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Health-related quality of life and physical activity in Ukrainian pediatric patients with heterozygous familial hypercholesterolemia

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Introduction. Familial hypercholesterolemia (FH) is a genetically determined disease characterized by elevated low-density lipoprotein levels since birth and predisposes a person to develop atherosclerosis-induced cardiovascular disease. Healthcare providers should monitor the health status and physical activity level in pediatric patients with FH, as a high-risk group for cardiovascular disease.

Purpose — to investigate the self-reported health-related quality of life (HRQoL) and physical activity energy expenditure based on the questionnaire data (PAEEq) in children with heterozygous FH compared with healthy peers to assess the health status.

Materials and methods. The HRQoL scores were assessed using the KINDL^R questionnaire in 15 patients with FH and 21 healthy peers. The physical activity level was evaluated using the C(Y)PAQ questionnaire. The KINDL^R data together with other variables such as age, weight, height, sex, BMI and the PAEEq scores were analyzed in SAS® OnDemand for Academics.

Results. HRQoL scores in FH children were similar to those of the control group ($p>0.05$). There was no association between PAEEq and the HRQoL scores in the FH ($r=0.37$, $p=0.29$) and the control group ($r=0.43$, $p=0.20$). The KINDL^R Physical well-being score in the 5–9 years age group was significantly higher for FH children than for controls ($p<0.01$), while the total HRQoL score was not significantly different between FH children and controls. The group of FH children aged 5–9 with an intermediate level of PAEEq was the most physically active among the surveyed children. The controls aged 15–18 with low levels of PAEEq was the least active. All other age groups were characterized by a low intermediate level of PAEEq.

Conclusions. Children with FH have HRQoL scores that are comparable to those of healthy peers. The FH and control groups were relatively satisfied with their quality of life. Thus, FH children consider themselves to be healthy, and from this underestimation of their cardiovascular risk they may have low adherence. Most FH children were found to have the low intermediate levels of PAEEq, which may indicate a lack of exercise and poor quality of life later on. Children with FH may have significant health problems in adulthood if they are not treated early and appropriately. In a similar manner, low PAEEq levels were demonstrated by the controls, so they should be also informed about the significance of regular physical activity and properly motivated.

The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the participating institution. The informed consent of the patients was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: children, familial hypercholesterolemia, dyslipidemia, health, health-related quality of life, physical activity.

Якість життя, пов'язана зі здоров'ям, та фізична активність в українських педіатричних пацієнтів із гетерозиготною сімейною гіперхолестеринемією

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Актуальність. Сімейна гіперхолестеринемія (СГ) — генетично детерміноване захворювання, що характеризується підвищеним рівнем ліпопротеїнів низької щільності від народження та схильністю до розвитку серцево-судинних захворювань, спричинених атеросклерозом. Медичні працівники повинні здійснювати моніторинг стану здоров'я та рівня фізичної активності в пацієнтів дитячого віку з СГ, як групи високого ризику розвитку серцево-судинних захворювань.

Мета — дослідити якість життя (ЯЖ), пов'язану зі здоров'ям, та енерговитрати на фізичну активність (ЕФА) у дітей з гетерозиготною формою СГ порівняно зі здоровими однолітками для оцінки стану здоров'я.

Матеріали та методи. Показники ЯЖ оцінено за допомогою опитувальника «KINDL»^{R} у 15 пацієнтів з СГ та 21 здорового однолітка. Рівень фізичної активності оцінено за допомогою опитувальника «C(Y)PAQ». Дані KINDL^R разом з іншими змінними, такими як вік, маса тіла, зріст, стать, індекс маси тіла та ЕФА, проаналізовано в SAS® OnDemand for Academics.

Результати. Показники ЯЖ у дітей з СГ майже не відрізнялися від показників контрольної групи ($p>0,05$). Не виявлено зв'язку між ЕФА та показниками ЯЖ у дітей з СГ ($r=0,37$, $p=0,29$) і в контрольній групі ($r=0,43$, $p=0,20$). Оцінка фізичного благополуччя за KINDL^R у віковій групі 5–9 років була достовірно вищою в дітей з СГ, ніж у контрольній групі ($p<0,01$), тоді як сумарна оцінка ЯЖ не мала достовірної різниці між групами дітей з СГ і здорових однолітків. Група дітей з СГ віком 5–9 років із середнім рівнем ЕФА була найбільш фізично активною серед обстежених дітей. Найменш активною була контрольна група віком 15–18 років із низьким рівнем ЕФА.

Висновки. У дітей з СГ показники ЯЖ не відрізняються від показників здорових однолітків. Діти з СГ і контрольна група відносно задоволені своєю ЯЖ. Отже, діти з СГ вважають себе здоровими, і через цю недооцінку власного серцево-судинного ризику в них може бути низький комплаєнс. У більшості пацієнтів відмічається середньо-низький рівень ЕФА, що може свідчити про недостатню фізичну активність та низьку ЯЖ в подальшому. Діти з СГ можуть мати значні проблеми зі здоров'ям у дорослому віці, якщо не отримають своєчасної та адекватної медичної підтримки. Аналогічно низькі рівні фізичної активності спостерігаються в контрольній групі, тому цих дітей також слід інформувати про важливість регулярної фізичної активності та належним чином мотивувати.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду пацієнтів.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: діти, сімейна гіперхолестеринемія, дисліпідемія, здоров'я, якість життя, пов'язана зі здоров'ям, фізична активність.

Introduction

Familial hypercholesterolemia (FH) is a genetically determined disease characterized by elevated low-density lipoprotein (LDL) levels since birth and predisposes a person to developing atherosclerosis-induced cardiovascular disease [24]. Healthcare providers should monitor the health status and physical activity level in pediatric patients with FH, as a high-risk group for cardiovascular disease, to implement a full spectrum of prompt preventive and curative medical interventions [20].

Health-related quality of life (HRQoL) is a multifactorial concept that can be used as patient-reported data to document patients' perspectives on their health and well-being [21]. HRQoL indices encompass physical, social and psychosocial aspects of a child's health, as well as the ability to participate fully in age-appropriate activities [18]. To design effective prevention programs for children, factors affecting the HRQoL must be identified [11]. These factors can then be used to promote positive physical and psychosocial health in the long term.

The World Health Organization (WHO) global status report on physical activity 2022 [1] documented that children and young adults are poorly involved in their own physical health care. According to the report, 81% of children aged 11–17 do not meet the levels of physical activity needed to maintain good health and well-being. The report findings highlight the important role played in clinical settings by pediatricians, primary care physicians and other health professionals in increasing opportunities for participation in physical activity among children and their families, especially those with disabilities and chronic illnesses, in view of the significant positive impact on their physical and mental health. Particular emphasis is placed on the importance of working with young and pre-school children to reinforce healthy behaviour that determines later well-being in adulthood.

The purpose of the study — to examine the self-reported HRQoL and physical activity energy expenditure based on the questionnaire data (PAEEq) in children with heterozygous FH compared with healthy peers to assess their health status.

Materials and methods of the research

A retrospective study was conducted of pediatric patients from all regions of Ukraine who were seen in the Department of Cardiology at Kyiv City Children's Clinical Hospital No.1.

Inclusion criteria for the study were: a confirmed diagnosis of FH for at least 6 months, age between 5 and 18 years, adherence to prescribed antilipid therapy and an appropriate diet (CHILD-1), signed informed consent by a child and parent(s) (or legal guardian(s)).

Exclusion criteria were withdrawal of informed consent, age less than 5 years, interruption of antilipid therapy >1 month, presence of an confirmed disease or condition other than FH that causes lipid metabolism disorders (diabetes mellitus, hypothyroidism, nephrotic syndrome, chronic kidney disease, primary cholangitis, obstructive jaundice, obesity, Cushing's syndrome, pheochromocytoma etc.); intake of medications that cause lipid metabolism disorders (amiodarone, thiazide diuretics, beta-blockers, glucocorticoids, estrogens, androgens, immunosuppressants, anticancer agents, antipsychotics, HIV-1 protease inhibitors, anticonvulsants, retinoids, growth hormones and others).

118 children were assessed between January and December 2021. 15 of these met the inclusion criteria and agreed to participate in the study, with informed consent given by both the children and their parent(s) (or legal guardian(s)). The following age groups were identified according to WHO guidelines: 5 to 9 years, 10 to 14 years, and 15 to 18 years.

Pediatric patients with FH were included in the FH group (hereinafter referred to as «FH children») (n=15). The Dutch Lipid Clinic Network criteria were used to establish the diagnosis of familial hypercholesterolemia [20]. FH children were mostly in the age range 5–17 years (53.4% girls and 46.6% boys). Each age group consisted of 5 subjects.

The control group consisted of healthy peers in the age range 6–17 years (hereinafter referred to as «Controls») (n=21, 47.7% girls and 52.3% boys). Each age group consisted of 7 subjects. The groups were representative of age and sex.

The auxological parameters (body weight, height, body mass index (BMI)) in the surveyed children were obtained by routine anthropometry.

The KINDL^R questionnaire [19] and the Child/Youth Physical Activity Questionnaire (C(Y)PAQ) [4] were used to establish quality-of-life and physical activity levels, respectively. The interview was conducted with parents present as it was requested by all patients. The KINDL^R is a compre-

hensive tool for assessing health-related quality of life in children and young people aged 3 years and over. The KINDL^R consists of 24 Likert scale items related to six modules: physical well-being, emotional well-being, self-esteem, family, friends and daily activities (school or kindergarten). The subscales of these six modules were combined to produce an overall score. Participants answered questions on a 5-point Likert scale (0 = never, 1 = rarely, 2 = sometimes, 3 = often and 4 = always). All subscales were then converted into scores from 0 to 100, where higher scores corresponded to a better quality-of-life index. Age-specific versions take into account the changes in the quality-of-life dimensions in the course of child development.

The Child Physical Activity Questionnaire (CPAQ) was administered to the youngest group (ages 5–9) and completed with partial parental help. The CPAQ questionnaire assesses the type, frequency and duration of physical activity and sedentary behaviour over the past 7 days. The Youth Physical Activity Questionnaire (YPAQ) was used among older children (10–14 years and 15–18 years). This tool allows to determine the frequency and duration of 47 different activities on both weekdays and weekends during the past week. As such, the YPAQ assesses the mode, frequency and duration of physical activity and sedentary behaviour across all parameters, including school hours and free time over the past 7 days. Estimates of energy expenditure for physical activity were derived from the CPAQ and YPAQ questionnaires. The calculation was based on the formula [4] used to estimate daily PAEEq, according to accepted metabolic equivalent of task (MET) values [6]. PAEEq levels were assessed according to the Sesso classification [22] as follows:

- Low: <2,100 kilojoules per week (kJ/wk)
- Low intermediate: 2,100–4,199 kJ/wk
- Intermediate: 4,200–8,399 kJ/wk
- Upper intermediate: 8,400–12,599 kJ/wk
- High: ⩾12,600 kJ/wk

The study was conducted in accordance with the Helsinki Declaration of Human Rights and the Council of Europe Convention on Human Rights and Biomedicine.

Statistical analysis. The KINDL^R data were analyzed in IBM® SPSS® Statistics (IBM Corp, New York, USA). The HRQoL scores together with other variables such as weight (kg), height (cm), sex, BMI and PAAEq levels were evaluated in SAS® OnDemand for Academics (SAS Institute Inc, North Carolina, USA) and described in terms of mean and standard deviation. Data were assumed to be normally distributed (verified analytically by Shapiro–Wilk and graphically by Q-Q plot).

Continuous variables with a normal distribution were indicated as a mean with standard deviation, and a t-test and a one-way analysis of variance (ANOVA) were used to compare the FH and control groups. The Pearson correlation test was used to search for possible associations between PAEEq, age, weight, BMI or sex variables with total quality-of-life score. Statistical significance was set at $p \leqslant 0.05$.

Results of the research

The Pearson correlation test found that there were no significant correlations between age and quality-of-life scores in patients and controls. A single-factor analysis of variance (ANOVA) revealed no statistically significant difference in quality-of-life scores between the age groups 5–9 years, 10–14 years and 15–18 years in FH children ($F=2.77$, $p=0.130$).

The total quality-of-life score for the 5–9-year-old FH group was virtually the same as the control group of the same age (67.71±6.83 vs 66.67±1.65, respectively; $t=0.48$, $p=0.23$, 95% confidence interval (CI) (-11.89; 15.54)). There was also no significant difference between FH children and healthy peers in the 10–14 years age group (58.33±1.04 vs 60.16±9.25; ($t=0.39$, $p=0.62$, 95% CI (-12.30; 16.41)) and in the 15–18 years age group (69.80±8.38 vs 73.54±14.76; $t=0.45$, $p=0.66$, 95% CI (-15.97; 23.46)).

A Pearson correlation test in the FH ($r=0.37$, $p=0.29$) and the control group ($r=0.43$, $p=0.20$) showed no such association between PAEEq and total quality-of-life score in the surveyed children. No statistically significant relationship was found between the variables weight, BMI, sex and PAEEq in the FH group and their control group counterparts.

The KINDL^R questionnaire data analysis (Table 1) showed that FH children in the 5–9 years age group had a significantly higher Physical well-being score than the control group of the same age ($p<0.01$), while the total score for quality of life was not significantly different.

The Self-esteem score in the 10–14 years age group was significantly lower in healthy children than in the FH group ($p<0.01$). There was also a decreasing trend in the Everyday functioning score in FH children of the same age ($p=0.07$).

Table 1

HRQoL data according to the KINDL^R questionnaire results in the surveyed children

Parameters	FH children		Controls		p-value
	Mean	±SD	Mean	±SD	
The 5–9 years age group					
Total quality-of-life score	67.71	6.83	66.67	1.65	0.90
Physical well-being	77.08	3.61	43.75	4.00	<0.01
Emotional well-being	62.50	25.00	50.00	12.74	0.70
Self-esteem	75.00	16.54	43.75	3.19	0.24
Family	62.50	16.54	87.50	6.64	0.32
Friends	79.17	21.95	50.00	21.24	0.36
Everyday Functioning	77.08	21.95	62.50	7.75	0.62
«Disease» Module	58.33	22.04	83.33	13.41	0.42
The 10–14 years age group					
Total quality-of-life score	58.33	1.04	60.16	9.25	0.72
Physical well-being	54.17	28.18	54.69	16.44	0.97
Emotional well-being	50.00	12.50	59.38	14.88	0.42
Self-esteem	83.33	13.01	51.56	7.86	<0.01
Family	68.75	10.83	67.19	16.44	0.89
Friends	52.08	3.61	64.06	16.44	0.27
Everyday Functioning	41.67	19.09	64.06	5.98	0.07
«Disease» Module	93.05	8.67	67.71	29.34	0.21
The 15–18 years age group					
Total quality-of-life score	69.80	8.38	73.54	14.76	0.66
Physical well-being	78.13	10.83	81.25	15.31	0.74
Emotional well-being	71.88	20.73	72.50	22.79	0.96
Self-esteem	70.31	16.44	68.75	19.26	0.90
Family	79.69	5.98	82.50	12.02	0.68
Friends	62.50	18.40	72.50	22.79	0.50
Everyday Functioning	56.25	8.84	63.75	28.09	0.62
«Disease» Module	71.88	28.34	86.67	17.28	0.36

Notes: statistically significant difference is highlighted in **bold**; M — mean values; SD — standard deviation.

Table 2

Daily physical activity energy expenditure based on the C(Y)PAQ questionnaire results (PAEEq) in the surveyed children, M±SD

Age groups	FH children		Controls		p-value
	Mean	±SD	Mean	±SD	
5–9 years age group	786.89	267.10	310.76	251.87	0.26
10–14 years age group	356.27	118.63	342.31	143.39	0.89
15–18 years age group	303.98	93.85	264.71	187.56	0.71

Note: M±SD* — mean values ± standard deviation.

There was no discernable difference in measures of subjective quality of life between FH children and controls in the 15–18 years age group.

Table 2 shows the daily PAEEq data. No statistically significant difference in PAEEq was found in FH children and controls.

We also estimated the weekly PAEEq using a simple calculation (Table 3). Thus, it can be concluded that the FH group aged 5–9 years with an intermediate level of PAEEq was the most physically active among the surveyed children (Fig.). The controls aged 15–18 with low levels of PAEEq was the least active. All other age groups were characterized by a low intermediate level of PAEEq.

Discussion

A diagnosis of FH, in addition to being associated with a very high risk of cardiovascular events such as cerebral apoplexy or acute coronary syndrome, can stimulate the adoption of unhealthy coping mechanisms out of a sense of despair facing the serious chronic condition-such lifestyle changes as overeating, smoking, excessive alcohol consumption, neglect of physical activity, passive participation in rehabilitation and low adherence [3].

There was no statistically significant difference in quality-of-life scores between the age groups in FH children, thus all age groups of FH children

Table 3

Estimated weekly PAEEq in kJ/wk (daily PAEEq x 7) in the surveyed children

Age groups	FH children	Controls
5–9 years age group	5,508.23	2,175.32
10–14 years age group	2,493.89	2,396.17
15–18 years age group	2,127.86	1,852.97

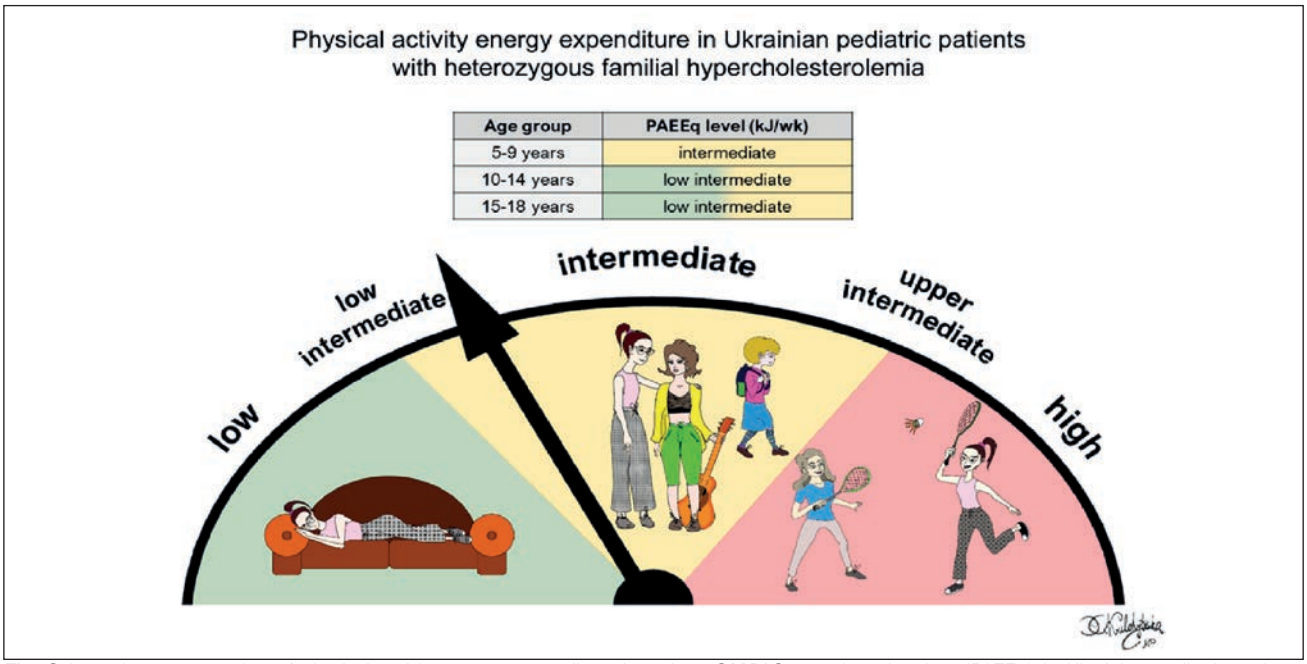

Fig. Schematic representation of physical activity energy expenditure based on C(Y)PAQ questionnaire data (PAEEq) in Ukrainian pediatric patients with heterozygous familial hypercholesterolemia

were generally equally satisfied with their quality of life. We also determined that children with FH, regardless of age, scored similarly to healthy peers on measures of quality-of-life. This result can be interpreted that the level of medical care they receive has improved over time, resulting in a reduction in the severity of their disease and alleviation of its burden. However, the literature suggests that most children with FH may not regard themselves as «patients» and underestimate the risks associated with the disease. Data from L.E. Akioyamen (2018) revealed that pediatric patients with FH showed generally lower anxiety scores and better mental quality of life than children without the disease. However, patients with FH may perceive their risk of cardiovascular disease as «controlled», which in turn may contribute to the underestimation of their cardiovascular risk, although this improves mental well-being [2]. In the study conducted by J. Mulder (2022), 75% of the patients with homozygous FH were found to be unable to describe themselves as «ill» [14]. The Mortensen study estimated that patients with FH before the onset of cardiovascular disease generally consider themselves to be healthy and view FH as a controllable condition with no significant impact on their quality of life [13].

In our study, we focused on children's perceptions of their quality of life and tried to remove as much parental influence from the assessment as possible (with the exception of 5–6-year-olds who completed the Kiddy-KINDL^R form with partial parental help). It should be noted that statistically significant differences in quality-of-life scores were observed in the 5–9 years and 10–14 years age groups — those groups that are more dependent on parents than young adults (15–18 years age group). Thus, for example, in the 5–9 years age group, FH children rated their physical well-being significantly higher than controls. Considering the average age of cardiovascular disease onset in patients with FH is 44 years [10], FH patients of primary school age without any symptoms of cardiovascular disease are not limited by their physical condition and cannot realize the consequences of the disease, and therefore do not comprehend its burden.

With regard to self-esteem, the M. Pinquart meta-analysis [18] found that children with a chronic illness have lower self-esteem than their

healthy peers, with parents' reports of their children's self-esteem being less positive than those of the children themselves. In our sample, the self-esteem of FH children aged 10–14 years was significantly higher than that of controls. This index may well be very fluctuating in healthy children in puberty who do not receive as much constant attention and care as unhealthy children with a potentially disabling illness may receive. Further research is recommended to focus on healthy children with low self-esteem.

No relationship was found between PAEEq and quality-of-life scores in the FH and control groups. Based on A.M. Marker's meta-analysis [12], there was a weak positive correlation between physical activity and better quality of life in healthy children and adolescents, although the magnitude of these effects did not present a minimal clinically significant difference in most studies.

There is little evidence in the available literature about the impact on a child's psychological well-being if one of their parents or siblings has suffered a major adverse cardiovascular event ascribed to FH. For example, Hollman points out that surviving cardiovascular disease or the death of family members had a lasting negative impact on patients with FH [7].

Parents are the primary decision-makers about their child's health until the children reach adulthood. P. Ge (2022) [5] has demonstrated that parents' perception of the severity of their child's condition and their self-reported ability to follow treatment regimen for the condition may affect whether or not children comply with the treatment. Ge concludes that there is a need to focus on improving the self-efficacy (or the ability to follow treatment regimen) in parents.

F.J. Kinnear (2019) [8] reports that parents of children with FH express high concern for their children's well-being and this parental responsibility has been identified as another factor contributing to high compliance with recommended preventive and treatment interventions. Therefore, the early years of adulthood present a challenge to maintaining compliance as young people move from being cared for by their parents to taking responsibility for their own treatment.

In addition to the disability stigma experienced by parents with FH themselves, other family members without FH may experience affiliated stigma, which can then influence the FH child's perception of his or her illness in one particular way or another. In general, all surveyed FH children expressed the belief that they kept their disease under control, with one of the highest «Disease module» scores (93.05±8.67) being observed in the FH group aged 10–14 years.

A parent-independent understanding of the illness and the ability to make independent choices and influence the treatment outcome with comprehensive information support from the healthcare provider are essential components of FH treatment. We are convinced of this by several examples from our practice, which unfortunately are far from isolated. In one such case, a mother of two children with FH who already had two valve replacements refused to take statins because «it doesn't help her». The attitude toward treatment in her children was similar — they refused to receive treatment.

To prevent early vascular ageing (EVA) [9], which is accelerated in patients with FH due to early exposure to high cholesterol levels, some level of physical activity should be maintained. There was no statistically significant association between the variables weight, BMI, gender and PAEEq in either the FH or control group in the population we examined.

Physical activity has a huge impact on physical and mental health, particularly in children with cardiovascular disorders [16]. All surveyed children showed in general the low intermediate level of PAEEq, despite the fact that respondents were asked to imagine what they would do if there were no current restrictions due to the COVID-19 pandemic, which in turn has led to reduced levels of physical activity among children and adolescents worldwide [23].

The patients aged 5–9 years with an intermediate level of PAEEq was the most physically active among the surveyed children. The controls aged 15–18 years with low levels of PAEEq was the least active. All other age groups were characterized by a low intermediate level of PAEEq. In the population we studied, there is an age-related decrease in physical activity, which is fully consistent with the literature over the past few decades [15]. There was no difference in PAEEq between FH children and healthy peers, representing the current trend towards sedentary lifestyles even in the pediatric population.

Conclusions

In summary, the overall quality-of-life scores of FH children and healthy peers did not differ from each other ($p>0.05$). The FH group and healthy

peers according to the KINDL[R] questionnaire results were relatively satisfied with their quality of life. The FH children considered themselves to be healthy or mostly healthy, and from this underestimation of their condition and cardiovascular risk they may develop low adherence with recommended preventive and therapeutic measures. As a result, children with FH can experience serious health problems in later life, so healthy behaviour development, patient and parent education and awareness are a key part of working with these patients.

According to the C(Y)PAQ questionnaire results, FH children had generally low PAEEq, which may have a negative impact on their physical and psychological well-being, both now and in later life.

The control group also had low PAEEq, indicating a lack of awareness among the pediatric population about the benefits of regular physical activity and the need for motivational building in all pediatrics populations.

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