

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Multivariable Linear Regression Analyses With Plasma Concentration of Vitamin B₁₂ as the Dependent Variable

| Variables | b | b (95% CI) | β | β (95% CI) | P-value |
|---------------------------------|---------|------------------|-------|----------------|-----------|
| Sex | 0.92 | [-9.97, 11.81] | 0.00 | [-0.04, 0.05] | 0.86 |
| Age | 0.14 | [-0.35, 0.63] | 0.01 | [-0.04, 0.06] | 0.58 |
| Ethnicity | -10.49 | [-29.20, 8.22] | -0.02 | [-0.05, 0.01] | 0.27 |
| Education (high) | 0.74 | [-7.89, 9.38] | 0.00 | [-0.03, 0.04] | 0.86 |
| BMI, kg/m ² | -0.58 | [-1.59, 0.43] | -0.02 | [-0.06, 0.02] | 0.26 |
| DBP, mm Hg | -0.16 | [-0.48, 0.17] | -0.03 | [-0.08, 0.03] | 0.35 |
| SBP, mm Hg | 0.62 | [-0.02, 1.25] | 0.05 | [0.00, 0.10] | 0.05 |
| Parental history of CKD | -7.70 | [-55.20, 39.80] | -0.01 | [-0.04, 0.03] | 0.75 |
| Parental history of T2D | -1.92 | [-11.97, 8.14] | -0.01 | [-0.04, 0.03] | 0.70 |
| T2D | 5.47 | [-16.78, 27.71] | 0.01 | [-0.03, 0.05] | 0.62 |
| Cancer history | 2.40 | [-15.54, 20.34] | 0.00 | [-0.03, 0.04] | 0.79 |
| CVD history | 1.48 | [-16.45, 19.40] | 0.00 | [-0.03, 0.04] | 0.87 |
| Smoking | -0.59 | [-3.98, 2.80] | -0.01 | [-0.04, 0.03] | 0.73 |
| Alcohol intake | -3.93 | [-9.60, 1.74] | -0.02 | [-0.06, 0.01] | 0.17 |
| Antihypertensive drugs | 8.63 | [-2.11, 19.37] | 0.03 | [-0.01, 0.07] | 0.11 |
| Lipid-lowering drugs | 15.42 | [0.60, 30.25] | 0.04 | [0.01, 0.07] | 0.04* |
| Ferritin, (μg/L) | 0.05 | [0.01, 0.08] | 0.05 | [0.02, 0.09] | 0.005** |
| Transferrin, (g/L) | -12.62 | [-22.66, -2.58] | -0.04 | [-0.08, -0.01] | 0.01* |
| Hemoglobin, mmol/L | 23.95 | [5.85, 42.04] | 0.15 | [0.04, 0.27] | 0.009** |
| Hematocrit, (%) | -333.02 | [-695.34, 29.30] | -0.10 | [-0.21, 0.01] | 0.07 |
| MCV, (fL) | -2.18 | [-3.11, -1.25] | -0.09 | [-0.12, -0.05] | <0.001*** |
| Homocysteine, (μmol/L) | -9.02 | [-10.00, -8.04] | -0.34 | [-0.38, -0.30] | <0.001*** |
| TC, mmol/L | 2.60 | [-1.60, 6.79] | 0.02 | [-0.01, 0.06] | 0.22 |
| HDL-C, mmol/L | 32.88 | [17.58, 48.18] | 0.09 | [0.05, 0.13] | <0.001*** |
| TG, mmol/L | -5.60 | [-10.73, -0.47] | -0.04 | [-0.08, -0.00] | 0.03* |
| Glucose, mmol/L | 3.04 | [-1.69, 7.76] | 0.03 | [-0.02, 0.07] | 0.20 |
| CRP, mg/L | 0.26 | [-0.44, 0.95] | 0.01 | [-0.02, 0.05] | 0.47 |
| eGFR, mL/min/1.73m ² | -0.78 | [-1.11, -0.46] | -0.11 | [-0.16, -0.07] | <0.001*** |
| UAE, mg/24h | 0.01 | [-0.01, 0.04] | 0.02 | [-0.01, 0.05] | 0.28 |
| ALT, (U/L) | 0.66 | [0.23, 1.09] | 0.08 | [0.03, 0.13] | 0.002** |
| AST, (U/L) | 0.74 | [0.05, 1.42] | 0.05 | [0.01, 0.10] | 0.03* |
| ALP, (U/L) | 0.18 | [-0.03, 0.38] | 0.03 | [0.00, 0.07] | 0.08 |
| GGT, (U/L) | 0.20 | [0.06, 0.33] | 0.06 | [0.02, 0.10] | 0.005** |

Standardized (β) and unstandardized (b) regression coefficients are shown. Significance codes: ‘***’: < 0.001; ‘**’: < 0.01; ‘*’: < 0.05.

eTable 2. Prospective Associations of Plasma Concentration of Vitamin B₁₂ With Risk of All-Cause Mortality After Excluding Individuals With History of Cardiovascular Disease

| | Vitamin B ₁₂ Per 1 SD Increment | | Q1 | Q2+Q3 | | Q4 | |
|------------------------|--|-----------------|-------|------------------|-----------------|------------------|-----------------|
| Participants, <i>n</i> | 5202 | | 1286 | 2607 | | 1309 | |
| Events, <i>n</i> | 167 | | 29 | 83 | | 55 | |
| | HR (95 % CI) | <i>P</i> -Value | | HR (95 % CI) | <i>P</i> -Value | HR (95 % CI) | <i>P</i> -Value |
| Crude Model | 1.32 [1.13;1.53] | <0.001 | (ref) | 1.40 [0.91;2.13] | 0.12 | 1.84 [1.17;2.88] | 0.007 |
| Model 1 | 1.32 [1.13;1.55] | <0.001 | (ref) | 1.37 [0.90;2.09] | 0.14 | 1.83 [1.16;2.87] | 0.008 |
| Model 2 | 1.35 [1.14;1.59] | < 0.001 | (ref) | 1.29 [0.83;2.00] | 0.25 | 1.86 [1.15;2.98] | 0.01 |
| Model 3 | 1.42 [1.20;1.69] | < 0.001 | (ref) | 1.40 [0.88;2.22] | 0.15 | 2.05 [1.24;3.38] | 0.005 |
| Model 4 | 1.40 [1.17;1.67] | < 0.001 | (ref) | 1.38 [0.86;2.22] | 0.18 | 1.93 [1.16;3.23] | 0.01 |
| Model 5 | 1.40 [1.17;1.67] | < 0.001 | (ref) | 1.36 [0.85;2.18] | 0.20 | 1.90 [1.13;3.18] | 0.01 |
| Model 6 | 1.42 [1.18;1.71] | < 0.001 | (ref) | 1.43 [0.87;2.37] | 0.16 | 2.13 [1.23;3.69] | 0.006 |
| Model 7 | 1.41 [1.17;1.71] | < 0.001 | (ref) | 1.44 [0.87;2.37] | 0.15 | 2.12 [1.22;3.68] | 0.007 |

Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). For HR of Vitamin B₁₂ per 1 SD increment, data was log_e transformed.

Model 1: Model adjusted for age and sex

Model 2: Model 1 + ethnicity + BMI + T2D + Smoking status (never, past, current) + Alcohol consumption (<1, 1-7,>7 drinks/week) + Education (low, medium, high) + SBP + homocysteine

Model 3: Model 2 + ferritin + hemoglobin + MCV

Model 4: Model 3 + TC / HDL-C ratio + glucose

Model 5: Model 4 + cancer history

Model 6: Model 5 + eGFR + UAE

Model 7: Model 6 + ALT + AST + ALP + GGT

eTable 3. Prospective Associations of Plasma Concentration of Vitamin B₁₂ With Risk of All-Cause Mortality After Excluding Individuals With History of Cancer

| | Vitamin B ₁₂ Per 1 SD Increment | | Q1 | Q2+Q3 | | Q4 | |
|------------------------|--|-----------------|-------|------------------|-----------------|------------------|-----------------|
| Participants, <i>n</i> | 5308 | | 1319 | 2655 | | 1334 | |
| Events, <i>n</i> | 203 | | 36 | 101 | | 66 | |
| | HR (95 % CI) | <i>P</i> -Value | | HR (95 % CI) | <i>P</i> -Value | HR (95 % CI) | <i>P</i> -Value |
| Crude Model | 1.21 [1.06;1.39] | 0.006 | (ref) | 1.38 [0.94;2.02] | 0.09 | 1.79 [1.19;2.69] | 0.004 |
| Model 1 | 1.21 [1.05;1.39] | 0.008 | (ref) | 1.37 [0.93;2.00] | 0.10 | 1.75 [1.17;2.63] | 0.007 |
| Model 2 | 1.25 [1.07;1.44] | 0.003 | (ref) | 1.35 [0.91;1.99] | 0.13 | 1.91 [1.25;2.92] | 0.002 |
| Model 3 | 1.25 [1.07;1.47] | 0.005 | (ref) | 1.42 [0.93;2.15] | 0.10 | 1.84 [1.17;2.92] | 0.008 |
| Model 4 | 1.25 [1.06;1.47] | 0.007 | (ref) | 1.42 [0.93;2.17] | 0.10 | 1.81 [1.13;2.87] | 0.01 |
| Model 5 | 1.23 [1.05;1.45] | 0.01 | (ref) | 1.40 [0.92;2.13] | 0.12 | 1.75 [1.10;2.80] | 0.01 |
| Model 6 | 1.23 [1.04;1.46] | 0.01 | (ref) | 1.46 [0.93;2.27] | 0.09 | 1.90 [1.16;3.11] | 0.01 |
| Model 7 | 1.23 [1.04;1.46] | 0.01 | (ref) | 1.45 [0.93;2.27] | 0.09 | 1.91 [1.16;3.13] | 0.01 |

Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). For HR of Vitamin B₁₂ per 1 SD increment, data was log_e transformed.

Model 1: Model adjusted for age and sex

Model 2: Model 1 + ethnicity + BMI + T2D + Smoking status (never, past, current) + Alcohol consumption (<1, 1-7,>7 drinks/week) + Education (low, medium, high) + SBP + homocysteine

Model 3: Model 2 + ferritin + hemoglobin + MCV

Model 4: Model 3 + TC / HDL-C ratio + glucose

Model 5: Model 4 + CVD history

Model 6: Model 5 + eGFR + UAE

Model 7: Model 6 + ALT + AST + ALP + GGT

eTable 4. Prospective Associations of Plasma Concentration of Vitamin B₁₂ With Risk of All-Cause Mortality After Excluding Individuals With Low Plasma Concentrations Vitamin B₁₂

| | Vitamin B ₁₂ Per 1 SD Increment | | Q1 | Q2+Q3 | | Q4 | |
|------------------------|--|-----------------|-------|------------------|-----------------|------------------|-----------------|
| Participants, <i>n</i> | 5376 | | 1344 | 2685 | | 1347 | |
| Events, <i>n</i> | 217 | | 36 | 111 | | 70 | |
| | HR (95 % CI) | <i>P</i> -Value | | HR (95 % CI) | <i>P</i> -Value | HR (95 % CI) | <i>P</i> -Value |
| Crude Model | 1.27 [1.12;1.45] | <0.001 | (ref) | 1.52 [1.04;2.21] | 0.02 | 1.91 [1.28;2.86] | 0.001 |
| Model 1 | 1.26 [1.11;1.44] | <0.001 | (ref) | 1.47 [1.01;2.14] | 0.04 | 1.87 [1.25;2.80] | 0.002 |
| Model 2 | 1.29 [1.13;1.48] | < 0.001 | (ref) | 1.48 [1.01;2.19] | 0.04 | 2.00 [1.31;3.05] | 0.001 |
| Model 3 | 1.29 [1.12;1.50] | < 0.001 | (ref) | 1.47 [0.98;2.21] | 0.06 | 1.87 [1.19;2.93] | 0.006 |
| Model 4 | 1.28 [1.10;1.48] | 0.001 | (ref) | 1.45 [0.96;2.17] | 0.07 | 1.79 [1.14;2.81] | 0.01 |
| Model 5 | 1.26 [1.08;1.46] | 0.002 | (ref) | 1.43 [0.96;2.15] | 0.08 | 1.75 [1.11;2.76] | 0.01 |
| Model 6 | 1.28 [1.09;1.49] | 0.002 | (ref) | 1.46 [0.95;2.26] | 0.08 | 1.93 [1.19;3.12] | 0.007 |
| Model 7 | 1.28 [1.10;1.50] | 0.001 | (ref) | 1.44 [0.93;2.22] | 0.09 | 1.93 [1.19;3.13] | 0.007 |

Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). For HR of Vitamin B₁₂ per 1 SD increment, data was log_e transformed.

Model 1: Model adjusted for age and sex

Model 2: Model 1 + ethnicity + BMI + T2D + Smoking status (never, past, current) + Alcohol consumption (<1, 1-7,>7 drinks/week) + Education (low, medium, high) + SBP + homocysteine

Model 3: Model 2 + ferritin + hemoglobin + MCV

Model 4: Model 3 + TC / HDL-C ratio + glucose

Model 5: Model 4 + cancer history + CVD history

Model 6: Model 5 + eGFR + UAE

Model 7: Model 6 + ALT + AST + ALP + GGT

eTable 5. Prospective Associations of Plasma Concentration of Vitamin B₁₂ With Risk of All-Cause Mortality After Excluding Individuals With High Plasma Concentrations Homocysteine

| | Vitamin B ₁₂ Per 1 SD Increment | | Q1 | Q2+Q3 | | Q4 | |
|------------------------|--|-----------------|-------|------------------|-----------------|------------------|-----------------|
| Participants, <i>n</i> | 4222 | | 1055 | 2105 | | 1062 | |
| Events, <i>n</i> | 120 | | 17 | 63 | | 40 | |
| | HR (95 % CI) | <i>P</i> -Value | | HR (95 % CI) | <i>P</i> -Value | HR (95 % CI) | <i>P</i> -Value |
| Crude Model | 1.38 [1.16;1.65] | <0.001 | (ref) | 1.85 [1.08;3.15] | 0.02 | 2.33 [1.32;4.11] | 0.003 |
| Model 1 | 1.26 [1.05;1.51] | 0.01 | (ref) | 1.47 [0.86;2.51] | 0.15 | 1.79 [1.01;3.16] | 0.04 |
| Model 2 | 1.23 [1.03;1.48] | 0.02 | (ref) | 1.43 [0.84;2.46] | 0.18 | 1.73 [0.98;3.06] | 0.06 |
| Model 3 | 1.24 [1.02;1.51] | 0.03 | (ref) | 1.22 [0.71;2.12] | 0.47 | 1.57 [0.87;2.84] | 0.13 |
| Model 4 | 1.23 [1.00;1.50] | 0.04 | (ref) | 1.23 [0.71;2.13] | 0.45 | 1.52 [0.84;2.77] | 0.17 |
| Model 5 | 1.21 [0.99;1.48] | 0.04 | (ref) | 1.24 [0.72;2.15] | 0.44 | 1.46 [0.80;2.66] | 0.21 |
| Model 6 | 1.24 [1.01;1.53] | 0.03 | (ref) | 1.25 [0.71;2.21] | 0.43 | 1.58 [0.85;2.93] | 0.14 |
| Model 7 | 1.25 [1.02;1.54] | 0.03 | (ref) | 1.27 [0.72;2.25] | 0.41 | 1.64 [0.88;3.05] | 0.12 |

Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). For HR of Vitamin B₁₂ per 1 SD increment, data was log_e transformed.

Model 1: Model adjusted for age and sex

Model 2: Model 1 + ethnicity + BMI + T2D + Smoking status (never, past, current) + Alcohol consumption (<1, 1-7,>7 drinks/week) + Education (low, medium, high) + SBP

Model 3: Model 2 + ferritin + hemoglobin + MCV

Model 4: Model 3 + TC / HDL-C ratio + glucose

Model 5: Model 4 + cancer history + CVD history

Model 6: Model 5 + eGFR + UAE

Model 7: Model 6 + ALT + AST + ALP + GGT

eTable 6. Prospective Associations of Plasma Concentration of Vitamin B₁₂ With Risk of All-Cause Mortality in All Individuals With Available Information

| | Vitamin B ₁₂ Per 1 SD Increment | | Q1 | Q2+Q3 | | Q4 | |
|------------------------|--|-----------------|-------|------------------|-----------------|------------------|-----------------|
| Participants, <i>n</i> | 5629 | | 1407 | 2813 | | 1409 | |
| Events, <i>n</i> | 233 | | 44 | 113 | | 76 | |
| | HR (95 % CI) | <i>P</i> -Value | | HR (95 % CI) | <i>P</i> -Value | HR (95 % CI) | <i>P</i> -Value |
| Crude Model | 1.23 [1.08;1.40] | 0.001 | (ref) | 1.27 [0.90;1.80] | 0.17 | 1.71 [1.18;2.48] | 0.004 |
| Model 1 | 1.20 [1.06;1.36] | 0.004 | (ref) | 1.26 [0.89;1.79] | 0.18 | 1.67 [1.15;2.42] | 0.006 |
| Model 2 | 1.25 [1.09;1.42] | 0.001 | (ref) | 1.28 [0.89;1.83] | 0.18 | 1.81 [1.22;2.68] | 0.002 |
| Model 3 | 1.24 [1.08;1.43] | 0.002 | (ref) | 1.33 [0.91;1.95] | 0.14 | 1.75 [1.15;2.68] | 0.009 |
| Model 4 | 1.24 [1.07;1.43] | 0.003 | (ref) | 1.32 [0.90;1.95] | 0.15 | 1.71 [1.11;2.63] | 0.01 |
| Model 5 | 1.20 [1.04;1.39] | 0.01 | (ref) | 1.32 [0.89;1.94] | 0.16 | 1.64 [1.07;2.53] | 0.02 |
| Model 6 | 1.21 [1.04;1.41] | 0.01 | (ref) | 1.35 [0.90;2.03] | 0.14 | 1.79 [1.13;2.83] | 0.01 |
| Model 7 | 1.23 [1.05;1.44] | 0.009 | (ref) | 1.32 [0.88;1.99] | 0.18 | 1.80 [1.14;2.86] | 0.01 |

Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). For HR of Vitamin B₁₂ per 1 SD increment, data was log_e transformed.

Model 1: Model adjusted for age and sex.

Model 2: Model 1 + ethnicity + BMI + T2D + Smoking status (never, past, current) + Alcohol consumption (<1, 1-7,>7 drinks/week) + Education (low, medium, high) + SBP

Model 3: Model 2 + ferritin + hemoglobin + MCV.

Model 4: Model 3 + TC/HDL-C ratio + glucose.

Model 5: Model 4 + cancer history + CVD history.

Model 6: Model 5 + eGFR + UAE.

Model 7: Model 6 + ALT + AST + ALP + GGT + B₁₂ supplementation

eTable 7. Prospective Associations of Plasma Concentration of Vitamin B₁₂ With Risk of All-Cause Mortality After Excluding Individuals With Mild to Moderated Loss of Kidney Function

| | Vitamin B ₁₂ Per 1 SD Increment | | Q1 | Q2+Q3 | | Q4 | |
|------------------------|--|-----------------|-------|------------------|-----------------|------------------|-----------------|
| Participants, <i>n</i> | 5342 | | 1333 | 2665 | | 1344 | |
| Events, <i>n</i> | 180 | | 34 | 89 | | 57 | |
| | HR (95 % CI) | <i>P</i> -Value | | HR (95 % CI) | <i>P</i> -Value | HR (95 % CI) | <i>P</i> -Value |
| Crude Model | 1.20 [1.04;1.39] | 0.01 | (ref) | 1.30 [0.87;1.92] | 0.20 | 1.64 [1.07;2.51] | 0.02 |
| Model 1 | 1.19 [1.03;1.38] | 0.01 | (ref) | 1.30 [0.88;1.93] | 0.19 | 1.63 [1.07;2.50] | 0.02 |
| Model 2 | 1.19 [1.01;1.39] | 0.03 | (ref) | 1.23 [0.82;1.85] | 0.32 | 1.63 [1.04;2.55] | 0.03 |
| Model 3 | 1.20 [1.02;1.43] | 0.03 | (ref) | 1.24 [0.80;1.91] | 0.33 | 1.62 [1.00;2.62] | 0.04 |
| Model 4 | 1.20 [1.01;1.43] | 0.03 | (ref) | 1.22 [0.78;1.89] | 0.38 | 1.58 [0.97;2.58] | 0.06 |
| Model 5 | 1.17 [0.99;1.40] | 0.06 | (ref) | 1.21 [0.78;1.88] | 0.39 | 1.52 [0.93;2.50] | 0.09 |
| Model 6 | 1.19 [0.99;1.43] | 0.06 | (ref) | 1.26 [0.79;2.01] | 0.33 | 1.70 [1.01;2.87] | 0.04 |
| Model 7 | 1.18 [0.98;1.42] | 0.07 | (ref) | 1.28 [0.80;2.05] | 0.29 | 1.70 [1.00;2.89] | 0.04 |

Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). For HR of Vitamin B₁₂ per 1 SD increment, data was log_e transformed.

Model 1: Model adjusted for age and sex.

Model 2: Model 1 + ethnicity + BMI + T2D + Smoking status (never, past, current) + Alcohol consumption (<1, 1-7,>7 drinks/week) + Education (low, medium, high) + SBP + homocysteine.

Model 3: Model 2 + ferritin + hemoglobin + MCV.

Model 4: Model 3 + TC/HDL-C ratio + glucose.

Model 5: Model 4 + cancer history + CVD history.

Model 6: Model 5 + eGFR + UAE.

Model 7: Model 6 + ALT + AST + ALP + GGT.

eTable 8. Prospective Associations of Plasma Concentration of Vitamin B₁₂ With Risk of All-Cause Mortality in a Design-Based Analysis

| | Vitamin B ₁₂ Per 1 SD Increment | | Q1 | Q2+Q3 | | Q4 | |
|------------------------|--|-----------------|-------|------------------|-----------------|------------------|-----------------|
| Participants, <i>n</i> | 5571 | | 1390 | 2787 | | 1394 | |
| Events, <i>n</i> | 226 | | 41 | 112 | | 73 | |
| | HR (95 % CI) | <i>P</i> -Value | | HR (95 % CI) | <i>P</i> -Value | HR (95 % CI) | <i>P</i> -Value |
| Crude Model | 1.36 [1.17;1.57] | <0.001 | (ref) | 1.19 [0.80;1.77] | 0.40 | 2.06 [1.37;3.10] | <0.001 |
| Model 1 | 1.32 [1.14;1.53] | <0.001 | (ref) | 1.19 [0.80;1.78] | 0.38 | 1.98 [1.31;2.98] | 0.001 |
| Model 2 | 1.38 [1.18;1.62] | <0.001 | (ref) | 1.20 [0.79;1.82] | 0.38 | 2.21 [1.43;3.43] | <0.001 |
| Model 3 | 1.38 [1.17;1.63] | <0.001 | (ref) | 1.23 [0.80;1.89] | 0.35 | 2.13 [1.34;3.38] | 0.001 |
| Model 4 | 1.33 [1.12;1.57] | 0.001 | (ref) | 1.16 [0.75;1.80] | 0.49 | 1.90 [1.19;3.05] | 0.007 |
| Model 5 | 1.30 [1.10;1.54] | 0.002 | (ref) | 1.15 [0.74;1.79] | 0.52 | 1.84 [1.15;2.97] | 0.01 |
| Model 6 | 1.33 [1.12;1.58] | 0.001 | (ref) | 1.17 [0.75;1.84] | 0.48 | 2.00 [1.22;3.25] | 0.005 |
| Model 7 | 1.33 [1.12;1.59] | 0.001 | (ref) | 1.16 [0.74;1.81] | 0.52 | 2.01 [1.23;3.30] | 0.005 |

Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). For HR of Vitamin B₁₂ per 1 SD increment, data was log_e transformed.

Model 1: Model adjusted for age and sex.

Model 2: Model 1 + ethnicity + BMI + T2D + Smoking status (never, past, current) + Alcohol consumption (<1, 1-7,>7 drinks/week) + Education (low, medium, high) + SBP + homocysteine

Model 3: Model 2 + ferritin + hemoglobin + MCV.

Model 4: Model 3 + TC/HDL-C ratio + glucose.

Model 5: Model 4 + cancer history + CVD history.

Model 6: Model 5 + eGFR + UAE.

Model 7: Model 6 + ALT + AST + ALP + GGT + B₁₂ supplementation

eTable 9. All-Cause Mortality Relative Risks for Each Stratum of Smoking Behavior

| | All-cause mortality | | | Proportion of deaths (all-cause mortality) (%) |
|--|---------------------|-------|-------|---|
| | Dead | Alive | Total | |
| <i>All participants^a</i> | | | | |
| Q1 of Vitamin B ₁₂ | 41 | 1349 | 1390 | 2.9 |
| Q2+Q3 of Vitamin B ₁₂ | 112 | 2675 | 2787 | 4.0 |
| Q4 of Vitamin B ₁₂ | 73 | 1321 | 1394 | 5.2 |
| <i>Participants who never smoked^b</i> | | | | |
| Q1 of Vitamin B ₁₂ | 7 | 372 | 379 | 1.8 |
| Q2+Q3 of Vitamin B ₁₂ | 13 | 765 | 778 | 1.7 |
| Q4 of Vitamin B ₁₂ | 12 | 408 | 420 | 2.9 |
| <i>Former smokers^c</i> | | | | |
| Q1 of Vitamin B ₁₂ | 25 | 556 | 581 | 4.3 |
| Q2+Q3 of Vitamin B ₁₂ | 61 | 1119 | 1180 | 5.2 |
| Q4 of Vitamin B ₁₂ | 42 | 575 | 617 | 6.8 |
| <i>Current smokers^d</i> | | | | |
| Q1 of Vitamin B ₁₂ | 9 | 400 | 409 | 2.2 |
| Q2+Q3 of Vitamin B ₁₂ | 37 | 759 | 796 | 4.6 |
| Q4 of Vitamin B ₁₂ | 19 | 323 | 342 | 5.6 |

a. Crude Relative Risk=5.2%/2.9%= 1.8.

b. Stratum-specific Relative Risk =2.9%/1.8%= 1.6.

c. Stratum-specific Relative Risk =6.8%/4.3%= 1.6.

d. Stratum-specific Relative Risk =5.6%/2.2%= 2.5.

eTable 10. All-Cause Mortality Relative Risks for Each Stratum of Alcohol Consumption Behavior

| | All-cause mortality | | | Proportion of deaths (all-cause mortality) (%) |
|---|---------------------|-------|-------|---|
| | Dead | Alive | Total | |
| <i>All Participants^a</i> | | | | |
| Q1 of Vitamin B ₁₂ | 41 | 1349 | 1390 | 2.9 |
| Q2+Q3 of Vitamin B ₁₂ | 112 | 2675 | 2787 | 4.0 |
| Q4 of Vitamin B ₁₂ | 73 | 1321 | 1394 | 5.2 |
| <i>Participants with alcohol intake <1 drinks/week^b</i> | | | | |
| Q1 of Vitamin B ₁₂ | 15 | 337 | 352 | 4.5 |
| Q2+Q3 of Vitamin B ₁₂ | 33 | 674 | 707 | 4.7 |
| Q4 of Vitamin B ₁₂ | 20 | 345 | 365 | 5.5 |
| <i>Participants with alcohol intake = 1-7 drinks/week^c</i> | | | | |
| Q1 of Vitamin B ₁₂ | 20 | 650 | 670 | 3.0 |
| Q2+Q3 of Vitamin B ₁₂ | 49 | 1316 | 1365 | 3.6 |
| Q4 of Vitamin B ₁₂ | 28 | 590 | 618 | 4.5 |
| <i>Participants with alcohol intake >7 drinks/week^d</i> | | | | |
| Q1 of Vitamin B ₁₂ | 15 | 337 | 352 | 4.3 |
| Q2+Q3 of Vitamin B ₁₂ | 33 | 674 | 707 | 4.7 |
| Q4 of Vitamin B ₁₂ | 20 | 345 | 365 | 5.5 |

a. Crude Relative Risk=5.2%/2.9%= 1.8.

b. Stratum-specific Relative Risk =5.5%/4.5%= 1.2.

c. Stratum-specific Relative Risk =4.5%/3.0%= 1.5.

d. Stratum-specific Relative Risk =5.5%/4.3%= 1.3.

eTable 11. All-Cause Mortality Relative Risks for Each Stratum of Age

| | All-cause mortality | | | Proportion of deaths (all-cause mortality) (%) |
|--|---------------------|-------|-------|---|
| | Dead | Alive | Total | |
| <i>All Participants^a</i> | | | | |
| Q1 of Vitamin B ₁₂ | 41 | 1349 | 1390 | 2.9 |
| Q2+Q3 of Vitamin B ₁₂ | 112 | 2675 | 2787 | 4.0 |
| Q4 of Vitamin B ₁₂ | 73 | 1321 | 1394 | 5.2 |
| <i>Participants <65 years old^b</i> | | | | |
| Q1 of Vitamin B ₁₂ | 12 | 1089 | 1101 | 1.1 |
| Q2+Q3 of Vitamin B ₁₂ | 31 | 2184 | 2215 | 1.4 |
| Q4 of Vitamin B ₁₂ | 20 | 1061 | 1081 | 1.9 |
| <i>Participants with ≥65 years old^c</i> | | | | |
| Q1 of Vitamin B ₁₂ | 29 | 260 | 289 | 10.0 |
| Q2+Q3 of Vitamin B ₁₂ | 81 | 491 | 572 | 14.2 |
| Q4 of Vitamin B ₁₂ | 53 | 260 | 313 | 16.9 |

a. Crude Relative Risk=5.2%/2.9%= 1.8.

b. Stratum-specific Relative Risk =1.9%/1.1%= 1.7.

c. Stratum-specific Relative Risk =16.9%/10%= 1.7.

eTable 12. Prospective Associations of Plasma Concentration of Vitamin B₁₂ With Risk of Cancer Mortality

| | Vitamin B ₁₂ Per 1 SD Increment | | Q1 | Q2+Q3 | | Q4 | |
|------------------------|--|----------------|-------|------------------|----------------|------------------|----------------|
| Participants, <i>n</i> | 5571 | | 1390 | 2787 | | 1394 | |
| Events, <i>n</i> | 172 | | 41 | 76 | | 55 | |
| | HR (95 % CI) | <i>P</i> Value | | HR (95 % CI) | <i>P</i> Value | HR (95 % CI) | <i>P</i> Value |
| Crude Model | 1.14 [0.98;1.33] | 0.08 | (ref) | 0.94 [0.64;1.37] | 0.73 | 1.36 [0.91;2.04] | 0.13 |
| Model 1 | 1.13 [0.97;1.31] | 0.10 | (ref) | 0.92 [0.63;1.35] | 0.67 | 1.33 [0.88;1.99] | 0.17 |
| Model 2 | 1.12 [0.96;1.32] | 0.15 | (ref) | 0.86 [0.58;1.28] | 0.45 | 1.32 [0.86;2.02] | 0.20 |
| Model 3 | 1.12 [0.94;1.33] | 0.20 | (ref) | 0.88 [0.58;1.33] | 0.53 | 1.26 [0.80;2.00] | 0.31 |
| Model 4 | 1.10 [0.92;1.31] | 0.29 | (ref) | 0.86 [0.56;1.30] | 0.47 | 1.18 [0.74;1.87] | 0.49 |
| Model 5 | 1.09 [0.91;1.30] | 0.35 | (ref) | 0.83 [0.55;1.27] | 0.39 | 1.17 [0.73;1.86] | 0.51 |
| Model 6 | 1.11 [0.92;1.33] | 0.26 | (ref) | 0.87 [0.57;1.35] | 0.54 | 1.22 [0.75;1.98] | 0.43 |
| Model 7 | 1.13 [0.93;1.36] | 0.21 | (ref) | 0.88 [0.57;1.36] | 0.55 | 1.28 [0.78;2.09] | 0.32 |

Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). For HR of Vitamin B₁₂ per 1 SD increment, data was log_e transformed.

Model 1: Model adjusted for age and sex.

Model 2: Model 1 + ethnicity + BMI + T2D + Smoking status (never, past, current) + Alcohol consumption (<1, 1-7,>7 drinks/week) + Education (low, medium, high) + SBP + homocysteine.

Model 3: Model 2 + ferritin + hemoglobin + MCV.

Model 4: Model 3 + TC/HDL-C ratio + glucose.

Model 5: Model 4 + cancer history + CVD history.

Model 6: Model 5 + eGFR + UAE.

Model 7: Model 6 + ALT + AST + ALP + GGT.

eTable 13. Prospective Associations of Plasma Concentration of Vitamin B₁₂ With Risk of Cardiovascular Mortality

| | Vitamin B ₁₂ Per 1 SD Increment | | Q1 | Q2+Q3 | | Q4 | |
|------------------------|--|----------------|-------|------------------|----------------|------------------|----------------|
| Participants, <i>n</i> | 5571 | | 1390 | 2787 | | 1394 | |
| Events, <i>n</i> | 53 | | 8 | 29 | | 16 | |
| | HR (95 % CI) | <i>P</i> Value | | HR (95 % CI) | <i>P</i> Value | HR (95 % CI) | <i>P</i> Value |
| Crude Model | 1.20 [0.91;1.57] | 0.19 | (ref) | 1.79 [0.82;3.91] | 0.14 | 1.97 [0.84;4.61] | 0.11 |
| Model 1 | 1.20 [0.92;1.58] | 0.18 | (ref) | 1.81 [0.83;3.97] | 0.13 | 1.99 [0.85;4.66] | 0.11 |
| Model 2 | 1.24 [0.93;1.66] | 0.14 | (ref) | 2.20 [0.97;4.98] | 0.05 | 2.07 [0.80;5.32] | 0.13 |
| Model 3 | 1.21 [0.90;1.64] | 0.21 | (ref) | 2.15 [0.94;4.92] | 0.07 | 1.91 [0.72;5.04] | 0.19 |
| Model 4 | 1.20 [0.88;1.62] | 0.25 | (ref) | 2.26 [0.97;5.27] | 0.05 | 1.79 [0.66;4.86] | 0.25 |
| Model 5 | 1.16 [0.85;1.59] | 0.34 | (ref) | 2.31 [0.98;5.42] | 0.05 | 1.62 [0.58;4.54] | 0.35 |
| Model 6 | 1.07 [0.76;1.51] | 0.69 | (ref) | 1.88 [0.79;4.51] | 0.15 | 1.37 [0.46;4.03] | 0.56 |
| Model 7 | 1.06 [0.75;1.51] | 0.74 | (ref) | 1.79 [0.74;4.32] | 0.19 | 1.33 [0.45;3.95] | 0.60 |

Data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). For HR of Vitamin B₁₂ per 1 SD increment, data was log_e transformed.

Model 1: Model adjusted for age and sex.

Model 2: Model 1 + ethnicity + BMI + T2D + Smoking status (never, past, current) + Alcohol consumption (<1, 1-7,>7 drinks/week) + Education (low, medium, high) + SBP + homocysteine.

Model 3: Model 2 + ferritin + hemoglobin + MCV.

Model 4: Model 3 + TC/HDL-C ratio + glucose.

Model 5: Model 4 + cancer history + CVD history.

Model 6: Model 5 + eGFR + UAE.

Model 7: Model 6 + ALT + AST + ALP + GGT.