

Supplementary Materials

Table S1. Breakpoints of the non-linear association between folate /vitamin B12 status and cognitive performance

| Marker | Cognitive tests | | | |
|-------------------------------------|-----------------|-----------------------|----------------|--------------|
| | Memory recall | Memory delayed recall | Animal Fluency | Digit Symbol |
| RBC folate (nmol/L) | | | | |
| Overall | 1450 | 1600 | 1280 | 1780 |
| ¹ Low vitamin B12 status | / | / | 1130 | 1510 |
| Normal vitamin B12 status | 1530 | 1640 | 1490 | 1820 |
| <i>p</i> Value for interaction | 0.317 | 0.809 | 0.291 | 0.423 |
| Serum total folate (nmol/L) | | | | |
| Overall | 67.4 | 67.1 | 64.6 | 79.3 |
| Low vitamin B12 status | / | 67.2 | 49.3 | 82.6 |
| Normal vitamin B12 status | 50.6 | 51.7 | 74.1 | 77.5 |
| <i>p</i> Value for interaction | 0.268 | 0.075 | 0.262 | 0.828 |
| 5MeTHF (nmol/L) | | | | |
| Overall | 58.7 | 57.1 | 57.1 | 70.2 |
| Low vitamin B12 status | 70.56 | 60.8 | 40.85 | 71.4 |
| Normal vitamin B12 status | / | 44.8 | 66.3 | 69.6 |
| <i>p</i> Value for interaction | 0.172 | 0.073 | 0.332 | 0.764 |
| Vitamin B12 (pmol/L) | | | | |
| Overall | 811.8 | 659 | 345.4 | 405.2 |

¹B12 deficiency was classified as < 148 pmol/L, while elevated MMA was defined as > 210 nmol/L. Low vitamin B12 status was operationally defined in this study as having a low serum B12, an elevated MMA, or both.

/ refers to non applicable for estimated breakpoints in non-linear model (*p* for non-linear > 0.05)

5MeTHF: 5-methyltetrahydrofolat

Table S2. Mean (SD) scores of each cognitive test according to folates and vitamin B12 status

| Cognitive tests | Test Scores | | | | P value |
|---------------------|--------------------------|---------------|---------------|---------------|---------|
| | Total Sample (N=2204) | Cluster | | | |
| | | A (N=654) | B (N=1493) | C (N=57) | |
| CERAD-WL, mean (SD) | 19.25 (4.50) | 19.16 (4.74) | 19.29 (4.39) | 19.19 (4.72) | 0.837 |
| CERAD-DR, mean (SD) | 6.07 (2.29) | 6.09 (2.32) | 6.07 (2.28) | 6.05 (2.46) | 0.039 |
| AF, mean (SD) | 17.00 (5.47) | 16.98 (5.35) | 17.01 (5.54) | 16.82 (5.17) | 0.965 |
| DSST, mean (SD) | 47.65 (16.93) | 49.42 (16.05) | 46.84 (17.29) | 48.75 (15.76) | 0.004 |

CERAD-WL/DR: consortium to establish a registry for Alzheimer's disease -word learning/ delayed recall, AF: animal fluency, DSST: digit symbol substitution test

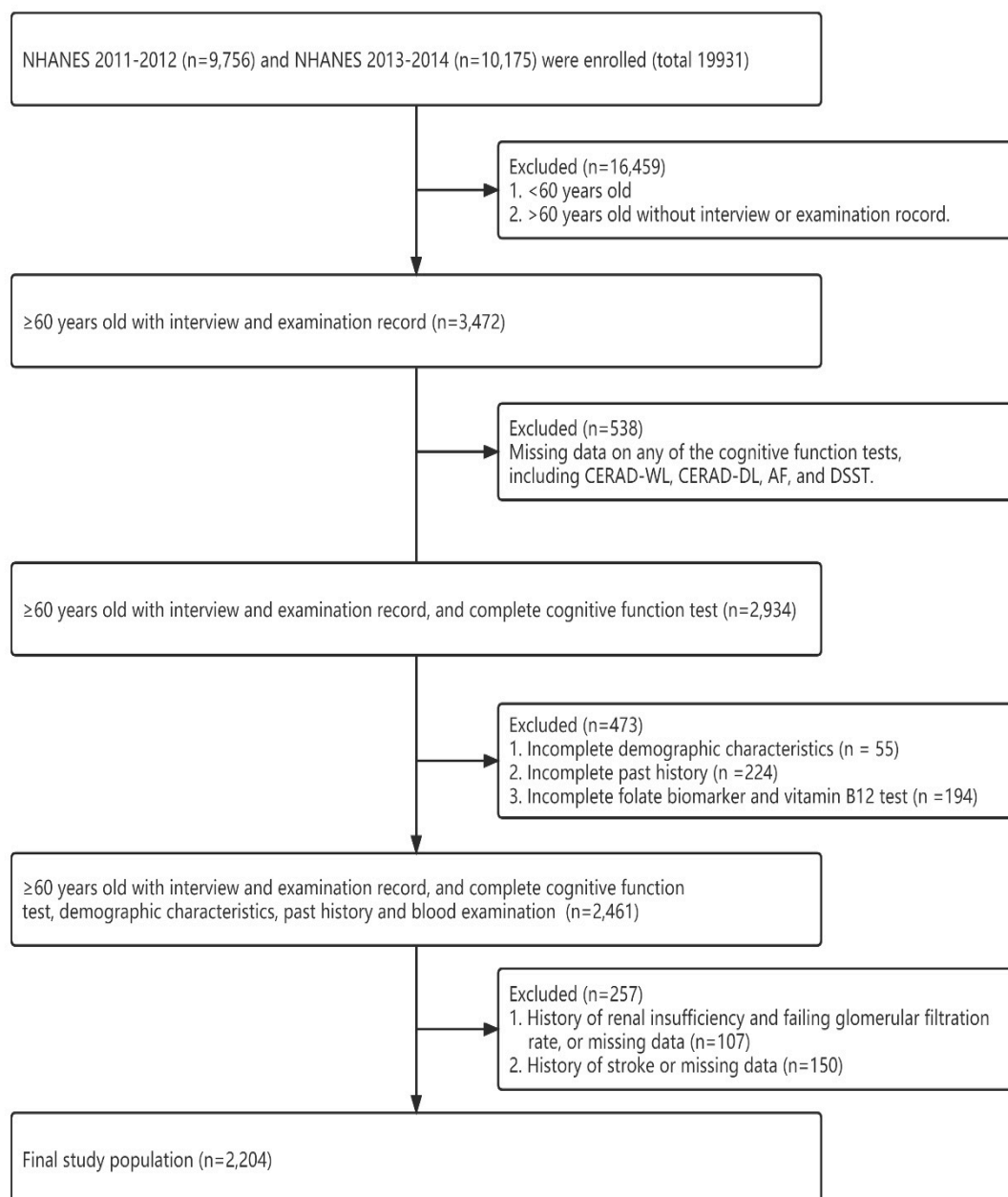


Figure S1. Flowchart illustrating sample stratification.

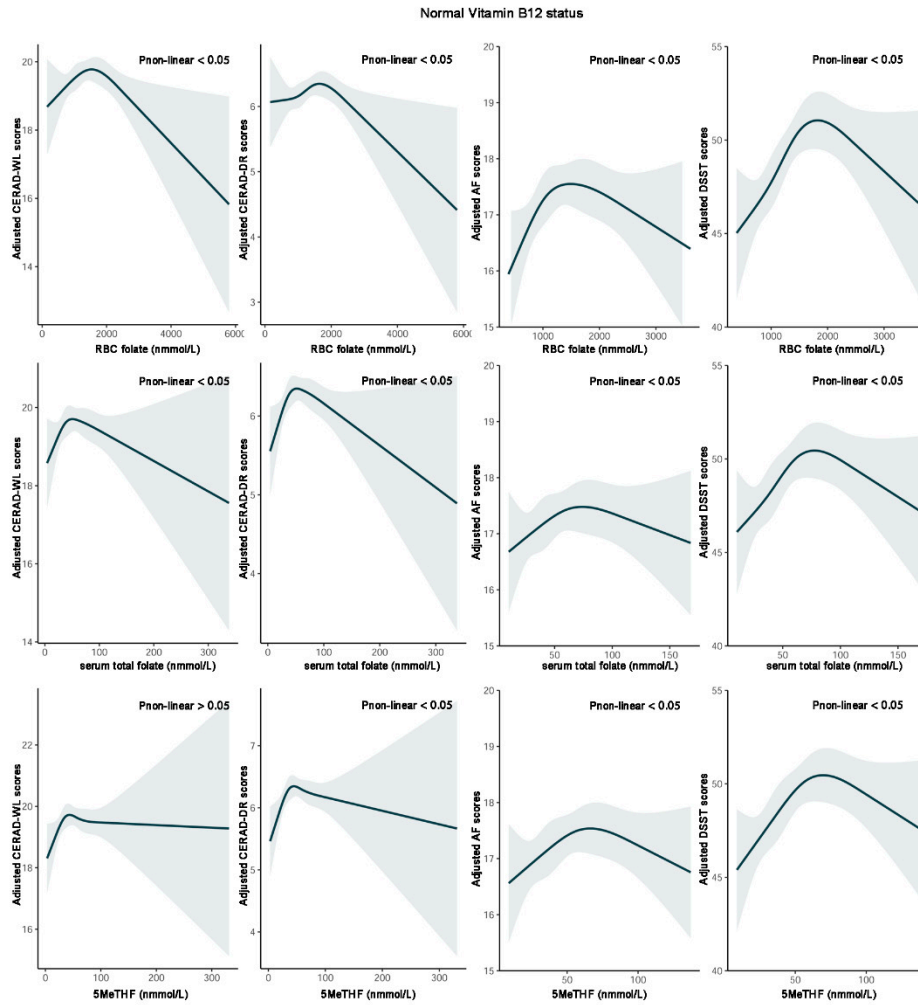


Figure S2. Association between folate status and cognitive performance in normal vitamin B12 status. The association between cognitive level and RBC folate, serum total folate, 5MeTHF was assessed by restricted cubic spline curves based on linear model estimation using ordinary least squares. The solid black lines with shaded regions indicate the adjusted recognition test scores and their corresponding 95% confidence intervals, respectively.

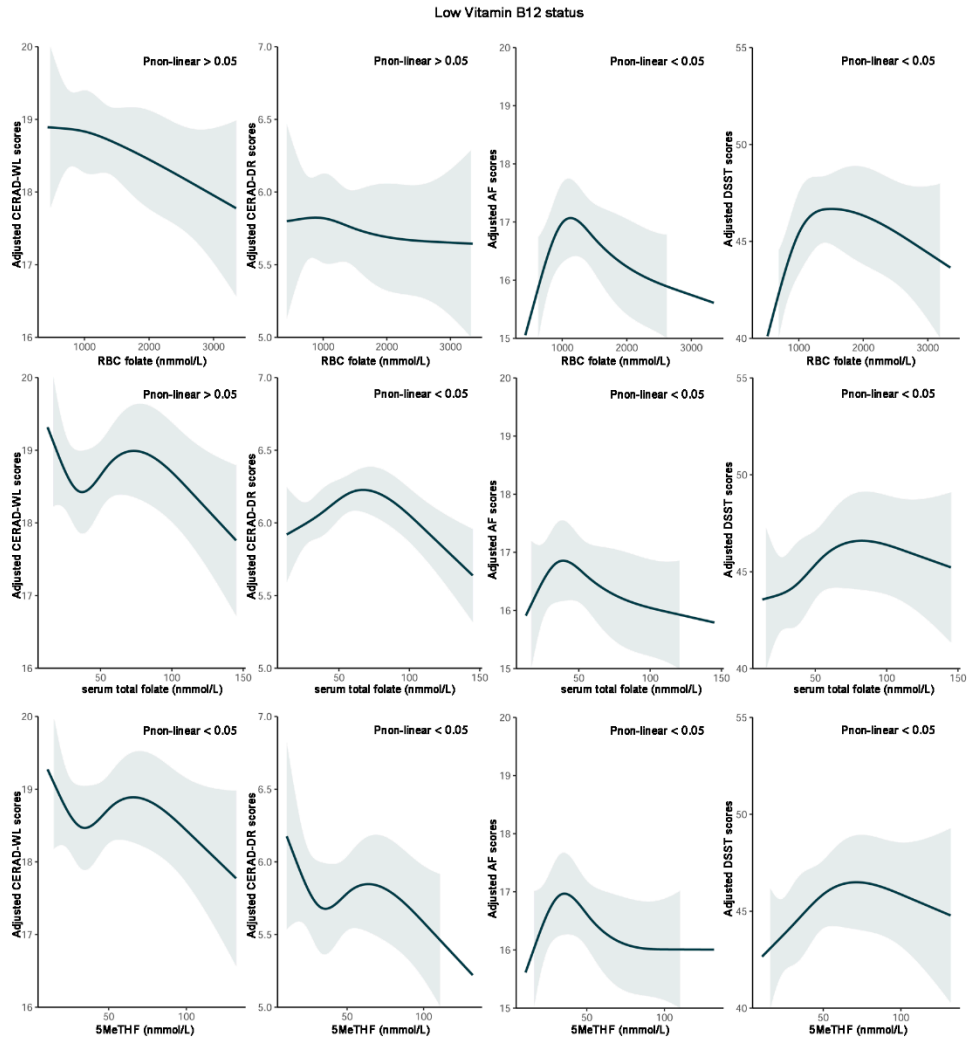


Figure S3. Association between folate status and cognitive performance in low vitamin B12 status. The association between cognitive level and RBC folate, serum total folate, 5MeTHF was assessed by restricted cubic spline curves based on linear model estimation using ordinary least squares. The solid black lines with shaded regions indicate the adjusted recognition test scores and their corresponding 95% confidence intervals, respectively.

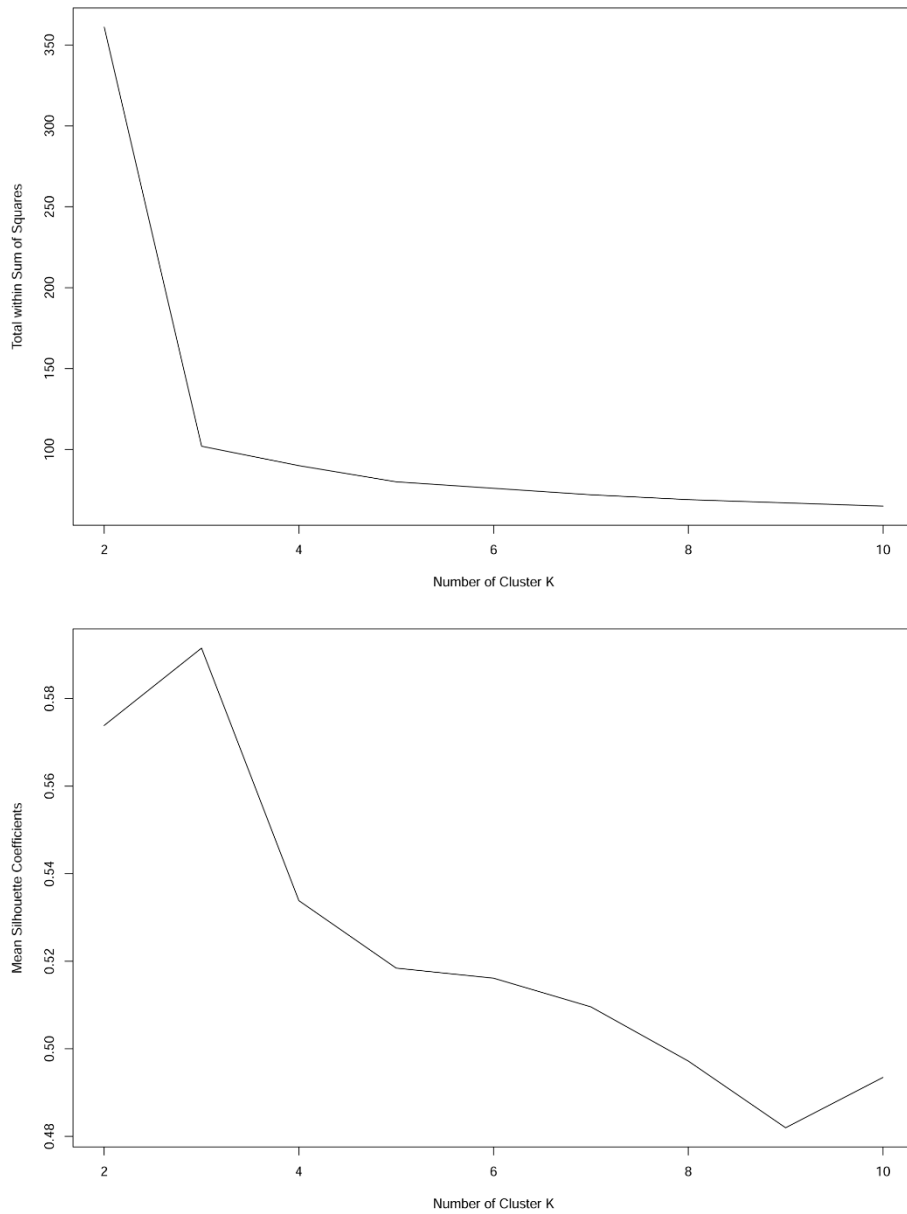


Figure S4. Elbow plot and Mean silhouette coefficients plot. Elbow plot and mean silhouette coefficients plot comparing cluster effect of different K. The elbow plot indicates the optimal number of clusters based on how tightly the clusters define their boundaries, and the mean silhouette coefficients define the compactness and separation of the clusters. When combining these 2 measures, one can estimate the optimal number of clusters, which in this case was determined to be 3.