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ORIGINAL ARTICLE

Association between neuropathy and B-vitamins: A systematic review and meta-analysis

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Abstract

Background: Peripheral neuropathy (PN) is common in patients with diseases that are in turn associated with deficiency of the B-vitamins, and vitamin treatment has shown mixed results.

Methods: This systematic review and meta-analysis studied the association between PN/pain and B-vitamin biomarkers and investigated whether vitamin treatment can ameliorate the symptoms. PubMed and Web of Science were searched according to the study protocol.

Results: A total of 46 observational and seven interventional studies were identified and included in the data synthesis. The presence of PN was associated with lowered B12 levels (pooled estimate [95% CIs] = 1.51 [1.23–1.84], n = 34, Cochran Q Test I^2 = 43.3%, p = 0.003) and elevated methylmalonic acid (2.53 [1.39–4.60], n = 9, I^2 = 63.8%, p = 0.005) and homocysteine (3.48 [2.01–6.04], n = 15, I^2 = 70.6%, p < 0.001). B12 treatment (vs. the comparators) showed a non-significant association with symptom improvement (1.36 (0.66–2.79), n = 4, I^2 = 28.9%). Treatment with B1 was associated with a significant improvement in symptoms (5.34 [1.87–15.19], n = 3, I^2 = 64.6%, p = 0.059). Analysis of seven trials combined showed a non-significant higher odds ratio for improvement under treatment with the B-vitamins (2.58 [0.98–6.79], I^2 = 80.0%, p < 0.001).

Conclusions: PN is associated with lowered plasma vitamin B12 and elevated methylmalonic acid and homocysteine. Overall, interventional studies have suggested that B-vitamins could improve symptoms of PN. Available trials have limitations and generally did not investigate vitamin status prior to treatment. Well-designed studies, especially in non-diabetes PN, are needed. This meta-analysis is registered at PROSPERO (ID: CRD42020144917).

KEYWORDS

diabetes, homocysteine, peripheral neuropathy, vitamin B1, vitamin B12, vitamin B6, vitamin deficiency

Responsible for statistical analyses and data integrity: J. Stein and R. Obeid

INTRODUCTION

Peripheral neuropathy (PN) is generalized nerve damage of the peripheral nerve system. The age-standardized prevalence of PN in the general population is 9.4%.[1] The etiology of PN is not well characterized. Approximately 31% of patients with PN have diabetes and 46% of neuropathies are idiopathic.[1]

Vitamin B12 deficiency causes spinal cord lesion or subacute combined degeneration where a demyelination process leads to decay of the myelin sheath in the dorsal and lateral columns.[2,3] In older patients with Parkinson's disease, neuropathy could be due to levodopa (L-dopa) treatment that causes vitamin B12 deficiency. Also, toxins such as alcohol and viral infections are associated with vitamin B12 deficiency and neuropathy.[2,3] Thus, vitamin B12 deficiency could be causally related to PN. The mechanisms could involve hypomethylation, phospholipid metabolism, and neurotoxic effects of homocysteine.[4]

Diagnosis of PN and differential diagnosis of similar disorders (i.e., myelopathy) [5] is challenging. Disease history and symptoms such as numbness, parenthesis, pain, and/or dysesthesias provide important clues to the diagnosis. The diagnosis relies on medical history, symptoms, clinical examination (i.e., ankle reflexes), and laboratory tests.[6] Additionally, nerve conduction studies (peroneal and posterior tibial nerves) help determine the type of nerve damage (axonal or demyelinating), distribution (symmetric or asymmetric, distal, or proximal), and severity.

Therapeutic doses of the B-vitamins (B1, B6, and/or B12) are commonly used in patients with PN but there are no evidence-based guidelines as to whether vitamin deficiency should be suspected or treated in such patients.[7] The present systematic review and meta-analysis investigated the association between low statuses of the B-vitamins and the presence of PN/pain and the effect of vitamin treatment on PN/pain symptoms. We studied the odds of patients with PN/pain having lowered vitamin biomarkers compared to those without PN/pain, and whether neuropathy symptoms are more likely to improve after treatment with vitamins B1, B6, and/or B12 than after a control treatment.

METHODS

The study is registered at the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42020144917). The protocol was prepared before starting the search.

Search and screening strategies

The search, screening, and data abstraction were independently conducted by JS and RO. The search was conducted in PubMed and Web of Science on 18 September 2018 using the terms shown in Table S1. A manual search of the grey literature and the references of relevant reviews was performed. We screened the titles and abstracts followed by the full texts of potentially relevant articles. The corresponding authors of relevant articles published between January 2010 and September 2018 were asked to provide additional data.

We included human studies of adult men and women. Neuropathy could be idiopathic or associated with viral infections, cancer, renal insufficiency, carpal tunnel syndrome, chemotherapy, alcoholism, diabetes, or Parkinson's disease. The design of observational studies could be cohort, case-control, or cross-sectional. Studies should report plasma/serum concentrations of vitamins B1, B6, and/or B12 (vitamin B12 [or holotranscobalamin], B1, B6); functional markers such as total homocysteine (tHcy) or methylmalonic acid (MMA); or functional enzymatic tests. We applied no restriction to the clinical tests used to diagnose PN and pain.

The design of interventional studies could be randomized- or quasi-randomized-controlled, open-labelled, or single or double-blind. The comparators could be placebo, no treatment, or non-drug comparators (i.e., Chinese herbs). All dosages, routes of administration, combinations, durations, and forms of the vitamins (i.e., thiamine-HCl, benfothiamine, cyanocobalamin, and methylcobalamin) were eligible. Studies testing vitamins plus a drug versus the drug without the vitamins could be included. The outcome of the intervention studies was improvement of PN/pain syndromes (vs. no improvement/worsened). No restriction was applied to the medical tests used to evaluate PN or pain. In studies applying multiple tests to diagnose PN, alternative tests were used in the sensitivity analyses.

We excluded multiple publications, non-English language articles, reviews, case series, case reports, studies not measuring biomarkers, studies with <20 participants, and when all patients were deficient or all received vitamins. We excluded studies in children, pregnant women, patients with liver disorders, inherited diseases associated with neuropathy, optic neuropathy, autonomic neuropathies, reports on vitamin B6 overdose-induced neuropathy, pain caused by an acute trauma, accidents, or operations, studies on cerebrospinal fluid biomarkers, and trials testing vitamins against drugs. Intervention studies in patients with herpes infection and carpal tunnel syndrome were excluded.

Data extraction

We documented PMID, first author, publication year, design, number (*n*) of participants, *n* male/*n* female, age, recruitment years, country, setting, inclusion and exclusion criteria, suspected main disease associated with PN, medications, comorbidities, PN/pain diagnostic tests, vitamin biomarkers, analytical methods used to measure the markers, study-specific definition of a low vitamin status, and *n* of deficient/sufficient patients with PN/pain and those without PN/pain. For treatment studies, we documented *n* of responders (improved) and non-responders (not improve/worsened) in each treatment arm. The information was captured in 2*2 contingency and Excel tables.

Data tabulation and statistical analyses

The effect size to be analyzed was the odds ratio (OR) and 95% confidence intervals (95% CIs) that were calculated for each vitamin marker and clinical test result. A Mantel–Haenszel-type estimator in a random effect model was used where each study is weighted by the inverse of its variance. Pooled estimates and 95% CIs were calculated from the individual OR. The results were meta-analyzed when the number of studies was ≥3 and Forest plot was used to plot the data. Cochran *Q* Test and I^2 were used to study the heterogeneity between the studies. Sources of heterogeneity were investigated in subgroup analyses. Publication bias was investigated by using Egger's regression that tests the hypothesis that the regression intercept is zero. Duval and Tweedie's "trim and fill" method was applied to correct the point estimates for publication bias. Funnel plot of the standard error (SE) by log-OR are presented for the main analyses. Values of $p < 0.05$ were considered statistically significant. The data analyses were conducted using the Comprehensive Meta-Analysis software programme (version 3.0).

Subgroup, sensitivity, and post hoc analyses

The association between PN and lowered vitamin B12 was studied according to the continent of the study origin (i.e., due to different medical practices and prevalence of deficiencies); the underlying diseases; publication years; and cut-off values used to define low vitamin B12. Studies in patients with diabetes were additionally analyzed according to metformin use. Moreover, we used a global definition of vitamin B12 deficiency that prioritizes the markers as follows: vitamin B12 as the first line marker, followed by MMA, and tHcy. The data analyses were repeated after excluding the studies one-by-one and evaluating the consistency of the estimates. We conducted post hoc analysis of the association between low plasma folate and PN from the studies that we identified in the present search.

For the primary analyses of intervention studies that included multiple clinical tests we used the most objective test (i.e., clinical examination by a physician) to define improvement. The sensitivity analyses included results of less certain tests (i.e., self-reported symptoms). In studies with several follow-up time points, the main analyses included the later time point (i.e., Parkinson's disease after receiving L-dopa), while the results in drug-näive subjects were analyzed in the sensitivity analyses.

We used the study quality and bias assessment tools according to the Newcastle–Ottawa Scale for case–control studies[8] and the revised form adapted for cross-sectional studies.[9] The overall quality was interpreted from the total scores.[10] The revised tool for assessing risk of bias in randomized trials (RoB 2) was used.[11] All studies were included in the data synthesis regardless of their quality.

RESULTS

Search results

The initial search identified 5174 articles, of which 1329 titles and abstracts were screened and 1078 were excluded (Figure 1). The remaining 251 articles plus one article that was identified from the reference list of a meta-analysis[7] passed to the full-text screening that led us to exclude a further 198 articles. We contacted 36 authors, of whom 13 provided additional data, while 16 potentially relevant articles were not included due to failed or implausible replies. The data were approximated from the figures or tables in nine studies.[12–20] The final analysis included 46 observational studies on B-vitamin markers in patients with and without PN[13–57] (Tables S2–S4) and seven intervention studies with B-vitamins in patients with PN [58–64] (Table 1 and Table S5). A study on non-neuropathic pain was excluded [65]

Observational studies

The prevalence of *lowered plasma vitamin B12* was reported in 32 independent studies among 2948 individuals with neuropathy and 9423 individuals without neuropathy (Tables S2–S4). One study was excluded from the data analyses because none of the participants had low vitamin B12.[53] Two studies had multiple groups of patients.[24,34] We found that neuropathy was associated with lowered vitamin B12 levels [pooled estimate (95% CIs) = 1.51 (1.23–1.84)] (Figure 2). The studies showed a moderate heterogeneity (Cochran *Q* Test I^2 = 43.3%, p = 0.003) and no publication bias (p = 0.065) (Figure S1A).

The association was not significant in a subgroup of Asian studies (1.43 [0.87–2.36], n = 10, I^2 = 63.5%, p = 0.003).[18,20,25,29,34,36,37,45,51] The European[14,17,22,26,28,30,32,38,42,46,47,57] and the North American studies[15,19,24,35,40,41,43,44,52,56] showed significant associations between lowered vitamin B12 and PN (1.66 [1.20–2.31], n = 12, I^2 = 13.4%, p = 0.314) and (1.55 [1.14–2.10], n = 11, I^2 = 44.8%, p = 0.053), respectively (Figure S2).

The presence of neuropathy was associated with lowered vitamin B12 concentrations among patients with diabetes (1.27 [0.87–1.85], n = 11, I^2 = 49.7%, p = 0.030) [22–24,26,32,34,37,45,51]; HIV infection (9.20 [1.85–45.82], n = 3, I^2 = 0%, p = 0.908) [19,35,40]; Parkinson's disease (2.74 [1.74–4.31], n = 7, I^2 = 0%, p = 0.894) [14,17,18,30,42,46,47]; and in idiopathic-[15,20,25,28,29,36,43,44,52,56,57] and alcohol-related neuropathies[15,57] combined (1.37 [1.06–1.78], n = 13, I^2 = 43.6%, p = 0.047) (Figure S3). Neuropathy was not significantly associated with lowered vitamin B12 in five studies among patients receiving metformin (1.50 [0.77–2.94], I^2 = 69.1%, p = 0.011) and in six studies among patients not exclusively treated with metformin (1.10 [0.72–1.68], I^2 = 16.3%, p = 0.309) (Figure S4).

The association between PN and lowered B12 was significant in 22 studies published between 2011 and 2018 (1.54 [1.22–1.94],

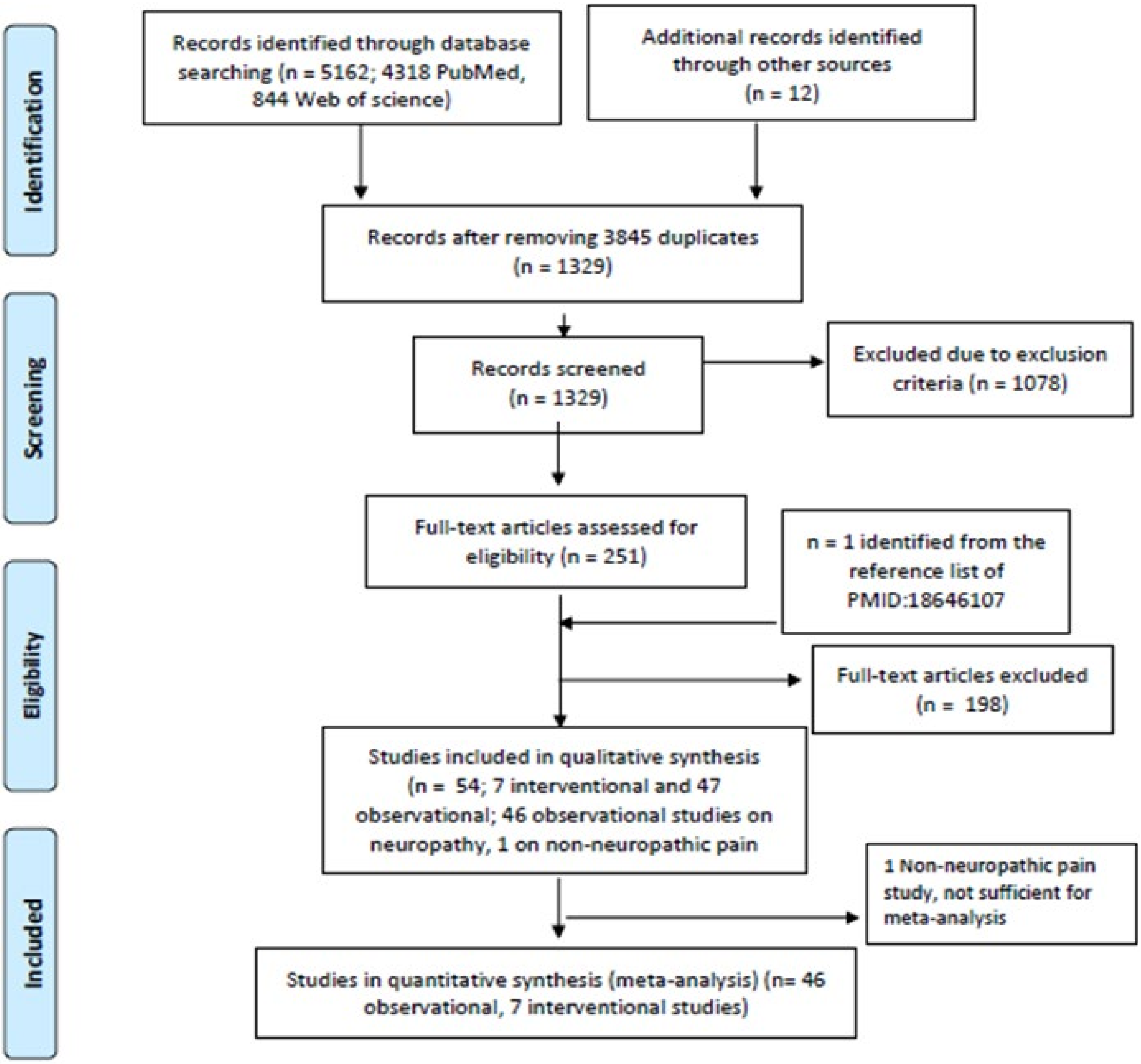


FIGURE 1 PRISMA study flow diagram. [Colour figure can be viewed at wileyonlinelibrary.com]

I^2 = 48.5%, p = 0.006), but not in studies published before 2000 (n = 5) or those published between 2000 and 2010 (n = 7) (Figure S5).

Neuropathy was associated with lowered vitamin B12 defined using cut-offs ≥205 ng/L (1.71 [1.20–2.43], n = 14, I^2 = 56.3%, p = 0.005) or below 205 ng/L (1.38 [1.04–1.83], n = 18, I^2 = 37.3%, p = 0.056) (Figure S6, Table S6).

Nine studies reported *concentrations of MMA* in relation to the presence of neuropathy in 827 individuals with neuropathy and 1492 without neuropathy.[18,21,30,36,38,49,50,52,53] An additional study reported a combination of lowered vitamin B12 or elevated MMA.[44] The presence of neuropathy was associated with elevated MMA (2.53 [1.39–4.60], I^2 = 63.8%, p = 0.005) (Figure 3). The studies showed a significant publication bias (p = 0.033). The pooled estimate after applying Duval and Tweedie's "trim and fill" method was 1.50 (0.81–2.78) (Figure S1B). Excluding studies one-by-one did not change the results (data not shown).

Neuropathy was associated with elevated plasma tHcy in 15 studies including 1047 patients with neuropathy and 4763 without neuropathy (3.48 [2.01–6.04], I^2 = 70.6%, p < 0.001).[12,14,17,22,27,30,33,38,39,42,44,47,48,52,53] No publication bias was observed (p = 0.276) (Figure 4 and Figure S1C) and no significant change of the estimate after one-by-one exclusion of the studies (data not shown).

Elevated tHcy was associated with neuropathy in studies among patients with Parkinson's diseases (n = 6) and idiopathic neuropathy (n = 4), while the association was not statistically significant in patients with diabetes (n = 5) (Figure S7).

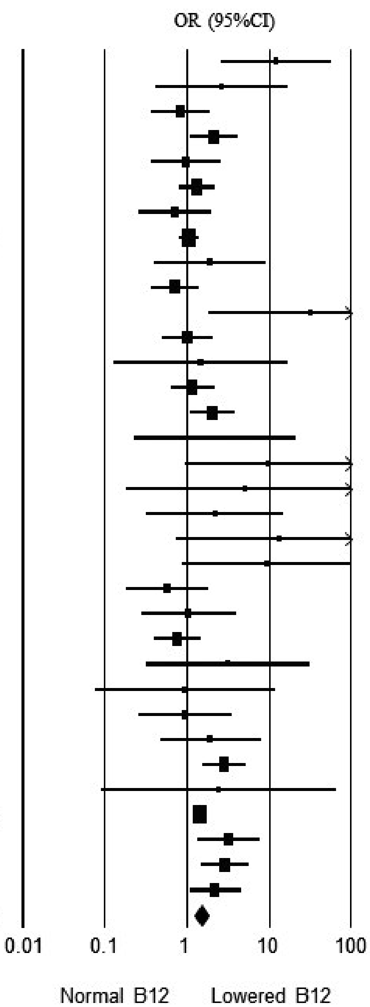
The sensitivity analysis showed that the association between neuropathy and lowered vitamin B12 remained significant after replacing one study reporting an alternative definition of lowered B12 status and six studies using alternative diagnosis of neuropathy (1.42 [1.14–1.78], n = 34, I^2 = 50.8%, p < 0.001) (Figure S8). This association showed publication bias (p = 0.006, Eggers regression

TABLE 1 Summary of intervention studies with B-vitamins in patients with neuropathy

Study	Design	Total *n*/*n* men	Primary aim	Country	Vitamin vs. comparator	Duration, days	Definition of PN/or pain	PN assessment
Li et al., 2016 [58]	Randomized double-blind controlled	232/122	Effect of oral Methyl B12 vs. acetyl-L-carnitine in patients with diabetic PN	China	1.5 mg Methyl B12 vs. 1500 mg acetyl-L-carnitine	168	Diabetic PN	Electrodiagnostic criteria from San Antonio Conference, abnormal NCV and/or amplitude in ≥1 nerve of the extremities
Haupt et al., 2005 [61]	Randomized double-blind controlled	40/23	Effect of oral benfothiamine vs. placebo in patients with distal diabetic PN	Germany	400 mg benfothiamine vs. placebo	21	Distal diabetic PN	Physical examination (motor/sensory function, coordination, reflexes), pain history
Abbas et al., 1997 [62]	Double-blind controlled	200/106	Effect of oral B1+B6 in high vs. low dose in patients with diabetic PN (28 days)	Tanzania	High dose: 50 mg B1 + 100 mg B6 (d 1–3), 25 mg B1 + 50 mg B6 (d 4–28) vs. low dose: (2 mg B1 + 2 mg B6 [d 1–3], 1 mg B1 + 1 mg B6 [d 4–28])	28	Diabetic PN	≥2 or more of the following: clinical symptoms, loss of light touch, impaired pain perception, absent ankle jerks, impaired temperature perception, impaired vibration sense at the medial malleolus or the great toe
Shindo et al., 1994 [59]	Open-label controlled	38/23	Effect of oral B12 vs. prostaglandin IV vs. no treatment in patients with diabetic PN	Japan	1.5 mg Methyl B12 vs. no treatment	28	Diabetic PN	Presence of subjective symptoms such as pain, numbness, hypesthesia, increased vibration threshold (upper and/or lower extremity)
McCann et al., 1983 [63]	Double-blind controlled	30	Effect of pyridoxine vs. placebo in patients with diabetic PN	Australia	25 mg pyridoxine vs. placebo	84	Diabetic PN	–
Vasudevan, 2014 [64]	Open randomized controlled trial	30/14	Pregabalin (±Methyl B12 and lipoic acid) in patients with diabetic PN associated with pain	India	Pregabalin 75 mg, 0.75 mg Methyl B12, 100 mg alpha lipoic acid * 2 daily vs. pregabalin 75 mg * 2 daily	84	Diabetic PN	Bilateral decreased or absent reflexes at the ankles, bilateral decreased vibration, pinprick, fine touch or temperature perception in the distal lower extremities for ≥6 months. confirmed by NCV studies; daily average pain score ≥4 on 11-point NRS (0–10)
Woelk 1998[60]	Randomized, placebo-controlled, double-blind	84/59	Effectiveness of benfotiamine and benfotiamine plus B6 and B12 in alcoholic neuropathy compared to placebo	Germany	Placebo; oral benfotiamine 320 mg/d for 4 weeks and 120 mg/d for another 4 weeks; benfotiamine 320 mg/d + 720 mg/d B6 + 2 mg/d B12 for 4 weeks, then 120 mg benfothiamine + 270 mg B6 + 0.75 B12 mg/d for 4 weeks	56	Alcohol-related neuropathy	Data on peripheral nerve function were recorded using a graduated tuning fork; vibration perception threshold at the great toe (major criterion): 8 is normal, 0 severely impaired; pain score on McGill's pain questionnaire ≤3 (5 = no pain, 0 = devastating pain); and sensory score ≤1 (0 = impaired perception, 2 = no impairment)

Abbreviations: d, day; IV, intravenous; NCV, nerve conduction velocity; NRS, numerical rating scale; PN, peripheral neuropathy.

	OR	Lower limit	Upper limit	n low B12/total PN present	n low B12/total PN absent	Relative weight
Gupta 2018	12.19	2.57	57.94	32 / 35	7 / 15	1.45
Cahill 2017	2.60	0.41	16.56	2 / 8	5 / 44	1.07
Ahmed 2016	0.82	0.35	1.90	11 / 43	23 / 78	3.70
Aroda 2016 (I)	2.12	1.10	4.10	13 / 100	43 / 653	4.89
Aroda 2016 (II)	0.96	0.37	2.52	5 / 95	35 / 641	3.08
Biemans 2015	1.30	0.80	2.12	32 / 96	88 / 317	6.37
de Groot-Kamphuis 2013	0.71	0.26	1.94	5 / 66	24 / 232	2.90
Leishear 2012	1.04	0.78	1.39	68 / 387	323 / 1900	8.44
Rajabally 2011	1.90	0.39	9.26	4 / 14	4 / 23	1.41
Baker 2010	0.70	0.36	1.35	28 / 46	132 / 191	4.84
Toth 2008	31.27	1.79	545.25	20 / 49	0 / 22	0.48
Hin 2006	1.00	0.48	2.07	15 / 30	400 / 800	4.39
Zambelis 2005	1.45	0.13	16.60	2 / 57	1 / 41	0.65
Gadoth 2006	1.17	0.63	2.15	20 / 53	93 / 272	5.30
Mold 2004	2.02	1.07	3.80	19 / 245	22 / 550	5.10
Ambrosch 2001	2.15	0.23	20.53	4 / 43	1 / 22	0.75
Fichtenbaum 1995	9.82	0.93	104.17	3 / 14	1 / 37	0.68
Veilleux 1995	5.00	0.18	139.16	1 / 1	7 / 19	0.36
Yao 1992	2.19	0.32	15.00	3 / 5	13 / 32	1.00
Kieburtz 1991	13.29	0.73	243.27	10 / 34	0 / 15	0.46
Merola 2015	9.17	0.86	97.69	5 / 11	1 / 12	0.68
Elhadd 2018 (I)	0.57	0.18	1.78	4 / 73	15 / 162	2.41
Elhadd 2018 (II)	1.03	0.27	3.90	4 / 21	8 / 43	1.88
Raizada 2017	0.76	0.39	1.46	19 / 68	39 / 115	4.92
Chen 2011	3.13	0.31	31.14	3 / 50	1 / 50	0.72
Rispoli 2017	0.94	0.07	12.00	1 / 9	2 / 17	0.59
Fennelly 1964	0.94	0.26	3.44	10 / 26	6 / 15	1.96
Crespo-Burillo 2016	1.93	0.47	7.86	4 / 26	5 / 58	1.72
Yang 2018	2.80	1.50	5.23	194 / 519	13 / 74	5.17
Park 2017	2.38	0.09	64.05	1 / 15	0 / 11	0.36
Oberlin 2013	1.44	1.20	1.72	273 / 600	887 / 2415	9.42
Mancini 2014	3.20	1.36	7.53	14 / 27	31 / 123	3.60
Ceravolo 2013	2.84	1.44	5.61	19 / 39	73 / 291	4.73
Sun 2014	2.17	1.07	4.41	20 / 43	38 / 133	4.54
	1.51 (1.23-1.84)			**868 / 2948**	**2341 / 9423**	



Cochran Q Test I^2 = 43.3%, p = 0.003

FIGURE 2 Forest plot of the association between the presence of peripheral neuropathy (PN) and low plasma concentrations of vitamin B12 in observational studies.

test). The estimate was 1.06 (0.94–1.19) after correcting for publication bias. Also, the association between PN and elevated plasma tHcy (2.93 [1.77–4.84], n = 15, I^2 = 77.9%, p < 0.001) or elevated MMA (2.20 [1.29–3.72], n = 9, I^2 = 67.8%, p = 0.002) remained significant when alternative definition of PN was used in the study of Hin et al.[38]

Neuropathy was associated with low vitamin B12 status defined using a global approach (i.e., B12 > MMA > tHcy) [(1.56 [1.31–1.86], n = 43, I^2 = 40.6%, p = 0.004) (Figure S9). A significant publication bias was detected (p = 0.023), but the adjusted estimate remained significant (1.37 [1.24–1.52]). Neuropathy was not significantly associated with lowered vitamin B1 or vitamin B6 (Figure S10).

Most observational studies were of good or fair quality (Table S7).

Intervention studies

Seven studies used at least one vitamin (B1, B6, or B12) to treat neuropathy[58–64] (Table 1). The OR of improvement in patients treated with B12 (vs. controls) was 1.36 (0.66–2.79), n = 4, I^2 = 28.9% (Figure S11A).[58–60,64] Similar results were seen when alternative tests were used to define improvement (1.23 [0.64–2.39], I^2 = 28.6%, p = 0.241).

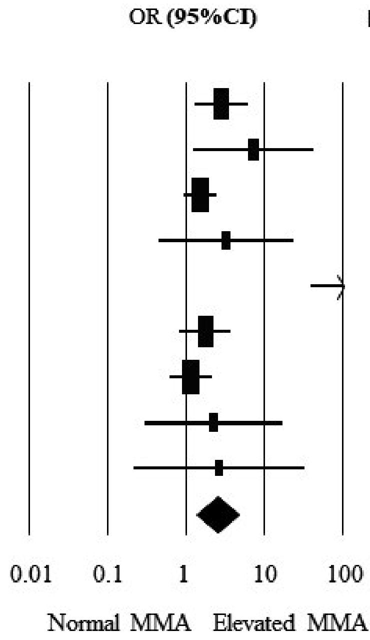
The association between symptom improvement after B12 alone or a combination of B12, B1, and B6 (n = 7) was not significant (2.58 [0.98–6.79], I^2 = 80.0%, p < 0.001) (Figure S11B). Alternative definitions of improvement yielded similar estimates (2.52 [0.98–6.50], I^2 = 80.8%, p < 0.001). The estimates were significant when the study of Li et al. [58] or that of McCann et al. [63] was excluded.

Treatment with vitamin B1 was associated with symptom improvement (5.34 [1.87–15.19], n = 3, I^2 = 64.6%, p = 0.059).[60–62] The sensitivity analysis showed similar results (4.60 [1.24–17.12]). Vitamin B6 was not associated with improvement (2.61 (0.42–16.36), n = 3, I^2 = 86.3%, p = 0.001).

There were similar or no side effects in three vitamin trials, while four trials did not report safety results[61–64] (Table S8).

Most intervention studies exhibited some concerns in the design (Table S9). Violations were often due to underreporting, rather than to a clear bias in the study designs.

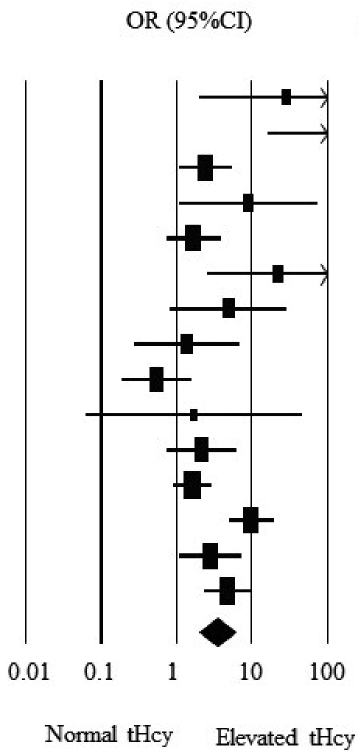
	Odds ratio	Lower limit	Upper limit	n elevated MMA/total PN +	n elevated MMA/total PN -	Relative weight
Adewumi 2013	2.86	1.33	6.15	55 / 118	11 / 47	16.55
Solomon 2011	7.31	1.25	42.81	13 / 15	8 / 17	7.64
Schrempf 2011	1.53	0.95	2.44	85 / 520	26 / 229	19.90
Toth 2010	3.24	0.45	23.11	2 / 5	7 / 41	6.60
Toth 2008	855.00	39.39	18557.28	47 / 49	0 / 22	3.26
Hin 2006	1.76	0.83	3.75	19 / 30	396 / 800	16.67
Gadoth 2006	1.17	0.63	2.15	20 / 53	93 / 272	18.37
Crespo-Burillo 2016	2.25	0.30	16.93	2 / 26	2 / 56	6.36
Park 2017	2.63	0.22	31.35	3 / 11	1 / 8	4.65
	2.53 (1.39-4.60)			**246 / 827**	**544 / 1492**	



Cochran Q Test $I^2 = 63.8\%$, $p = 0.005$

FIGURE 3 Forest plot of the association between the presence of peripheral neuropathy (PN) and elevated plasma methylmalonic acid (MMA) in observational studies.

	OR	Lower limit	Upper limit	n elevated tHcy/total PN present	n elevated tHcy/total PN absent	Relative weight
Toth 2010	28.67	1.98	414.19	2 / 5	1 / 44	3.10
Toth 2008	301.15	16.22	5590.05	43 / 49	0 / 22	2.71
Hin 2006	2.40	1.09	5.31	21 / 30	394 / 800	9.26
Ambrosch 2001	9.10	1.10	74.98	13 / 43	1 / 22	4.27
Buysschaert 2000	1.67	0.73	3.81	27 / 77	11 / 45	9.12
Merola 2015	22.50	2.60	194.51	9 / 11	2 / 12	4.15
Andréasson 2017	4.90	0.84	28.73	14 / 16	10 / 17	5.25
de Luis 2005	1.38	0.28	6.85	2 / 11	20 / 144	5.81
Hoogeveen 1999	0.54	0.18	1.60	4 / 25	148 / 569	7.93
Rispoli 2017	1.73	0.06	46.77	9 / 9	16 / 17	2.24
Crespo-Burillo 2016	2.13	0.73	6.26	8 / 26	10 / 58	7.97
Russo 2016	1.62	0.89	2.94	24 / 79	39 / 184	10.11
Oberlin 2013	9.80	4.95	19.39	28 / 600	12 / 2415	9.75
Mancini 2014	2.81	1.11	7.13	20 / 27	62 / 123	8.64
Ceravolo 2013	4.78	2.38	9.60	24 / 39	73 / 291	9.69
	3.48 (2.01-6.04)			**248/1047**	**799/4763**	



Cochran Q Test $I^2 = 70.6\%$, $p < 0.001$

FIGURE 4 Forest plot of the association between the presence of peripheral neuropathy (PN) and elevated plasma total homocysteine (tHcy) in observational studies.

DISCUSSION

We have shown that patients with PN had higher probabilities of lowered vitamin B12 (OR = 1.51 [1.23–1.84]) and elevated MMA (2.53 [1.39–4.60]) and tHcy concentrations (3.48 [2.01–6.04]) compared to patients without PN. The associations between lowered vitamin B12 and PN were rather consistent in subgroups of countries, comorbidities, publication years, and according to cut-off values of vitamin B12 concentrations. Studies conducted in patients with type 2 diabetes explained some of the observed heterogeneity. Furthermore, we found a non-significant higher OR of patients with PN to show improvement after vitamin B12 treatment compared to the comparators. Treatment with vitamin B1 was associated with improvement of PN symptoms compared to the control treatments.

Interpretation and translation into practice

Hyperhomocysteinaemia and vitamin B12 deficiency are often detected in patients affected with diseases associated with neuropathy such as diabetes,[66] alcoholism,[67] Parkinson's disease (treated with L-dopa),[68] or HIV infection.[69] Vitamin B12 deficiency could be a modifiable risk factor for neuropathy in those patients. A previous systematic review on the effect of B-vitamins among patients with alcohol- and diabetes-neuropathy was inconclusive.[7] Our results strongly suggest that screening for and treating vitamin B12 deficiency should be recommended for patients at risk for neuropathy and those with neuropathy. We have shown that the OR of elevated tHcy or MMA in patients with PN was higher than that of lowered vitamin B12. This observation supports using tHcy as a screening marker, since MMA measurement is expensive and requires highly equipped laboratories. Although the vitamin B12 test is widely used, lowered vitamin B12 concentrations show low sensitivity in detecting deficiency. Moreover, higher MMA and tHcy in elderly people and those with renal insufficiency, especially in patients with diabetes, may have increased the heterogeneity of the analysis and reduced the chance of detecting significant associations in subgroup analysis.

There is a need for consensus regarding the selection of markers to be used in detecting vitamin B12 deficiency in patients with PN. The German Society of Neurology recommended screening for vitamin B12 deficiency in patients with PN using vitamin B12 (or holotranscobalamin) and MMA.[70] Yetley et al. suggested using circulating vitamin B12 or holotranscobalamin and one functional marker, such as MMA or tHcy, to diagnose vitamin B12 deficiency.[71] The cut-off values for vitamin B12 are debatable and some authors proposed using cut-off values up to 258 or 300 nmol/L (or 191–222 pg/L) to capture all patients with probable deficiency.[72] Detection of low vitamin B12 in patients with PN could identify a subgroup of patients who may benefit from treatment.

A causal role for low B12 or elevated tHcy or MMA in neuropathy is uncertain, although the consistency in the evidence from observational and treatment studies in the present meta-analysis is suggestive of causality. Individuals who showed elevated tHcy after 6 years follow-up had lower nerve conduction velocity and abnormalities in monofilament compared to patients whose tHcy remained normal.[41] Longitudinal studies are needed to show if low B-vitamins in subjects who are free of neuropathy may predict future risk of the disease.

The associations between neuropathy and lowered vitamin B1 and B6 were inconclusive possibly due to the low number of studies, although some studies that showed significant associations[73,74] could not be analyzed in the present study.

Limitations

The present study has some limitations. The search was limited to English language articles published in PubMed and Web of Science, which may have caused publication bias or overestimation of the associations. However, our study depending on biomarkers and including PN associated with several diseases enabled us to synthesize evidence from a large number of studies, compared to previous systematic reviews.[7,75] Overall the results were consistent in the direction and the strength of the associations. The sensitivity and subgroup analyses have shown small variations in the pooled estimates, while the loss of significance in the subgroup analyses could be due to the low number of studies. Finally, the association of low vitamin B12 status and the presence of neuropathy was confirmed by using three independent markers of vitamin B12 status, suggesting that the results were not due to chance.

Gaps in the literature and recommendations for future research

There are mechanistically plausible data on a possible role of folic acid as a neuroprotective vitamin. We did not intend to capture studies on folate concentrations because the widely applied fortification with folic acid can bias the associations. We encountered and analyzed data from 12 studies reporting on plasma folate and neuropathy (results are not based on systematic search). Most of the studies did not find lower concentrations of folate or higher prevalence of deficiency in patients with PN compared to those without PN (Table S10). Plasma concentrations of tHcy could be elevated due to vitamin B12 and/or folate deficiency. Identifying elevated tHcy levels implies exploring the cause and lowering tHcy by using the appropriate vitamins or their combinations, since tHcy itself could be neurotoxic.

Notably, the vitamin trials have shortcomings that limit extrapolation of the results to all patients with PN. The limitations include small sample size, short treatment duration (3–24 weeks), and inclusion of mainly diabetes neuropathy (with rather high heterogeneity). Moreover, it is not clear whether the treatment with the vitamins should be better tailored to patients with low vitamin concentrations who are more likely to benefit. Future interventions should investigate vitamin statuses prior to administrating the vitamins.

CONCLUSIONS

We found that neuropathy was associated with lowered vitamin B12 status as indicated by plasma vitamin B12, MMA, and tHcy. This association was observed regardless of the primary disease that was believed to be the cause of neuropathy. The associations between neuropathy and vitamin B1 and B6 deficiencies were inconclusive. Treatment of neuropathy is a challenge. The association between vitamin B1 and B12 status and neuropathy symptoms or improvement after treatment suggests that treating nutritional deficiencies (including lowering plasma tHcy) should be part of the healthcare management of neuropathy and all morbidities associated with high risk of neuropathy.

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CONFLICT OF INTEREST

JS and JG: nothing to disclose. RO: received speaker honoraria from Merck Selfmedikation.

AUTHOR CONTRIBUTIONS

JS (MD Candidate, Homburg, Germany): developed the protocol, search, author contact, data extraction, data analysis, and revision of the publication. JG (MD, PhD, Homburg, Germany): provided input to the design and the intellectual content of the final draft of the manuscript. RO (PhD, Homburg, Germany): planned, designed, and conceptualized the study, prepared the first draft of the protocol, participated in the search, review, data extraction, supervised data analyses, and wrote the manuscript.

DATA AVAILABILITY STATEMENT

All data related to this article can be made available to investigators on request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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