

Examining the Clinical Usefulness of Urine Methylmalonic Acid for Diagnosis of Vitamin B-12 Deficiency in Older Adults: A Pilot Study

Charlotte Bédard-Delisle^{1,2}, Guillaume Leonard^{1,2}, Christiane Auray-Blais^{1,3}, Isabelle Reid², Mohamed Gamrani^{1,3}, Hassiba Chebbihi^{1,2}, Nancy Presse^{1,2,†}

¹Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, Quebec, Canada; ²Research Centre on Aging, CIUSSS de L'Estrée-CHUS, Sherbrooke, Quebec, Canada; ³Centre Hospitalier Universitaire de Sherbrooke Research Center, CIUSSS de l'Estrée-CHUS, Sherbrooke, Quebec, Canada

[†]Nancy Presse passed away on February 7, 2025

Correspondence: Guillaume Leonard, Research Centre on Aging, CIUSSS de L'Estrée-CHUS, 1036 rue Belvedere Sud, Sherbrooke, Quebec, J1H 4C4, Canada, Tel +1 819 821 2220 ext. 45246, Fax +1 819 829 7141, Email guillaume.leonard2@usherbrooke.ca

Aim: Vitamin B-12 deficiency is common among older adults and can lead to irreversible neurological damage and severe complications if not treated early. Despite its clinical significance, effective management remains challenging due to the absence of simple and sensitive biomarkers for early detection and for monitoring treatment response.

Purpose: This pilot study evaluated the feasibility and potential of the urinary methylmalonic acid (uMMA)/creatinine ratio as a biomarker of vitamin B-12 deficiency in older adults, while exploring clinical responses following supplementation.

Participants and Methods: A 3-month quasi-experimental pre-post study was conducted with 53 community-dwelling adults aged ≥ 70 years. Participants provided 4 monthly fasting urine samples to enable tandem mass spectrometry analysis of the uMMA/creatinine ratio before and after 1200 $\mu\text{g/day}$ of peroral vitamin B-12 supplementation. Balance (Berg Balance Scale, Activities-specific Balance Confidence Scale), cognitive function (Montreal Cognitive Assessment), and neurophysiological markers (motor evoked potentials [MEP] latency) were assessed before and after supplementation.

Results: All urine filter paper samples were successfully received and analyzed, with most participants ($n = 45$) maintaining a supplementation adherence rate of 95% or higher. Supplementation led to a statistically significant reduction in uMMA/creatinine levels, accompanied by significant improvements in both balance and cognitive performance. A significant correlation was observed between the reduction in the uMMA/creatinine ratio and cognitive improvement. No significant changes were detected in MEP latency.

Conclusion: Urinary methylmalonic acid is a promising biomarker for assessing vitamin B-12 deficiency and treatment response in older adults. Larger, well-designed studies with extended supplementation periods are needed to confirm its clinical utility and better evaluate the impact of prolonged supplementation on balance, cognitive and neurophysiological outcomes.

Keywords: vitamin B-12 deficiency, aging, methylmalonic acid, cognition, transcranial magnetic stimulation, motor evoked potential

Introduction

Vitamin B-12 deficiency affects 5–15% of older adults, and up to 42% of hospitalized older patients.^{1–8} If left untreated, vitamin B-12 deficiency can lead to potentially irreversible neurological complications, including neuropathies and cognitive impairment.^{9–12} Over time, neurological symptoms become harder to reverse, limiting the window for effective intervention.^{13–15} Despite advances in clinical practice, vitamin B-12 deficiency often remains undiagnosed due to its subtle and diverse manifestations, highlighting the need for simple and sensitive biomarkers to enable early detection and monitor treatment response.^{16–18}

Total serum vitamin B-12 – the standard diagnostic marker – correlates poorly with clinical symptoms and often yields false negatives, as normal or high serum levels do not necessarily reflect adequate cellular availability.^{2,19,20} During the last

decades, research efforts have been focusing on identifying markers of vitamin B-12 status in older adults that can be sensitive and specific, as well as practical and cost-effective.²¹

Vitamin B-12 is a cofactor in the conversion of L-methylmalonyl-CoA to succinyl-CoA,¹¹ and deficiency leads to increased methylmalonic acid (MMA) in blood and urine.²² While serum MMA is considered the gold standard, its measurement via gas chromatography/mass spectrometry (GC/MS) is costly and not widely available, and its levels can be falsely elevated in individuals with impaired kidney function.²³ Urinary MMA has been proposed as a non-invasive and cost-effective alternative.²² Early studies demonstrated elevated urinary MMA in B-12-deficient individuals, with normalization after supplementation.^{22,24,25} Moreover, in contrast to serum MMA, urinary MMA appears to be less influenced by mild to moderate renal impairment and, when expressed relative to urinary creatinine, remains unaffected by reduced renal function.^{26,27} However, urinary MMA remains underexplored in older adults. A validated UPLC-MS/MS method developed by our group allows the simultaneous, high-throughput quantification of MMA and creatinine in urine, including from dried urine filter paper samples suitable for home collection and mail-in.^{28,29}

Briefly, 1 mL of urine specimen from each participant was deposited on a 5 cm filter paper disk (GE Healthcare, IL, USA) and left to dry for 4 hours at room temperature. The chosen internal standards were creatinine-D3 (methyl-D3 99 atom%D) and MMA-D3 (methyl-D3 99 atom%D) (CDN, Canada). Two hundred microliters of the internal standard solution were deposited on each filter disk, left to dry at room temperature, and eluted under mild alkaline conditions (ammonium hydroxide) prior to UPLC-MS/MS analysis. The eluate was filtered to remove particulate matter before injection. The analyses (MMA, creatinine, and deuterated internal standards) were then chromatographically separated on a reversed-phase C18 column coupled to a tandem mass spectrometer, allowing sensitive and precise quantification. This approach ensures minimal matrix interference and is well suited for remote sampling in large-scale studies.²⁹

Previous experience with a neonatal screening program for amino acids and organic acids (including MMA) demonstrated the feasibility and utility of non-invasive urine collection on filter paper by parents.^{30–32} Recent studies conducted by our team support urinary MMA as a valid biomarker in older adults, showing correlations with serum MMA, serum B-12, and dietary intake.^{28,29,33} However, its clinical utility ultimately hinges on confirming its predictive value for clinical outcomes and if it detects B-12 deficiency at all stages, including early deficiency states.

The main overall objective of this study was to assess the utility of using urinary MMA/creatinine ratio as a biomarker in individuals aged 70 years and older who may be at risk of vitamin B-12 deficiency. Specific objectives were to: 1) evaluate feasibility through recruitment, attrition rates, compliance to supplementation, and urine sample return rates; and 2) collect preliminary data on clinical responses – including changes in MMA/creatinine ratio, motor evoked potentials (MEP) latency, balance, and cognition – following vitamin B-12 supplementation, and to explore associations among these outcomes.

Materials and Methods

Design and Study Population

This 3-month pre-post quasi-experimental pilot study aimed to include French-speaking individuals, aged ≥ 70 years, living in the community of Sherbrooke, Quebec, Canada. Participants were recruited from a registry of more than 2000 community-dwelling, socially active volunteers aged 65 and older. None of them had been diagnosed with vitamin B-12 deficiency or were taking vitamin B-12 supplements (prescribed or over-the-counter). Other exclusion criteria included: to be under dialysis, being anuric, being diagnosed with peripheral neuropathy, being diagnosed with diabetes, have an active cancer or have been in remission for less than a year, not able to come to the research center for assessment, not able to stand on two legs, not able to provide informed consent, and the case where an eligible participant has not taken their first initial urine sample before visit 1. People with contraindications to transcranial magnetic stimulation (eg, metal implants in the skull, epilepsy, pacemaker) were also excluded.³⁴ Reasons for non-eligibility or refusal to participate were noted. Ethics approval was obtained from the Research Ethics Board of the CIUSSS de l'Estrie-CHUS (#2024-5174), and this study complied with the Declaration of Helsinki ethical standards.

Sample Size

The required sample size was estimated at 50 participants (25 men and 25 women), sufficient to detect a correlation of 0.40 or greater between changes in MMA/creatinine ratio, electrophysiological measures and clinical outcomes. To account for potential attrition rate of ~10%, the recruitment target was increased to 56 participants. This sample size aligns with Julious et al's³⁵ recommendation of including at least 12 participants per group for pilot studies.

Urine Collection Kit

Fasting urine specimens were collected using an at-home urine collection kit, designed by our team for this study, and fasting urine MMA/creatinine ratio ($\mu\text{mol}/\text{mmol}$) measured on dried urine filter paper samples at baseline and after 1, 2 and 3 months of vitamin B-12 supplementation. The kit included a letter to the participant, the instruction sheet, an identification form, a piece of folded aluminum foil containing a Whatman-GE 903 filter paper, a disposable urine collection bag, and a prepaid return envelope. Participants were asked to follow the instructions and return by regular mail their dried urine collected on the filter paper as well as the identification form to the laboratory. One or two days before the first visit, participants mailed their first fasting urine sample collected using the urine collection kit to the laboratory as a baseline measurement for the MMA/creatinine ratio ($\mu\text{mol}/\text{mmol}$) prior to vitamin B-12 supplementation. To make sure this was done properly, the research assistant (IR) called the participants when the first kit was sent to their home to ensure that the participant expected to receive a package and to explain the urine collection procedure. In the event that the return envelope with this first filter paper urine sample was not received by the laboratory by regular mail as planned, the research assistant (IR) made a follow-up phone call to determine whether the participant had experienced any problems with the urine collection kit. If necessary, a new urine collection kit was sent to the participant.

Visits 1 and 2

Recruited participants came twice to the Research Center on Aging, 3 months apart, for the assessments scheduled. The consent form was reviewed and signed with the participants during the first visit, and sample characteristics (birth date, sex, education level, ethnicity, weight [measured], body mass index [calculated] and frailty status) were noted. Frailty was assessed using the Edmonton Frail Scale (EFS), a validated, multidimensional questionnaire grading frailty along a 5-level continuum, to collect additional data and monitor changes in participants' health status throughout the follow-up period. A score of ≥ 6 is considered positive (moderately frail).

Feasibility

Feasibility was evaluated through recruitment and attrition rates, compliance to supplementation, and the return rate and quality of urine samples. These quantitative indicators served as proxies for the utility, acceptability, and overall feasibility of the intervention and study procedures in an older adult population. Compliance was calculated for each participant as the proportion of vitamin B-12 tablets taken over the expected supplementation period. Reasons for non-compliance were documented. The proportion of urine samples returned and deemed usable by the laboratory was used to assess the practicality of the biological sample collection method. Participant feedback, reports of discomfort, and observations from the research assistant were also reviewed to identify any necessary adjustments to the data collection procedures.

Clinical Assessments

Cognitive status, balance and electrodiagnostic evaluation were assessed in all participants at both visits.

- Cognition was assessed using the Montreal Cognitive Assessment (MoCA), a screening tool designed for the early detection of mild cognitive impairment. The MoCA consists of short-answer questions and simple tasks, assessing six cognitive domains: short-term memory, visuospatial abilities, executive functions, attention and concentration, working memory, language, and temporal and spatial orientation. A score of ≥ 26 is considered normal.³⁶ Two different versions of the MoCA test were used for the first and second visits to prevent memory bias.

- Balance was assessed using the Berg Balance Scale (BBS), which measures static and dynamic balance abilities during 14 tasks.³⁷ Each task of the BBS is scored on a 5-point ordinal scale ranging from 0 to 4, with a score <45 suggesting impaired balance. Confidence in performing activities of daily living without losing balance was also evaluated as a patient-centered outcome by using the Activities-specific Balance Confidence Scale (ABC Scale).^{38–40} The ABC Scale consists of 16 items representing daily activities; participants rate their confidence in performing each task on a scale from 0% to 100%, with the total score reflecting overall balance confidence. Scores below 67% have been associated to an increased risk of falling in older adults.
- Vibratory perception and stretch reflexes were evaluated to gather additional information on somatosensory and motor functions. Using a 128 Hz tuning fork, the non-dominant foot was randomly touched 10 times, and participants were asked to indicate whether they felt a vibration or not (while covering their ears and closing their eyes). The score is calculated based on the number of correct answers (out of 10). The Achilles reflex was also assessed by using a reflex hammer on the Achilles tendon of each foot, and a qualitative rating was assigned for each response: hyporeflexia, normal, or hyperreflexia. These procedures followed standardized protocols, as described by Mold et al.⁴¹

Electrophysiological Testing

Electrophysiological evaluation was conducted using transcranial magnetic stimulation (TMS) before and after vitamin B-12 supplementation. Evaluations were performed unilaterally, on the primary motor cortex (M1) of the non-dominant leg, with a Magstim 200² TMS apparatus, using standardized protocols³⁴ and SENIAM recommendations.⁴² MEP of the tibialis anterior (TA) were specifically targeted as they appear to be particularly sensitive to change in vitamin B-12 status.^{43–45} Ten electrical pulses were delivered at 110% of the motor threshold to the TA of the non-dominant leg for each participant; the first pulse was excluded from analyses. Electromyographic signals elicited by magnetic stimulation were amplified directly via the PicoEMG recording system (sampled at 2000 Hz, filtered at 1000 Hz, with a 20–2000 Hz bandwidth), and transferred to the acquisition computer using a 1401 Micro MKII device and Spike 2 software (version 7.10; Cambridge Electronic Design Ltd., Cambridge, UK) for subsequent offline analysis. A neuronavigation system (Brainsight, Rogue Research Inc., Montreal, Quebec, Canada) was used to ensure the consistency of brain stimulation location over M1. Participants were invited to express their concerns or if they experienced any discomfort during evaluations.

All clinical and electrophysiological assessments were conducted under double-blind conditions, ensuring that neither the participant, nor the assessors had access to urine test results. Reasons for attrition over the 3-month follow-up were noted. During the course of this study, a member of the research team (CBD) noted in a logbook any comments from participants or any relevant observations that might improve data collection procedures in future studies.

Vitamin B-12 Supplementation

After visit 1, participants were provided with 1200 µg/day vitamin B-12 (methylcobalamin) supplements, approved by Health Canada as a natural health product (NPN 00480878). This daily dose of 1200 µg falls within the range of standard high oral doses commonly prescribed by clinicians and nutritionists for the treatment of vitamin B12 deficiency.⁴⁶ The labeling requirements of taking 1 tablet per day were appropriate for the target population and were consistently followed. High intakes of vitamin B-12 pose no safety concerns, as excess amounts are readily excreted in urine; accordingly, no tolerable upper intake level is recommended and was required for this study. Compliance to supplementation was assessed by unused tablets, which were returned to the research team (CBD) at visit 2. The vitamin B-12 supplements used are tasteless small tablets and are not known to cause side effects. Nonetheless, participants were told to report any potential new symptoms or side effects that might arise while on supplementation.

Urine Collection and Analysis

At the end of visit 1, participants received three additional urine collection kits to provide 3 monthly urine samples to the laboratory, scheduled for specific dates with a member of the research team (CBD). They were scheduled in the participants' personal calendar to measure the uMMA/creatinine ratio (µmol/mmol) at 30, 60 and 90 days after the first day of vitamin B-12 supplementation. All analyses were performed at the Waters-CHUS Expertise Centre in Clinical

Mass Spectrometry (CAB) using our validated UPLC-MS/MS (Acquity I-Class-Xevo TQ-S micro (Waters Corp.) method.^{28,29} The results are expressed as the uMMA/creatinine ratio, which accounts for urine dilution variations due to individual differences in water intake. For practical reasons, all mass spectrometry analyses were performed at once, at the end of the study. All not usable filter papers were noted. All suspected cases of vitamin B-12 deficiency were contacted and received medical attention by their family physician or the geriatrician (HC) to ensure investigation and further supplementation if needed. Based on our previous research, a threshold of $>2.0 \mu\text{mol}/\text{mmol}$ has been established to indicate metabolic vitamin B-12 deficiency.²⁸ This cut-off demonstrated both high sensitivity and specificity for detecting B-12 deficiency, as determined by serum MMA levels $>400 \text{ nmol}/\text{L}$, a recognized threshold for older adults.^{28,47} Given this evidence, we adopted the $>2.0 \mu\text{mol}/\text{mmol}$ cut-off in the present study.

Statistical Analysis

Statistical analyses were performed using SPSS version 30 (SPSS Inc, Chicago, IL). Feasibility outcomes (eg, recruitment and attrition rate) were reported using descriptive analyses. Compliance to vitamin B-12 supplementation was calculated for each participant and main reasons for non-compliance were reported. The proportion of filter papers returned by mail to the laboratory as planned, as well as the proportion of “usable” filter papers, were calculated. Problems regarding the use of the urine collection kit were noted and analyzed to improve urine collection procedures. Comments on the data collection procedures or discomforts expressed by the participants, as well as observations by the research assistant, were analyzed to determine if any modifications should be made regarding the data collection procedures.

To assess changes in clinical outcomes, baseline and post-supplementation values were compared using paired-sample *t*-tests. An ANOVA was also used to test for time-related variations in uMMA/creatinine levels relative to baseline, and Pearson correlation analyses were conducted to examine associations between 3-month changes in uMMA/creatinine levels, electrophysiological measures, and clinical outcomes. Normality of the data was confirmed through visual inspection of histograms and the Kolmogorov–Smirnov test, supporting the use of parametric analyses.

Results

Participants Characteristics

Data collection took place from April to August 2024. A total of 146 individuals were contacted for recruitment. Among them, 56 (38.4%) agreed to participate and scheduled their first visit. Five participants (3.5%) withdrew from the study after receiving the baseline urine collection kit but before visit 1, citing fatigue, study burden, or personal health concerns. These participants were replaced, as they had not yet signed the consent form. An attrition rate of 2% was observed after visit 1, as 3 participants withdrew from the study due to self-reported common cold symptoms (low-grade fever, mild headache, feeling generally unwell...), hospitalization, or fatigue, resulting in 53 participants completing the study (Figure 1).

Baseline participant characteristics are shown in Table 1. Participants were aged between 70 and 86 years, with a predominance of individuals in their early seventies (mean age = 75.6). The sample had a balanced sex distribution, and all participants were of Caucasian ethnicity.

Main reasons for exclusion, refusal and attrition were determined and are summarized in Figure 1. Participant characteristics are presented as means ($\pm$ SD) or proportions (%), as appropriate (Table 1).

Education levels averaged 15.3 years, corresponding to approximately one year of university studies. BMI values indicated that most participants were within the normal to overweight range. Frailty scores were generally low, reinforcing the idea that the sample consisted of functionally independent older adults.

Feasibility

Two participants completed the TMS at visit 1 but choose not replicated it at visit 2 due to discomfort experienced during the first visit. One participant was excluded from the data analyses due to inconsistent TMS results, and 4 participants with contraindications to TMS (eg, skull metal implants, epilepsy, pacemaker) were excluded from this assessment but completed all other evaluations. In total, 46 out of the 53 participants (87%) completed both TMS evaluations.

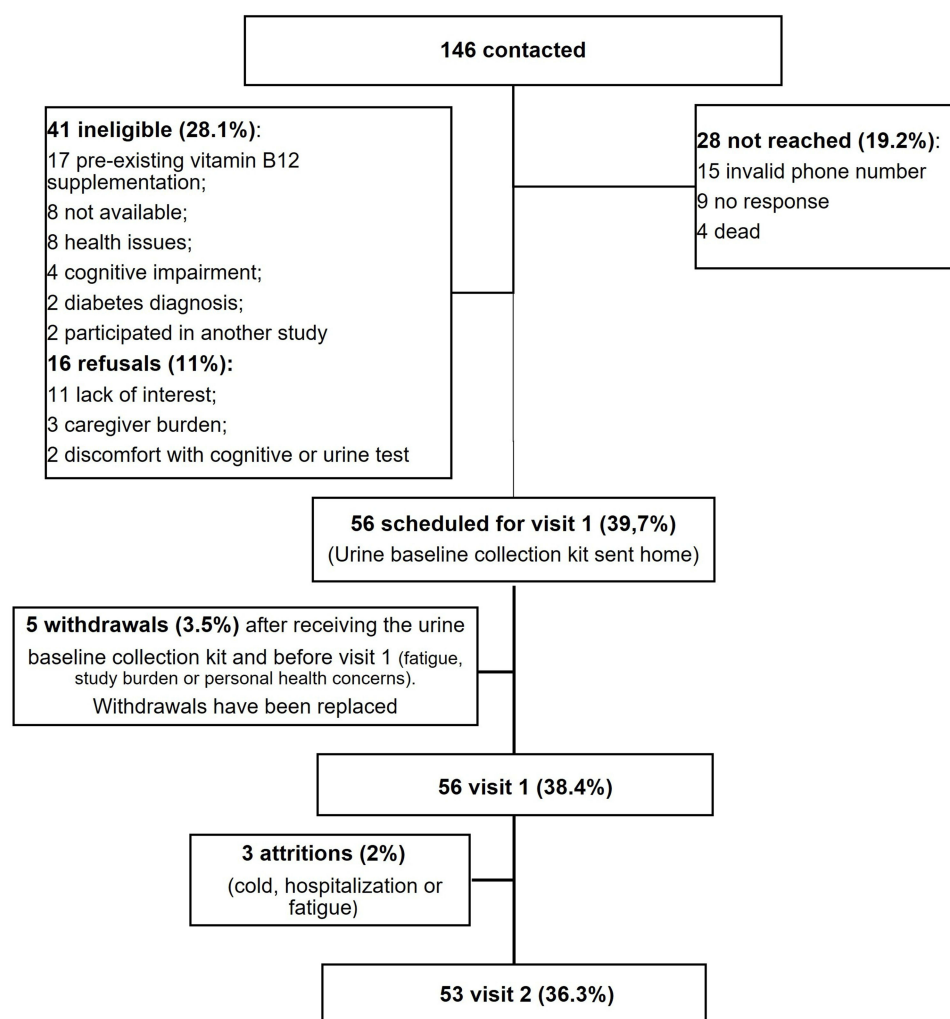


Figure 1 Recruitment.

The average compliance rate among participants was 99.1%, indicating a high level of adherence to the supplementation protocol. Compliance below 100% was mainly due to missed doses ($n = 19$; 35.8%), and compliance above 100% was due to unintentional double dosing after missing a previous dose ($n = 10$; 18.9%) (Table 2).

All 53 urine samples were properly received as planned and analyzed; no follow-up or replacement kits were required. However, certain steps or elements of the kit make it difficult to use and need to be revised for better future use, whether in a large-scale study or a screening program. While most of the participants found the procedure straightforward, some encountered difficulties related to specific aspects of the kit's design and instructions. Specifically, concerns were raised regarding the collector bag, with reports of minor leakage and challenges in handling. Several participants suggested including a dropper or pipette to facilitate controlled urine transfer onto the filter paper, as the current method sometimes led to excess or insufficient application. Additionally, the drying process posed logistical challenges for some, particularly in terms of finding an appropriate contamination-free space. Clarifications were also requested for certain instructions, such as the acceptable urine volume to apply to the filter paper. These insights will be used to refine the kit and to enhance user experience in future studies.

Response to a Standard Daily Dose of Vitamin B-12 Supplementation for 3 months

Values of uMMA/creatinine ratio at baseline and at each timepoint (months 1, 2, and 3) for the 53 participants over the course of the intervention are illustrated in Figure 2. The ANOVA revealed a significant reduction in the uMMA/

Table 1 Baseline Characteristics of the Study Sample (n=53)

Characteristics	Mean ($\pm$ SD) or n (%)
Age (years)	75.6 ($\pm$ 3.8)
Age group	
- 70–79 years	46 (86.8)
- 80+ years	7 (13.2)
Male	27 (50.9)
Female	26 (49.1)
Ethnicity	
- Caucasian	53 (100)
Education level (years)	15.3 ($\pm$ 2.6)
- High school or less	11 (20.8)
- Postsecondary non-university	16 (30.2)
- University/Post-graduate	26 (49.0)
BMI	26.4 ($\pm$ 4.6)
Edmonton Frail Scale	1.9 ($\pm$ 1.4)

Table 2 Compliance Rate to Vitamin B-12 Supplementation

Compliance Rate (%)	Frequency	Percentage (%)
< 90	1	1.9
90–94.9	7	13.2
95–99.9	11	20.8
100	24	45.3
> 100	10	18.9
Total	53	100.0

creatinine ratio, with the post-hoc *t*-test confirming a significant decrease from 1.36 to 1.10 after 3 months of supplementation ($p < 0.001$).

Paired-sample *t*-tests were used to compare 3-month MEP latency and amplitude of tibialis anterior, vibration perception test scores, BBS scores, ABC Scale scores, and MoCA with baseline measurements (Table 3). Compared with baseline, significant improvements were observed in both balance (BBS, $p < 0.001$) and cognitive performance (MoCA, $p = 0.017$). In contrast, tibialis anterior MEP latency and amplitude, vibration perception, and ABC Scale scores did not change significantly (all *p*-values > 0.05).

Association Between uMMA/Creatinine Ratio and the Signs and Symptoms of Vitamin B-12 Deficiency

Correlations between 3-month changes in urinary MMA/creatinine ratios and changes in MEP, balance and cognition were examined (Table 4). No significant correlations were found between changes in uMMA/creatinine levels and variations in MEP, balance, vibration perception or self-perceived balance test results (all *p*-values > 0.05). However, a significant and positive correlation was observed between the reduction in uMMA/creatinine levels and improvements in cognitive performance, as measured by the MoCA test ($r = 0.32$, $p < 0.05$).

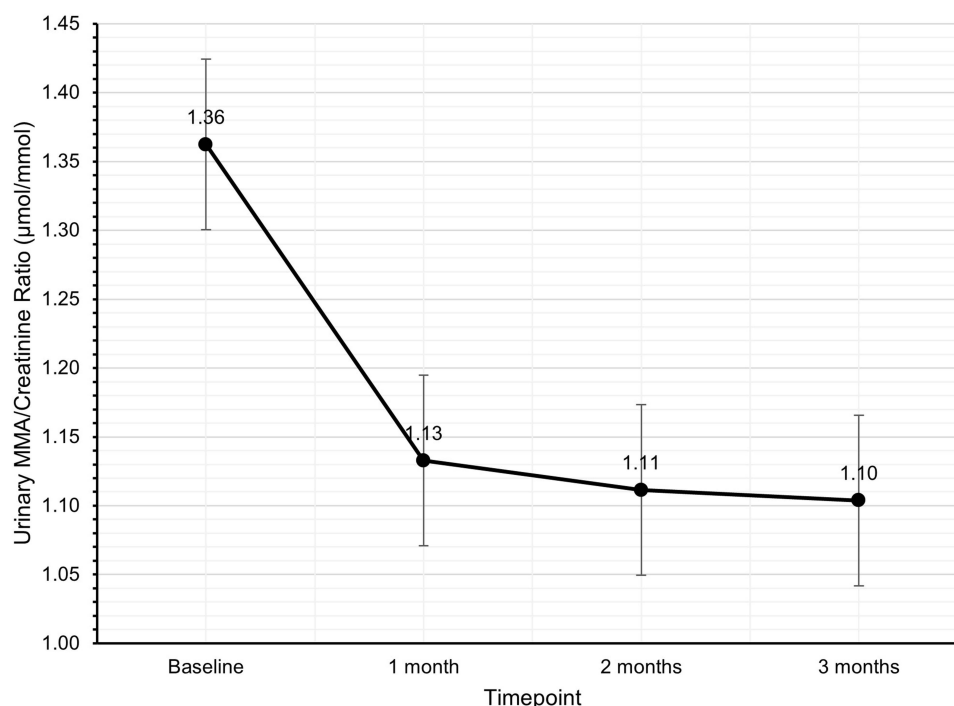


Figure 2 Urinary MMA/Creatinine Reduction Over 3 Months of Vitamin B-12 Supplementation (n=53).

Discussion

The aims of this study were to: 1) assess the feasibility, including recruitment and attrition rates, compliance with supplementation, and the proportion of urine samples successfully collected; and 2) gather preliminary data on the relationship between changes in the urinary MMA/creatinine ratio and variations in electrophysiological responses

Table 3 Baseline Values Compared to 3-Month Post-Supplementation with 1200 μg/Day of Vitamin B-12

Variable	Baseline Mean (± SD)	3 Months Mean (± SD)	p-value
Urinary MMA/Creatinine Ratio (N=53)	1.36 (± 0.65)	1.10 (± 0.40)	<0.001
Tibial Anterior MEP Latency (N=46)	33.47 (± 3.11)	33.32 (± 3.05)	0.591
Tibial Anterior MEP Amplitude (N=46)	0.19 (± 0.13)	0.24 (± 0.30)	0.164
Tuning Fork Test Score (N=53)	8.13 (± 1.97)	8.15 (± 2.12)	0.947
Berg Balance Scale Score (N=53)	53.04 (± 2.86)	54.40 (± 2.48)	<0.001
ABC Scale Total Score (N=53)	89.25 (± 8.42)	88.98 (± 8.49)	0.763
MoCA Score (N=53)	26.11 (± 2.06)	26.74 (± 2.17)	0.017

Note: significant data (p-value <0.05) are in bold.

Table 4 Correlations Between Changes in Urinary MMA/Creatinine Levels and Neurological Symptoms Over 3 Months

Variable	Pearson's r	p-value
Urinary MMA/creat. and MEP Latency	0.13	0.38
Urinary MMA/creat. and MEP Amplitude	0.04	0.81
Urinary MMA/creat. and Tuning Fork Test	0.16	0.26
Urinary MMA/creat. and Berg Balance Scale	-0.06	0.65
Urinary MMA/creat. and ABC Scale	0.06	0.69
Urinary MMA/creat. and MoCA Score	0.32*	0.02

Note: *Significant correlation at p-value <0.05.

(motor evoked potential [MEP] latency), as well as clinical outcomes related to balance and cognition following vitamin B-12 supplementation.

Feasibility

The recruitment and low attrition rates suggest that the study protocol was feasible and well-tolerated among older adults, supporting the practicality of similar interventions in this population. However, participants were recruited from a volunteer registry of individuals already interested in research, introducing a potential selection bias. Such bias may limit the generalizability of the findings, as the sample may not fully represent the broader older adult population.

In the medical literature, a compliance rate of over 80% is generally considered satisfactory.⁴⁸ However, some researchers suggest higher thresholds to guarantee therapeutic efficacy. For example, one study suggests that a compliance rate of over 95% is necessary to ensure treatment efficacy.⁴⁹ In this study, compliance was relatively good, with the lowest compliance rate being 83.52%, and 64.2% of participants having a compliance rate of 100% (M = 99%).

All urine samples were properly received and analyzed. Although some participants showed no change in urinary measures (n = 16), an overall decrease in the uMMA/creatinine ratio was observed after 3 months of vitamin B-12 supplementation, suggesting an improvement in vitamin B-12 status in several participants.

A portion of the TMS data could not be recorded or retained for analysis, and a few participants did not complete the TMS assessment. Ultimately, usable TMS data were available for 46 of the 53 participants. Data loss arose from multiple factors, including non-participation or incomplete assessments, the absence of repeated measurements at visit 2 for some participants, poor EMG recordings, and medical contraindications that prevented completion of the procedure.

Effect of Supplementation and Association with Electrophysiological and Clinical Responses

Analysis of the effects of supplementation revealed several significant changes after 3 months. The uMMA/creatinine ratio significantly decreased after supplementation (from 1.36 to 1.10), consistent with the expected physiological response to vitamin B-12. These changes paralleled the improvement observed in the BBS and the MoCA. However, observed changes were minimal and not clinically significant, making it unlikely to have a substantial impact at the group level.

No significant change was observed for the other outcomes measures. These findings suggest that, while vitamin B-12 supplementation led to improvements in metabolic markers, as well as modest gains in balance and cognition, its effects on neuromuscular conduction, vibration sense and self-perceived balance confidence were not apparent over the 3-month period.^{50,51} The lack of significant changes in MEP latency, vibration perception, and ABC Scale scores suggests that some neuromuscular and perceptual functions may be less responsive to short-term supplementation. A longer-term supplementation or additional therapies, such as physical rehabilitation, may be necessary to achieve measurable improvements in these areas.⁵² Future research studies should explore these possibilities.

Regarding the association between changes in uMMA/creatinine levels and improvements in neurological symptoms, Pearson correlation analyses revealed a significant moderate relationship between reductions in uMMA/creatinine and increases in MoCA scores, suggesting that individuals with the greatest reductions in urinary MMA/creatinine levels tended to exhibit the most notable improvements in cognitive function. On the contrary, no correlation was observed between uMMA/creatinine changes and either MEPs or balance. This observed correlation suggests a potential link between metabolic vitamin B-12 status and cognitive function. This finding aligns with previous studies⁵³ indicating that vitamin B-12 plays a crucial role in neurological health, particularly in cognitive processes. For instance, Ueno and coll.⁵³ demonstrated that vitamin B-12 supplementation resulted in improved cognitive function in patients with vitamin B-12 deficiency, with significant reductions in homocysteine levels and enhancements in Mini-Mental State Examination (MMSE) scores.⁴³

While vitamin B-12 is essential for maintaining myelin health and promoting nerve regeneration,⁵⁴ the absence of significant correlations between uMMA/creatinine reduction and improvements in electrophysiological motor responses, vibration sense or balance suggests that these functions may be influenced by additional factors beyond vitamin B-12 status alone. It is also possible that the 3-month intervention period was insufficient to observe measurable electrophysiological

improvements, or that participants may not have had a sufficiently severe B12 deficiency to influence this parameter. Recovery may be limited by coexisting nutrient deficiencies and age-related neurodegenerative changes.^{55,56} Deficiencies in folate and iron, for instance, have been linked to impaired nerve conduction and balance issues in older adults.⁵⁷ Additionally, structural degeneration in the central and peripheral nervous systems may further constrain improvement regardless of vitamin B-12 status.^{58,59} Methodological and population-specific factors—such as baseline vitamin B-12 levels, comorbidities, and variation in intervention protocols—may also influence outcomes. One study, for example, found that individuals with Alzheimer's disease showed slower cognitive decline under cholinesterase inhibitor therapy only when baseline vitamin B-12 levels were optimal (>436 ng/L), underscoring the relevance of individual nutritional and clinical profiles in treatment efficacy.⁶⁰ Moreover, the lack of change in MEP latency raises questions about whether electrophysiological mechanisms truly underlie the cognitive improvements observed (eg, MoCA), warranting further investigation.

At baseline, the uMMA/creatinine ratio observed in our participants ($M = 1.36$) was comparable to those reported in previous studies conducted in similar older community-dwelling populations. For instance, Boutin et al²⁸ reported a median uMMA/creatinine ratio of 1.22 (interquartile range: 0.80–1.81) of a sample of 34 among 1753 participants from the NuAge biobank study. Moreover, Flatley et al²⁶ found a median ratio of 1.50 (0.40–10.1) in a sample of 591 participants. These comparable values suggest that our baseline measurements are consistent with previously published data obtained using the same analytical approach (UPLC-MS/MS) in similarly healthy, community-dwelling older adults.

Limitations

Several factors may explain the absence of statistically significant findings. The 3-month supplementation may have been too short to produce detectable physiological changes. Significant improvements often require longer periods, as shown by Sharma and Sucharita,⁶¹ who observed increased sensory conduction after 4 months, and Stabler,¹⁰ who noted neurological improvements in 6 months. The external validity of this study is limited by its single-site design and the homogeneous Caucasian sample. Although this was not an inclusion criterion, recruitment in the Sherbrooke region naturally led to this demographic composition, restricting the generalizability of the findings to similar populations. Moreover, the relatively healthy status and high education level of participants may have contributed to a ceiling effect, limiting observable changes and facilitating comprehension and better task performance. The BBS may lack sensitivity to detect subtle balance improvements in healthy older adults, and evidence from Lima et al⁶² further indicates that it may not adequately discriminate between fallers and non-fallers in this population. A limited sample may have reduced statistical power, particularly for detecting subtle neurophysiological effects like changes in MEPs. Additionally, the absence of a control group limits the ability to attribute observed changes solely to vitamin B12 supplementation, as factors such as learning effects or lifestyle modifications could have influenced the results. However, regarding urinary MMA, our previous work demonstrated a strong correlation with its serum counterpart,²⁸ supporting the validity of this biomarker. Future perspectives should consider extended supplementation durations, larger and more diverse sample sizes, the utilization of more sensitive or more challenging assessment tools (eg, Timed Up and Go Dual Task) and the incorporation of a control group to better elucidate the effects of vitamin B-12 on nerve conduction and balance in older adults.

Additionally, the loss of electrophysiological data due to invalid or unusable recordings may have reduced the statistical power of the analyses, limiting the detection of potential vitamin B-12-related effects on TMS measures. In addition, this partial exclusion could introduce a selection bias, as participants who completed the TMS assessment may be less likely to have severe neurological abnormalities or comorbidities that could influence response to TMS.

Despite these limitations, at baseline, 11 participants were either deficient or borderline deficient in vitamin B-12, compared to only 2 after three months of supplementation. This indicates that about 17–20% of seemingly healthy older adults may have early-stage B-12 deficiency. This prevalence is higher than the 5–15% typically reported in population-based studies of adults over 60 years in Canada and the United States, emphasizing the need for earlier and more frequent screening in this population.^{1–8} These results highlight the importance of targeted screening (or high-risk screening), even among asymptomatic older adults at higher risk. Additionally, Scott et al⁶³ recently showed in the Baltimore Longitudinal Study of Aging that B-12 status is positively associated with appendicular lean mass in women, suggesting a link between B-12 deficiency and sarcopenia. Since sarcopenia contributes to frailty, falls, and disability among older adults,⁶⁴ early detection and

treatment of B-12 deficiency could help prevent these adverse outcomes. Overall, daily oral B-12 supplementation appears to be a simple and effective strategy to improve B-12 status and support healthy aging at low cost.

Conclusion

This pilot study provides preliminary evidence on the association between urinary MMA/creatinine levels and neurological signs of B-12 deficiency, as well as biomarker and symptom responses to supplementation. It marks the beginning of a broader research effort aimed at improving the diagnosis of vitamin B-12 deficiency in older adults with the aim of developing a non-invasive, accessible, and cost-effective screening program for at-risk populations, including older individuals who are losing weight or have low dietary intakes and, long-term users of metformin or gastric acid suppressants. A large-scale study is warranted to further investigate these findings, with potential long-term benefits for the prevention of neurological disorders associated with B-12 deficiency, as well as improvements in balance and fall prevention. If the clinical validity of the urinary test is confirmed, it could provide clinicians with a simple, non-invasive, and affordable tool for assessing B-12 status in older patients. Ultimately, this test could form the basis of a screening program, particularly for high-risk groups.

Abbreviations

MMA, methylmalonic acid; UPLC-MS/MS, ultra-performance liquid chromatography coupled to tandem mass spectrometry; GC/MS, gas chromatography/mass spectrometry; NuAge, Quebec Longitudinal Study on Nutrition and Successful Aging; TMS, transcranial magnetic stimulation; MoCA, Montreal Cognitive Assessment; EFS, Edmonton Frail Scale; ABC Scale, Activities-specific Balance Confidence Scale; BBS, Berg Balance Scale.

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Disclosure

The authors report no conflicts of interest in this work.

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