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# EFFECT OF HYPOHOMOCYSTEINEMIC THERAPY ON COGNITIVE FUNCTION IN HYPERTENSIVE PATIENTS

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The purpose of the study was to evaluate the effect of hypohomocysteinemic therapy on cognitive function in patients with hypertension. This open-label, prospective, randomized clinical study included 46 patients aged 40–65 years with stage I–III hypertension depending on severity of target organ damage. Patients of the study group were supplemented with an oral hypohomocysteinemic combination in addition to standard antihypertensive therapy. The follow-up lasted three months. The control group consisted of 34 apparently healthy individuals. Total plasma homocysteine levels were measured using ELISA before and after treatment. Short-term memory performance was assessed by Luria´s Memory Words test. The addition of hypohomocysteinemic therapy to standard antihypertensive treatment significantly reduces plasma homocysteine levels and was associated with meaningful improvement in cognitive performance. These findings support a potential neuroprotective role of homocysteine-lowering therapy in patients with hypertension.

**Key words:** hypertension, homocysteine, B group vitamins, cognitive function, Luria´s Memory Words test.

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# ВПЛИВ ГІПОГОМОЦИСТЕЇНЕМІЧНОЇ ТЕРАПІЇ НА КОГНІТИВНІ ФУНКЦІЇ У ПАЦІЄНТІВ З АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ

Метою дослідження було оцінити вплив гіпогомоцистеїнемічної терапії на когнітивні функції у пацієнтів з артеріальною гіпертензією. Відкрите проспективне рандомізоване клінічне дослідження включало 46 пацієнтів віком 40–65 років з артеріальною гіпертензією I–III стадій залежно від наявності та ступеня ураження органів-мішеней. Пацієнти основної групи додатково отримували пероральну гіпогомоцистеїнемічну комбінацію на тлі стандартної антигіпертензивної терапії. Тривалість спостереження становила три місяці. Контрольну групу склали 34 практично здорові особи. Загальний рівень гомоцистеїну визначали методом імуноферментного аналізу до та після лікування. Обсяг короткочасної пам'яті оцінювали за тестом «10 слів» Лурії. Додавання гіпогомоцистеїнемічної терапії до стандартного антигіпертензивного лікування достовірно знижувало рівень гомоцистеїну в плазмі крові та було асоційоване з вірогідним покращенням когнітивної продуктивності. Отримані результати підтверджують потенційну нейропротекторну роль терапії, спрямованої на зниження рівня гомоцистеїну, у пацієнтів з артеріальною гіпертензією.

**Ключові слова:** артеріальна гіпертензія, гомоцистеїн, вітаміни групи В, фолієва кислота, когнітивні функції, тест 10 слів Лурія.

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Elevated plasma total homocysteine (Hcy) has been recognized as an independent cardiovascular risk factor and a contributor to cognitive impairment, as demonstrated in multiple observational and clinical studies, including those by Karger [5], Lauriola [6], and Periñán et al. [8]. Hyperhomocysteinemia (HHcy) can affect the central nervous system through both direct neurotoxic effects and vascular-mediated mechanisms. As reviewed by Luzzi [7], HHcy is associated with impaired performance across various cognitive domains, including motor planning, long-term episodic memory, total episodic memory, and global cognition.

Homocysteine is a sulfur-containing amino acid derived from methionine metabolism and is involved in several biochemical pathways requiring the coenzymes vitamins $B_6$, $B_9$ (folate), and $B_{12}$ for its metabolism. Evidence from systematic reviews suggests that folic acid supplementation may improve cognitive function by reducing Hcy concentrations, enhancing vascular health, attenuating inflammatory responses, correcting cerebral folate deficiency, and exerting antioxidant effects. However, the results of randomized controlled trials investigating the cognitive benefits of Hcy reduction through B-vitamin supplementation remain inconsistent.

A retrospective cohort study conducted by Rabensteiner [9] evaluated the association between biochemical markers of vitamin $B_{12}$ and folate status, cognitive function, and MRI-based brain atrophy in 378 cognitively healthy elderly individuals and 217 patients with Alzheimer's disease. Their findings indicated that variations in direct and indirect biomarkers of vitamin $B_{12}$ and folate status were not

significantly associated with cognitive dysfunction or brain atrophy.

In contrast, a meta-analysis by Xu [12], which included 22 randomized controlled trials with 3,604 participants, demonstrated that folic acid supplementation was associated with improved cognitive performance in patients with mild cognitive impairment and Alzheimer's disease, particularly at doses ≥ 3 mg daily.

Several studies examining healthy populations reported inconsistent associations between folate and vitamin $B_{12}$ levels and cognition, with benefits observed only in selected domains such as word recall, verbal fluency, and attention, as discussed by Luzzi [7].

Important methodological limitations must be considered when interpreting these findings, including variability in fasting status during blood sampling, differences in biochemical assay sensitivity, inconsistent adherence to standardized protocols, and confounding factors such as age-related decline in glomerular filtration rate, smoking, sex, alcohol consumption, and coffee intake.

Although observational studies strongly support a causal relationship between HHcy and cognitive impairment, most randomized controlled trials have failed to demonstrate robust cognitive benefits from Hcy-lowering therapy. These discrepancies may reflect limitations in study design, including late-stage intervention, insufficiently sensitive cognitive assessments, potential safety concerns of prolonged high-dose vitamin supplementation, and the influence of unaccounted confounding factors. Further well-designed trials are needed to elucidate the underlying mechanisms and clarify the preventive and therapeutic role of homocysteine-lowering strategies in cognitive decline, as emphasized by Ji [4].

Therefore, study findings should be interpreted in the context of limited available data, and the absence of evidence of an effect should not necessarily be regarded as evidence of no effect.

**The purpose** of the study was to evaluate the potential neuroprotective effects of hypohomocysteinemic therapy in hypertensive patients over a three-month period.

**Materials and methods.** An open-label, prospective, randomized clinical study was conducted by the Clinical Pharmacy and Clinical Pharmacology Department at the cardiology clinic of the Vinnytsia Military Medical Clinical Center (Ukraine), which serves as the clinical base of the National Pirogov Memorial Medical University (Vinnytsya). Patient enrollment was carried out between 2010 and 2012. The study was conducted in compliance with the main provisions of GCP ICH E6(R1), the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), the Declaration of Helsinki of the World Medical Association for the Ethical Principles of Scientific Medical Research Involving Human Subjects (1964–2000), and the Order of the Ministry of Health of Ukraine No. 281 of 01.11.2000. The study protocol was approved by the Bioethics Committee of National Pirogov Memorial Medical University (protocol No. 7 of September 1, 2010, and No. 5 of September 3, 2012).

The study included patients aged 40–65 years with stage I–III hypertension (HTN), depending on the stage of target organ damage. The diagnosis of hypertension (HTN) was established based on comprehensive clinical, laboratory, and instrumental examinations performed in the cardiology department, in accordance with Guideline No. 00069 "Hypertension: Examination and Initial Treatment" dated March 7, 2017, Order of the Ministry of Health of Ukraine No. 384 "On the Approval and Implementation of Medical and Technological Documents for the Standardization of Medical Care for Arterial Hypertension" dated May 24, 2012, and the 2023 clinical practice guidelines of the European Society of Hypertension.

Inclusion criteria were stage I-III arterial hypertension, hypertensive encephalopathy, and age 40–65 years. Age stratification according to WHO standards was not applied. All participants provided written informed consent before enrollment. Exclusion criteria were secondary hypertension, psychiatric disorders, decompensated renal or hepatic disease, acute or subacute cerebrovascular events, primary degenerative disorders, advanced heart failure, hematologic disorders, severe diabetes mellitus, malignancy, bilateral renal artery stenosis, rheumatic heart disease, heart rhythm disturbances, cardiac interventions in previous 4 weeks, pregnancy, lactation, and known hypersensitivity to the study medications.

After screening, 51 patients with stage I–III hypertension were enrolled. Data from 46 patients (mean age was 59.07±1.32 years) were included in the final analysis, as five patients were lost to follow-up. Patients were prescribed valsartan tablets ("Valsacor", KRKA, Slovenia) at a dose of 80–160 mg/day, with the addition of indapamide 2.5 mg in tablets ("Indapamid", Hemofarm, Serbia) if required. All patients received an oral homocysteine-lowering combination consisting of one tablet "Neurorubin-forte Lactab" (Mepha, Mepha Schweiz AG) containing 200 mg thiamine mononitrate (vitamin $B_1$), 50 mg pyridoxine hydrochloride (vitamin $B_6$), 1 mg cyanocobalamin (vitamin $B_{12}$), and 1 mg of folic acid ("Technolog", Ukraine). The vitamin dosage was chosen to provide sufficient amounts for HHcy reduction. High doses of folic acid (5 mg) were not administered, as concerns regarding vitamin $B_9$-associated carcinogenesis remain controversial [10].

According to the study protocol, the follow-up lasted three months.

The control group comprised 34 practically healthy individuals with normal blood pressure (BP), including 18 women (53.3 %) and 16 men (46.7 %), aged 25–52 years (mean age 38.3±1.77 years).

Table 1

**Baseline demographic and clinical characteristics of patients in the clinical and control groups (M±m)**

| | Clinical groups | |
|---|---|---|
| | Study group (n=46) | Control group (n=34) |
| Age, years | 59.07±1.32* | 38.3±1.77 |
| Females (%) | 16 (34.78 %) | 18 (53.3 %) |
| HTN stage I | 1 (2.17 %) | - |
| HTN stage II | 36 (78.26 %) | - |
| HTN stage III | 9 (19.56 %) | - |
| Mean SBP, mm Hg | 167.22±2.31** | 128.49±4.21 |
| Mean DBP, mm Hg | 100.67±1.55* | 79.41±1.34 |
| History of HTN, years | 11.94±1.29 | - |

Notes: 1. * – significance of differences compared to the control group at the level of $p<0.05$; 2. ** – significance of differences compared to the control group at the level of $p<0.01$.

Biochemical analyses were performed at the Research Clinical Diagnostic Laboratory of Vinnytsia National Pirogov Memorial Medical University, certified by the Ministry of Health of Ukraine (re-certification certificates No. 002/10 dated January 11, 2010, and No. 049/15 dated March 2, 2015). The study protocol included laboratory assessment of baseline Hcy and repeat measurement at the end of the follow-up period. Blood samples were collected in the morning after overnight fasting from the ulnar vein using vacutainer systems (Vacuette®, Greiner Bio-One, Austria) without anticoagulants. Serum was obtained by centrifugation at 1500 g for 15 minutes at 18–22 °C. Plasma Hcy concentrations were measured using an enzyme-linked immunosorbent assay (ELISA; Homocysteine EIA, Axis-Shield, UK) on a STAT FAX 303/PLUS analyzer. For biochemical and enzyme-linked immunosorbent assays, serum aliquots were transferred into Eppendorf microtubes and stored at -20 °C until analysis (Ilchenko O. et al, 2002). Hyperhomocysteinemia (HHcy) was ranged according to the recommendations of D.W. Jacobsen (1998): 10–15 μmol/L – subnormal level; 15–25 μmol/l – mild HHcy; 25–50 μmol/l – moderate HHcy; and >50 μmol/l – severe HHcy.

Vitamin $B_6$ status was assessed by the degree of activation of erythrocyte aspartate aminotransferase (AST) after the addition of pyridoxal-5-phosphate (PAF effect). Venous blood was collected into EDTA tubes, centrifuged, and erythrocytes were washed three times with isotonic saline. Hemolysates were prepared by dilution with distilled water (1:4). AST activity was determined spectrophotometrically at 340 nm in the absence and presence of PAF. The PAF effect was calculated as the percentage increase in enzyme activity after the addition of PAF. A PAF effect greater than 80 % was interpreted as evidence of vitamin $B_6$ deficiency, while values between 70 % and 80 % were regarded as indicative of marginal deficiency (Ilchenko O. et al, 2002).

Vitamin $B_{12}$ status was evaluated by the determination of methylmalonic acid (MMA) in urine involves passing 1 ml of urine through an ion-exchange column packed with the strongly basic anion-exchange resin DOWEX 1×4, followed by elution of methylmalonic acid and subsequent performance of a colorimetric diazo reaction. A 2M sodium chloride solution was used as the eluent. Then the eluate was purified with activated charcoal, and spectrophotometric analysis of the final solution was carried out at 620 nm against a reagent blank. MMA excretion of less than 20 μg/g creatinine was considered indicative of optimal vitamin $B_{12}$ status, values of 20–25 μg/g creatinine indicated a subnormal level, and values exceeding 25 μg/g creatinine were regarded as evidence of cyanocobalamin deficiency (Rasmussen K, 1990).

Short-term verbal memory was assessed using the Luria Memory Words Test. Participants listened to a list of 10 unrelated words and were asked to recall as many words as possible after each presentation across five trials [0].

Statistical analysis was performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean±standard error of the mean. Intergroup differences were evaluated using Student's *t*-test or the Mann–Whitney *U* test, as appropriate. Statistical significance was defined as $p<0.05$.

**Results of the study and their discussion.** Titration of the baseline antihypertensive medication was performed over a two-week period. The effectiveness of pharmacotherapy was assessed using office blood pressure (BP) measurements. The advantage of this method in the present study was the ability to dynamically monitor BP normalization over a three-month period: once weekly during the first month and once monthly thereafter. Baseline plasma Hcy levels in the study group were elevated compared with those in the control group and were classified as subnormal (Table 2).

Table 2

**Serum Hcy, vitamin $B_6$, and $B_{12}$ status of patients in the study group compared to the control group**

| | Study group (n=46) | | Control group (n=34) | $P_{1-2}$ | $P_{2-3}$ | $P_{1-3}$ |
|---|---|---|---|---|---|---|
| | Baseline | After follow-up | | | | |
| Homocysteine, μmol/l | 14.5±0.93 | 11.2±0.56 | 9.20±0.56 | 0.0004 | 0.04 | 0.0005 |
| PAF effect, % | 70.0±1.07 | 68.8±0.98 | 66.8±0.86 | 0.001 | 0.03 | 0.0003 |
| Urinary excretion of MMA, μg/g creatinine | 19.9±0.43 | 19.3±0.44 | 18.2±0.44 | 0.001 | 0.011 | 0.012 |

Notes: 1. $P_{1-2}$: significance of difference between baseline values in patients and controls. 2. $P_{2-3}$ : significance of the difference between repeated markers in patients and control subjects. 3. $P_{1-3}$ : significance of the difference between baseline and repeated indicators in patients of the third clinical group.

After three months of vitamin B supplementation, serum Hcy levels decreased by 22.7 % compared with baseline, with no statistically significant difference between post-treatment Hcy levels and those of the control group. Vitamin $B_6$ status assessed using the PAF differed significantly between patients and controls at baseline, although values remained within the normal range. Following treatment, a small but significant decrease in vitamin $B_6$ levels (4.57 %) was observed ($p<0.05$). Vitamin $B_{12}$ status also differed significantly between patients and controls at baseline, while remaining within normal limits in both groups. After three months of follow-up, urinary methylmalonic acid (MMA) excretion did not differ significantly from that of the control group and was 8.04 % lower than baseline values. Neuropsychological assessment of short-term memory was performed using the Luria 10-Word Test (Fig. 1).

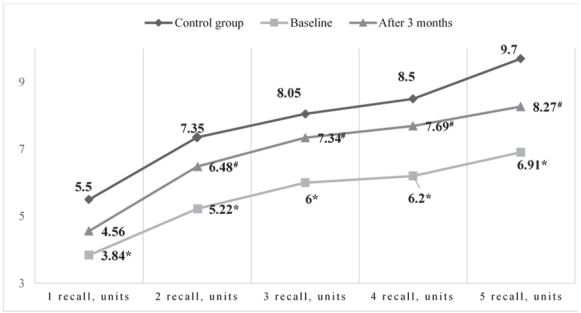


Fig. 1. Changes of cognitive performance in hypertensive patients and comparison with the control group. Notes: 1. * – difference between the baseline parameters of patients and the control group at the level 0.05; 2. # – difference between the baseline and repeated indicators of patients at the level 0.05.

At baseline, patients with hypertension demonstrated significantly poorer performance than the control group across all recall trials ($p<0.05$). Assessment of short-term memory capacity using the Luria 10-Word Test revealed a significant reduction in the number of recalled words in hypertensive patients during the first recall compared with healthy controls (3.84±0.20 vs. 5.50±0.94 words, p=0.002). During the second recall, patients in the study group reproduced, on average, 2.13±0.04 fewer words than controls (p=0.004). In the third trial, participants in the control group recalled 8.05±0.82 words, which was 25.6 % higher than that of hypertensive patients ($p<0.05$). During the fourth recall, hypertensive patients continued to reproduce significantly fewer words than controls (6.20±0.21 vs. 8.50±0.42 words, p=0.0001). The greatest difference between groups was observed during the final recall, with a mean difference of 2.79±0.01 words.

After three months of therapy, a significant improvement in short-term memory performance was observed at all recall stages. Overall, short-term memory capacity increased by 21.9 % compared with baseline values, with no statistically significant differences between treated patients and the control group.

Specifically, repeated testing demonstrated a significant increase in the number of recalled words during the second recall compared with baseline ($p<0.05$), with performance comparable to that of healthy individuals. During the third recall, the number of recalled words increased by 1.34±0.20 compared with baseline ($p>0.05$), although it remained lower than in the control group ($p<0.05$). At baseline, performance during the third recall was 25.46 % lower than that of controls ($p<0.05$).

Following three months of treatment, hypertensive patients recalled nearly the same amount of verbal material as healthy individuals during the fourth recall. At baseline, performance at this stage was 24.0 % lower than that of the control group. The final recall, reflecting the maximum test score, demonstrated a 19.68 % increase in short-term memory capacity compared with baseline ($p<0.05$). Notably, performance during the final recall did not differ significantly between hypertensive patients receiving combined pharmacotherapy and healthy controls.

The greatest improvement was observed during the final recall, which reflects maximal memory capacity and learning efficiency. This finding suggests that hypohomocysteinemic therapy may positively influence higher-order cognitive processes involved in memory consolidation. The observed cognitive improvement may be attributed, at least in part, to the reduction of plasma homocysteine levels, which is known to exert neurotoxic effects. Lowering homocysteine levels may therefore improve neuronal

metabolism and cerebral microcirculation, thereby enhancing cognitive performance.

Importantly, memory improvement was observed despite the relatively short follow-up period, suggesting that cognitive changes associated with homocysteine reduction may be at least partially reversible. However, performance during intermediate recall trials remained lower than in controls, indicating that residual cognitive vulnerability may persist in hypertensive patients even after biochemical correction.

In the present study, hypertensive patients exhibited significantly elevated plasma homocysteine (Hcy) levels (14.5±0.93 μmol/l), a recognized modifiable cardiovascular risk factor, compared with healthy individuals. These findings are consistent with the results reported by Karger et al. (2025), who demonstrated that mild hyperhomocysteinemia (Hcy >12 μmol/l) in patients with cardiovascular disease was significantly associated with an increased risk of heart failure [3, 5]. Given the well-established adverse vascular effects of hyperhomocysteinemia, reduction of Hcy levels through vitamin supplementation appears to be a rational therapeutic approach.

Furthermore, hypertensive patients showed significantly poorer short-term memory performance compared with the control group. This impairment may be attributed to arterial hypertension as a causative factor of hypertensive encephalopathy, as well as to the direct neurotoxic and vascular-mediated effects of elevated homocysteine. These results are in agreement with the findings summarized by Luzzi et al. (2022), who reported that hyperhomocysteinemia is associated with impaired performance across multiple cognitive domains, including motor planning, long-term episodic memory, total episodic memory, and global cognition [6, 7, 8].

However, the present findings are not fully supported by the study conducted by Rabensteiner et al. (2020), which reported no significant association between homocysteine levels, global cognitive performance, and MRI-based markers of brain atrophy [9]. These discrepancies may reflect differences in study populations, cognitive assessment tools, and methodological approaches, highlighting the need for further large-scale, well-designed studies to clarify the relationship between hyperhomocysteinemia and cognitive dysfunction.

Vitamin B supplementation administered over a three-month period resulted in a significant reduction in serum Hcy levels in hypertensive patients, indicating that the selected vitamin dosages and duration of intervention were sufficient to achieve a therapeutic effect. These findings are consistent with the results reported by Ueno et al. (2022), who also demonstrated a significant Hcy-lowering effect following combined B-vitamin supplementation. Moreover, the combined administration of vitamins $B_6$, $B_9$, and $B_{12}$ enables modulation of multiple metabolic pathways involved in Hcy utilization, allowing effective Hcy reduction without the need for high-dose folic acid supplementation [11, 12].

In the present study, the reduction in Hcy levels was accompanied by significant improvement in short-term memory performance, which corresponds to the cognitive benefits observed by Ueno et al. (2022) [11]. However, these findings contrast with the results reported by Ford et al. (2019), who found no significant improvement in Mini-Mental State Examination scores following B-vitamin supplementation in individuals with cognitive impairment [3]. Such discrepancies may be attributed to differences in study populations, baseline cognitive status, intervention duration, vitamin dosages, and sensitivity of cognitive assessment tools.

Overall, these results support the hypothesis that hypohomocysteinemic therapy, when added to standard antihypertensive treatment, may exert beneficial effects on cognitive function in patients with hypertension. The findings highlight the potential neuroprotective role of homocysteine-lowering strategies and underscore the importance of addressing metabolic risk factors in the prevention and management of hypertension-associated cognitive decline.

**Limitations.** Several limitations should be considered when interpreting these results. The open-label design, modest sample size, and relatively short follow-up period may limit generalizability. Additionally, practice effects from repeated neuropsychological testing cannot be entirely excluded, although the magnitude of improvement and convergence with control values suggest a true therapeutic effect rather than test-retest bias.

## Conclusions

1. Hypertensive patients demonstrated a significant decline in cognitive performance, particularly in the domain of short-term memory, compared with practically healthy individuals ($p<0.05$), highlighting the negative impact of arterial hypertension on cognitive functioning.

2. Supplementation with B-group vitamins resulted in a marked reduction in serum homocysteine levels by 22.7 % compared with baseline values, accompanied by a modest improvement in serum concentrations of vitamins $B_6$ and $B_{12}$. Given the established role of hyperhomocysteinemia as a modifiable risk factor for vascular and cognitive disorders, these biochemical changes may contribute to the observed clinical benefits.

3. In this small interventional trial, B vitamin supplementation was associated with a significant improvement in short-term memory performance in hypertensive patients compared with baseline ($p<0.05$). This suggests a potential neuroprotective effect of B vitamins mediated through homocysteine lowering and optimization of vitamin status. Although the study was limited by a relatively small sample size and short follow-up duration, the results support the rationale for incorporating B vitamin supplementation into comprehensive therapeutic strategies aimed at improving cognitive outcomes in patients with arterial hypertension.

## References

1. Andreichenko DI, Kalbus OI. Diagnostic value of the Luria 10-word memorization technique and Schulte tables in the diagnosis of mild cognitive dysfunction in patients with multiple sclerosis. Bulletin of problems biology and medicine. 2024;(4):243–252.
2. Enderami A, Zarghami M, Darvishi-Khezri H. The effects and potential mechanisms of folic acid on cognitive function: a comprehensive review. Neurol Sci. 2018;39(10):1667–1675. doi:10.1007/s10072-018-3473-4.
3. Ford AH, Almeida OP. Effect of vitamin B supplementation on cognitive function in the elderly: a systematic review and meta-analysis. Drugs Aging. 2019;36(5):419–434. doi:10.1007/s40266-019-00649-w.
4. Ji Y. Homocysteine: A modifiable culprit of cognitive impairment for us to conquer? J Neurol Sci. 2019;404:128–136. doi:10.1016/j.jns.2019.06.012.
5. Karger AB, Nomura SO, Guan W, Garg PK, Tison GH, Szklo M, et al. Association between elevated total homocysteine and heart failure risk in the Multi-Ethnic Study of Atherosclerosis cohort. J Am Heart Assoc. 2025;14(5):e038168. doi:10.1161/JAHA.124.038168.
6. Lauriola M, D'Onofrio G, Ciccone F, Germano C, Cascavilla L, Paris F, et al. Relationship of homocysteine plasma levels with mild cognitive impairment, Alzheimer's disease, vascular dementia, psychobehavioral, and functional complications. J Alzheimers Dis. 2021;82(1):235–248. doi:10.3233/JAD-210166.
7. Luzzi S, Cherubini V, Falsetti L, Viticchi G, Silvestrini M, Toraldo A. Homocysteine, cognitive functions, and degenerative dementias: State of the art. Biomedicines. 2022;10(11):2741. doi:10.3390/biomedicines10112741.
8. Periñán MT, Macías-García D, Jesús S, Martín-Rodríguez JF, Muñoz-Delgado L, Jimenez-Jaraba MV, et al. Homocysteine levels, genetic background, and cognitive impairment in Parkinson's disease. J Neurol. 2023;270(1):477–485. doi:10.1007/s00415-022-11361-y.
9. Rabensteiner J, Hofer E, Fauler G, Fritz-Petrin E, Benke T, Dal-Bianco P, et al. The impact of folate and vitamin B12 status on cognitive function and brain atrophy in healthy elderly and demented Austrians, a retrospective cohort study. Aging (Albany NY). 2020;12(15):15478–15491. doi:10.18632/aging.103714.
10. Thabet RH, Alessa REM, Al-Smadi ZKK, Alshatnawi BSG, Amayreh BMI, Al-Dwaaghreh RBA, et al. Folic acid: Friend or foe in cancer therapy. J Int Med Res. 2024;52(1):3000605231223064. doi:10.1177/03000605231223064.
11. Ueno A, Hamano T, Enomoto S, Shirafuji N, Nagata M, Kimura H, et al. Influences of vitamin B12 supplementation on cognition and homocysteine in patients with vitamin B12 deficiency and cognitive impairment. Nutrients. 2022;14(7):1494. doi:10.3390/nu14071494.
12. Xu M, Zhu Y, Chen J. Effects of folic acid supplementation on cognitive impairment: A meta-analysis of randomized controlled trials. *J* Evid Based Med*.* 2024;17:134–144. doi:10.1111/jebm.12588.

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