IN VIVO *39*: 1703-1718 (2025)
doi: 10.21873/invivo.13972

Impact of Genetic Mutations in Hyperhomocysteinemia and Metabolic Syndrome on Physiological Parameters and Quality of Life in Healthy Individuals

BOGDAN MIHAI TARCAU[1], ANDRA NEGRU[2], ALEXANDRA MANUELA BUZLE[1], TIMEA CLAUDIA GHITEA[3] and ELEONORA MARIAN[3]

[1]Doctoral School of Biological and Biomedical Sciences, University of Oradea, Oradea, Romania;
[2]Department of Internal Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania;
[3]Pharmacy Department, University of Oradea, Faculty of Medicine and Pharmacy, Oradea, Romania

Abstract

Background/Aim: Hyperhomocysteinemia (HH) is a metabolic condition linked to cardiovascular and cognitive health risks. This study investigated the prevalence of HH and cardiovascular metabolic syndrome (MS) among patients with symptoms such as fatigue, joint pain, muscle weakness, vertigo, paresthesia, and aphthous stomatitis. The objective was to explore the associations between HH, MS, and quality of life, emphasizing the role of personalized dietary interventions.

Patients and Methods: A prospective study was conducted between 2019 and 2023, including 86 patients aged 18 years or older who underwent nutrigenetic testing and provided anthropometric data. Participants were divided into three groups: those with HH (45.3%), those without HH or MS (31.4%), and those with MS but without HH (23.3%). Nutrigenetic analyses assessed genetic predispositions related to nutrient metabolism.

Results: Patients with HH exhibited reduced quality of life, with lower Short Form-12 Health Survey (SF-12) scores compared to other groups. Sex-specific nutrient needs and age-related changes in dietary requirements were identified. Metabolic conditions, including obesity, hypertension, and hypercholesterolemia, inversely impacted nutrient utilization. Physical activity positively correlated with higher demands for folic acid, vitamin B12, zinc, and magnesium.

Conclusion: Nutritional interventions targeting these needs effectively improved metabolic health and alleviated symptoms. HH significantly impacts quality of life and metabolic health. Personalized dietary and lifestyle modifications tailored to genetic predispositions, sex, and age are critical for mitigating cardiometabolic risks. These findings lay the groundwork for targeted interventions aimed at improving health outcomes in individuals with HH and MS.

Keywords: Hyperhomocysteinemia, metabolic syndrome, fatigue, quality of life (QoL).

Timea Claudia Ghitea, Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, Piața 1 Decembrie 10, 410068 Oradea, Romania. Tel: +40 723546427, e-mail: timea.ghitea@csud.uoradea.ro

Received January 17, 2025 | Revised January 31, 2025 | Accepted February 4, 2025

Introduction

Hyperlipidemia, a chronic metabolic disorder characterized by abnormal lipoprotein metabolism, poses significant health risks and remains a major public health challenge (1, 2). It is a well-established independent risk factor for cardiovascular and cerebrovascular diseases, including atherosclerosis, myocardial infarction, cerebral infarction, and coronary heart disease. In the United States, approximately 28 million adults exhibit cholesterol levels exceeding 240 mg/dl, doubling their risk of developing atherosclerotic cardiovascular disease (ASCVD) compared to individuals with normal lipid levels. Effective control of blood lipid levels has been shown to reduce both recurrence and mortality rates associated with cardiovascular diseases (CVDs), underscoring its clinical importance (3).

Homocysteine (Hcy), a sulfur-containing amino acid and intermediate product in methionine metabolism, has also emerged as a critical factor in cardiovascular health. Hyperhomocysteinemia (HH), characterized by elevated plasma Hcy levels, is increasingly recognized as a modifiable risk factor for CVD (4-9). Epidemiological studies have revealed that each 25% increase in plasma Hcy elevates the risk of CVDs by 10% and stroke by 20%. Hcy contributes to vascular pathology through mechanisms such as endothelial dysfunction, oxidative stress, smooth muscle proliferation, and enhanced low-density lipoprotein (LDL) oxidation (10).

Additionally, a potential interplay between HH and dyslipidemia has been observed. Studies suggest that HH may exacerbate dyslipidemia by impairing high-density lipoprotein cholesterol (HDL-C) metabolism, reducing ApoA-I synthesis, and accelerating HDL-C clearance (11). This dynamic disrupts the delicate balance necessary for lipid and homocysteine metabolism. While dietary and lifestyle factors such as folate, vitamin B12 intake, physical activity, and smoking cessation influence Hcy levels, the precise mechanistic links between HH, lipid profiles, and CVD remain incompletely understood (12).

Metabolic syndrome is a cluster of interrelated risk factors for CVD and type 2 diabetes, characterized by central obesity, elevated triglycerides, reduced HDL cholesterol, hypertension, and hyperglycemia. According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the presence of three or more of these factors confirms a diagnosis of metabolic syndrome (13). Metabolic syndrome contributes to reduced physical functioning, fatigue, and psychological distress due to its association with chronic diseases such as cardiovascular disorders, diabetes, and obesity. These conditions negatively impact mobility, energy levels, and mental health, thereby diminishing overall quality of life. Studies show that individuals with metabolic syndrome have significantly lower scores in quality of life assessments, particularly in domains related to physical and mental health (14, 15).

The co-occurrence of metabolic syndrome and hyperhomocysteinemia accelerates cardiovascular morbidity and increases the risk of complications such as stroke, peripheral arterial disease, and myocardial infarction (16). These conditions result in significant physical and psychological burdens, reducing patients' functional abilities, increasing fatigue, and impairing emotional well-being. Studies have shown that individuals with both metabolic syndrome and hyperhomocysteinemia exhibit worse scores on health-related quality of life (HRQoL) metrics compared to those with either condition alone (17).

Emerging evidence also highlights the importance of the metabolic balance involving S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), and related compounds in regulating Hcy metabolism (18). Dysregulation in this balance may exacerbate lipid abnormalities, liver dysfunction, and cardiovascular risk. Genetic polymorphisms, particularly in the MTHFR gene, further influence Hcy levels, although their role in cardiovascular outcomes is debated (19).

Beyond cardiovascular implications, Hcy has been identified as a neurotoxin. In mice deficient in the cystathionine β-synthase (CBS) enzyme, Hcy levels are elevated up to 2-50 times compared to wild-type mice, depending on the genotype and dietary conditions (20). These animals exhibit severe neuronal impairments, including altered neuronal plasticity, cognitive dysfunction,

growth restrictions, and energy metabolism deficiencies. Furthermore, elevated Hcy levels in these models are associated with neurodegenerative features, severe developmental retardation, and early mortality (21).

Human studies corroborate these findings, linking HH to disrupted neural plasticity and various neuro-degenerative disorders. Accumulation of Hcy in the brain is associated with neural and cognitive dysfunction, impaired energy metabolism, and increased vulnerability to neurodegeneration. The role of HH as a contributing factor in dementia and other neurological conditions has been increasingly recognized (22).

This study aimed to explore the multifaceted roles of HH in both cardiovascular and neurological health, focusing on its toxic effects on endothelial and neuronal cells. By examining genetic and metabolic factors contributing to HH and its interaction with lipid profiles and neuronal health, this study sought to enhance our understanding of the underlying mechanisms and inform targeted prevention and therapeutic strategies.

Patients and Methods

Study design. This prospective study was conducted with patients presenting fatigue, arthralgia, muscle weakness, vertigo, paresthesia, and aphthous stomatitis, seeking dietary consultations and undergoing nutrigenetic testing. Anthropometric measurements and physical activity levels were also recorded. All participants provided written informed consent before enrollment, which took place between January 2019 and December 2023. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the University of Oradea (protocol code CEFMF/03 from 28 November 2022 and date of approval).

A total of 342 Caucasian individuals were enrolled, of whom only 86 met the inclusion criteria. The patients were followed for six months. The patients were not receiving medication for any chronic disease, had an average/good socioeconomic status, and adhered to a strict diet for six months, with monthly evaluations.

Inclusion criteria. Participants were eligible for inclusion if they were aged 18 years or older, presented with the above symptoms, underwent nutrigenetic testing, and were committed to improving their quality of life through dietary and lifestyle interventions.

Exclusion criteria. Patients were excluded if they were under 18 years of age or unwilling to participate in the study.

Participant grouping. Participants were recruited from a nutrition clinic and stratified based on obesity severity and the presence or absence of MS or HH. A total of 86 patients were classified into three groups: (I) Group HH: 39 patients (45.3%) with HH. (II) Control Group: 27 patients (31.4%) with neither HH nor metabolic syndrome. (III) Group without HH with MS: 20 patients (23.3%) with metabolic syndrome but without HH.

Data collection. Through detailed anamnesis and objective examination, demographic and clinical data, including age, sex, height, weight [for body mass index (BMI) calculation], and physical activity levels, were collected. Physical activity levels were categorized into four distinct groups. The food plans for each participant were primarily intended for MS and additionally HH with increased intake of foods rich in vitamin B12 and folic acid. Control group (II) did not follow any diet therapy.

Nutrigenetic testing. Nutrigenetic testing was performed using the Advanced NutriGenetx system (Rainbow Court Cary, NC, USA). This validated genetic test evaluates individual nutrient needs, metabolic risks, genetic predispositions to chronic diseases, and pharmacogenetic responses. It specifically includes analyses of genes such as MTHFR (Marker rs1801133) and TCF7L2 (Marker rs12255372), which influence metabolic pathways and nutrient management.

Nutrigenetic management. The genetic analysis provided insights into physical activity potential, metabolic response to exertion, and optimal nutritional requirements based on

Table I. *The demographic description of the study patients in each study group.*

Parameters		HH		Without HH and MS		Without HH with MS	
		N	%	N	%	N	%
Sex	Male	15	17.4	14	16.3	6	7,0
	Female	24	27.9	13	15.1	14	16.3
Age (mean±SD)		43.56±11.73		40.00±12.17		47.55±14.51	
Environment	Urban	18	20.9	16	18.6	11	12.8
	Rural	21	24.4	11	12.8	9	10.5
Physical activity (mean±SD)		2.21±1.03		2.41±0.97		1.95±1.05	

HH: Hyperhomocysteinemia; MS: metabolic syndrome; SD: standard deviation.

genetic predispositions. This information was used to develop personalized nutritional and exercise plans tailored to individual needs, targeting optimal weight, muscle strength, cardiorespiratory function, glucose and insulin metabolism, and lipid profiles. The test also included a genetic score for non-alcoholic fatty liver disease (NAFLD), aiding in its nutritional management and reducing the risk of metabolic complications due to misaligned diets.

SF-12 quality of life assessment. The Short Form-12 (SF-12) Health Survey was used to assess the quality of life in participants. This validated tool evaluates two key components: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Scores for each domain range from 0 to 100, with higher scores indicating better health status. The SF-12 was administered during consultations, and participants self-reported their health status through 12 items addressing physical and mental health. Scores were calculated using the standard SF-12 scoring algorithm, which normalizes results against population norms to interpret health-related quality of life comprehensively.

Statistical analysis. Data were analyzed using IBM SPSS Statistics (version 20, IBM, Armonk, NY, USA). Descriptive statistics, including means, frequency ranges, and standard deviations, were calculated. Differences between groups and time points were assessed using Student's *t*-test and chi-square test, with a significance threshold of $p<0.05$ and high significance defined as $p<0.01$. The Bravais-Pearson correlation coefficient was employed to evaluate relationships between variables. Post hoc analysis using the Holm-Bonferroni method further examined group differences to ensure robust statistical inferences. The pathway analysis of metabolic syndrome, hyperhomocysteinemia, and their impact on quality of life is presented in the flowchart (Figure 1).

Results

The demographic characteristics of the study population are summarized in Table I. A total of 86 participants were included, with a slightly higher proportion of females (59.3%) compared to males (40.7%). The mean age of the participants was 43.37 years, with a standard deviation of 12.71, indicating a moderately diverse age distribution within the study cohort.

In terms of residential environment, the population was nearly evenly split, with 52.3% living in urban areas and 47.7% residing in rural areas. This distribution allows for a comparative analysis of lifestyle and environmental factors that might influence the study outcomes.

Physical activity levels were also recorded, with a mean activity score of 2.21 (standard deviation 1.02). This score reflects a range of activity levels among participants, which may contribute to variations in the observed health metrics.

This demographic data provides a comprehensive overview of the study population, highlighting diversity in

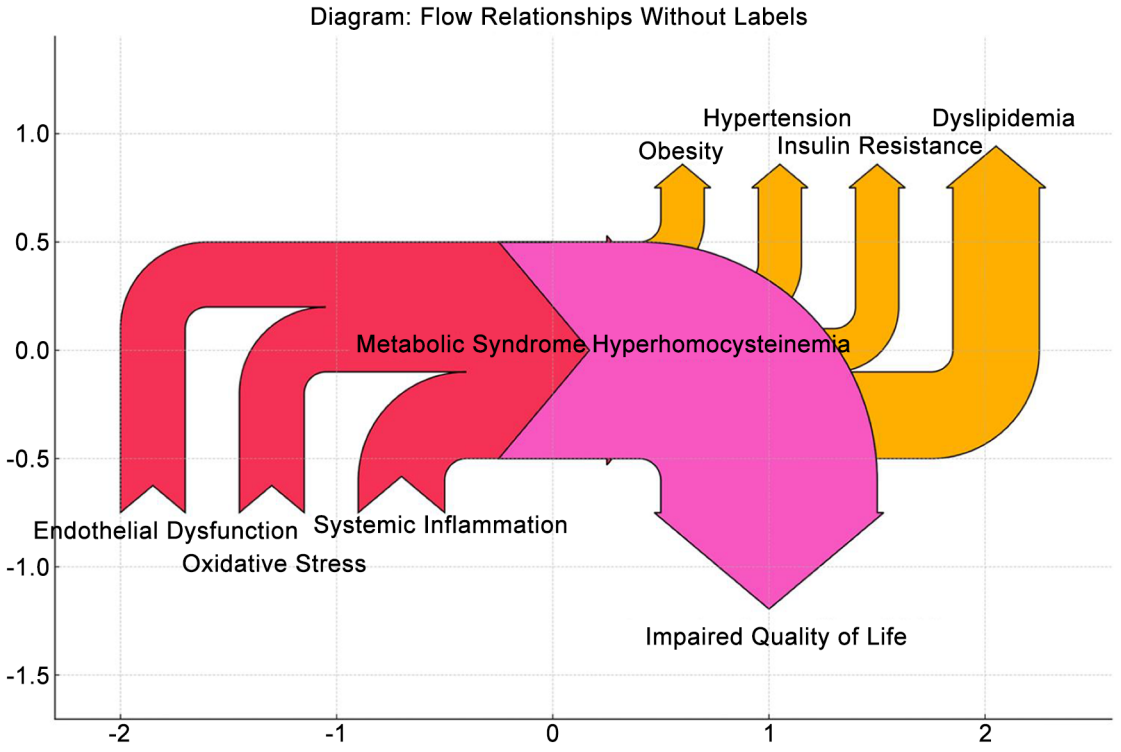

Figure 1. *Pathway analysis of metabolic syndrome, hyperhomocysteinemia, and their impact on quality of life. This Sankey diagram illustrates the progression from early pathophysiological factors (endothelial dysfunction, oxidative stress) to systemic inflammation and metabolic disturbances (metabolic syndrome, hyperhomocysteinemia), ultimately leading to chronic conditions like obesity, hypertension, insulin resistance, and dyslipidemia. These interconnected pathways contribute to impaired quality of life. The color-coded arrows indicate different stages, emphasizing the cascading impact of metabolic and vascular dysfunction.*

sex, age, environment, and physical activity levels, essential for interpreting the study findings in context.

The metabolic parameters description. Table II presents a comparison of metabolic parameters among three groups: individuals with HH, those without HH and without MS, and those without HH but with MS. The data highlights differences in glucose and lipid profiles both initially and after a follow-up period.

In the HH group, there was one person with grade II obesity, five individuals with grade I obesity, and eight overweight participants. The remaining individuals were initially of normal weight, with an average BMI of 25.28 (SD=4.86) for the cohort. By the end of the study, there were five people with grade I obesity, eight overweight individuals, and the rest were of normal weight.

In the "Without HH and MS" group, initially, one person had grade I obesity and one was overweight. By the end, only one person remained overweight, while the rest were normal weight.

In the "Without HH with MS" group, there was one person with grade III obesity, three individuals with grade II obesity, two with grade I obesity, and seven overweight participants. The remaining participants were initially of normal weight. By the end of the study, there were two individuals with grade II obesity, three with grade I obesity, seven overweight participants, and the rest were normal weight, with a final cohort BMI of 24.13 (SD=4.38).

At baseline, initial glucose levels were similar across the groups, with minimal variation. However, individuals with HH exhibited slightly higher total cholesterol (197.44 mg/dl) and LDL cholesterol (102.33 mg/dl)

Table II. *The metabolic parameters description.*

Parameters	HH Mean±SD	Without HH and MS Mean±SD	Without HH with MS Mean±SD	*p*-Value
		Initial		
BMI	25.42±4.26	23.06±2.69	27.99±6.68	0.002
Glucose	95.23±7.41	94.63±7.39	94.40±7.44	0.905
Cholesterol	197.44±18.56	189.74±13.44	189.30±13.67	0.082
LDL cholesterol	102.33±30.96	91.74±15.09	90.15±14.02	0.091
HDL cholesterol	37.13±3.40	37.52±3.02	37.45±3.10	0.872
Triglycerides	132.62±15.97	131.63±16.16	130.70±15.79	0.906
		Final		
BMI	24.34±4.28	22.14±1.95	26.42±5.72	0.003
Glucose	86.90±5.11	86.37±4.76	86.90±5.00	0.901
Cholesterol	180.87±14.04	176.63±12.52	177.50±13.21	0.405
LDL cholesterol	83.08±15.48	79.15±10.79	78.45±10.38	0.328
HDL cholesterol	42.74±3.17	42.78±3.02	42.65±3.17	0.990
Triglycerides	119.36±13.61	118.52±13.64	118.25±13.53	0.947

HH: Hyperhomocysteinemia; MS: metabolic syndrome; SD: standard deviation; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

compared to the other groups. HDL cholesterol levels and triglyceride levels were relatively comparable among the groups, showing only minor differences.

Over the course of the intervention, all groups exhibited reductions in glucose, cholesterol, LDL cholesterol, and triglycerides, reflecting metabolic improvements. HDL cholesterol levels increased slightly across the groups. Despite these improvements, individuals with HH consistently maintained slightly higher final cholesterol and LDL cholesterol levels compared to the other groups, suggesting persistent differences in lipid metabolism associated with HH.

These findings highlight the metabolic impact of HH, particularly its association with lipid dysregulation, and emphasize the need for further research on its role in metabolic and cardiovascular health.

The paired samples *t*-test (Table III) results reveal significant changes in glucose and lipid parameters between initial and final measurements for the 86 participants. All parameters demonstrate statistically significant differences ($p<0.001$), indicating meaningful improvements or changes over time.

Figure 2A illustrates the mean BMI difference (kg/m^2) across three groups: HH, Without HH and MS, and Without HH with MS. The smallest reduction in BMI was observed in the HH group, with a mean difference of approximately −1.0 kg/m^2, indicating less weight loss compared to the other groups. The Without HH and MS group showed a moderate reduction, with a mean BMI difference of around −1.2 kg/m^2. The largest reduction was seen in the Without HH with MS group, with a mean difference close to −1.6 kg/m^2, suggesting the most significant weight loss. These results indicate that the presence of HH may negatively impact weight management, as individuals with HH experienced the least reduction in BMI despite similar dietary and lifestyle interventions.

Glucose levels decreased by an average of 8.12 mg/dl (SD=8.06), with a 95% confidence interval of 6.39 to 9.84 mg/dl. This substantial reduction, confirmed by a

Table III. *The paired samples t-test for the metabolic parameters.*

Parameters		Mean	SD	Paired samples test	Paired differences		*t*	*p*-Value
					Lower	Upper		
Pair 1	BMI initial - BMI final	1.14	1.15	0.12	0.89	1.39	9.18	0.001
Pair 2	Glucose initial - Glucose final	8.11	8.06	0.86	6.38	9.84	9.33	0.001
Pair 3	Total cholesterol initial - Total cholesterol final	14.37	7.82	0.84	12.69	16.04	17.03	0.001
Pair 4	LDL cholesterol initial - LDL cholesterol final	15.40	14.61	1.57	12.27	18.53	9.77	0.001
Pair 5	HDL cholesterol initial - HDL cholesterol final	−5.40	1.30	0.14	−5.68	−5.12	−38.42	0.001
Pair 6	Triglycerides initial - Triglycerides final	13.02	5.93	0.63	11.75	14.29	20.35	0.001

SD: Standard deviation; *t*: *t* student coefficient; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

t-value of 9.34, suggests improved glucose regulation, potentially reflecting the effectiveness of the intervention or other influencing factors.

Total cholesterol levels showed a significant mean reduction of 14.37 mg/dl (SD=7.82), with a confidence interval of 12.69 to 16.05 mg/dl. The large t-value of 17.03 emphasizes the strength of this improvement, indicating a notable decrease in overall cholesterol levels. Similarly, LDL cholesterol levels dropped by 15.41 mg/dl (SD=14.61), with a confidence interval of 12.27 to 18.54 mg/dl and a t-value of 9.78. This reduction highlights a meaningful decline in "bad cholesterol".

Triglycerides also decreased significantly, with a mean reduction of 13.02 mg/dl (SD=5.93) and a confidence interval of 11.75 to 14.30 mg/dl. The *t*-value of 20.36 underscores the magnitude of this improvement, suggesting enhanced lipid control. However, HDL cholesterol, often referred to as "good cholesterol", experienced a slight decrease. The mean reduction of −5.41 mg/dl (SD=1.30) is statistically significant (*t*=−38.42), with a confidence interval of −5.69 to −5.13 mg/dl. While unexpected, this result warrants further investigation to understand its implications on overall lipid health.

In summary, the results indicate significant improvements in glucose regulation and reductions in total cholesterol, LDL cholesterol, and triglycerides. However, the decrease in HDL cholesterol suggests the need for additional analysis to evaluate its impact within the context of the overall lipid profile.

Figure 2 summarizes the differences between final and initial values of glucose and lipid parameters across the three groups: individuals with HH, those without HH and without MS, and those without HH but with MS. For glucose, all groups showed significant decreases, with the largest reduction observed in the HH group (−8.33 mg/dl) compared to −8.26 mg/dl and −7.50 mg/dl in the other groups, respectively. Similar trends were seen for total cholesterol, where the HH group had the most substantial decrease (−16.56 mg/dl), followed by −13.11 mg/dl and −11.80 mg/dl in the other groups.

LDL cholesterol also showed the greatest reduction in the HH group (−19.26 mg/dl), compared to −12.59 mg/dl and −11.70 mg/dl. In contrast, HDL cholesterol increased in all groups, with a slightly higher improvement in the HH group (+5.62 mg/dl) than the others. Triglycerides demonstrated consistent reductions across all groups, with similar decreases of −13.26 mg/dl, −13.11 mg/d, and −12.45 mg/dl, respectively.

These results suggest that while all groups showed improvements in metabolic parameters, individuals with HH exhibited the largest differences; however, none reached statistical significance. The most notable differences were observed in cholesterol and LDL levels, highlighting potential variations in metabolic responses based on their condition. This finding may be explained by the inclusion of participants without chronic diseases but with specific genetic mutations in the study.

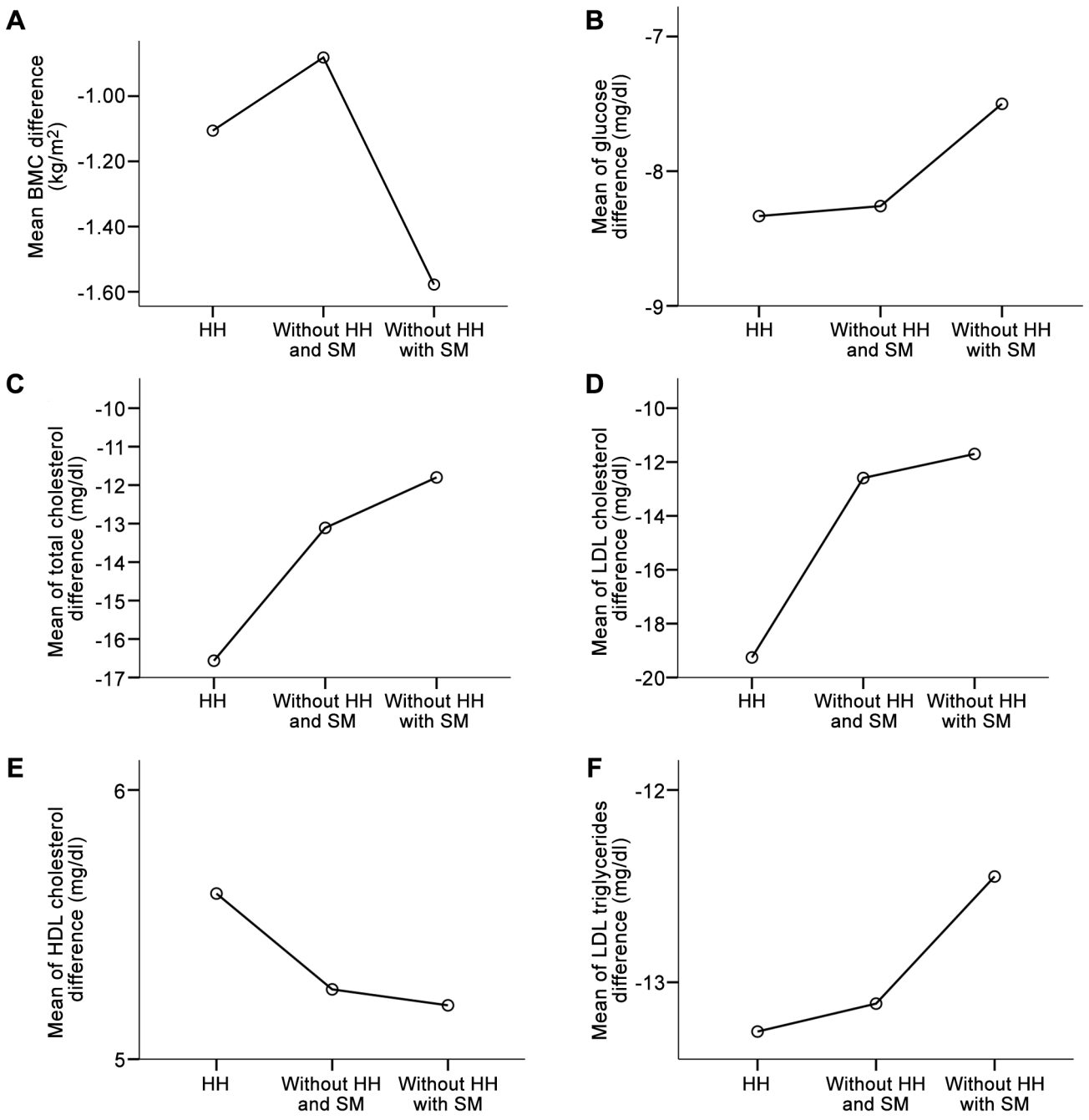

Figure 2. *Graphical presentation of metabolic parameters (A) glucose, (B) total cholesterol, (C) LDL cholesterol, (D) HDL cholesterol and (E) triglycerides in each study group.*

The study of the physical condition parameters. This study (Figure 3) presents the recorded improvements in physical condition on a scale from 1 to 10 across three groups: individuals with HH, those without HH and without MS, and those without HH but with MS. All participants began the study with some degree of health

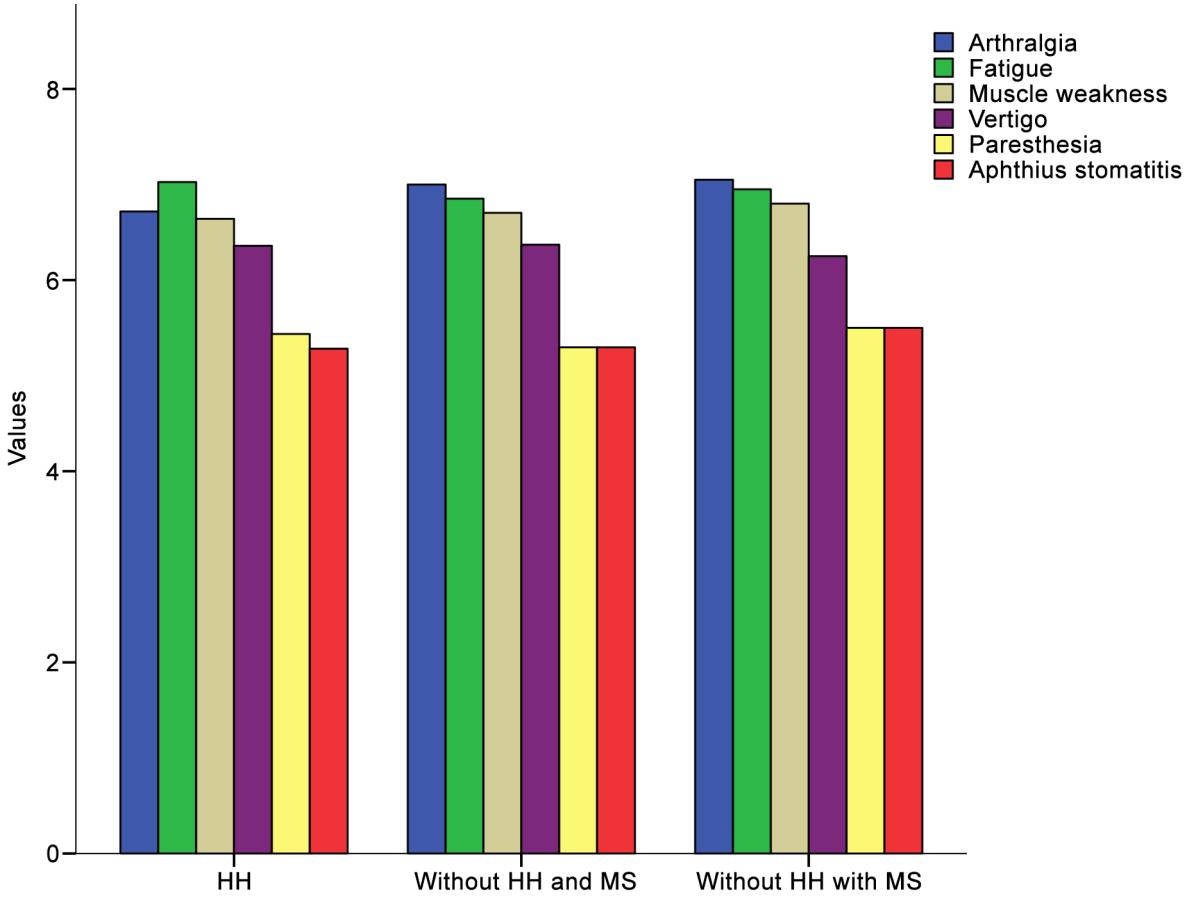

Figure 3. *Graphical presentation of the physical condition parameters.*

impairment, and their progress was assessed in terms of arthralgia, fatigue, muscle weakness, vertigo, paresthesia, and aphthous stomatitis.

Fatigue levels showed a moderate improvement, with mean scores of 7.03 in the HH group, 6.85 in the group without HH and MS, and 6.95 in the group without HH but with MS. Arthralgia improved slightly less, with mean scores of 6.72, 7.00, and 7.05, respectively. Muscle weakness also showed consistent improvements across the groups, with mean scores ranging from 6.64 to 6.80.

Vertigo demonstrated similar levels of improvement across groups, with scores around 6.25 to 6.37. Paresthesia saw the lowest mean improvement, with scores between 5.30 and 5.50. Finally, reduction in the severity of aphthous stomatitis was recorded with mean scores of 5.28 to 5.50, showing mild progress in this symptom.

Overall, the recorded improvements reflect positive changes in physical condition, albeit with variability across symptoms and groups. The HH group exhibited comparable or slightly greater symptom improvement, suggesting that managing HH may enhance overall health outcomes.

Life quality. Table IV presents the results of the SF-12 Health Survey, summarizing the mean scores, standard deviations, and distribution of participants across interpretation ranges for three groups: individuals with HH, those without HH and without MS, and those without HH but with MS. The mean SF-12 scores, which reflect

Table IV. *The SF-12 score in each one of study groups.*

	HH		Without HH and MS		Without HH with MS			
SF 12	N	%	N	%	N	%	*t*	*p*-Value
31-54 points	10	11.6	1	1.2	1	1.2	6.966	0.001
55-77 points	11	12.8	7	8.1	6	7.0	10.537	0.001
78-100 points	18	20.9	19	22.1	13	15.1	17.029	0.001

HH: Hyperhomocysteinemia; MS: metabolic syndrome; N: number of patients; *t*: coefficient *t* student.

overall quality of life, differ significantly between the groups. The HH group scored an average of 70.46 (SD=20.18), indicating moderate impairments in quality of life. In contrast, the group without HH and MS had the highest scores, averaging 84.07 (SD=13.45), reflecting better health. The group without HH but with MS scored slightly lower, with a mean of 80.50 (SD=16.73), suggesting relatively good health but slightly below the second group.

Table IV presents the distribution of SF-12 quality of life scores across three groups: participants with HH, those without HH and MS, and those without HH but with MS. The scores are divided into three ranges to reflect varying levels of quality of life.

For 31-54 points (Low Quality of Life): A significantly higher percentage of participants in the HH group (11.6%) reported low quality of life compared to only 1.2% in both the group without HH and MS and the group without HH but with MS. The observed difference was statistically significant (t=6.966, p=0.001), highlighting a greater impact of HH on quality of life.

For 55-77 points (Moderate Quality of Life): In the moderate range, 12.8% of participants in the HH group fell into this category, compared to 8.1% in the group without HH and MS and 7.0% in the group without HH but with MS. This difference was also statistically significant (t=10.537, p=0.001), indicating that HH contributes to moderate impairments in quality of life.

For 78-100 points (High Quality of Life): A higher proportion of participants without HH and MS (22.1%) reported high quality of life compared to 20.9% in the HH group and 15.1% in the group without HH but with MS. The difference remained statistically significant (t=17.029, p=0.001), suggesting that the absence of HH and MS is associated with better quality of life outcomes.

Therefore, these results highlight disparities in quality of life across the groups. The HH group had more individuals with moderate to severe impairments (lower scores), while the group without HH and without MS consistently demonstrated better health outcomes, as reflected by higher scores. These findings emphasize the impact of HH on quality of life and the importance of interventions to improve health in affected individuals (Figure 4).

Correlations. The analysis revealed significant correlations between changes in metabolic parameters and physical symptoms. Improvements in glucose and LDL cholesterol levels were associated with reduced arthralgia, indicated by negative correlations with glucose difference (r=−0.453, p<0.001) and LDL difference (r=−0.353, p=0.001). Similarly, reductions in glucose, cholesterol, and LDL levels were strongly linked to decreases in vertigo (r=−0.641, p<0.001, r=−0.248, p=0.021, and r=−0.269, p=0.012, respectively). Interestingly, an increase in HDL levels was positively correlated with vertigo (r=0.332, p=0.002). Improvements in glucose levels also showed a significant association with fewer occurrences of canker sores (r=−0.396, p<0.001). Conversely, glucose and triglyceride improvements were positively correlated with increased reports of muscle weakness (r=0.308, p=0.004 and r=0.300, p=0.005, respectively), suggesting a complex relationship between metabolic adjustments and physical

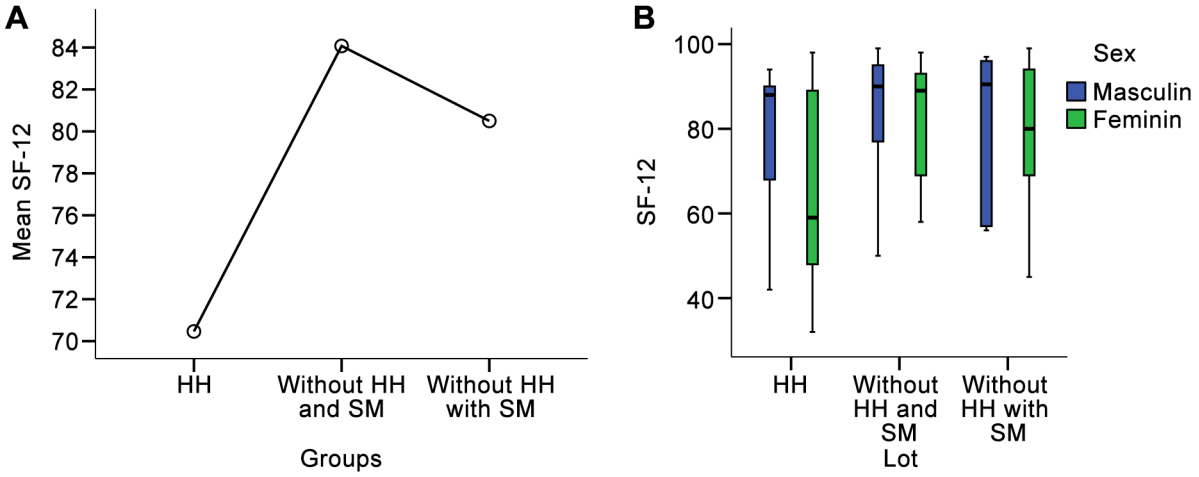

Figure 4. *The graphical presentation of the mean of SF-12 score in each group of the study (A), and depending on sex (B).*

symptoms. These findings emphasize the role of metabolic regulation in mitigating specific physical complaints while highlighting the need for a nuanced understanding of symptom changes during health interventions (Table V).

Discussion

The findings of this study highlight the interconnected roles of genetics, environment, personal lifestyle, and medical care in influencing individual and population health. The results underscore the importance of lifestyle modifications, particularly dietary changes and increased physical activity, in managing conditions such as hyperhomocysteinemia (HH) and metabolic syndrome (MS). These interventions play a crucial role in improving health outcomes, as evidenced by the observed modifications in BMI within the study groups. This approach emphasizes the necessity of addressing multiple factors to achieve effective management of metabolic and health conditions (9, 23, 24). This perspective has formed the foundation for promoting healthy lifestyles, particularly in addressing chronic diseases such as cardiovascular disorders and metabolic conditions (25).

Homocysteine, a sulfur-containing amino acid derived from methionine metabolism, plays a dual role in human health. While essential for various metabolic processes, elevated homocysteine levels, or HH, have been implicated in vascular calcification, cognitive decline, and reproductive health issues. Research, including studies by Karger *et al.* (2020) and Luzzi *et al.* (2022), highlights the association between HH and CVD, as well as its role in accelerating cognitive dysfunction, particularly in patients with dementia. In this study, HH was linked to significant metabolic and health impairments, emphasizing its impact on quality of life (26-28).

The causes of HH are multifaceted, including genetic polymorphisms in homocysteine-metabolism-related enzymes, deficiencies in B vitamins (such as folate and B12), and comorbid conditions like kidney disease and hypothyroidism (29). These genetic and metabolic factors contribute to the prevalence of HH in various chronic diseases, such as diabetes mellitus, and can be influenced by medications, including anti-Parkinson's and anti-epileptic drugs. Addressing these factors through targeted nutritional and lifestyle interventions is crucial (30).

Hyperhomocysteinemia is common in patients with erectile dysfunction (ED). Our study reveals a correlation between elevated homocysteine levels and penile duplex ultrasound parameters, supporting its role in arterial-origin ED. The link involves nitric oxide (NO) metabolism

Table V. *The Pearson correlation between changes in metabolic parameters and physical symptoms.*

Pearson correlation		BMI	Glucose	Cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides
SF-12	r	−0.120	0.018	0.123	0.174	−0.062	−0.014
	p-Value	0.271	0.867	0.258	0.110	0.568	0.900
Fatigue	r	0.117	0.026	0.021	−0.123	−0.004	0.227*
	p- Value	0.283	0.814	0.845	0.258	0.972	0.035
Arthralgia	r	0.008	−0.453**	−0.135	−0.353**	0.133	−0.155
	p- Value	0.941	0.000	0.215	0.001	0.223	0.155
Muscle weakness	r	0.157	0.308**	0.062	0.017	−0.183	0.300**
	p- Value	0.150	0.004	0.572	0.875	0.092	0.005
Vertigo	r	0.039	−0.641**	−0.248*	−0.269*	0.332**	−0.104
	p- Value	0.718	0.000	0.021	0.012	0.002	0.340
Paresthesia	r	−0.158	0.040	0.063	0.113	−0.068	0.166
	p- Value	0.147	0.713	0.564	0.300	0.532	0.128
Aphthous stomatitis	r	−0.134	−0.396**	−0.075	−0.132	0.192	0.144
	p- Value	0.220	0.000	0.491	0.225	0.077	0.185
	N				86		

SF-12: Short Form-12 Health Survey; r: Pearson coefficient; *p*-Value: statistical significance; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; N: number of patients; *Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed).

and oxidative stress, leading to endothelial dysfunction. As this process also drives CVD, targeting hyperhomocysteinemia may help prevent progression from endothelial damage to atherosclerosis (31, 32).

This study demonstrated that sex-specific and individualized dietary recommendations are essential for effectively managing HH. Nutritional interventions focusing on increased intake of folic acid and vitamin B12 were employed to achieve reductions in homocysteine levels without pharmacological support (33). Additionally, emerging evidence supports the use of N-acetylcysteine (NAC) as a potential adjunct therapy, although this study relied exclusively on dietary strategies (34). The findings reinforce the role of tailored nutritional therapy in mitigating the health risks associated with HH, improving metabolic profiles, and enhancing overall quality of life (35). These results underscore the importance of integrating genetics, lifestyle, and targeted dietary approaches into personalized healthcare strategies for managing HH and related conditions (36).

The role of Hcy in vascular pathology is well-documented, with elevated levels linked to increased risks of cardiovascular, cerebrovascular, peripheral vascular diseases, and vitamin D deficiency (20, 37, 38). These associations are largely attributed to heightened inflammation and oxidative stress. Mechanisms such as endothelial dysfunction, platelet activation, and oxidative damage to vascular cells highlight homocysteine's contribution to these conditions (39-41). Elevated inducible nitric oxide synthase (iNOS) activity has been identified as a key factor in collagen/elastin remodeling in vascular tissues, further emphasizing homocysteine's detrimental effects on vascular health (42).

Beyond vascular implications, HH has been associated with cognitive decline and an increased risk of Alzheimer's disease and dementia (43, 44). Elevated homocysteine levels impair cognitive function, with older adults particularly vulnerable. The study also underscores the role of HH in reproductive health, linking it to pregnancy complications and birth defects. Supplementation with B vitamins, particularly folic acid, has shown potential in reducing homocysteine levels and preventing associated complications, although the evidence remains inconclusive (8).

The relationship between HH and nutrient requirements highlights the complex interplay between metabolic conditions and dietary needs. Obesity,

hypertension, and hypercholesterolemia inversely affect nutrient utilization, while age and physical activity levels influence the demand for nutrients like vitamin B6, zinc, and magnesium. These findings emphasize the need for tailored nutritional strategies to address the specific needs of individuals with HH and related metabolic conditions (45-47).

Despite its significant implications, interventional studies on B vitamin supplementation to reduce vascular and cognitive risks have produced mixed results (8). While some studies demonstrate benefits in lowering homocysteine levels, others fail to show a significant impact on major vascular or cognitive outcomes. These discrepancies highlight the need for further research to refine therapeutic approaches (48).

The current study also examined the association between HH and MS, emphasizing the importance of identifying HH as metabolic issues are becoming increasingly prevalent. However, limitations such as the relatively small sample size, reliance on data from individuals with pre-existing health conditions, and the high cost of genotyping HH were noted. Expanding the study to include a larger and more diverse cohort could provide more comprehensive insights into the relationship between HH and cardiometabolic risks.

The connection between metabolic syndrome and hyperhomocysteinemia is rooted in shared patho-physiological mechanisms, including insulin resistance, low-grade systemic inflammation, and endothelial dysfunction. Elevated homocysteine levels impair nitric oxide availability, leading to vascular damage, whereas metabolic syndrome exacerbates this process through dyslipidemia and hypertension. These synergistic effects contribute to cardiovascular complications and lower quality of life (49).

To assess the impact on quality of life, validated instruments such as the SF-36 Health Survey or EQ-5D are commonly applied. These tools capture the multi-dimensional impact of metabolic syndrome, including limitations in physical activity, social functioning, and emotional well-being (50).

Personalized dietary strategies, including folate and vitamin B12 supplementation, have shown promise in reducing homocysteine levels and mitigating the cardiovascular risks associated with metabolic syndrome (51). Tailored interventions targeting specific genetic polymorphisms (*e.g*., MTHFR) that influence homocysteine metabolism can further optimize health outcomes and enhance quality of life for these patients.

The findings reinforce the importance of personalized nutrition as a cornerstone for managing HH. A diet rich in folic acid and vitamin B12 can mitigate cardiometabolic risks and improve the quality of life for affected individuals. Additionally, sex-specific dietary recommendations and adjustments for age and activity levels are essential to address the evolving nutritional needs of different populations. These insights pave the way for targeted interventions aimed at optimizing health outcomes globally, particularly in the context of HH and its metabolic and cognitive impacts.

Conclusion

Patients with HH demonstrated poorer quality of life and persistent symptoms, emphasizing the need for targeted interventions. Personalized dietary strategies, focusing on increased intake of folic acid and vitamin B12, effectively reduced cardiometabolic risks and improved symptom management in patients with HH. Nutrigenetic testing provided valuable insights into individual nutrient needs, enabling tailored interventions for optimal health outcomes. Improvements in glucose, LDL cholesterol, and triglycerides correlated with reduced symptoms such as joint pain and dizziness, may support the role of metabolic regulation in symptom control. This study highlights the importance of integrating personalized nutrition and lifestyle modifications to enhance the quality of life in patients with HH and related metabolic conditions.

Funding

The APC was funded by University of Oradea, Oradea, Romania.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: B.M.T. and T.C.G.; methodology: T.C.G.; software: T.C.G.; validation: B.M.T. and A.N.; formal analysis: T.C.G.; investigation: B.M.T.; resources: B.M.T.; data curation: B.M.T.; writing—original draft preparation: T.C.G.; writing—review and editing: T.C.G.; visualization: T.C.G. and A.M.B.; supervision: E.M.; project administration: B.M.T.; funding acquisition: B.M.T. All Authors have read and agreed to the published version of the manuscript.

Acknowledgements

The Authors would like to thank the University of Oradea, for supporting the payment of the invoice, through an internal project.

References

1 Morvaridzadeh M, Zoubdane N, Heshmati J, Alami M, Berrougui H, Khalil A: High-density lipoprotein metabolism and function in cardiovascular diseases: what about aging and diet effects? Nutrients 16(5): 653, 2024. DOI: 10.3390/nu16050653

2 Ghitea TC, Aleya L, Tit DM, Behl T, Stoicescu M, Sava C, Iovan C, El-Kharoubi A, Uivarosan D, Pallag A, Bungau S: Influence of diet and sport on the risk of sleep apnea in patients with metabolic syndrome associated with hypothyroidism — a 4-year survey. Environ Sci Pollut Res Int 29(16): 23158-23168, 2022. DOI: 10.1007/s11356-021-17589-x

3 Vinci P, Di Girolamo FG, Panizon E, Tosoni LM, Cerrato C, Pellicori F, Altamura N, Pirulli A, Zaccari M, Biasinutto C, Roni C, Fiotti N, Schincariol P, Mangogna A, Biolo G: Lipoprotein(a) as a risk factor for cardiovascular diseases: pathophysiology and treatment perspectives. Int J Environ Res Public Health 20(18): 6721, 2023. DOI: 10.3390/ijerph20186721

4 González-Lamuño D, Arrieta-Blanco FJ, Fuentes ED, Forga-Visa MT, Morales-Conejo M, Peña-Quintana L, Vitoria-Miñana I: Hyperhomocysteinemia in adult patients: a treatable metabolic condition. Nutrients 16(1): 135, 2023. DOI: 10.3390/nu16010135

5 Valente FX, Campos Tdo N, Moraes LF, Hermsdorff HH, Cardoso Lde M, Pinheiro-Sant'Ana HM, Gilberti FA, Peluzio Mdo C: B vitamins related to homocysteine metabolism in adults celiac disease patients: a cross-sectional study. Nutr J 14: 110, 2015. DOI: 10.1186/s12937-015-0099-8

6 Ganguly P, Alam SF: Role of homocysteine in the development of cardiovascular disease. Nutr J 14: 6, 2015. DOI: 10.1186/1475-2891-14-6

7 Guieu R, Ruf J, Mottola G: Hyperhomocysteinemia and cardiovascular diseases. Ann Biol Clin (Paris) 80(1): 7-14, 2022. DOI: 10.1684/abc.2021.1694

8 Herrmann W, Herrmann M: The controversial role of HCY and vitamin B deficiency in cardiovascular diseases. Nutrients 14(7): 1412, 2022. DOI: 10.3390/nu14071412

9 Tarcau BM, Negru A, Ghitea TC, Marian E: Is there a connection between hyperhomocysteinemia and the cardiometabolic syndrome? Biomedicines 12(6): 1135, 2024. DOI: 10.3390/biomedicines12061135

10 Lu J, Chen K, Chen W, Liu C, Jiang X, Ma Z, Li D, Shen Y, Tian H: Association of serum homocysteine with cardiovascular and all-cause mortality in adults with diabetes: a prospective cohort study. Oxid Med Cell Longev 2022: 2156483, 2022. DOI: 10.1155/2022/2156483

11 Heeren J, Scheja L: Metabolic-associated fatty liver disease and lipoprotein metabolism. Mol Metab 50: 101238, 2021. DOI: 10.1016/j.molmet.2021.101238

12 Dankner R, Chetrit A, Ken Dror G, Sela BA: Physical activity is inversely associated with total homocysteine levels, independent of C677T MTHFR genotype and plasma B vitamins. Age (Dordr) 29(4): 219-227, 2007. DOI: 10.1007/s11357-007-9041-0

13 Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C, American Heart Association, National Heart, Lung, and Blood Institute: Definition of metabolic syndrome. Circulation 109(3): 433-438, 2004. DOI: 10.1161/01.CIR.0000111245.75752.C6

14 Ford ES, Li C, Sattar N: Metabolic syndrome and incident diabetes: current state of the evidence. Diabetes Care 31(9): 1898-1904, 2008. DOI: 10.2337/dc08-0423

15 Bruno G, Merletti F, Biggeri A, Bargero G, Ferrero S, Runzo C, Prina Cerai S, Pagano G, Cavallo-Perin P: Metabolic syndrome as a predictor of all-cause and cardiovascular mortality in type 2 diabetes. Diabetes Care 27(11): 2689-2694, 2004. DOI: 10.2337/diacare.27.11.2689

16 Elshorbagy AK, Nurk E, Gjesdal CG, Tell GS, Ueland PM, Nygård O, Tverdal A, Vollset SE, Refsum H: Homocysteine, cysteine, and body composition in the Hordaland Homocysteine Study: does cysteine link amino acid and lipid metabolism? Am J Clin Nutr 88(3): 738-746, 2008. DOI: 10.1093/ajcn/88.3.738

17 Das D, Shruthi NR, Banerjee A, Jothimani G, Duttaroy AK, Pathak S: Endothelial dysfunction, platelet hyperactivity, hypertension, and the metabolic syndrome: molecular insights

and combating strategies. Front Nutr 10: 1221438, 2023. DOI: 10.3389/fnut.2023.1221438
18 Ouyang Y, Wu Q, Li J, Sun S, Sun S: S-adenosylmethionine: A metabolite critical to the regulation of autophagy. Cell Prolif 53(11): e12891, 2020. DOI: 10.1111/cpr.12891
19 Raghubeer S, Matsha TE: Methylenetetrahydrofolate (MTHFR), the one-carbon cycle, and cardiovascular risks. Nutrients 13(12): 4562, 2021. DOI: 10.3390/nu13124562
20 Moretti R, Caruso P: The controversial role of homocysteine in neurology: from labs to clinical practice. Int J Mol Sci 20(1): 231, 2019. DOI: 10.3390/ijms20010231
21 Nieraad H, Pannwitz N, Bruin N, Geisslinger G, Till U: Hyperhomocysteinemia: Metabolic role and animal studies with a focus on cognitive performance and decline-a review. Biomolecules 11(10): 1546, 2021. DOI: 10.3390/biom 11101546
22 Jindal A, Rajagopal S, Winter L, Miller JW, Jacobsen DW, Brigman J, Allan AM, Paul S, Poddar R: Hyperhomocysteinemia leads to exacerbation of ischemic brain damage: Role of GluN2A NMDA receptors. Neurobiol Dis 127: 287-302, 2019. DOI: 10.1016/j.nbd.2019.03.012
23 Tulchinsky TH: Marc Lalonde, the Health Field Concept and Health Promotion. Case Studies in Public Health: 523-541, 2018. DOI: 10.1016/B978-0-12-804571-8.00028-7
24 Wang Y, Jiang Y, Wang N, Zhu M, Liu X, Wang R, Jiang F, Chen Y, Zhao Q, Zhao G: Central but not general obesity is positively associated with the risk of hyperhomocysteinemia in middle-aged women. Nutrients 11(7): 1614, 2019. DOI: 10.3390/ nu11071614
25 Ghitea TC: Correlation of periodontal bacteria with chronic inflammation present in patients with metabolic syndrome. Biomedicines 9(11): 1709, 2021. DOI: 10.3390/biomedicines 9111709
26 Miller AL: The methionine-homocysteine cycle and its effects on cognitive diseases. Altern Med Rev 8(1): 7-19, 2003. DOI: 10.1007/978-3-322-81541-5_2
27 Azzini E, Ruggeri S, Polito A: Homocysteine: its possible emerging role in at-risk population groups. Int J Mol Sci 21(4): 1421, 2020. DOI: 10.3390/ijms21041421
28 Karger AB, Steffen BT, Nomura SO, Guan W, Garg PK, Szklo M, Budoff MJ, Tsai MY: Association between homocysteine and vascular calcification incidence, prevalence, and progression in the MESA cohort. J Am Heart Assoc 9(3): e013934, 2020. DOI: 10.1161/JAHA.119.013934
29 Luzzi S, Cherubini V, Falsetti L, Viticchi G, Silvestrini M, Toraldo A: Homocysteine, cognitive functions, and degenerative dementias: state of the art. Biomedicines 10(11): 2741, 2022. DOI: 10.3390/biomedicines10112741
30 Ocal P, Ersoylu B, Cepni I, Guralp O, Atakul N, Irez T, Idil M: The association between homocysteine in the follicular fluid with embryo quality and pregnancy rate in assisted reproductive techniques. J Assist Reprod Genet 29(4): 299-304, 2012. DOI: 10.1007/s10815-012-9709-y
31 Salvio G, Ciarloni A, Cordoni S, Cutini M, Delli Muti N, Finocchi F, Firmani F, Giovannini L, Perrone M, Balercia G: Homocysteine levels correlate with velocimetric parameters in patients with erectile dysfunction undergoing penile duplex ultrasound. Andrology 10(4): 733-739, 2022. DOI: 10.1111/andr.13169
32 Salvio G, Ciarloni A, Cutini M, Balercia G: Hyperhomocysteinemia: focus on endothelial damage as a cause of erectile dysfunction. Int J Mol Sci 22(1): 418, 2021. DOI: 10.3390/ijms22010418
33 Langman LJ, Cole DE: Homocysteine. Crit Rev Clin Lab Sci 36(4): 365-406, 1999. DOI: 10.1080/10408369991239231
34 Brustolin S, Giugliani R, Félix TM: Genetics of homocysteine metabolism and associated disorders. Braz J Med Biol Res 43(1): 1-7, 2010. DOI: 10.1590/s0100-879x2009007500021
35 Cordaro M, Siracusa R, Fusco R, Cuzzocrea S, Di Paola R, Impellizzeri D: Involvements of hyperhomocysteinemia in neurological disorders. Metabolites 11(1): 37, 2021. DOI: 10.3390/metabo11010037
36 Wiklund O, Fager G, Andersson A, Lundstam U, Masson P, Hultberg B: N-acetylcysteine treatment lowers plasma homocysteine but not serum lipoprotein(a) levels. Atherosclerosis 119(1): 99-106, 1996. DOI: 10.1016/0021-9150(95)05635-1
37 Kaplan P, Tatarkova Z, Sivonova MK, Racay P, Lehotsky J: Homocysteine and mitochondria in cardiovascular and cerebrovascular systems. Int J Mol Sci 21(20): 7698, 2020. DOI: 10.3390/ijms21207698
38 Trifan DF, Tirla AG, Moldovan AF, Moș C, Bodog F, Maghiar TT, Manole F, Ghitea TC: Can vitamin D levels alter the effectiveness of short-term facelift interventions? Healthcare (Basel) 11(10): 1490, 2023. DOI: 10.3390/healthcare11101490
39 Prtina A, Rašeta Simović N, Milivojac T, Vujnić M, Grabež M, Djuric D, Stojiljković MP, Soldat Stanković V, Čolić MJ, Škrbić R: The effect of three-month vitamin D supplementation on the levels of homocysteine metabolism markers and inflammatory cytokines in sera of psoriatic patients. Biomolecules 11(12): 1865, 2021. DOI: 10.3390/biom11121865
40 Trifan DF, Tirla AG, Mos C, Danciu A, Bodog F, Manole F, Ghitea TC: Involvement of vitamin D3 in the aging process according to sex. Cosmetics 10(4): 114, 2023. DOI: 10.3390/ cosmetics10040114
41 Danciu AM, Ghitea TC, Bungau AF, Vesa CM: The relationship between oxidative stress, selenium, and cumulative risk in metabolic syndrome. In Vivo 37(6): 2877-2887, 2023. DOI: 10.21873/invivo.13406
42 Yang Q, He GW: Imbalance of homocysteine and H(2)S: significance, mechanisms, and therapeutic promise in vascular injury. Oxid Med Cell Longev 2019: 7629673, 2019. DOI: 10.1155/2019/7629673
43 Price BR, Wilcock DM, Weekman EM: Hyperhomocysteinemia as a risk factor for vascular contributions to cognitive impairment and dementia. Front Aging Neurosci 10: 350, 2018. DOI: 10.3389/fnagi.2018.00350

44 Nilsson K, Gustafson L, Hultberg B: Elevated plasma homocysteine level in vascular dementia reflects the vascular disease process. Dement Geriatr Cogn Dis Extra 3(1): 16-24, 2013. DOI: 10.1159/000345981
45 Cena H, Calder PC: Defining a healthy diet: evidence for the role of contemporary dietary patterns in health and disease. Nutrients 12(2): 334, 2020. DOI: 10.3390/nu12020334
46 Wilborn C, Beckham J, Campbell B, Harvey T, Galbreath M, La Bounty P, Nassar E, Wismann J, Kreider R: Obesity: prevalence, theories, medical consequences, management, and research directions. J Int Soc Sports Nutr 2(2): 4-31, 2005. DOI: 10.1186/1550-2783-2-2-4
47 Tershakovec AM, Jawad AF, Stouffer NO, Elkasabany A, Srinivasan SR, Berenson GS: Persistent hypercholesterolemia is associated with the development of obesity among girls: the Bogalusa Heart Study. Am J Clin Nutr 76(4): 730-735, 2002. DOI: 10.1093/ajcn/76.4.730
48 Kwok T, Wu Y, Lee J, Lee R, Yung CY, Choi G, Lee V, Harrison J, Lam L, Mok V: A randomized placebo-controlled trial of using B vitamins to prevent cognitive decline in older mild cognitive impairment patients. Clin Nutr 39(8): 2399-2405, 2020. DOI: 10.1016/j.clnu.2019.11.005
49 Boushey CJ, Beresford SA, Omenn GS, Motulsky AG: A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: Probable benefits of increasing folic acid intakes. JAMA 274(13): 1049-1057, 1995. DOI: 10.1001/jama.1995.03530130055028
50 Chichlowska KL, Rose KM, Diez-Roux AV, Golden SH, McNeill AM, Heiss G: Individual and neighborhood socioeconomic status characteristics and prevalence of metabolic syndrome: the Atherosclerosis Risk in Communities (ARIC) Study. Psychosom Med 70(9): 986-992, 2008. DOI: 10.1097/PSY.0b013e318183a491
51 Selhub J: Homocysteine metabolism. Annu Rev Nutr 19(1): 217-246, 1999. DOI: 10.1146/annurev.nutr.19.1.217