0.991 |
| ‘low B12/normal folate’ | 1.18 | 0.07 | 1.05 | 1.33 | 0.005 | 1.10 | 0.06 | 0.99 | 1.24 | 0.075 | 1.07 | 0.07 | 0.95 | 1.20 | 0.279 |
| **MoCA** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ‘normal B12/high folate’ | 0.87 | 0.05 | 0.78 | 0.98 | 0.026 | 0.90 | 0.04 | 0.82 | 1.00 | 0.061 | 0.90 | 0.05 | 0.81 | 1.00 | 0.070 |
| ‘low B12/high folate’ | 0.97 | 0.09 | 0.80 | 1.17 | 0.737 | 0.86 | 0.08 | 0.72 | 1.03 | 0.113 | 0.89 | 0.09 | 0.73 | 1.09 | 0.250 |
| ‘low B12/normal folate’ | 1.08 | 0.03 | 1.01 | 1.15 | 0.016 | 1.04 | 0.03 | 0.98 | 1.10 | 0.169 | 1.02 | 0.03 | 0.96 | 1.09 | 0.506 |

Reference group = ‘normal B12/normal folate', IRR =1.00,  \*P<0•05, \*\*P<0•01, \*\*\*P<0•001

**Supplementary Table 7. Associations between concentrations of folate (continuous) and quintiles of vitamin B12 with global cognition in those aged ≥ 60 years (incidence rate ratios; IRR, standard errors; SE and 95% Confidence Intervals; 95% CIs)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Model 1** | | | | | **Model 2** | | | | |
|  | IRR | SE | 95% CIs | | *P* | IRR | SE | 95% CIs | | *P* |
| *n* | 1,972 | | | | | 1,761 | | | | |
| **MMSE** |  |  |  |  |  |  |  |  |  |  |
| Folate (Cont.): B12 Q1 | 1.00 | 0.01 | 0.99 | 1.01 | 0.838 | 1.00 | 0.01 | 0.99 | 1.01 | 0.804 |
| Folate (Cont.): B12 Q2 | 1.00 | 0.01 | 0.99 | 1.01 | 0.702 | 1.00 | 0.01 | 0.99 | 1.01 | 0.697 |
| Folate (Cont.): B12 Q3 | 1.00 | 0.01 | 0.99 | 1.01 | 0.835 | 1.00 | 0.01 | 0.99 | 1.01 | 0.898 |
| Folate (Cont.): B12 Q4 | 1.00 | 0.01 | 0.99 | 1.00 | 0.321 | 0.99 | 0.00 | 0.99 | 1.00 | 0.265 |
| **MoCA** |  |  |  |  |  |  |  |  |  |  |
| Folate (Cont.): B12 Q1 | 1.00 | 0.00 | 1.00 | 1.01 | 0.523 | 1.00 | 0.00 | 1.00 | 1.01 | 0.635 |
| Folate (Cont.): B12 Q2 | 1.00 | 0.00 | 0.99 | 1.00 | 0.464 | 1.00 | 0.00 | 0.99 | 1.00 | 0.575 |
| Folate (Cont.): B12 Q3 | 1.00 | 0.00 | 1.00 | 1.01 | 0.869 | 1.00 | 0.00 | 1.00 | 1.01 | 0.768 |
| Folate (Cont.): B12 Q4 | 1.00 | 0.00 | 0.99 | 1.00 | 0.096 | 0.99 | 0.00 | 0.99 | 1.00 | 0.029 |

Reference group = ‘Folate (Continuous): B12 Q5, IRR =1.00; Q1 vitamin B12 , 45.4 - 225 pmol/L (*n* 409), Q2 225 – 289 pmol/L (*n* 427), Q3 289 – 350 pmol/L (*n* 408); Q4 350 - 428 pmol/L (*n* 415); Q5 428 – 719 pmol/L (*n* 412)

**Supplementary Table 8. Associations between concentrations of vitamin B12 (continuous) and quintiles of folate with global cognition in those aged ≥ 60 years (incidence rate ratios; IRR, standard errors; SE and 95% Confidence Intervals; CIs)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Model 1** | | | | | **Model 2** | | | | |
|  | IRR | SE | 95% CIs | | *P* | IRR | SE | 95% CIs | | *P* |
| *n* | 1,972 | | | | | 1,761 | | | | |
| **MMSE** |  |  |  |  |  |  |  |  |  |  |
| **B12** (Cont.): Folate Q2 | 1.00 | 0.00 | 1.00 | 1.00 | 0.588 | 1.00 | 0.00 | 1.00 | 1.00 | 0.867 |
| **B12** (Cont.): Folate Q3 | 1.00 | 0.00 | 1.00 | 1.00 | 0.254 | 1.00 | 0.00 | 1.00 | 1.00 | 0.559 |
| **B12** (Cont.): Folate Q4 | 1.00 | 0.00 | 1.00 | 1.00 | 0.637 | 1.00 | 0.00 | 1.00 | 1.00 | 0.820 |
| **B12** (Cont.): Folate Q5 | 1.00 | 0.00 | 1.00 | 1.00 | 0.438 | 1.00 | 0.00 | 1.00 | 1.00 | 0.560 |
| **MoCA** |  |  |  |  |  |  |  |  |  |  |
| **B12** (Cont.): Folate Q2 | 1.00 | 0.00 | 1.00 | 1.00 | 0.342 | 1.00 | 0.00 | 1.00 | 1.00 | 0.558 |
| **B12** (Cont.): Folate Q3 | 1.00 | 0.00 | 1.00 | 1.00 | 0.534 | 1.00 | 0.00 | 1.00 | 1.00 | 0.882 |
| **B12** (Cont.): Folate Q4 | 1.00 | 0.00 | 1.00 | 1.00 | 0.687 | 1.00 | 0.00 | 1.00 | 1.00 | 0.764 |
| **B12** (Cont.): Folate Q5 | 1.00 | 0.00 | 1.00 | 1.00 | 0.400 | 1.00 | 0.00 | 1.00 | 1.00 | 0.389 |

Reference group = ‘B12 (Continuous): Folate Q1, IRR =1.00; Q1 folate, 1 - 11 nmol/L (*n* 376), Q2 11 – 16 nmol/L (*n* 401), Q3 16 – 22 nmol/L (*n* 379); Q4 22 – 33 nmol/L (*n* 439); Q5 33 – 81 nmol/L (*n* 475)