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Homocysteine as a biomarker of physical activity and exercise tolerance in adolescent children

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Abstract

Purpose: To determine the homocysteine content in children and adolescents with different levels of physical activity, to establish the relationship between homocysteine content, indicators of physical development, level of physical activity and tolerance to physical activity in adolescence.

Material and Methods. We examined 83 children aged 11 to 17 years, who were examined by a pediatrician, an endocrinologist, and the girls by a pediatric gynecologist. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Committee on Bioethics and Deontology. Height, body weight and body mass index were assessed; physical activity tolerance by the Ruffier test; physical activity was assessed using a questionnaire; serum homocysteine was determined by enzyme-linked immunosorbent assay.

Results. 81% of adolescents with high physical activity had regular sports training at least three times a week. In the group with low physical fitness, only 25.6 % attended sports sections, and 44.2 % of adolescents were completely physically inactive. The level of homocysteine in the blood did not depend on the sex of adolescents and physical development. Moderate hyperhomocysteinemia was detected in 41 adolescents, 68.3 % of whom had poor and low exercise tolerance and/or low physical activity. Statistically significantly higher homocysteine levels were observed in children with low physical activity ($p<0.05$), those who did not have sports training ($p=0.027$) or had reduced adaptation to physical activity ($p<0.01$).

Conclusions. The level of homocysteine in the blood serum of adolescents did not depend on gender, physical development and the presence of somatic pathology. Low physical activity of adolescents is accompanied by increased levels of homocysteine in the blood. On the contrary, adolescents with high physical activity have lower levels. The lowest levels of homocysteine are observed in adolescents with good to excellent exercise tolerance. Unsatisfactory and weak Ruffier test results are associated with elevated homocysteine levels in adolescents.

Keywords: homocysteine, physical activity, children, adolescents, exercise tolerance, sport.

Introduction.

Interest in the study of the pathophysiological role of homocysteine in the human body has increased in recent years, due to the establishment of its association with chronic cardiovascular diseases. Homocysteine (HC) is a non-proteinogenic amino acid containing sulphur and is a homologue of cysteine. Homocysteine is not supplied by the diet and is predominantly synthesized in the methionine cycle (Kamat et al., 2016). Its concentration is regulated by two key pathways: remethylation back to methionine or transsulfuration to cysteine with the simultaneous formation of hydrogen sulfide (H_2S), which occurs with the participation of vitamins B6, B12 and folic acid. Their deficiency in the body may be one of the reasons for elevated homocysteine levels. The level of homocysteine is determined by various factors, including heredity, diet, lifestyle, medicines, etc.

Increased HC levels are considered a risk factor for cardiovascular disease (Chrysant & Chrysant, 2018). It causes damage to the vascular endothelium, promotes inflammation and endothelial dysfunction, which ultimately leads to heart and vascular disease (Balint et al., 2020). It has also been established that hyperhomocysteinemia is associated not only with the risk of atherosclerosis and cardiovascular disease, but also with various systemic and neurological diseases (Tawfik et al., 2020). And although clinical manifestations of cardiovascular disease are usually more common in adulthood, there is evidence that these diseases can begin in childhood and adolescence (Shi, et al., 2022).

To date, it remains controversial whether high HC concentrations are a risk factor or a risk marker (Ganguly & Alam, 2015; Fournier et al., 2015). A study by de Leite, Pitangueira, Damascena, & de Farias Costa (2021) showed that more than half of children with hereditary homocysteinemia died as a result of premature vascular events. It is suggested that hyperhomocysteinemia is a causative risk factor for cardiovascular disease in childhood (Shi et al., 2022).

There are a number of factors that influence HC concentrations: age, gender, heredity, and medicines. In addition, lifestyle factors, such as alcohol consumption, smoking, dietary habits, and physical activity, also influence HC levels (Joubert & Manore, 2006).

Over the course of a lifetime, blood levels of HC gradually increase. Evidence suggests that HC levels are higher in men than in women, and this gender effect is likely to be most pronounced during puberty. At the same time, in prepuberty, HC levels in boys and girls are approximately equal. It is believed that lower HC levels in women are due to digestive and hormonal characteristics (Kuo, et al., 2006), the gradual increase in HC levels with age is explained by a decrease in renal function, and higher homocysteine levels in men are due to greater muscle mass (Bates et al., 2002; van Beynum et al., 2005).

Regular exercise is known to affect all physiological systems of the body. Their benefits for health and prevention of cardiovascular and other chronic diseases are well documented in the literature (Heine et al., 2019; Bocharova et al., 2020; Solovyov et al., 2020; Pojednic et al., 2022). Physical activity has also been shown to be an important factor in reducing cardiovascular risks (Hamilton, 2018; Bratland-Sanda et al., 2022). However, it remains unclear how exercise or physical activity (PA) changes or influences HC concentrations (Fournier et al., 2015; Maroto-Sánchez, Lopez-Torres, Palacios, & González-Gross, 2016). Some studies have been devoted to the association of PA with HC levels (Bates et al., 2002; Choi et al., 2014; Costa, Kinra, D'Almeida, & Assis, 2018), but their results were contradictory, which is explained by different research methodologies, composition of observation groups and characteristics of physical activity.

Some researchers have demonstrated a decrease in HC concentrations immediately after a period of physical activity (Randeva et al., 2002; Choi et al., 2014). Others have associated high levels of PA and cardiorespiratory fitness with lower HC concentrations (Kuo et al., 2005; Ruiz et al., 2007). At the same time, some studies have shown higher HC concentrations after intense physical activity, training periods, or after certain sports competitions (König et al., 2003; Herrmann et al., 2003; Duncan et al., 2005).

The relationship between physical activity and HC levels in people of different ages is also controversial. Studies of the effect of low and high PA on serum HC levels in young (18-50 years) and elderly (>65 years) men and women have shown that HC levels are significantly associated with PA, age, and gender. Lower levels of HC have been demonstrated in patients with higher PA, regardless of the level of other factors that may affect HC, such as vitamin B12 (Alomari, Khabour, Gharaibeh, & Qhatan, 2016).

Most of the studies concerned groups of people with active or sedentary lifestyles, and in these groups, the acute effects had the same response of HC increase. The authors suggested that intense exercise accelerates protein catabolism and amino acid accumulation in the muscles (Sotgia et al., 2005). As a result, this can lead to increased intermediate metabolic catabolism and the formation of HC (Deminice, Vannucchi, Simões-Ambrosio, & Jordao, 2011). Thus, the results of these studies suggest that intense exercise usually causes an increase in HC immediately after training, regardless of its intensity, duration, and previous fitness level (Maroto-Sánchez et al., 2016).

Interestingly, Okura and colleagues found different responses to PA depending on the baseline HC status (Okura et al., 2006). An increase in HC was observed after training in those who had HC levels within the normal range at baseline. The opposite effect was observed in people with baseline hyperhomocysteinemia, in whom HC decreased after exercise.

Di Santolo, Banfi, Stel, & Cauci (2009) showed that recreational exercise does not reduce HC levels in young women, and the risk of hyperhomocysteinemia is significantly increased only in the presence of low folic acid levels.

Thus, despite the close attention paid to HC in recent years, the impact of physical activity on its level remains controversial. Meanwhile, in order to prevent the onset and development of cardiovascular disease in adulthood, it is important to identify risk factors for cardiovascular disease in childhood and adolescence.

*Objective***.** To determine the homocysteine content in children and adolescents with different levels of physical activity, to establish the relationship between homocysteine content, indicators of physical development, level of physical activity and tolerance to physical activity in adolescence.

Materials and methods of the study

Participants

The study included 83 children aged 11 to 17 years who agreed to participate in the study and were examined at the clinic of the State Institution «ICAHC NAMS» in 2021-2022. Exclusion criteria for the study were the presence of acute and chronic diseases in the acute stage; conditions requiring hormonal (corticosteroid, replacement), anti-inflammatory therapy.

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Committee on Bioethics and Deontology of the State Institution «ICAHC NAMS». Informed consent was obtained from parents of children aged 11-17 years and adolescents aged 14 years and older to participate in the study.

Research design

All the adolescents underwent clinical, instrumental and laboratory examinations, and were examined by a pediatrician and an endocrinologist, and the girls by a pediatric gynecologist.

The parameters of physical development - height, body weight and body mass index (BMI) and the main indicators of haemodynamics - heart rate, systolic and diastolic blood pressure - were assessed.

Physical activity tolerance was determined by the Ruffier test, which is used to determine the physical education group at school (as recommended by the Ministry of Health of Ukraine). Excellent, good, satisfactory (middle), weak, and unsatisfactory tolerance were distinguished (Rak, Yeshchenko, Kashina-Yarmak, & Muzhanovskyi, 2023). Since there were not enough excellent results for the Ruffier test (2 results), they were combined with the good options. Weak and unsatisfactory tolerance together indicate reduced adaptive capacity of children.

Physical activity (PA) of adolescents was assessed using a modified questionnaire that allows taking into account the presence and duration of activity during the week (Kowalski, Crocker, & Donen, 2004; Morozov & Budreyko, 2013). The child noted what types of activity (morning exercises, physical education classes at school, classes in sports sections, active sports games in the open air, and walking) they had every day of the week and how much time they spent on them. The total average score was calculated, on the basis of which children were divided into groups: children with low physical activity had up to 7 points; 7 to 8.9 points indicated middle physical activity; 9 points and above were children with high physical activity.

Depending on the availability of training in sports sections, children were also divided into groups: children who regularly attended sports sections three or more times a week over the past year; children who used to attend sports sections but did not do so over the past year; children who never attended sports sections.

Serum analysis

Blood was taken for the study of HC levels on an empty stomach, and in the group of sports-active adolescents - on a rest day after training.

HC was determined in blood serum by enzyme-linked immunosorbent assay (ELISA) using commercial kits (Axis-Shield, UK).

Statistical analysis

Statistical analysis of the data was performed using the SPSS 26.0 statistical software package. All data were subject to normal distribution. The mean value ± standard deviation/error of the mean (M (SD), M (m)) was used for the total assessment of quantitative variables. Nominal data were characterized by the number of observations (n) and frequency (%). A one-way ANOVA with three groups was used to compare data between groups. We included HC concentration as a continuous variable in general linear models with age, sex, and body mass index (BMI) as covariates to test the association with PA. The Bonferroni test was used for post hoc comparisons. The significance level was set at $p < 0.05$.

Research results

The general characteristics of the children who participated in the study are presented in Table 1. Boys and girls did not differ in age, although girls had significantly lower height and weight. Meanwhile, the groups did not differ significantly in terms of BMI.

It was found that 48.2% of adolescents had functional disorders of the gastrointestinal tract. Menstrual dysfunction was diagnosed in 12 girls (33.4%), and puberty (delayed or accelerated) in 4 boys. In isolated cases, gastroesophageal reflux disease (3), hypothalamic puberty syndrome (8), and cardiac rhythm disorders (3) were observed.

Almost half of the children who participated in the study had unsatisfactory and poor adaptation to physical activity and low PA without significant differences by gender (Table 1).

A detailed analysis of the groups showed that in the group with high physical activity, the vast majority of adolescents (81.0%) regularly attended sports sections and had normal physical development indicators (76.2%). In the group with medium physical activity, one in three adolescents had regular sports training at the time of the study and one in three had been involved in sports before, and two thirds of the children (60.0%) in the group had indicators of harmonious physical development.

Table 1. General characteristics of children depending on gender

Indicator	Total	Boys	Girls	
	n=83	n=47	n=36	p
Homocysteine (μmol/l), M (m)	15,65 (6,82)	15,72 (6,83)	15,56 (6,91)	0,92
Age (Years), M (SD)	14,69 (1,85)	14,63 (1,68)	14,77 (2,07)	0,74
Height (sm), M (SD)	167,49 (11,61)	171,97 (11,02)	161,60 (9,67)	0,000
Weight (kg), M (SD)	57,23 (13,78)	60,63 (14,84)	52,98 (11,08)	0,013
BMI, M (SD)	20,23 (3,16)	20,29 (3,35)	20,16 (2,94)	0,86
< 5 ‰, n (%)	4 (4,8)	1 (2,1)	3 (8,3)	
≥5-85 ‰, n (%)	64 (77,1)	35 (74,5)	29 (80,6)	
>85-≤95‰, n (%)	12 (14,5,)	8 (17,0)	4 (11,1)	
>95 ‰, n (%)	3 (3,6)	3 (6,4)	0 (0)	
Tolerance to physical activity				
Unsatisfactory and weak, n (%)	38 (45,8)	20 (42,6)	18 (50,0)	
Satisfactory, n (%)	28 (33,7)	17 (36,2)	11(30,6)	
Good or excellent, n (%)	17 (20,5)	10 (21,3)	7 (19,4)	
PA				
Low, n (%)	43 (51,8)	24 (51,1)	19 (52,8)	
Middle, n (%)	12 (14,5)	7 (14,8)	5 (13,9)	
High, n (%)	28 (33,7)	16 (34,1)	12 (33,3)	
Sports sections				
On a regular basis, n (%)	38 (45,8)	25 (53,2)	13 (36,1)	
did not attend, n (%)	26 (31,3)	14 (29,8)	12 (33,3)	
ever visited, n (%)	19 (22,9)	8 (17,0)	11 (30,6)	

40.0% of adolescents in this group did not have any sports training, neither amateur nor of their own free will, but achieved sufficient (moderate) physical activity during the week. In the low PA group, only a quarter (25.6%) attended sports sections, 30% had attended sports sections in the past, and 44.2% were completely physically inactive (Figure 1.).

Serum HC levels did not depend on the sex of adolescents (Table 1). Moderate hyperhomocysteinemia (over 15 μmol/l) was present in 41 adolescents (23 boys and 18 girls). It should be noted that most of these children had poor and weak adaptation to physical activity and/or low physical activity (68.3%). Interestingly, there were no adolescents with good or excellent adaptation among children with hyperhomocysteinemia, and only 5 people (12.2%) had high PA. No specific patterns were found between the level of HC and the presence of pathology in adolescents.

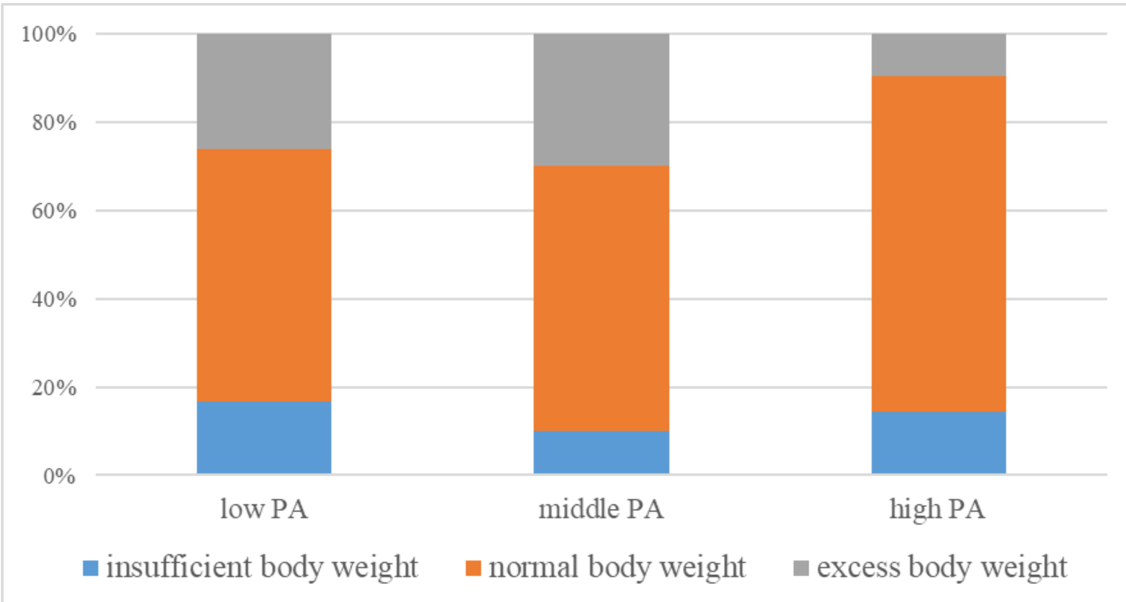


Figure 1. Distribution of children with different physical activity by body weight

The study showed that the level of HC in children depended on the adaptation of the cardiovascular system to physical activity. The lowest levels of HC were observed in children with good and excellent adaptation ($p<0.05$, Table 2), regardless of gender (Figure 2). The level of HC in adolescents with reduced physical activity tolerance significantly exceeded their indicators ($p<0.01$) and was slightly higher on average ($p=0.065$) than in adolescents with satisfactory adaptation.

Table 2. Homocysteine level in children's blood depending on physical activity tolerance

Indicator	Good and Excellent (n=14)	Satisfactory (n=30)	Unsatisfactory and week, (n=36)	p
Homocysteine, (µmol/l), M (m)	7,46 (1,55)	16,81 (1,11)[1]	17,97 (0,96)[1]	0,000

Note. [1]- significance of differences in relation to the group of children with good adaptation

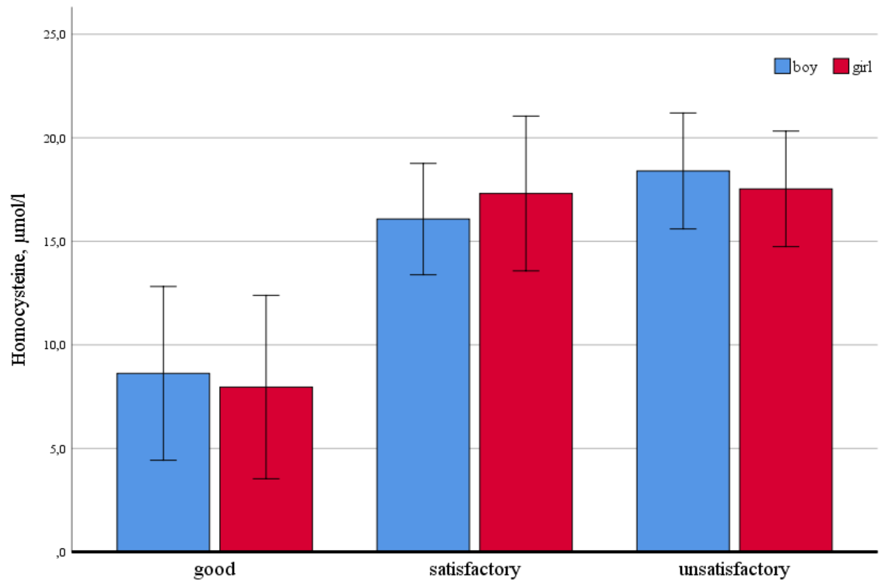


Figure 2. Homocysteine levels in boys and girls depending on exercise tolerance (M±m)

Analysis of serum HC levels in relation to PA levels in adolescents showed that HC levels were significantly lower in children who regularly participated in sports sections compared with children who did not train and did not differ from children who had previously had sports training (Table 3).

Table 3. Homocysteine levels in children's blood depending on the regularity of attendance at sports sections (µmol/l), M (m)

Indicator	Regular attendance, (n=38)	Previously attended, (n=19)	Did not attend (n=26)	p
Homocysteine, (µmol/l), M (m)	13,72 (1,16)	14,50 (1,61)	18,38 (1,32)[1]	0,027

Note. [1] – significance of differences in relation to children who regularly attended sports sections, p=0,01

In children who did not attend sports sections at all, the level of HC tended to increase relative to their peers who stopped training regularly (p=0.065). There were no significant differences in the level of HC by gender in these groups of children (Figure 3).

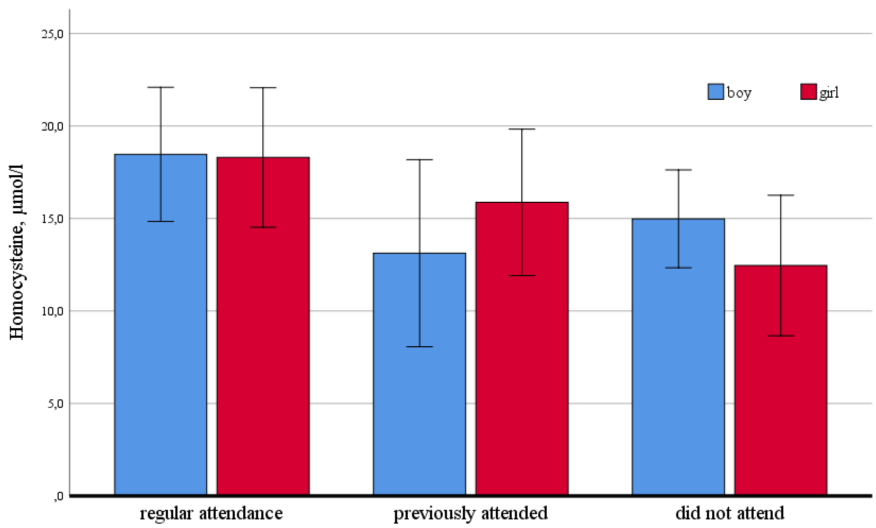


Figure 3. Homocysteine levels in boys and girls depending on the regularity of attendance at sports sections, (M±m)

The level of HC also depended on adolescents' total PA and was significantly lower in children with high PA compared to children with moderate and low activity (Table 4). These changes were similar in girls and boys with no significant differences by sex (Figure 4).

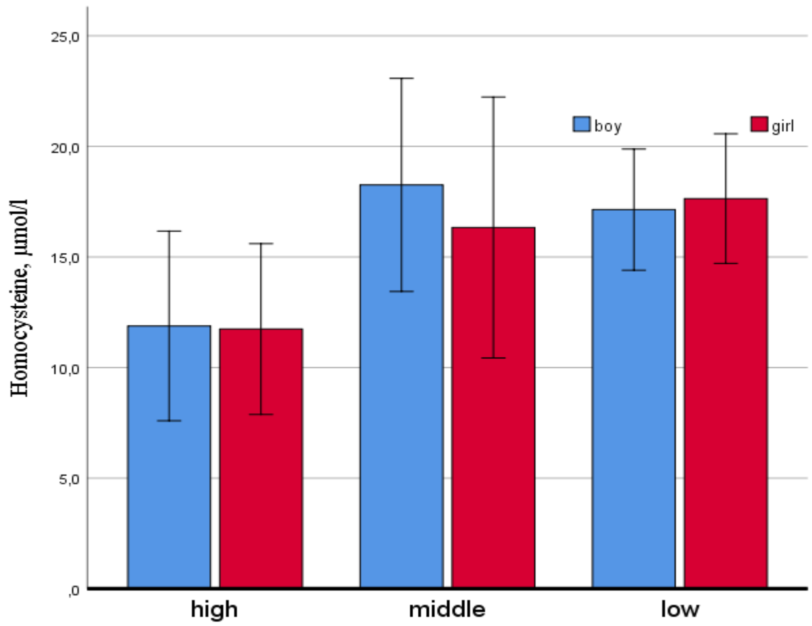
Table 4. Homocysteine levels in children's blood depending on physical activity

Indicator	High PA, (n=24)	Middle PA, (n=17)	Low PA, (n=42)	p
Homocysteine (µmol/l), M (m)	11,30 (1,39)	17,17 (1,71)[1]	17,27 (1,0)[1]	0,001

[1] - *significance of differences in relation to children with high physical activity p<0,009*

Discussion.

Our cross-sectional study has several limitations, as it did not include the study of adolescent eating behavior and potential factors that may influence HC levels, such as vitamins B12 and folic acid. The aim of our study was to establish the association of HC levels with exercise tolerance and PA in adolescents during puberty. Our findings are in line with current knowledge about the association of HC levels with PA (Choi et al., 2014; Fournier et al., 2015; Maroto-Sánchez et al., 2016; Costaet al., 2018). We did not find a significant difference in HC content depending on physical development and gender, unlike some studies (Kuo et al., 2006). Meanwhile, we did not find any information in the literature on the relationship between HC levels and puberty in adolescents. At the same time, it is known that puberty is a critical period of immune and hormonal restructuring of the child's body and affects all human systems (Shliakhova & Plekhova, 2014). Thus, this issue is promising for further research.



Picture 4. Homocysteine levels in boys and girls depending on physical activity, (M±m)

Based on a comprehensive clinical examination, it was found that half of the subjects had somatic pathology of a predominantly functional nature. There were no significant differences in the level of HC depending on the clinical diagnosis.

The analysis of serum HC levels in relation to PA levels showed that they were significantly lower in children who had regular training in a sports club or had recently stopped training. Children who did not attend sports sections at all had significantly higher levels of HC. It can be said that regular sports activities at least three times a week, together with the activation of metabolic processes, lead to a decrease in blood HC levels. Thus, our findings are consistent with those reported in the literature on the positive effect of physical activity on HC levels (Choi et al., 2014; Costa et al., 2018).

In the literature available to us, we did not find any studies that investigated the relationship between HC and exercise tolerance. Our studies have shown that the level of HC in adolescents differed depending on the adaptive capacity of their cardiovascular system. Children with reduced exercise tolerance (poor and weak results) had significantly higher HC levels than those with good and excellent tolerance. In our future studies, we plan to analyze the relationship between cardiovascular parameters and HC content.

The high proportion of children with low PA and reduced exercise tolerance is worrying. Presumably, one possible explanation could be the rather low PA of children during the quarantine restrictions caused by the Covid-19 lockdown (Rak, Kashina-Yarmak & Yeshchenko, 2023). In addition, there is insufficient attention from parents and society in engaging adolescents in active sports. Therefore, this issue requires more careful attention from the family and the state.

Conclusion

The level of homocysteine in the blood serum of adolescents did not depend on gender, physical development and the presence of somatic pathology.

Low physical activity of adolescents is accompanied by increased levels of homocysteine in the blood. Adolescents with high physical activity, on the contrary, have lower levels.

The lowest levels of homocysteine are observed in adolescents with good to excellent exercise tolerance. Unsatisfactory and weak Ruffier test results are associated with elevated homocysteine levels in adolescents.

Authors Contributions

Conceptualization, N.S and L.R; methodology, N.S and L.R; software, N.S; check, N.S and L.R; formal analysis, V.M; investigation, N.S, L.R and V.M; resources, N.S, L.R and V.M; data curation,V.M; writing - rough preparation, N.S and L.R; writing - review and editing, N.S and L.R; visualization, N.S and L.R; supervision, L.R; project administration, N.S and L.R. All authors have read and agreed with the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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