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SPECIAL ISSUE

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Impact of supplementation with vitamins B_6, B_{12}, and/or folic acid on the reduction of homocysteine levels in patients with mild cognitive impairment: A systematic review

Gloria Olaso-Gonzalez[1] | **Marco Inzitari**[2,3] | **Giuseppe Bellelli**[4] | **Alessandro Morandi**[2,5] | **Núria Barcons**[6] | **José Viña**[1]

[1]Department of Physiology, Faculty of Medicine, Universitat de València, Valencia, Spain

[2]REFiT Barcelona Research Group, Parc Sanitari Pere Virgili and Vall d'Hebrón Institute of Research, Barcelona, Spain

[3]Department of Health Sciences, Universitat Oberta de Catalonia, Barcelona, Spain

[4]School of Medicine and Surgery, University of Milano-Bicocca and Acute Geriatric Unit, San Gerardo Hospital, Monza, Italy

[5]Department of Rehabilitation and Aged Care, Fondazione Teresa Camplani, Hospital Ancelle, Cremona, Italy

[6]Medical Affairs, Nestlé Health Science, Vevey, Switzerland

Correspondence
José Viña, Department of Physiology, Faculty of Medicine, University of Valencia, Avenida Blasco Ibañez 15, 46010 Valencia, Spain.
Email: jose.vina@uv.es

Funding information
Nestlé Health Science, Switzerland

Abstract

Hyperhomocysteinemia is an independent predictor of the risk for cognitive decline and may be a result of low levels of vitamins B_{12}, B_6, and folate. Previous findings suggest that adequate intake of these vitamins may reduce homocysteine levels. This review aimed to assess the effects of treatment with vitamins B_6, B_{12}, and/or folic acid in the homocysteine levels in patients with mild cognitive impairment (MCI). A systematic literature review was conducted in EMBASE, MEDLINE®, PsycINFO, and Cochrane Central Register of Controlled Trials. The research question was formulated using the Population, Intervention, Comparison, and Outcome (PICO) framework: in patients with MCI (P); what is the efficacy of vitamins B_6, B_{12}, and/or folic acid intake (I); compared with baseline values, and/or compared with controls (C); in reducing homocysteine levels from baseline (O). A total of eight primary studies with a total of 1,140 participants were included in the review. Four were randomized controlled trials, one was a quasi-controlled trial, and three were observational studies. All studies included folic acid in their intervention, seven vitamin B_{12}, and four vitamin B_6. Mean (*SD*) length of the intervention period was 18.8 (19.3) months, ranging from 1 to

Abbreviations: AD, Alzheimer disease; BHMT, betaine-homocysteine methyltransferase; C, comparison; CBS, cystathionine β-synthase; CT, controlled trial; GPx, glutathione peroxidase; I, intervention; m, month; MCI, mild cognitive impairment; MMSE, mini-mental state examination; MTR, methionine synthase; NR, not reported; GSH, glutathione; GST, glutathione reductase and glutathione s-transferase; O, outcome; P, population; PICO, population, intervention, comparison, and outcome; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCT, randomized controlled trial; ROB 2, Cochrane risk-of-bias version 2; ROS, reactive oxygen species; tHcy, total homocysteine concentration; vit, vitamin.

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60 months. All studies showed a statistically significant decrease in homocysteine levels in groups treated with vitamins B_6, B_{12}, and/or folic acid compared to controls, with a mean decline of homocysteine concentration of 31.9% in the intervention arms whereas it increased by 0.7% in the control arm. This review identified evidence of a reduction of plasma homocysteine levels in MCI patients taking vitamins B_6, B_{12}, and/or folic acid supplements, with statistically significant declines being observed after 1 month of supplementation. Findings support that supplementation with these vitamins might be an option to reduce homocysteine levels in people with MCI and elevated plasma homocysteine.

KEYWORDS

folic acid, homocysteine, mild cognitive impairment, vitamin B_6, vitamin B_{12}

1 | INTRODUCTION

Mild cognitive impairment (MCI) is a condition that is prodromal to Alzheimer's disease (AD) and marked by a subjective memory impairment and modest deficits in at least one of the following cognitive domains: executive function, memory, language, processing speed or attention.[1] The main distinction between MCI and mild dementia is that the latter involves more than one cognitive domain and there is a substantial interference with daily activities, while MCI may affect only one cognitive domain and does not substantially interfere with daily activities.[2] MCI is common among older people and its prevalence increases with age, being estimated that 6.7% of people aged 60–64 years old suffer from this condition, 8.4% of those aged 65–69, 10.1% of those aged 70–74, 14.8% of those aged 75–79, and 25.2% of those aged 80–84 years old.[3] MCI patients are at high risk of progressing to dementia[2-4] and around 50% of cases are estimated to progress to AD within 5 years.[1,4] As such, early therapeutic interventions are required to prevent degenerative neurological damage.[5,6]

Patients suffering from MCI have increased oxidative damage even before the onset of symptoms.[7] Oxidative damage is caused by a high production of reactive oxygen species (ROS) that cannot be managed by antioxidant defenses. Glutathione-dependent enzymes such as glutathione peroxidase (GPx), glutathione reductase, and glutathione S-transferase (GST) are antioxidant enzymes responsible for controlling ROS.[8] Cysteine is a major contributor to Glutathione (GSH) synthesis that can be obtained from the transsulfuration pathway from homocysteine to cysteine (Figure 1).

Homocysteine is a sulfur-containing amino acid and an intermediate in the biochemical conversion of methionine to cysteine and eventually glutathione.[9,10] Cysteine is easily autoxidized to the dimer cystine and H_2O_2,[11] and thus, in high concentrations, may be toxic to cells.[12] Homocysteine is also able to autoxidize in the presence of molecular oxygen and transition metal catalysts, promoting the formation of ROS such as hydrogen peroxide, hydroxyl, and thiol free radicals[11,13] (Figure 1). Plasma/serum total homocysteine concentration (tHcy) is the sum of homocysteine in all its three forms (protein-bound, free circulating disulfide, and sulfhydryl), and under conditions of maximal metabolic efficiency, tHcy levels of homocysteine range from 4 to 10 μmol/L.[10] Elevated blood levels of homocysteine (hyperhomocysteinemia) may be defined as a tHcy level >15 μM, although there may also be increased risks for people with tHcy concentrations of 10–15 μM.[14] The normal functioning of the homocysteine metabolism is dependent on the adequate intake of three vitamins: vitamin B_9 (folate/folic acid), vitamin B_{12} (cobalamin), and vitamin B_6 (pyridoxal phosphate), and a low level of these vitamins is a key cause of hyperhomocysteinemia[10,15] (Figure 1).

Strategies aimed at improving nutrition are increasingly being studied, in light of evidence that B vitamin deficiencies may contribute to the pathogenesis of cognitive impairment, through elevated blood levels of homocysteine.[16–20] Moderately elevated levels of tHcy are common in the population and increase with aging.[21–23] Increased prevalence of hyperhomocysteinemia is observed both in non-institutionalized elderly and in those living in care-facility homes, population where deficits of vitamin B_{12} and folate are also frequent.[24–27] Studies suggest that citizens of several European countries do not have adequate intakes of folic acid and B_{12} vitamins with respect to the recommendations.[28] Besides inadequate intake, there are other factors that may cause B vitamins deficiency, such as malabsorption, drug–nutrient interactions, specific medical conditions, or increased requirements.[29] Older people are more prone to have B vitamin deficiency, with the prevalence of vitamin B_{12} deficiency among older adult being estimated to

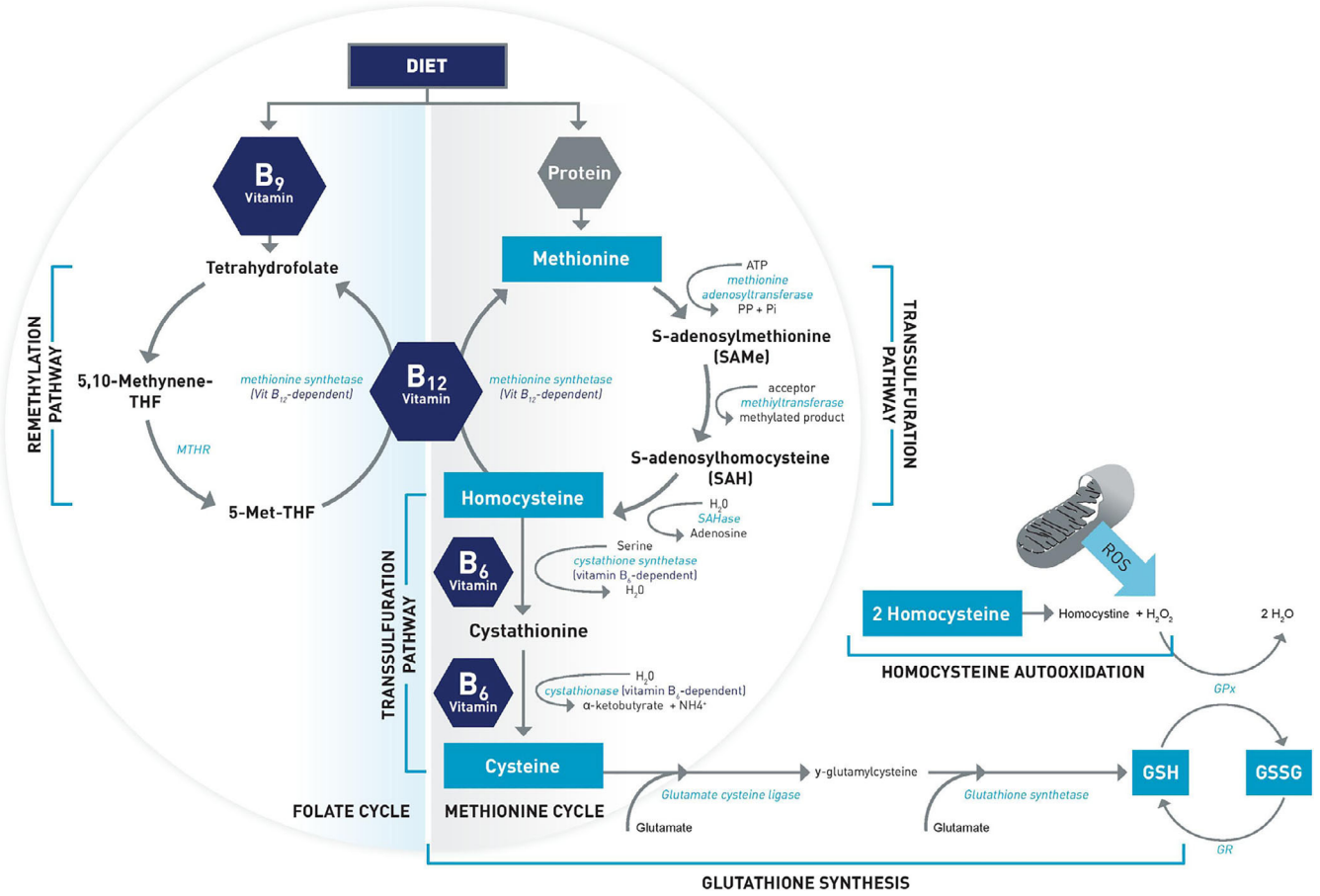

FIGURE 1 Homocysteine pathways and role of B vitamins. Reproduced with permission of Nestlé Health Science

range between 10 and 38%,[30] of folate between 29 and 35%, and of vitamin B_6 between 24 and 31%.[29]

Hyperhomocysteinemia is a potential risk factor for several diseases.[31] It has been associated with increased risk of neurodegenerative diseases (such as brain atrophy, cognitive impairment, and AD) and of cardiovascular diseases, amongst others.[10,32–35] Low blood levels of folate and vitamin B_{12}, and elevated tHcy levels have been associated with AD and vascular dementia: prospective studies in healthy older people have reported that individuals with tHcy concentrations >14 mmol/L had a two-fold higher risk of AD after adjustment for known risk factors.[36–38] Distinct, not mutually exclusive, biological mechanisms could explain the connection between raised tHcy and cognitive impairment (such as regional brain atrophy, neuronal death, vascular mechanisms, neurofibrillary tangle and amyloid plaque formation, and epigenetic mechanism), being likely that several alternative pathways are involved.[39] Recently, an international consensus on homocysteine and dementia concluded that raised tHcy is a strong modifiable risk factor for both cognitive decline, dementia and AD,[39] conclusion which is supported by a large body of evidence.[21,32,36–38,40–45]

Normalization of laboratory vitamin status may be accomplished with oral vitamins, and there is evidence that supplements containing folate, vitamins B_{12}, and/or B_6, decrease homocysteine concentrations.[26,36,40,46] Moreover, the international consensus recommended specific public health interventions, such as screening for raised tHcy in memory clinics or in people over 65 years old, and prescription of supplementary B vitamins to people who present raised tHcy,[39] in order to avoid the risks of hyperhomocysteinemia.[27]

The aim of this systematic review was to evaluate the impact on homocysteine levels of supplementation with vitamins B_6, B_{12}, and/or folic acid, specifically in patients with MCI.

2 | MATERIALS AND METHODS

2.1 | Research question and search strategy

A systematic search was conducted on July 2020 in EMBASE, MEDLINE®, PsycINFO, and Cochrane Central Register of Controlled Trials. The research question was

formulated using the following Population, Intervention, Comparison, and Outcome (PICO) framework[47]: in patients with MCI* (P); what is the efficacy of vitamins B_6, B_{12}, and/or folic acid intake (I); compared with baseline values and/or compared with placebo or any other intervention (C); in reducing homocysteine levels from baseline (O).

Keywords and free text words used to search from the above-mentioned databases included: (mild cognitive impairment), (mild cognitive dysfunction), (mild cognition), (MCI), (incipient dementia), (early stage dementia), (B complex vitamins), (Vitamin B complex), (vitamin B6), (pyridoxine), (vitamin B9), (folate), (vitamin B12), (cobalamin). Detailed search string for Embase is provided in the supporting information (Table S1). Additional references were searched from the bibliography of selected systematic reviews and meta-analyses. There was no restriction on publication timeframe or language.

2.2 | Eligibility criteria

Articles were included if they followed pre-defined inclusion/exclusion criteria (Table S2). In particular, whenever the studies included mixed populations, such as patients with AD, they were only included if results were separately published for MCI.

2.3 | Review methodology

Abstracts identified during the search were reviewed by two independent researchers against pre-determined eligibility (inclusion/exclusion) criteria using the previously described PICO frame. Cases of uncertainty about the inclusion of a publication were resolved either through "reconciliation" (discussion between the two reviewers) or through "arbitration" by a third reviewer. Excluded publications were disregarded. After abstract review, full texts were reviewed by one researcher and checked by another, based on the eligibility criteria. The approach to resolving disagreements was the same as outlined above during the abstract review process. All papers included after the full text review were retained for data extraction. The inclusion and exclusion of studies are summarized in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.[48]

2.4 | Data extraction

A standardized extraction template on excel was developed to extract data from included publications. Data extracted were: population characteristics, clinical history, study design, and treatment details such as medication dose, frequency, composition, and duration. Measures included were mean, median, numbers with variables such as *SD*, *SE*, CI, and *p*-values.

The growth in homocysteine concentration was computed as the percentage increase between the mean homocysteine concentration reported at baseline and the one reported at the end of the intervention in each study. The mean homocysteine growth across identified studies was computed in a pooled analysis, by weighting the homocysteine growth from each single study by the respective population sample in the intervention arm.

2.5 | Assessment of the methodological quality of the studies

The quality of each study was assessed to ensure that the conclusions and findings of this review are based on the best available evidence and that any potential sources of bias in the data are identified. Eligible studies were assessed for bias using the Cochrane risk-of-bias version 2 (RoB 2) tool for randomized trials.[49] For non-randomized controlled trials (RCTs), this review utilized the Brown and Black checklist to assess the quality of those studies.[50]

The RoB 2 tool provides a framework for considering the risk of bias in the findings of any type of randomized trial. The tool is structured into five domains through which bias might be introduced into the results, namely: (a) bias arising from the randomization process; (b) bias due to deviations from intended interventions; (c) bias due to missing outcome data; (d) bias in measurement of the outcome; (e) bias in the selection of the reported result. The Brown and Black checklist considers the following possible biases: (a) reporting bias; (b) external validity bias; (c) internal validity—bias; (d) internal validity—confounding (selection bias); (e) power of the study.

3 | RESULTS

3.1 | Search results

The review identified a total of 457 citations after removal of duplicates. Following title and abstract review, 53 publications were retained for full-text review. During the full-text review, 41 were excluded due to the study design ($n = 3$), population ($n = 6$), intervention ($n = 5$), or outcomes ($n = 26$) not being of interest; thus, resulting in the inclusion of 12 publications, which correspond to 8 primary studies. The details of the selection process of articles are shown in Figure 2.

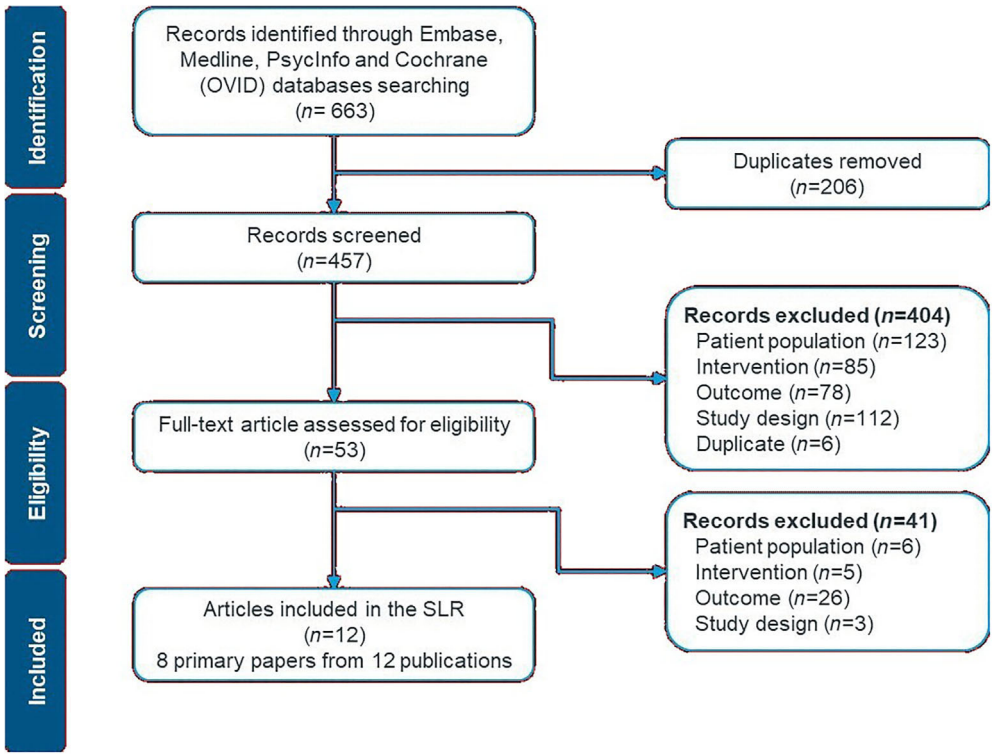

FIGURE 2 PRISMA flow chart of the study selection process

3.2 | Characteristics of the retrieved studies

Eight primary studies with 1,140 participants were included in the review. Four were RCTs, one was a quasi-controlled trial, and three were observational studies (Table 1). MCI patients sample sizes ranged from 16[51] to 279.[52] Seven primary studies used the Mini-Mental State Examination (MMSE) as diagnostic criteria for inclusion,[17–19,32,53,54] and one study did not report the diagnostic criteria, but was included since mean, minimum and maximum MMSE was reported and fit the MCI criteria[35] (Table S3).

The mean age of included patients ranged from 68 years[17] to 78 years,[18] resulting in a mean (*SD*) of 74.1 (3.1) years for the B vitamins intervention groups. As for gender distribution, the mean (*SD*) percentage of females was 56.7% (10.3). Medical history was reported in five studies, of which all reported diabetes (range: 2.5%[35] to 62.5%[18]) and heart disease (range: 6.6%[17] to 16.6%[18]), four reported stroke (range: 7.8%[19] to 22.2%[35]), and three hypertension (range: 6.6%[19] -58.3%[18]) (Table S4).

Mean (*SD*) length of the intervention period was 18.8 (19.3) months, with intervention period ranging from 1[54] to 60 months.[35] Oral B vitamins supplementation was used in the included studies, with the following ingredients and dosage: all studies included folic acid in their intervention with a daily intake ranging from 400 to 30,000 μg/day; seven studies included vitamin $B_{12,}$ with a daily intake ranging from 25 to 2,000 μg/day; and four studies included vitamin $B_{6,}$ with a daily intake ranging from 20 to 300 mg/day (Table 1). One study did not report the dose of the intervention, but was included as it specified the combination of B vitamins which was used, which met this review criteria.[18]

3.3 | Methodological quality of the studies

Three of the studies showed an overall high risk of bias measured by the RoB 2[17,19,53]—in two studies, the high risk of bias was due to measurement of outcome, and, in the other, due to the selection of reported results. One study showed an overall low risk of bias.[52] As for the quality of the observational studies and of the quasi-controlled trial—whose quality was assessed using the Downs and Black Quality checklist, based on the scores, one out of three included articles of observational studies[35] and one quasi controlled study[18] were categorized as fair and the remaining two were categorized as poor quality[32,54] (Table 1).

3.4 | Impact of the interventions in homocysteine levels

The evaluation time point of homocysteine concentration levels (μmol/L) ranged from 1 month[51,54] to 60 months[35]

TABLE 1 Design of the included studies

Variable/study	Kwok (2020)[52]	Ma (2019)[17]	Ma (2019)[19]	Lee (2016)[18]	Blasko (2012)[35]	De Jager (2012)[53]	Schroecksnadel (2006)[51,54]			Lehmann (2003)[32]
Study design	RCT	RCT	RCT	Quasi CT	Observational	RCT	Observational			Observational
MCI patients (including controls)	279	240	180	48	81	266	16	15	9	30
Overall quality assessment	Low risk of bias	High risk of bias	High risk of bias	Fair quality level	Fair quality level	High risk of bias	Poor quality level			Poor quality level
Intervention period	24 m	6 m	24 m	3 m	60 m	24 m	1 m	2 m	3 m	9 m (270 days)
Folic acid (μg/day)	500	800	400	NR	1,800 ± 2,100[a]	800	5,000	15,000	30,000	10,000
Vit B_{12} (μg/day)	400	25	—	NR	146 ± 259[a]	500	50	150	300	2,000
Vit B_6 (mg/day)	—	—	—	NR	—	20	50	150	300	80
Other	—	—	—	—	—	—	50 mg vit B_1	150 mg vit B_1	300 mg vit B_1	—
Route	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral	Oral

Abbreviations: CT, controlled trial; m, month(s); MCI, mild cognitive impairment; NR, not reported; RCT, randomized controlled trial; vit, vitamin.

[a]Mean daily dose of on folic acid and vitamin B_{12} supplementation obtained from study participants during a clinical interview.

after treatment. At baseline, mean homocysteine levels were above >15 mmol/L in the group B vitamin intervention arm in three studies,[17,32,55] and between 10 and 15 mmol/L in five studies.[19,35,52–54] All studies showed a statistically significant decrease in homocysteine levels in vitamin B group compared to the control group (Table 2).

In the B vitamins intervention groups, the decline of mean homocysteine concentration from baseline to the end of study ranged between 9.8%[35] and 48.6%.[32] The weighted mean growth across studies is −31.9% in the intervention arms versus 0.7% in the control arm.

Figure 3 displays the growth of mean homocysteine concentration per study in each of the reported evaluation time points, per type of intervention. A significant decline in homocysteine was observed as early as after 1 month of supplementation.[54] Only two studies provided mean levels of homocysteine concentrations across time. Ma et al. reported a progressive decline through time (a 30.5% decline in mean homocysteine concentration was observed 6 months after treatment initiation, which increased to a 44.8% decline at 24 months of treatment).[19] Kwok et al. report a 31.9% decline in mean homocysteine concentration at 12 months which is consistent with the decline observed at 24 months (32.6%).[52]

The study which had a longer duration had the lowest decline in mean homocysteine concentration (9.8%).[35] However, in this study, the data on folic acid and vitamin B_{12} supplementation was collected during a clinical interview at baseline and at the end of the 5 years observation period and includes patients who have used a combination of folic acid and vitamin B_{12} for more than a year, but not necessarily throughout the whole period, nor at a prespecified dose.

The highest decline in homocysteine concentration is observed in the combination of vitamins B_6, B_{12}, and folic acid.[32] Overall, the highest declines in homocysteine concentrations were observed in some combination of vitamins B_6, B_{12}, and/or folic acid.[17–19,32,35,52] Ma et al. reported a higher decline in homocysteine when using a combination of folic acid and vitamin B_{12} (33.0%) than when using either supplements alone (25.0% with folic acid and 23.4% with vitamin B_{12}).[17]

3.5 | Impact of the interventions in B vitamin levels

3.5.1 | Folate

Folate levels (ng/mL) were reported in seven studies. All studies showed statistically significant increase in

TABLE 2 Effects on the levels of plasma homocysteine concentrations

Author and year	Intervention/ comparator	*n*	Time point	Homocysteine concentrations (μmol/L)	% change to baseline	*p*-value
Kwok (2020)[52]	Vitamin B_{12} + folic acid	138	Baseline	Mean (*SD*): 13.8 (3.4)	—	NR
	Placebo	141		Mean (*SD*): 13.8 (3)	—	
	Vitamin B_{12} + folic acid	121	12 months	Mean (*SD*): 9.4 (2.2)	**−31.9%**	**<.0001**
	Placebo	125		Mean (*SD*): 13.5 (3.6)	−2.2%	NR
	Vitamin B_{12} + folic acid	118	24 months	Mean (*SD*): 9.3 (2.4)	**−32.6%**	**<.0001**
	Placebo	120		Mean (*SD*): 14 (4.1)	1.4%	NR
Ma (2019)[17]	Folic acid alone	60	Baseline	Mean (*SD*): 19.88 (1.93)	—	NR
	Vitamin B_{12} alone	60		Mean (*SD*): 20.99 (1.1)	—	
	Vitamin B_{12} + folic acid	60		Mean (*SD*): 21.98 (1.71)	—	
	Control	60		Mean (*SD*): 19.22 (1.66)	—	
	Folic acid alone	60	6 months	Mean (*SD*): 14.91 (0.35)	**−25.0%**	**.027**
	Vitamin B12 alone	60		Mean (*SD*): 16.07 (0.64)	**−23.4%**	**.017**
	Vitamin B_{12} + folic acid	60		Mean (*SD*): 14.72 (0.39)	**−33.0%**	**.012**
	Control	60		Mean (*SD*): 18.21 (0.67)	−5.3%	NR
Ma (2019)[19]	Folic acid supplementation	90	Baseline	Mean (*SD*): 13.65 (4.82)	—	NR
	Control	90		Mean (*SD*): 12.19 (3.85)	—	
	Folic acid supplementation	90	6 months	Mean (*SD*): 9.49 (5.72)	−30.5%	NR
	Control	90		Mean (*SD*): 10.97 (2.42)	−10.0%	
	Folic acid supplementation	90	12 months	Mean (*SD*): 8.21 (1.22)	−39.9%	NR
	Control	90		Mean (*SD*): 11.33 (1.51)	−7.1%	
	Folic acid supplementation	90	18 months	Mean (*SD*): 8.01 (1.26)	−41.3%	NR
	Control	90		Mean (*SD*): 11.36 (1.49)	−6.8%	
	Folic acid supplementation	90	24 months	Mean (*SD*): 7.54 (1.33)	**−44.8%**	**.028**
	Control	90		Mean (*SD*): 11.37 (1.21)	−6.7%	NR
Lee (2016)[18]	Vitamin B_6, B_{12}, and folic acid	24	Baseline	Mean (*SD*): 19.29 (7.09)	—	NR
	Control	24		Mean (*SD*): 17.57 (5.4)	—	
	Vitamin B_6, B_{12}, and folic acid	24	3 months	Mean (*SD*): 10.92 (1.67)	**−43.4%**	**.001**
	Control	24		Mean (*SD*): 19.08 (5.57)	8.6%	NR
Blasko (2012)[35]	Non user	51	Baseline	Mean (*SD*): 15 (4.7)	—	NR
	Inconsistent users	20		Mean (*SD*): 14 (4.4)	—	
	Combination users	10		Mean (*SD*): 12.3 (2.5)	—	
	Non user	51	60 months	Mean (*SD*): 15.2 (6.3)	1.3%	NR
	Inconsistent users	20		Mean (*SD*): 12.7 (4.7)	**−9.3%**	**.044**
	Combination users	10		Mean (*SD*): 11.1 (1.6)	**−9.8%**	**.007**
De Jager (2012)[53]	Vitamin B_6, B_{12}, and folic acid	110	Baseline	Mean (95%CI): 11.3 (10.7–11.9)	—	NR
	Placebo	113		Mean (95%CI): 11.6 (10.9–12.9)	—	

TABLE 2 (Continued)

Author and year	Intervention/ comparator	*n*	Time point	Homocysteine concentrations (μmol/L)	% change to baseline	*p*-value
	Vitamin B_6, B_{12}, and folic acid	110	24 months	Mean (95%CI): 8.7 (8.2–9.1)	**−23.0%**	**<.001**
	Placebo	113		Mean (95%CI): 12.4 (11.8–13.1)	6.9%	NR
Schroecksnadel (2006)[51,54]	Vitamin B_1, B_6, B_{12}, and folic acid	15	0	Mean (*SD*): 13 (1.3)	—	NR
		15	1 month	Mean (*SD*): 8.33 (NR)	**−34.6%**	**.001**
Lehmann (2003)[32]	Vitamin B_6, B_{12}, and folic acid	30	0	Mean (*SD*): 18.5 (4.7)	—	NR
		30	9 months	Mean (*SD*): 9.5 (2.6)	**−48.6%**	**<.0001**

Abbreviation: NR, not reported.
p-value of less than .05 considered statistically significant was in bold.

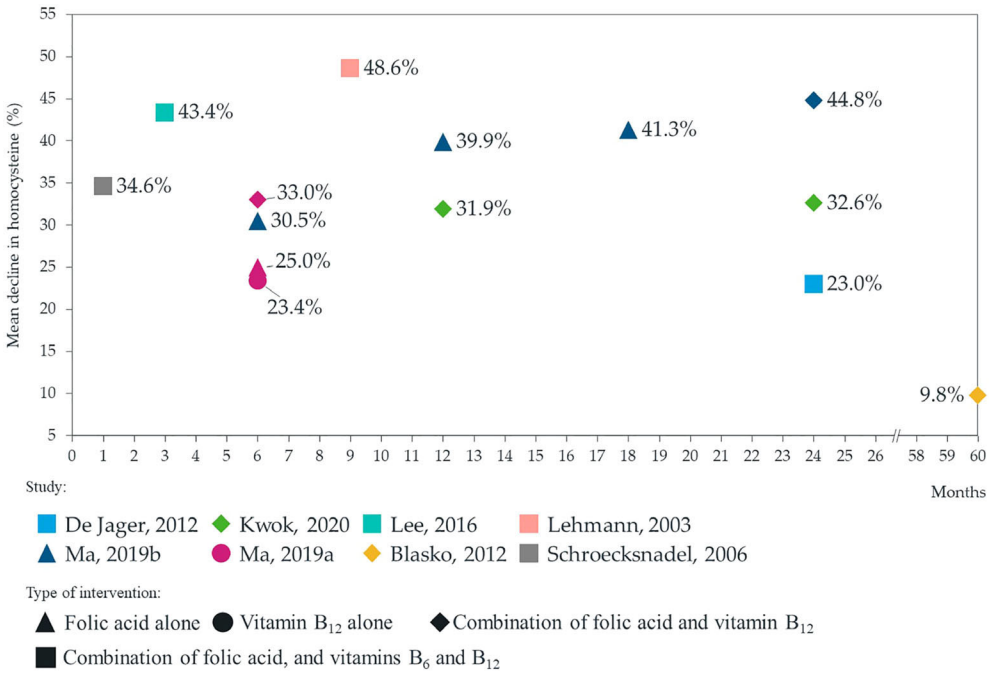

FIGURE 3 Mean decline in homocysteine from baseline per study, time point, and type of intervention. X-axis: months from the beginning of the study (baseline). Y-axis: mean decline in homocysteine (%) from the beginning of the study, given the following formula:

$$\text{Mean decline in homocysteine} = \frac{(\text{Mean homocysteine at month m}) - (\text{Mean homocysteine at baseline})}{\text{Mean homocysteine at baseline}}$$

folate levels in vitamin B group compared to the respective control groups (Table S5).[17,19,32,35,51–54] In the B vitamins intervention groups, the increase of mean folate concentration per study ranged between 16.7%[17] and 302.3%[51,54] from baseline to the end of study. The weighted mean change across the seven studies was 103.8% in the intervention arms versus 0.7% in the control arm.

3.5.2 | Vitamin B_{12}

Vitamin B_{12} levels (pg/mL) were reported in seven studies. Four studies showed a statistically significant increase in vitamin B_{12} levels in the treatment group compared to the control group. The weighted mean change across the six studies with vitamin B_{12} supplementation in the intervention is 65.6% in the intervention arms versus 2.1% in the control arm.

3.5.3 | Vitamin B_6

Although four studies included vitamin B_6 in their intervention, none of them has reported the vitamin B_6 levels of their population, neither at baseline nor at the end of the intervention.

4 | DISCUSSION

This systematic literature review, which included results from 1,140 patients from eight primary studies, has identified consistent evidence of a statistically significant decrease in homocysteine concentration in MCI patients treated with vitamins B_6, B_{12}, and/or folic acid compared to the control groups, with a mean decline in homocysteine of 31.9%. Results are aligned with those from Clarke et al., whom, in a meta-analysis from 11 trials, not specific to MCI, found that allocation to B vitamins was associated with a 26.1–28.4% reduction in plasma concentrations of homocysteine, including patients with distinct cognitive status.[36] In our review, the mean age of included patients was 74.1 years old across studies, whereas patients included in Clarke et al. review were younger (68 years old in the cognitive-domain trials and 66 years old in the global cognition trials). The highest tHcy reduction reported in Clarke et al. was 34.9% and the lowest 12.4%,[36] while in the present review it ranged between 9.8%[35] and 48.6%.[32] The decline in homocysteine levels was higher than the maximum reported by Clarke et al. in three of the studies.[18,19,32]

Clinically relevant and statistically significant results were observed in all studies, irrespective of the duration of the intervention. The studies reporting the highest homocysteine-lowering effects have used a combination of vitamins B_6, B_{12}, and/or folic acid, and one study specifically reports higher results when using a combination of folic acid and vitamin B_{12}, than when using either ingredients alone.[17] As previously mentioned, the mechanisms behind the connection between raised homocysteine levels, vitamins B_6, B_{12}, and/or folic acid levels and cognitive impairment are various and not mutually exclusive.[39] Homocysteine metabolism may occur through three pathways: (a) the homocysteine remethylation to form methionine catalyzed by the methionine synthase (MTR) enzyme (a vitamin B_{12} and folate-dependent reaction); (b) the transsulfuration pathway, through which homocysteine is converted to cystathionine by cystathionine β-synthase (CBS); and by (c) homocysteine remethylation to methionine via betaine-homocysteine methyltransferase (BHMT).[15,56]

Vitamin B_6 is thought to activate the transsulfuration pathway, potentially leading to lower Hcy levels.[57] In this metabolic pathway—fundamental to maintain optimal cellular function[12,58,59]—sulfur is transferred from homocysteine to cysteine[58] which can be used to form GSH and enhancing the antioxidant defenses of the organism. Nonetheless, as there is a significant heterogeneity in the ingredients, dosage, and duration of the intervention across studies, no specific conclusion can be drawn as to the most effective treatment duration, combination and dosage of vitamins B_6, B_{12}, and/or folic acid supplementation to achieve an optimal homocysteine-lowering effect. This limitation was also identified in a previous review analyzing the benefits of B vitamins on cognitive function.[60]

The present review has focused on the impact of supplementations with vitamins B_6, B_{12}, and/or folic acid on the reduction of homocysteine levels, as this reduction might be associated with benefits for cognition. The research question was not extended to the direct association between supplementations with vitamins B_6, B_{12}, and/or folic acid and cognitive status due to the heterogeneity of tests used to assess cognitive function in these studies (Table S6). Future high-quality studies with homogenous evaluations of cognitive function are required to enable a robust assessment of the relation between supplementation with vitamins B_6, B_{12}, and/or folic acid and cognitive function in MCI patients.

5 | CONCLUSIONS

The present systematic review corroborates the beneficial effect of supplementation with vitamins B_6, B_{12}, and/or folic acid on reducing homocysteine levels in MCI patients, from as early as 1 month. The differences in controls are significant and clinically relevant, supporting a potential use of these supplements as a strategy to compensate low levels of these vitamins and reduce the risk of hyperhomocysteinemia.

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CONFLICT OF INTEREST

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ORCID

José Viña https://orcid.org/0000-0001-9709-0089

ENDNOTE

* Mild cognitive dysfunction was used in the search strategy as it is a MeSH term.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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