**Supplemental table 1: Multivariate regression models to assess association
between vitamin B-12 status and nerve conduction outcomes (unadjusted analyses)1.**

|  |  |
| --- | --- |
|  |  |
|  | Unadjusted coefficients(95% CI) | B-12 (pmol/l) | HoloTC (pmol/l) | cB-12 |
| Sensory SAP amplitudes (µV)2 | n | 164 | 158 | 158 |
|  | Median  | -0.01 (-0.03, 0.00) | -0.01 (-0.04, 0.03) | -0.84 (-3.10, 1.26) |
|  | Ulnar | -0.01 (-0.02, -0.00) | -0.00 (-0.03, 0.03) | -0.61 (-2.09, 0.80) |
|  | Sural | -0.00 (-0.01, 0.01) | -0.01 (-0.04, 0.03) | 0.01 (-1.48, 1.47) |
|  | Superficial peroneal | -0.00 (-0.01, 0.01) | -0.00 (-0.02, 0.02) | 0.33 (-0.92, 1.44) |
|  |  | p=0.17 | p=0.99 | p=0.75 |
| Sensory nerve conduction velocities (m/s) | n | 115 | 110 | 110 |
|  | Median  | 0.00 (-0.02, 0.02) | 0.02 (-0.02, 0.06) | 1.31 (-1.51, 4.34) |
|  | Ulnar | -0.01 (-0.03, 0.00) | -0.03 (-0.07, 0.00) | -1.80 (-3.64, 0.10) |
|  | Sural | -0.01 (-0.03, 0.00) | -0.01 (-0.05, 0.03) | -2.54 (-4.90, -0.01) |
|  | Superficial peroneal | -0.01 (-0.03, 0.01) | 0.00 (-0.05, 0.05) | -1.05 (-3.67, 1.79) |
|  |  | p=0.10 | p=0.10 | p=0.00 |
| Motor CMAP amplitudes (mV) | n | 164 | 158 | 158 |
|  | Median | -0.01 (-0.01, -0.00) | -0.00 (-0.02, 0.01) | -0.18 (-0.76, 0.54) |
|  | Ulnar | 0.01 (-0.00, 0.01) | 0.01 (-0.01, 0.03) | 0.85 (-0.11, 1.75) |
|  | Tibial | -0.01 (-0.01, 0.00) | -0.00 (-0.03, 0.02) | -0.11 (-1.79, 1.38) |
|  | Common peroneal | 0.00 (-0.00, 0.01) | 0.00 (-0.01, 0.02) | 0.58 (-0.15, 1.24) |
|  |  | p=0.01 | p=0.60 | p=0.05 |
| Motor nerve conduction velocities(m/s) | n | 153 | 148 | 148 |
|  | Median | -0.00 (-0.02, 0.01) | 0.00 (-0.04, 0.04) | -0.22 (-2.22, 2.39) |
|  | Ulnar | 0.00 (-0.02, 0.02) | 0.01 (-0.04, 0.05) | 0.71 (-1.84, 2.77) |
|  | Tibial | 0.00 (-0.01, 0.02) | 0.00 (-0.03, 0.05) | 0.28 (-1.88, 2.44) |
|  | Common peroneal | -0.01 (-0.02, 0.01) | -0.02 (-0.05, 0.02) | -0.38 (-2.17, 1.84) |
|  |  | p=0.79 | p=0.76 | p=0.93 |
| Central motor conduction (ms) | n | 147 | 142 | 142 |
|  | ADM CMCT | 0.00 (-0.00, 0.01) | -0.00 (-0.01, 0.00) | 0.17 (-0.34, 0.62) |
|  | AH CMCT | 0.00 (-0.01, 0.01) | -0.00 (-0.03, 0.03) | 0.02 (-1.78, 1.84) |
|  |  | p=0.40 | p=0.66 | p=0.74 |
|  | n | 164 | 158 | 158 |
|  | Mean ADM MEP amplitude (mV) | -0.00 (-0.00, 0.00) | -0.00 (-0.01, 0.01) | -0.01 (-0.61, 0.60) |
|  |  | p=0.99 | p=0.61 | p=0.98 |

1HoloTC,holotranscobalamin; SAP, sensory action potential; CMAP, compound muscle action potential; ADM, abductor digiti minimi;
 CMCT, central motor conduction time; AH, abductor hallucis; MEP, motor evoked potential.

2 Percentage of absent (SAP amplitude=0) responses= 3 for median, 4 for ulnar, 14 for sural and 20 for superficial peroneal nerves.

**Supplemental table 2: Logistic regression models to assess association between vitamin B-12 status and clinical markers of
nerve function**

**Vitamin B12 (pmol/L)**

|  |  |  |
| --- | --- | --- |
|  | **Unadjusted** | **Adjusted for age and sex** |
| **Clinical marker** | **Absent** | **Mean (sd)**  | **Present** | **Mean (sd)**  | **OR (95% CI)** | **OR (95% CI)** |
| Right knee jerk | 15 | 246.71 (61.09) | 150 | 231.83 (54.09) | 1.01 (1.00, 1.01) | 1.01 (1.00, 0.02) |
| Right ankle jerk | 45 | 235.60 (51.75) | 120 | 232.28 (55.99) | 1.00 (1.00, 1.01) | 1.00 (0.99, 1.01) |
| Joint position sense (right great toe) | 12 | 257.27 (58.46) | 153 | 231.30 (54.17) | 1.01 (1.00, 1.02) | 1.01 (1.00, 1.02) |
| Vibration sense (right great toe) | 105 | 229.20 (52.73) | 60 | 240.16 (57.85) | 0.97 (0.99, 1.00) | 1.00 (0.99, 1.00) |

**Holotranscobalamin (pmol/L)**

|  |  |  |
| --- | --- | --- |
|  | **Unadjusted** | **Adjusted for age and sex** |
| **Clinical marker** | **Absent** | **Mean (sd)**  | **Present** | **Mean (sd)**  | **OR (95% CI)** | **OR (95% CI)** |
| Right knee jerk | 15 | 51.16 (18.81) | 144 | 52.75 (19.93) | 1.00 (0.97, 1.02) | 1.00 (0.97, 1.03) |
| Right ankle jerk | 43 | 51.57 (19.87) | 116 | 52.98 (19.81) | 1.00 (0.98, 1.01) | 1.00 (0.98, 1.02) |
| Joint position sense (right great toe) | 11 | 51.57 (19.82) | 148 | 52.67 (19.84) | 1.00 (0.97, 1.03) | 1.00 (0.97, 1.03) |
| Vibration sense (right great toe) | 101 | 51.55 (18.54) | 58 | 54.43 (21.81) | 0.99 (0.98, 1.01) | 0.99 (0.98, 1.01) |

**cB-12**

|  |  |  |
| --- | --- | --- |
|  | **Unadjusted** | **Adjusted for age and sex** |
| **Clinical marker** | **Absent** | **Mean (sd)**  | **Present** | **Mean (sd)**  | **OR (95% CI)** | **OR (95% CI)** |
| Right knee jerk | 15 | -0.19 (0.35) | 144 | -0.23 (0.37) | 1.32 (0.30, 5.79) | 1.32 (0.26, 6.66) |
| Right ankle jerk | 43 | -0.24 (0.41) | 116 | -0.22 (0.35) | 0.85 (0.33, 2.18) | 0.90 (0.33, 2.43) |
| Joint position sense (right great toe) | 11 | -0.20 (0.52) | 148 | -0.22 (0.36) | 1.17 (0.22, 6.29) | 1.34 (0.25, 7.38) |
| Vibration sense (right great toe) | 101 | -0.25 (0.37) | 58 | -0.17 (0.36) | 0.52 (0.21, 1.30) | 0.52 (0.21, 1.30) |

**Supplemental table 3: Multivariate regression models to assess association between vitamin B12 status and nerve conduction outcomes (subjects with carpal tunnel syndrome excluded)1,2**.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Adjusted coefficients2(95% confidence interval) | B-12 (pmol/l) | HoloTC (pmol/l) | cB-12 |
| Sensory SAP amplitudes (µV) |  | n=139 | n=133 | n=133 |
|  | Median  | -0.01 (-0.02, 0.01) | -0.02 (-0.06, 0.01)3 | -1.30 (-3.34, 0.87) 3 |
|  | Ulnar | -0.01 (-0.02, -0.00) | -0.01 (-0.04, 0.02) 3 | -0.53 (-1.96, 0.87) 3 |
|  | Sural | -0.00 (-0.01, 0.01) | -0.02 (-0.05, 0.02) 3 | -0.26 (-2.02, 1.49) 3 |
|  | Superficial peroneal | 0.00 (-0.01, 0.01) | -0.00 (-0.02, 0.02) 3 | 0.55 (-1.03, 1.76) 3 |
|  |  | p=0.23 | p=0.733 | p=0.483 |
| Sensory nerve conduction velocities (m/s) |  | n=99 | n=94 | n=94 |
|  | Median  | 0.00 (-0.02, 0.01) | 0.01 (-0.05, 0.02) | 0.17 (-2.45, 2.31) |
|  | Ulnar | -0.01 (-0.03, 0.00) | -0.03 (-0.07, 0.01) | -1.33 (-3.44, 0.70) |
|  | Sural | -0.01 (-0.03, 0.00) | -0.01 (-0.05, 0.03) | -1.62 (-4.12, 0.53) |
|  | Superficial peroneal | -0.01 (-0.02, 0.01) | -0.00 (-0.05, 0.04) | -0.04 (-2.97, 2.75) |
|  |  | p=0.24 | p=0.63 | p=0.34 |
| Motor CMAP amplitudes (mV) |  | n=139 | n=133 | n=133 |
|  | Median | -0.01 (-0.01, -0.00) | -0.01 (-0.02, 0.01) | -0.38 (-0.95, 0.26) |
|  | Ulnar | 0.01 (-0.00, 0.01) | 0.02 (-0.00, 0.03) | 0.97 (-0.01, 1.85) |
|  | Tibial | -0.00 (-0.02, 0.01) | -0.01 (-0.03, 0.02) | -0.16 (-1.82, 1.33) |
|  | Common peroneal | 0.00 (-0.00, 0.01) | 0.00 (-0.01, 0.02) | 0.58 (-0.24, 1.33) |
|  |  | p=0.01 | p=0.14 | p=0.01 |
| Motor nerve conduction velocities (m/s) |  | n=131 | n=126 | n=126 |
|  | Median | -0.00 (-0.02, 0.01) | -0.00 (-0.04, 0.04 | -0.73 (-2.57, 1.19) |
|  | Ulnar | 0.00 (-0.02, 0.02) | 0.02 (-0.03, 0.06) | 0.97 (-1.97, 3.34) |
|  | Tibial | 0.00 (-0.01, 0.02) | 0.01 (-0.03, 0.06) | 0.70 (-1.37, 2.83) |
|  | Common peroneal | -0.00 (-0.02, 0.01) | -0.02 (-0.05, 0.01) | -0.28 (-2.09, 1.96) |
|  |  | p=0.85 | p=0.52 | p=0.72 |

1SAP, sensory action potential; CMAP, compound muscle action potential.

2All analyses adjusted for age, sex and foot skin temperature, unless otherwise stated.

3Adjusted for age, sex, skin temperature (foot) and mean corpuscular volume.

**Supplemental table 4: Multivariate regression models to assess interaction between vitamin B12 status and age for nerve conduction outcomes1, 2.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Coefficients(95% CI) for interaction parameter2 | B-12 (pmol/l) | HoloTC (pmol/l) | cB-12 |
| Sensory SAP amplitudes (µV) |  | n=164 | n=158 | n=158 |
|  | Median  | -0.00 (-0.01, 0.00) | -0.00 (-0.01, 0.01)3 | 0.03 (-0.73, 0.63) 3 |
|  | Ulnar | -0.00 (-0.01, 0.00) | -0.00 (-0.01, 0.00) 3 | -0.28 (-0.60, 0.05) 3 |
|  | Sural | -0.00 (-0.00, 0.00) | 0.00 (-0.01, 0.01) 3 | 0.07 (-0.39, 0.52) 3 |
|  | Superficial peroneal | 0.01 (-0.00, 0.00) | -0.00 (-0.01, 0.00) 3 | 0.05 (-0.42, 0.46) 3 |
|  |  | p=0.42 | p=0.743 | p=0.353 |
| Sensory conduction velocities (m/s) |  | n=115 | n=110 | n=110 |
|  | Median  | 0.00 (-0.01, 0.01) | 0.00 (-0.01, 0.02) | 0.40 (-0.33, 1.34) |
|  | Ulnar | 0.00 (-0.00, 0.01) | -0.00 (-0.01, 0.00) | -0.11 (-0.62, 0.31) |
|  | Sural | -0.00 (-0.01, 0.01) | -0.00 (-0.01, 0.01) | -0.46 (-1.33, 0.31) |
|  | Superficial peroneal | 0.00 (-0.00, 0.01) | -0.01 (-0.02, 0.00) | -0.70 (-1.45, -0.05) |
|  |  | p=0.54 | p=0.57 | p=0.38 |
| Motor CMAP amplitudes (mV) |  | n=164 | n=158 | n=158 |
|  | Median | -0.00 (-0.00, 0.00) | -0.00 (-0.01, 0.00) | -0.13 (-0.29, 0.07) |
|  | Ulnar | -0.00 (-0.00, 0.00) | 0.00 (-0.00, 0.00) | -0.02 (-0.30, 0.25) |
|  | Tibial | -0.00 (-0.00, 0.00) | 0.00 (-0.01, 0.01) | 0.03 (-0.36, 0.44) |
|  | Common peroneal | 0.00 (-0.00, 0.00) | -0.00 (-0.01, 0.00) | -0.18 (-0.40, 0.01) |
|  |  | p=0.95 | p=0.06 | p=0.23 |
| Motor conduction velocities (m/s) |  | n=153 | n=148 | n=148 |
|  | Median | 0.00 (-0.00, 0.01) | 0.00 (-0.01, 0.02) | 0.45 (-0.17, 1.26) |
|  | Ulnar | -0.00 (-0.01, 0.00) | -0.00 (-0.01, 0.01) | -0.40 (-1.16, 0.23) |
|  | Tibial | 0.00 (-0.00, 0.01) | -0.00 (-0.01, 0.01) | 0.01 (-0.75, 0.77) |
|  | Common peroneal | 0.00 (-0.00, 0.00) | -0.01 (-0.02, -0.00) | -0.40 (-0.99, 0.44) |
|  |  | p=0.76 | p=0.09 | p=0.21 |
| Central Motor Conduction Time (ms) |  | n=147 | n=142 | n=142 |
|  | ADM | 0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) | -0.03 (-0.17, 0.12) |
|  | AH | -0.00 (-0.01, 0.00) | -0.01 (-0.01, -0.00) | -0.55 (-0.99, -0.18) |
|  |  | p=0.70 | p=0.06 | p=0.03 |
|  |  | n=164 | n=158 | n=158 |
|  | Mean ADM MEP amplitude (mV) | -0.00 (-0.00, 0.00)4 | 0.00 (-0.00, 0.00) 4 | -0.14 (-0.31, 0.02) 4 |
|  |  | p=0.164 | p=0.834 | p=0.114 |

1SAP, sensory action potential; CMAP, compound muscle action potential; ADM, abductor digiti minimi; CMCT, central motor conduction time; AH, abductor hallucis; MEP, motor evoked potential.

2All analyses adjusted for sex and foot skin temperature, unless otherwise stated.

3Adjusted for sex, skin temperature (foot) and mean corpuscular volume.

4Adjusted for sex and skin temperature (hand)

**Supplemental table 5: Multivariate regression models to assess interaction between vitamin B12 status and folate status for nerve conduction outcomes1, 2.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Coefficients(95% CI) for interaction parameter2 | B-12 (pmol/l) | HoloTC (pmol/l) | cB-12 |
| Sensory SAP amplitudes (µV) |  | n=162 | n=156 | n=156 |
|  | Median  | 0.00 (-0.00, 0.00) | 0.00 (-0.00, 0.00)3 | 0.03 (-0.13, 0.21) 3 |
|  | Ulnar | -0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) 3 | -0.04 (-0.14, 0.06) 3 |
|  | Sural | 0.00 (0.00, 0.00) | 0.00 (-0.00, 0.00) 3 | 0.05 (-0.05, 0.18) 3 |
|  | Superficial peroneal | -0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) 3 | -0.01 (-0.09, 0.07) 3 |
|  |  | p=0.32 | p=0.753 | p=0.583 |
| Sensory conduction velocities (m/s) |  | n=114 | n=109 | n=109 |
|  | Median  | -0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) | -0.08 (-0.31, 0.11) |
|  | Ulnar | -0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) | -0.10 (-0.25, 0.07) |
|  | Sural | 0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) | -0.10 (-0.30, 0.09) |
|  | Superficial peroneal | -0.00 (-0.00, 0.00) | 0.00 (-0.00, 0.00) | -0.12 (-0.30, 0.06) |
|  |  | p=0.78 | p=0.83 | p=0.45 |
| Motor CMAP amplitudes (mV) |  | n=162 | n=156 | n=156 |
|  | Median | -0.00 (-0.00, 0.00) | 0.00 (-0.00, 0.00) | -0.02 (-0.07, 0.03) |
|  | Ulnar | -0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) | 0.02 (-0.04, 0.08) |
|  | Tibial | -0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) | 0.01 (-0.08, 0.10) |
|  | Common peroneal | -0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) | -0.03 (-0.07, 0.02) |
|  |  | p=0.85 | p=0.60 | p=0.41 |
| Motor conduction velocities (m/s) |  | n=152 | n=147 | n=147 |
|  | Median | 0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) | -0.05 (-0.27, 0.14) |
|  | Ulnar | -0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) | -0.14 (-0.31, 0.03) |
|  | Tibial | 0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) | -0.06 (-0.19, 0.07) |
|  | Common peroneal | -0.00 (-0.00, 0.00) | 0.00 (-0.00, 0.00) | -0.02 (-0.13, 0.10) |
|  |  | p=0.42 | p=0.82 | p=0.46 |
| Central Motor Conduction Time (ms) |  | n=146 | n=141 | n=141 |
|  | ADM | -0.00 (-0.00, 0.00) | -0.00 (-0.00, 0.00) | -0.03 (-0.07, 0.00) |
|  | AH | -0.00 (-0.01, 0.00) | -0.01 (-0.00, 0.00) | -0.55 (-0.22, 0.03) |
|  |  | p=0.36 | p=0.20 | p=0.10 |
|  |  | n=162 | n=156 | n=156 |
|  | Mean ADM MEP amplitude (mV) | -0.00 (-0.00, 0.00)~~4~~ | -0.00 (-0.00, 0.00) 4 | -0.03 (-0.07, 0.00) 4 |
|  |  | p=0.344 | p=0.614 | p=0.104 |

1SAP, sensory action potential; CMAP, compound muscle action potential; ADM, abductor digiti minimi; CMCT, central motor conduction time; AH, abductor hallucis; MEP, motor evoked potential.

2All analyses adjusted for age, sex and foot skin temperature, unless otherwise stated.

3Adjusted for age, sex, skin temperature (foot) and mean corpuscular volume.

4Adjusted for age, sex, skin temperature (hand)

**Supplementary Figure 1: Participant flowchart from Dangour *et al.* (2015)(11)**

Placebo (n=102)

Withdrew (n=4)

Died (n=1)

No final data (n=0)

Withdrew (n=2)

Died (n=0)

No final data (n=3)

Vitamin B12 (n=99)

Data available (n=201)

Not randomized (n=16)

No data available (n=8)

(randomised in error)

Randomized (n=209)

Eligible (n=225)

Interviewed (n=487)

Not eligible (n=262)

Vitamin B12 not in range (n=208)

Withdrew interest (n=35)

Anemic (n=25)

Vitamin B12 taken daily (n=4)

No consent (n=3)

Pacemaker (n=2)

MMSE <24 (n=1)

Invitation sent (n=3071)

Not interviewed (n=2584)

Not interested (n=1605)

No reply (n=738)

Ineligible (n=197)

Eligible not interviewed (n=44)

All final data (n=92)

Postal data only (n=4)

Nerve and cognitive data only (n=1)

All final data (n=91)

Postal data only (n=3)

Nerve and cognitive data only (n=0)