## Title

Relationship between vitamin B12 and sensory and motor peripheral nerve function in older adults.



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# The Relationship of Vitamin B12 and Sensory and Motor Peripheral Nerve Function in Older Adults

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## Abstract

**Objectives—**To examine whether deficient B12 status or low serum B12 levels are associated with worse sensory and motor peripheral nerve function in older adults.

**Design—**Cross-sectional.

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**Conflict of Interest:** The authors report no conflict of interest.

**Author Contributions:** KL, ESS: study design, data analysis, data interpretation, and manuscript preparation; ABN, RMB, LF, SAS, CR: study design, data interpretation, and manuscript preparation; DKH, EH, KY, TBH, ND, SBK, AVS, AIV: data interpretation and manuscript preparation

**Setting—**Health, Aging and Body Composition Study.

**Participants—**Two thousand two hundred eighty-seven adults aged 72–83 years [mean age: 76.5 ± 2.9 years; 51.4% female; 38.3% black].

**Measurements—**Low serum B12 was defined based solely on serum B12 of <260 pmol/L, whereas deficient B12 status was defined as B12 <260 pmol/L, methylmalonic acid [MMA] >271 nmol/L and MMA >2-methylcitrate. Peripheral nerve function was assessed by peroneal nerve conduction amplitude and velocity [NCV] (motor); 1.4g/10g monofilament detection; average vibration threshold detection; and peripheral neuropathy symptoms [numbness; aching/burning pain] (sensory).

**Results—**B12 deficient status was found in 7.0% and an additional 10.1% had low serum B12 levels. B12 deficient status was associated with greater insensitivity to light (1.4g) touch (OR: 1.50; 95% CI: [1.06, 2.13]) and worse NCV [42.3 m/s vs. 43.5 m/s] (β =−1.16; p=0.01), after multivariable adjustment for demographics, lifestyle factors, and health conditions. Associations were consistent for the alternative definition using low serum B12 only. No significant associations were found for deficient B12 status or the alternative low serum B12 definition and vibration detection, nerve conduction amplitude, or peripheral neuropathy symptoms.

**Conclusion—**Poor B12 (deficient B12 status and low serum B12) is associated with worse sensory and motor peripheral nerve function. Nerve function impairments may lead to physical function declines and disability in older adults, suggesting that prevention and treatment of low B12 levels may be important to evaluate.

### Keywords

low B12; deficient B12; sensory peripheral nerve function; motor nerve conduction; older adults

## INTRODUCTION

Vitamin B12 deficiency affects 5–20% of older adults and low serum B12 levels are highly prevalent among older adults, affecting 15–40%[1–4]. Studies have reported a wide range of prevalence rates, due to different population characteristics as well as a lack of agreement on diagnostic criteria for low or deficient B12. Some studies only use serum B12 levels to define deficiency (cutpoints ranging from 74 to 148 pmol/L) and low (cutpoints from 185 to 260 pmol/L). Other studies use a combined definition with low serum B12 and high methylmalonic acid [MMA] (e.g., > 2 or 3 SD above the mean), since MMA is considered a highly sensitive and specific marker to determine B12 deficiency[1, 4–8]. While no agreed-upon cutpoint for low or deficient B12 serum levels exists, the most commonly used cutpoints are 148 pmol/L for deficiency and 260 pmol/L for low B12.

There are many different causes of B12 deficiency in older adults. More than half of older adults with B12 deficiency have food-cobalamin malabsorption, defined as impaired digestion and absorption of protein-bound B12[3, 9–10]. Other causes of low or deficient B12 are insufficient intake either from diet or supplements, pernicious anemia, gastric surgery, gastrointestinal disease, and certain medications (e.g., proton-pump inhibitors, metformin)[3].

Vitamin B12 deficiency is clinically recognized to be associated with neurological disorders, such as dementia, cognitive impairment, and depression[1, 3, 11–12]. B12 deficiency may cause demyelination of nerves in the peripheral and central nervous system[13] and has been associated with peripheral neuropathy, loss of sensation in peripheral nerves, and weakness in lower extremities in older adults[1, 14–16]. In particular, vitamin B12 deficiency is associated with large fiber (type A) neuropathy; type A nerve fibers act as both sensory and

motor fibers[17]. Thus, vitamin B12 may be associated with both sensory and motor peripheral nerve function.

In older adults, the prevalence of poor peripheral nerve function and neuropathy is high and increases with age[18–21]. Poor peripheral nerve function, often undiagnosed or at subclinical levels, is related to lower strength, bone mineral density, and physical performance in older adults[22–26]. Identifying risk factors for poor peripheral nerve function is crucial. While B12 deficiency is a recognized risk factor for clinical peripheral neuropathy, little is known about the relationship between low B12 and subclinical sensory and motor peripheral nerve function in older adults. The purpose of this study is to examine whether deficient B12 status or an alternative definition using low serum B12 levels are associated with worse sensory and motor peripheral nerve function in older adults and whether the same relationship exists for low serum B12 levels as deficient B12 status.

## METHODS

### Study population

We conducted a cross-sectional study of vitamin B12 levels and status and peripheral nerve function in 2287 participants of the Health, Aging and Body Composition (Health ABC) Study. The Health ABC Study is an ongoing, prospective cohort study of 3,075 well-functioning black and white men and women, aged 70–79 years at the 1997–98 baseline examination. Participants were recruited from a random sample of Medicare-eligible white adults and all eligible black community-dwelling residents in Pittsburgh, PA and Memphis, TN. Individuals were ineligible if they had difficulty walking a ¼ mile (400m), climbing 10 steps, performing activities of daily living; had life-threatening cancer or treatment for cancer in the last 3 years; or were planning to move out of the study area within 3 years. The study was approved by the Institutional Review Boards at the University of Pittsburgh and the University of Tennessee Health Science Center, and informed consent was obtained from all participants.

Of 3075 participants at baseline, 2405 had a 2000–01 clinic examination. The remaining cohort had a home visit (n=88), telephone follow-up (n=233), proxy interview only (n=49), were deceased (n=187), withdrew (n=9), or missed the examination (n=104). We excluded participants missing: all peripheral nerve function measures (n=1), serum B12 levels (n=98), fasting blood glucose levels (n=14), or with diabetes onset at ≤20 years of age (n=5). Thus, 2287 participants (48.6% male, 38.3% black) were included, representing 74.4% of baseline participants and 95.1% of those attending the 2000–01 examination.

### Assays

Serum samples were frozen at −70°C in cryogenic vials at the time of collection. Tests for serum B12 used 300 ul sera from the 2000–01 visit and were performed at the Clinical Chemistry Laboratory at Fletcher Allen Health Care, University of Vermont, by a competitive immunoassay on the ADVIA Centaur (Bayer HealthCare, LLC) with direct chemiluminescent technology. The normal range was 72 to 1427 pmol/L, previously determined from 272 serum samples. The assay coefficient of variation [CV] ranged from 4% to 10% and a 6.7% CV was observed for 5% of our sample blinded for quality control.

For samples with low serum B12 (<260 pmol/L), we measured serum MMA, total homocysteine (Hcy), serum 2-methylcitrate (2-MCA), and cystathionine in order to determine deficiency status. These additional metabolite assays for the subset with low serum B12 (N=391) were tested by the University of Colorado Health Sciences Center using capillary gas chromatography-mass spectrometry[27]. The normal ranges were 73–271 nmol/L for MMA, 5.4–13.9 μmol/L for Hcy, 60–228 nmol/L for 2-MCA, and 44–342 nmol/L for

cystathionine. Inflammatory markers, tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), were measured at the 1997–98 and 2000–01 visit, respectively, as previously described[28].

We used 2 definitions for poor vitamin B12 in the analyses. We first classified participants based on serum B12 and MMA levels with deficient B12 status defined as B12 <260 pmol/L and MMA >271 nmol/L with MMA >2-MCA and low B12 status defined as B12 <260 pmol/L and (MMA ≤271 nmol/L or MMA ≤2-MCA). The reference group was B12 ≥260 pmol/L;[29] We then used an alternative definition based solely on serum B12 with low serum B12 levels defined as B12 <260 pmol/L and normal levels defined as B12 ≥260 pmol/L[30]. Thus, "low serum B12 levels" in this alternate definition is further divided into "deficient B12 status" or "low B12 status" in our original definition based on MMA levels.

## Peripheral nerve function

Sensory and motor peripheral nerve function was measured on the right leg/foot unless contraindicated by amputation, knee replacement, surgery, trauma, or ulcer. Motor nerve conduction amplitude (compound motor action potential [CMAP]) in millivolts and nerve conduction velocity [NCV] in meters per second were measured between the popliteal fossa and ankle (NeuroMax 8; XLTEK). Poor CMAP was defined as <1 mV and poor NCV as <40 m/s[31]. To assess sensory nerve function, monofilament testing was done on the dorsum of the great toe. Reduced sensation was defined as being unable to detect 3 out of 4 touches for each 1.4g (light) and 10g (standard) monofilaments. Average vibration threshold detection in microns was recorded at the great toe [range: 0–130 μ] (VSA-3000 Vibratory Sensory Analyzer; Medoc). To assess symptoms of peripheral neuropathy, participants were asked "in the past 12 months, have you ever had: "numbness, an asleep feeling, or a prickly feeling in your legs or feet?" (yes/no); "sudden stabbing, burning pain, or a deep aching in your legs or feet?" (yes/no).

## Covariates

Data on questionnaire and clinical measures were collected at the 2000–01 exam unless otherwise indicated. Demographics included age, sex, race, and clinic site (Memphis, TN or Pittsburgh, PA). Lifestyle factors included alcohol use [1997–98], smoking status (never, former, current) [1999–2000], and weekly physical activity from walking and stair-climbing (kcal/kg/wk). To measure body composition, height and weight were used to calculate body mass index (BMI) as weight (kg)/ height$^2$ (m$^2$). Whole body mineral–free lean mass and fat mass was measured using Dual-energy X-ray absorptiometry (Hologic 4500A, software version 9.03; Hologic)[32]. Physiological factors included blood pressure, cholesterol, ankle-brachial index (low: <0.9; normal: 0.9-<1.3; stiffening: ≥1.3); high cystatin-C (≥1 mg/L); and thyroid stimulating hormone [1998–99]. Medications (e.g., fibrate, niacin, statin, thyroid, metformin) and B12 supplement use (i.e.., multivitamin or supplemental B12 [oral or intramuscular]) were assessed by medication inventory[33] at the 1999–2000 visit. Health conditions included diabetes mellitus (determined by fasting glucose ≥126 mg/dl, medications, self-reported physician diagnosis)[34], hypertension (determined by physiological exam, medications, and self-reported physician diagnosis); cerebrovascular disease, coronary heart disease, congestive heart failure, and peripheral arterial disease (each determined by self-reported physician diagnosis at the 1997–98 exam). For cognitive function, we assessed processing speed, using the Digit Symbol Substitution Test (DSST)[35] [1997–98] and global cognitive function, using the Modified Mini-Mental State Examination (3MS) (range: 0–100)[36] [1999–2000].

### Statistical analyses

Differences were tested by vitamin B12 status in demographics, lifestyle factors, body composition, physiological factors, medication and supplement use, and health conditions, using Pearson $\chi^2$ tests or Fisher's exact test for categorical variables and Kruskal-Wallis, analysis of variance, or t-tests for continuous variables.

Logistic regression was performed for outcomes of 1.4g (light) and 10g (standard) monofilaments, and peripheral neuropathy symptoms. Linear regression was done for outcomes of nerve conduction amplitude and velocity. Tobit regression, which is censored linear regression used for an outcome which is censored, was performed for average vibration threshold because of a ceiling effect.

Multivariable regression modeling was performed separately for each peripheral nerve function variable with vitamin B12 status as the predictor variable. There was low correlation between peripheral nerve measures ($-0.29 < r < 0.34$), indicating different aspects of nerve function are being captured, thus each measure was considered separately as an outcome. Adjusting for potential confounders, the models were built progressively in the following order: demographics, diabetes, lifestyle factors, body composition, physiological factors, medication and supplement use, health conditions, and inflammatory markers. DSST and 3MS were additionally included for vibration detection, monofilament detection, and peripheral neuropathy symptoms, due to the cognitive aspects of these outcomes. Age, sex, race, clinic site, and diabetes were adjusted for in all models; other variables were removed if $p>0.10$.

Sensitivity analyses were conducted in several ways. First, we excluded participants with diabetes to verify that associations were consistent in older adults without diabetes. We also performed analyses using two additional definitions for vitamin B12 in order to confirm whether results were consistent for other definitions of B12 deficiency. For our first additional definition, we defined deficient serum B12 levels as B12 <148 pmol/L[30]. For our second additional definition, we defined deficient B12 status as B12 <148 pmol/L or [normal renal function and Hcy ≥13.9 μmol/L], estimating normal renal function using MMA ≤271 nmol/L, Hcy ≤13.9 μmol/L, cystathionine ≤342 nmol/L, and 2-MCA ≤228 nmol/L)][27]. Results of the analyses for these two additional definitions were not significant; however, we had a very small number of participants with B12 deficiency using these definitions (26 participants [1.1%] with B12 <148 pmol/L, and 55 participants [2.4%] using the deficient B12 status definition based on additional markers from the vitamin B12 pathway). Multicollinearity for independent variables was assessed using the variance inflation factor (VIF); no VIF was >2. All analyses were conducted with SAS, version 9.2 (SAS Institute Inc., Cary, NC).

## RESULTS

B12 deficient status was found in 7.0% of the participants and an additional 10.1% had low serum B12 but did not have high MMA levels to have deficient status. Thus, the prevalence of low serum B12 levels (<260 pmol/L) was 17.1%. Table 1 shows the descriptive characteristics by B12 deficiency status (i.e., deficient: <260 pmol/L and MMA >271 nmol/L with MMA >2-MCA, low: B12 <260 pmol/L and (MMA ≤271 nmol/L or MMA ≤2-MCA), and normal: B12 ≥260 pmol/L). Participants with deficient B12 status were more likely to be older, male, white, have lower cholesterol levels, and were less likely to take supplemental B12, compared to those with normal B12 levels. As expected, those with deficient B12 status were more likely to have lower serum B12 levels and were more likely to be white compared to those with low B12 status, although other characteristics were not different. Among the participants taking a supplement containing vitamin B12, 96% were

taking a multivitamin. About 8% of those with normal B12 levels and 3% of those with low or deficient B12 status were specifically taking a B12 supplement (oral or intramuscular).

Nearly half (45.6%) of the participants were unable to detect 1.4g monofilament; 5.9% were unable to detect the maximum vibration (130 μ); 11.0% had poor CMAP (<1 mV); and 22.2% had poor NCV (<40 m/s). Table 2 demonstrates peripheral nerve function by B12 deficiency status. Participants with deficient B12 status were less likely to detect 1.4g monofilament, and more likely to have worse (higher) average vibration threshold detection and lower NCV compared to those with normal B12 levels. No significant differences were found univariately between deficient B12 status and normal B12 in ability to detect standard (10g) monofilament, CMAP amplitude, or peripheral neuropathy symptoms. When using the alternative definition of low serum B12, univariate associations with peripheral nerve function were similar; however, low serum B12 levels were associated with lower CMAP compared to those with normal B12 levels [3.1 ± 1.9 mV vs. 3.4 ± 2.0 mV; p=0.04].

Table 3 illustrates the multivariable regression results for deficient B12 status. Those with deficient B12 status were 1.5 times more likely to be unable to detect 1.4g (light) monofilament after adjusting for age, sex, race, clinic site, diabetes, height, alcohol use, and 3MS score (OR: 1.5; 95% CI: [1.06, 2.13]). Deficient B12 status was associated univariately with worse vibration detection, but not after adjusting for covariates. Sex, race, clinic site, diabetes, and 3MS score attenuated the association. Lower NCV was associated with deficient B12 status, after adjusting for demographics, diabetes, height, weight, alcohol use, ankle-brachial index, and systolic blood pressure. CMAP was not associated with B12 deficiency. Low B12 status was not associated with any nerve function outcome. However, using the low serum B12 definition (B12 <260 pmol/L), findings were consistent with the deficient B12 status definition: low serum B12 was significantly associated with greater insensitivity to 1.4g (light) monofilament (OR: 1.28; 95% CI: [1.01, 1.62]) and lower NCV (β= −0.63; p=.04), after adjusting for covariates. Consistent with deficient B12 status, low serum B12 was not associated with CMAP or vibration detection. In addition, no significant association was found between deficient B12 status or low serum B12 and standard (10g) monofilament detection or symptoms in the multivariable regression models (data not shown). Sensitivity analysis was performed removing participants with diabetes, and the results were consistent.

## DISCUSSION

Older community-dwelling adults with deficient B12 status had both worse sensory and motor peripheral nerve function. This study is unique in comparing different definitions of poor B12 and their relationship with several measures of sensory and motor nerve function in community-dwelling older adults. These findings are of importance since poor peripheral nerve function may lead to impaired physical function and disability in older adults[20, 22, 25–26] and it is thus vital to establish potentially modifiable risk factors.

Our results show that the association between B12 and peripheral nerve function was consistent for both definitions of deficient B12 status (using MMA) and using solely low serum B12 levels. This is important since much controversy exists over how to define poor vitamin B12. Using serum B12 levels alone may not be very sensitive or specific to determine a tissue deficiency, while MMA is considered to be a highly sensitive marker of B12 deficiency[7]. However, since MMA is expensive and is not often used in clinical practice[37], it is important to investigate whether only using serum B12 is adequate and specific to disease-related outcomes in older adults. Our results suggest that using MMA with serum B12 may be best for determining B12 deficiency, since the associations were stronger than using serum B12 alone. However, we found that using low serum B12 only

(<260 pmol/L) was sufficient, since the associations were consistent with deficient B12 status, using serum B12 with MMA.

The prevalence of poor NCV (22.2%) was more than twice as high as poor CMAP (11.0%), which may be why we did not find a significant association with CMAP. Low CMAP is thought to be related to nerve axonal damage and low NCV is related to nerve demyelination[38]. Our results suggest that demyelination may be occurring more often in older adults than axonal damage. We expected the prevalence of poor NCV to be higher than that of poor CMAP since demyelination is thought to occur before axonal degeneration[39]. There was no association with deficient B12 status and ability to detect standard (10g) monofilament or peripheral neuropathy symptoms, common clinical screens for peripheral nerve problems. Light (1.4g) monofilament may be more sensitive compared to using a standard (10g) monofilament, detecting sensory neuropathy at an earlier stage[40–41]. The symptoms of numbness and deep aching/burning pain in the legs or feet may not be specific for peripheral neuropathy in older adults in the context of B12 deficits. Importantly, peripheral nerve impairments have been shown to be largely asymptomatic in older adults, even among those with diabetes[21] .

Strengths of this analysis were that we had a large cohort of older men and women and tested MMA levels for those with serum B12 levels <260 pmol/L[37]. We had measures of both sensory and motor peripheral nerve function. Sensory nerve function was assessed using both average vibration threshold and monofilament detection, which even though it is less sensitive, it is highly specific and has clinical significance (i.e., it is a low-cost and quick test that can easily be done in an exam room)[42]. Measuring motor nerve function with nerve conduction is considered the gold standard, because it is highly sensitive, reliable, and reproducible[43].

A limitation of this study was having a small percentage of participants (1.1%) with serum B12 levels <148 pmol/L. Thus, we likely did not have sufficient statistical power to examine a relationship between clinically deficient serum B12 levels (<148 pmol/L) and peripheral nerve function. The participants in this study were likely to be healthier than older adults in the general population and 39.2% of participants took a supplement containing vitamin B12. We also did not have a sensory nerve conduction test (e.g., sural nerve).

We found that deficient B12 status is associated with worse sensory and motor nerve function in older adults. These findings have important implications for functioning and disability in older adults. Several studies have shown an association between peripheral neuropathy or poor peripheral nerve function and impaired mobility and falls[22, 25, 44–48].

In the aftermath of the 1998 mandatory folic acid fortification in the United States, it is important to study vitamin B12 and consequences of poor B12 status in older adults[2]. A high intake of folic acid may correct megaloblastic anemia, which is caused by a deficiency in B12 and/or folic acid[14, 49]. Since the classic sign of anemia may not be present, B12 deficiency may go unnoticed while neurological damage may progress and not be easily reversible[2]. Although current recommendations do not advise monitoring B12 levels in older adults, our results suggest that low levels are associated with peripheral nerve impairments which have been associated with lower musculoskeletal function in our population[22–23, 26]. Supplemental B12 is easily available, adequately absorbed, highly tolerated in older adults[50], and may potentially correct vitamin B12 deficits associated with impaired peripheral nerve function. Randomized clinical trials are needed to establish that sufficient B12 supplementation can improve peripheral nerve function.

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**Table 1**

Descriptive Characteristics by Vitamin B12 Status

| | Normal (n=1896) | Low (n=232) | Deficient (n=159) | p-value |
|---|---|---|---|---|
| *Demographics* | | | | |
| Age (years) | 76.5 ± 2.9 | 76.4 ± 2.8 | 77.2 ± 2.9† | .009 |
| Male (%) | 47.0 | 55.6* | 57.2† | .004 |
| Black (%) | 39.6 | 36.6 | 25.2†,‡ | .001 |
| Diabetes status | | | | .66 |
| Impaired fasting glucose (%) | 16.0 | 18.1 | 16.4 | .71 |
| Diabetes (%) | 21.5 | 19.4 | 25.2 | .39 |
| Metformin use (%) | 15.6 | 27.9* | 23.1 | .08 |
| *Lifestyle Factors* | | | | |
| Smoking status | | | | .56 |
| Former (%) | 47.1 | 47.4 | 53.9 | .27 |
| Current (%) | 7.0 | 7.9 | 6.5 | .85 |
| Alcohol use | | | | .70 |
| Former (%) | 21.1 | 21.2 | 20.3 | .97 |
| <1 per week (%) | 21.3 | 21.2 | 19.6 | .89 |
| 1–7 per week (%) | 22.7 | 22.1 | 24.1 | .90 |
| >1 per day (%) | 6.7 | 10.2 | 9.5 | .09 |
| Physical activity (kcal/kg/wk) | 31.4 ± 50.7 | 41.4 ± 76.4 | 26.1 ± 39.3 | .11 |
| *Body Composition* | | | | |
| BMI (kg/m$^2$) | 27.2 ± 4.8 | 27.5 ± 4.4 | 26.9 ± 4.2 | .35 |
| Height (mm) | 1654.1 ± 93.2 | 1670.9 ± 99.1 | 1663.5 ± 94.2 | .02 |
| Weight (kg) | 74.9 ± 15.1 | 77.9 ± 15.2 | 75.2 ± 14.9 | .02 |
| Total fat mass (kg) | 26.1± 8.8 | 27.1 ± 8.4 | 25.6 ± 8.1 | .11 |
| Total lean mass (kg) | 48.8 ± 10.2 | 50.5 ± 10.6 | 49.7 ± 10.4 | .06 |
| *Physiological Factors* | | | | |
| SBP (mmHg) | 134.9 ± 19.8 | 137.1 ± 20.6 | 135.4 ± 22.7 | .40 |
| DBP (mmHg) | 71.4 ± 10.7 | 72.7 ± 11.2 | 70.9 ± 12.4 | .16 |
| Ankle-brachial index | | | | .27 |
| Low (%) | 15.8 | 16.4 | 18.1 | .75 |
| Stiffening (%) | 5.6 | 2.7 | 3.2 | .09 |
| Total cholesterol (mg/dL) | 192.6 ± 37.9 | 190.5 ± 35.7 | 182.1 ± 34.9 | .009 |
| Cystatin-C ≥1 mg/L (%) | 44.7 | 46.1 | 56.1† | .02 |
| B12 supplement use (%) | 42.9 | 19.6* | 22.1† | <.001 |
| *Medication use* | | | | |
| Fibrate use (%) | 1.1 | 0.5 | 1.4 | .68 |
| Niacin use (%) | 1.1 | 0.5 | 0.7 | .90 |
| Statin use (%) | 20.1 | 18.4 | 19.1 | .81 |
| Thyroid medication (%) | 12.7 | 11.0 | 12.1 | .76 |

| | Normal (n=1896) | Low (n=232) | Deficient (n=159) | p-value |
|---|---|---|---|---|
| *History of comorbidities* | | | | |
| Hypertension (%) | 72.7 | 75.1 | 74.7 | .67 |
| CBVD (%) | 6.5 | 8.7 | 7.7 | .41 |
| CHD (%) | 15.2 | 20.0 | 20.0 | .07 |
| CHF (%) | 0.9 | 0.0 | 0.6 | .38 |
| PAD (%) | 4.3 | 3.1 | 5.7 | .45 |
| *Inflammatory markers* | | | | |
| IL-6 (pg/mL) | 3.6 ± 3.7 | 3.7 ± 3.8 | 3.7 ± 4.4 | .85 |
| TNF-α (pg/mL) | 3.4 ± 1.5 | 3.4 ± 1.9 | 3.7 ± 1.5† | .01 |
| *Cognitive tests* | | | | |
| 3MS score | 90.4 ± 8.1 | 90.8 ± 7.2 | 90.0 ± 7.7 | .50 |
| DSST score | 36.8 ± 14.8 | 35.8 ± 13.9 | 35.2 ± 11.9 | .15 |
| B12 level (pmol/L) | 474.5 ± 203.0 | 223.2 ± 30.4* | 200.7 ± 39.8†,‡ | <.001 |

Pairwise: p<0.05 for *: Low vs. Normal;

†Deficient vs. Normal;

‡Deficient vs. Low;

Normal: B12 ≥260 pmol/L; Low status: B12 <260 pmol/L & (MMA ≤271 nmol/L or MMA ≤2-methylcitrate); Deficient status: B12 <260 pmol/L & MMA >271 nmol/L & MMA >2-methylcitrate

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CBVD: cerebrovascular disease; CHD: coronary heart disease; CHF: congestive heart failure; PAD: peripheral arterial disease; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; 3MS: Modified Mini-Mental Examination; DSST: Digit Symbol Substitution Test; MMA: methylmalonic acid

## Table 2

Peripheral Sensory and Motor Nerve Function by Vitamin B12 Status

| | Normal (n=1896) | Low (n=232) | Deficient (n=159) | p-value |
|---|---|---|---|---|
| Monofilament | | | | |
| Unable to detect 10g (%) | 8.8 | 8.3 | 9.0 | .97 |
| Unable to detect 1.4g (%) | 44.4 | 48.3 | 56.1 * | .01 |
| Vibration threshold (μ) | 50.5 ± 35.3 | 53.8 ± 36.9 | 59.8 ± 36.4 * | .003 |
| Unable to detect vibration (%) | 5.7 | 5.8 | 7.9 | .54 |
| CMAP (mV) | 3.4 ± 2.0 | 3.2 ± 1.9 | 3.0 ± 2.0 | .14 |
| <1 mV (%) | 10.7 | 12.0 | 13.7 | .54 |
| NCV (m/s) | 43.8 ± 5.4 | 43.1 ± 5.5 | 42.2 ± 5.2 * | .006 |
| <40 m/s (%) | 21.6 | 23.0 | 28.7 | .21 |
| Numbness (%) | 29.3 | 28.1 | 25.2 | .53 |
| Aching/burning pain (%) | 16.8 | 19.8 | 13.8 | .29 |

Pairwise: $p<0.05$ for *: Deficient vs. Normal;

Normal: B12 ≥260 pmol/L; Low status: B12 <260 pmol/L & (MMA ≤271 nmol/L or MMA ≤2- methylcitrate); Deficient status: B12 <260 pmol/L & MMA >271 nmol/L & MMA >2- methylcitrate

CMAP: compound motor action potential; NCV: nerve conduction velocity; MMA: methylmalonic acid

**Table 3**

Multivariable Regression Models for the Association between Vitamin B12 Status and Peripheral Nerve Function

| | Model 1: unadjusted | | | | Model 2: adjusted for demographics | | | | Model 3: fully adjusted* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Low status*† | | *Deficient status* | | *Low status* | | *Deficient status* | | *Low status* | | *Deficient status* | |
| **Nerve function** | **OR** | **95% CI** | **OR** | **95% CI** | **OR** | **95% CI** | **OR** | **95% CI** | **OR** | **95% CI** | **OR** | **95% CI** |
| Inability to detect 1.4g monofilament | 1.17 | [0.89, 1.54] | 1.60 | [1.15, 2.23] | 1.13 | [0.86, 1.50] | 1.51 | [1.08, 2.11] | 1.15 | [0.85, 1.54] | 1.50 | [1.06, 2.13] |
| | **β** | **p** | **β** | **p** | **β** | **p** | **β** | **p** | **β** | **p** | **β** | **p** |
| Vibration detection (μ) | 3.37 | .21 | 9.68 | .002 | 1.97 | .43 | 5.23 | .08 | 1.27 | .61 | 5.23 | .08 |
| CMAP (mV) | −.176 | .26 | −.347 | .06 | −.120 | .44 | −.187 | .30 | −.127 | .40 | −.159 | .38 |
| NCV (m/s) | −.670 | .13 | −1.58 | .002 | −.280 | .48 | −.891 | .06 | −.256 | .52 | −1.16 | .01 |

Ref: Normal: B12 ≥260 pmol/L; CMAP: compound motor action potential; NCV: nerve conduction velocity

† Low status: B12 <260 pmol/L & (MMA ≤271 nmol/L or MMA ≤2- methylcitrate);

‡ Deficient: B12 <260 pmol/L & MMA >271 nmol/L & MMA >2- methylcitrate

* in addition to demographics (age, sex, race, clinic site) and diabetes: monofilament: adjusted for height, alcohol use, 3MS score; vibration: adjusted for height, weight, ankle-brachial index, high cystatin-C, 3MS score, vibration variance; CMAP: adjusted for height, ankle-brachial index, cholesterol level, high cystatin-C; NCV: adjusted for height, weight, alcohol use, ankle-brachial index, systolic blood pressure

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