ОГЛЯД ЛІТЕРАТУРИ

UDC 616-056.52-053.2:616.71-007.234
DOI https://doi.org/10.32782/2226-2008-2024-6-10

N. I. Hnida https://orcid.org/0000-0001-6055-1611

CHILDHOOD OBESITY AND OSTEOPOROSIS

Odesa National Medical University, Odesa, Ukraine

UDC 616-056.52-053.2:616.71-007.234

N. I. Hnida
CHILDHOOD OBESITY AND OSTEOPOROSIS
Odesa National Medical University, Odesa, Ukraine
Introduction. Sufficient accumulation of bone tissue is extremely important for the growth and development of the child's body. Among the factors that can adversely affect this process, deviations from normal body weight cause the greatest concern today due to the significant increase around the globe.

The purpose of the present review article is to analyze current research on the relationship between obesity in children and the development of osteoporosis.

Material and methods. The narrative literature review was conducted using data published in the PubMed database in 2022–2024, as well as by manually searching the reference lists for relevant studies. The search query included a combination of words such as child, obesity, osteoporosis. In total, 58 studies were identified following the results of the literature search. The final number from 30 sources was included in this review.

Results and discussion. Studies conducted on sufficiently large samples indicate that the real impact of obesity on bone mass in children can be determined primarily by its degree. An increase in body mass index (BMI) can indeed be directly related to an increase in bone mineral density (BMD), but up to a certain BMI value. Further, the dependence of BMD on BMI can become either zero, or the reverse.

In addition, the real impact of obesity on bone mass in children is also determined by the presence or absence of a concomitant metabolic syndrome. Many modern studies indicate that it is the presence of metabolic syndrome in overweight and obese children that adversely affects BMD.

The negative impact of metabolically unhealthy obesity on BMD may be mediated by a deficiency of important micronutrients in the child's body, primarily vitamin D, the metabolism of which in obesity can be significantly impaired.

Conclusion. Measures to normalize body weight are necessary already in childhood. Among other things, they will prevent osteoporosis in the future. It is necessary not only to correct the nutritional status but also to use special sets of exercises for overweight and obese children and adolescents.

Key words: child, obesity, osteoporosis, metabolic syndrome.

УДК 616-056.52-053.2:616.71-007.234

Н. І. Гніда
ОЖИРІННЯ В ДИТИНСТВІ Й ОСТЕОПОРОЗ
Одеський національний медичний університет, Одеса, Україна
Наративний огляд літератури проводився з використанням даних, опублікованих у наукометричній базі PubMed у 2022–2024 роках, а також шляхом ручного пошуку за списками літератури відповідних досліджень. Аналіз показав, що ожиріння у дітей і підлітків частіше сприяє збільшенню, ніж зниженню мінеральної щільності кісткової тканини (МЩКТ). Але існує певний рівень насиченості індексу маси тіла (ІМТ), після якого пряма залежність МЩКТ від ІМТ може стати зворотною. Крім того, у разі метаболічно нездорового типу ожиріння ця залежність також частіше зворотна. Це призводить до підвищеного ризику остеопенії та остеопорозу, як у дитинстві, так і пізніше в дорослому віці. Тому заходи щодо нормалізації маси тіла необхідні вже в дитячому віці і служать у тому числі профілактикою остеопорозу в майбутньому.

Ключові слова: дитина, ожиріння, остеопороз, метаболічний синдром.

Introduction. Bone growth is not only a critical process for body development and growth [1]. Childhood is a unique time during which individuals accrue bone rapidly, and peak bone mass is achieved early in the third decade of life [2]. Hardness and rigidity are key bone structural attributes that determine specific properties of this organ [1]. Therefore, when these attributes change, especially in childhood, it leads to impaired physical development of the child. These attributes are evaluated on an indicator such as bone mineral density (BMD) [2].

Several factors may adversely influence bone accrual, including primary skeletal disorders as well as secondary causes of low bone density such as specific endocrinopathies, altered weight-bearing, and certain medications [2]. Among these factors, the greatest concern, due to its high prevalence in the world, is caused today by deviations from normal body weight [3]. Children with low

weight-for-age are known as underweight. A child who is underweight may be stunted. Stunting holds children back from reaching their physical and cognitive potential [4]. A low body weight is also a well-known risk factor for fragility fracture [5].

But even excess body weight, according to the latest data, can adversely affect bone health and fragility [6]. As well as affecting a child's immediate physical and mental health, educational attainment and quality of life, unhealthy body weight in early life can increase the risk of obesity and noncommunicable diseases, such as cardiovascular disease, cancer, and diabetes, later in life [7]. The World Obesity Atlas 2024 establishes that obesity rates are rising – at a very concerning rate – among children and adolescents [8]. Overweight and obesity among children remain one of the major public health challenges facing the WHO European Region [7]. It is projected that 88% of children with overweight and obesity will be living in low- and middle-income countries by 2035 [8]. Ukraine is one of them.

Thus, obesity has become an alarming disease with growing prevalence and multiple metabolic comorbidities, resulting in a significant burden on healthcare and increased mortality [6]. The imbalance between increased food ingestion and decreased energy expenditure leads to pathological adipose tissue distribution and function, with increased secretion of proinflammatory markers and harmful consequences for body tissues, including bone tissue [6]. However, previous studies on the effects of obesity on bone health have been insufficient and often contradictory, especially studies involving children.

The aim of the present article is to analyze current research on the relationship between childhood obesity and the development of osteoporosis.

Research materials and methods. The narrative literature review was performed using data published in the PubMed database between 2022 and 2024, and through a manual search of the reference lists of relevant studies. The search query included a combination of words, such as child, obesity, and osteoporosis. A total of 58 studies were identified following the literature search. A final number of 30 references were included in this review.

Research results and discussion

The Impact of Obesity in Childhood and Adolescence on the Development of Osteoporosis

Historically, the common belief was that obesity has a protective effect against osteoporosis [6]. But the results of newer studies have sometimes begun to show the opposite effect. This is evidenced by a large review by K.G. Lopes et al. conducted in 2022. The authors examined 167 studies on the relevant topic available at that time. The scientists concluded that in the specific literature, there are still disagreements about the real consequences of adiposity on bone mass in children. Some pointed to a negative impact, while others indicated positive or neutral effects [9]. Since then, several more original studies have been published on the subject. The authors have tried to explain those discrepancies.

Thus, Y. Ouyang et al. used multiple linear regression models, smoothed curve fitting, and saturation effect analysis models to examine the relationship between body mass index (BMI) and BMD in 6143 US adolescents aged 8–19 years [10]. An individual's BMI is known to be important in the determination of potential future health issues and has been widely used as a factor in the determination of various public health policies [11]. The scientists found not only a simple linear positive correlation between BMI and BMD but also a saturation value that persisted across gender and age subgroups in the analysis [10]. This work suggests that keeping BMI at saturation values may provide benefits for adolescents to maintain optimal BMD and reduce other obesity-related diseases [10]. Accordingly, an increase in BMI above the saturation value, i.e. excessive obesity, is harmful to health.

This opinion is also shared by G.X. Wang et al., who included 4056 adolescents aged 12–19 years in a cross-sectional study of the saturation effect between BMI and BMD. The authors found that appropriate obesity status allows adolescents to have better bone mass development but not excessive obesity [12].

Therefore, studies conducted on sufficiently large samples indicate that the real impact of obesity on bone mass in children can be determined primarily by its degree. An increase in BMI can indeed have a direct relationship with an increase in BMD, but up to a certain BMI value. Further, the dependence of BMD on BMI can become either zero or reversed.

Mechanisms of Interaction between Bone and Adipose Tissues

Several mechanical and biochemical mechanisms have been suggested to understand the complex communication between the adipose tissue and bone tissue [6]. The positive effects can be explained by the following mechanisms. Higher body mass results in increased mechanical load on bone, leading to an increase in BMD to adapt to mechanical stress [6]. Adipose tissue also plays a vital biochemical role in bone metabolism, mainly due to the production of adipokines, some of which act positively in bone formation [9].

However, despite a higher BMD, accumulating data demonstrate a negative effect of obesity on bone tissue with a site-dependent fracture risk, secondary to increased mechanical loads on some bones, excess of visceral, ectopic (including hepatic adipose tissue) and bone marrow adipose tissue, with a metabolic profile specific to each tissue, and secretion of inflammatory cytokines, adipokines, hormones and bone remodeling factors [6]. Thus, obesity can increase bone reabsorption through the increased release of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6), which stimulate the formation and activity of osteoclasts through the receptor activator of the nuclear factor kappa-B ligand (RANKL)/(RANK)/Osteoprotegerin (OPG) pathway [9].

Such differences may be related to the fact that there are heterogeneous obesity phenotypes among populations, depending on body fat distribution, each one with a different metabolic risk profile, leading to the concept of metabolically healthy obese (MHO) and metabolically unhealthy obese (MUHO) phenotypes [6]. The main hypothesis is that MHO, with less visceral and ectopic fat than MUHO and no evidence of metabolic syndrome, is defined by better bone structure and mass, as well as a potentially lower risk of fractures and osteoporosis [6].

Therefore, the real impact of obesity on bone mass in children may depend not only on its degree, as mentioned above, but also on the presence or absence of concomitant metabolic syndrome.

Impact of Obesity with Metabolic Syndrome on Bone Health in Children

The definition and criteria for metabolic syndrome in children and adolescents are currently unclear. But there is a strong association between obesity and the prevalence of metabolic syndrome [13]. The integration of waist measurements is believed to improve metabolic risk stratification among children, suggesting that waist measurements should be considered in routine pediatric screening [13]. Waist circumference, as an indicator for assessing visceral fat accumulation, has also been included in studies of the effect of MUHO on bone structure and mass. Just like those indicators that reflect the accumulation of ectopic fat. Muscle mass, fat mass, lean body mass, and water content were also often assessed to analyze body mass composition as a predictor of overweight and obesity in children and adolescents [14].

Thus, in a study by C. Cristi-Montero et al., a principal component analysis was performed to obtain a factor made up of four fatness indicators (a) neck circumference, (b) kilograms of fat, (c) visceral fat area, and (d) waist-to-height ratio. The skeletal muscle mass index (SMMI) was also calculated. The sample comprised 1,296 adolescents (50% girls) aged 10–14. It has been found that the inverse relationship between fatness and bone mineral content is mediated by the SMMI of adolescents [15]. This, in turn, provides opportunities for correcting impaired indicators. A 20-week exercise program that didn't target specific bones has already been shown to cause a small but significant improvement in overall body and leg weight, as well as BMD, in overweight or obese children [16].

Data from a review by R. Franceschi et al. suggest that overweight or obese children-adolescents have at the forearm increased volumetric BMD, normal/increased bone size, but altered bone geometry with a high proportion of fat relative to muscle in the forearm, negatively associated with bone strength [17]. The local fat mass/lean mass ratio may give a mismatch between bone strength and the load experienced by the distal forearm during a fall, resulting in increased risk of forearm fractures [17].

K.G. Lopes et al. also reviewed the factors related to bone health and their association with obesity and metabolic syndrome in adolescents. They concluded that obesity (specifically, accumulated visceral fat) harms bones in the infant–juvenile phase, thereby increasing osteopenia/osteoporosis in adults and the elderly [9].

A study by R. Khwanchuea examined correlations among anthropometric parameters, body composition, bone parameters and predictive factors of bone mass in adolescent girls with different body fat percentages. Body fat and waist circumference were found to be negative predictors of bone mass [18].

R. Lin et al. also analyzed the relationship between abdominal obesity and bone metabolism. A total of 1557 adolescent participants were included in the study. Research has shown a significant negative correlation between abdominal obesity index A Body Shape Index (ABSI) and BMD at the four detection sites of the femur, and this correlation may vary slightly due to age, race, family income, and different detection sites [19]. The research results indicate that compared to overall body weight, fat distribution and content may be more closely related to bone metabolism [19].

Some researchers believe that as opposed to waist circumference or body mass index, weight-adjusted waist index (WWI) is a superior method for assessing obesity. WWI also indicates centripetal obesity independently of the weight of the individual [20]. Through multivariate linear regression, G. Ma et al. discovered that WWI was negatively linked with lumbar, trunk, and total BMD but not pelvis BMD in this study, which included 6828 adolescents [20]. In passing, it can be noted here that the place on the skeleton where BMD is measured is also important.

I. Labayen et al. examined 106 children (aged 10.6 ± 1.1 years, 53.8% girls) with overweight/obesity. Their findings suggested that hepatic steatosis, rather than overall excess adiposity, was associated with greater bone marrow adipose tissue in preadolescent children with overweight/obesity, which in turn, was related to lower BMD [21].

The relationship between adipose tissue and bone can be explained by the fact that both bone marrow adipocytes and osteoblasts originate from the same cells, the mesenchymal multipotent stem cells [9]. Depending on a balance through the regulating key transcription factors to which these cells are subjected, they will follow one or another path of differentiation [9]. Modified selection from the mesenchymal lineage to the adipogenic lineage rather than the osteogenic lineage might involve several mechanisms, such as oxidative stress, proinflammatory factors (TNF-α and IL-6) and adipokines [6]. These mechanisms are triggered more often in obese people with metabolic syndrome, which, in fact, triggers them [9].

Therefore, it is the presence of metabolic syndrome in overweight and obese children that adversely affects bone mineral density, which can further lead to the development of osteopenia and osteoporosis, to an increase in the risk of osteoporotic fractures and disability, which is a heavy burden on the public health system.

Relationship of Obesity with Other Factors that also Affect Bones

It is known that nutrient deficiencies, especially calcium and vitamin D, associated with a sedentary lifestyle, lack of sun exposure, and epigenetic aspects represent some of the main risk factors for poor bone quality [9]. Vitamin D is a mediator in the regulation of skeletal, calcium and phosphate metabolism and has already been shown to play an important role in musculoskeletal health as well as in the prevention of nutritional rickets, osteomalacia and osteoporosis [22]. One of the causes of vitamin D deficiency is obesity [23]. It has been proven that the combination of chronic vitamin D, calcium, and phosphorus deficiencies, particularly in obese people, enhances the risk of osteoporosis and fractures [6].

The potential causes of the increased risk of vitamin D deficiency among patients with overweight or obesity include (a) limited cutaneous cholecalciferol synthesis associated with lower exposure to sunlight (lower physical activity and social exclusion), (b) abnormal eating habits, (c) accumulation/sequestration in adipose tissue ("fat

trap") and (d) disruption of hepatic hydroxylation of cholecalciferol at position 25 [22].

A multidisciplinary panel of clinical experts suggests empiric vitamin D supplementation for all children and adolescents aged 1 to 18 years to prevent nutritional deficiency. At the same time the panel suggests against routine 25(OH)D testing in the absence of established indications in the general population, nor in those with obesity [24]. Indeed, a trial by B. O'Sullivan et al. confirmed that even a 50.000 IU loading dose plus 8.000 IU daily oral vitamin D as safe and effective in increasing serum 25(OH) D levels in children/adolescents with overweight/obesity to levels ≥ 40 ng/mL. Given the critical role of vitamin D in many conditions complicating childhood obesity, these data close a critical gap in our understanding of vitamin D dosing in children [25].

A deficit of Mg, Zn or vitamin K is associated with, and can even contribute to, the occurrence or progression of the same illnesses as in the case of vitamin D deficiency, e.g., musculoskeletal diseases, obesity, etc. [26; 27]. The results of H. Qi et al. indicate that inadequate micro- and macronutrient intake at an early age interacts with adulthood general obesity and significantly increases the risk of low-energy fracture later in life in women [28]. Thus, it becomes evident that forming and maintaining healthy eating habits is necessary during infancy and adolescence to reduce the risk of fractures caused by bone-metabolic diseases in adulthood and to promote healthy ageing [4].

A review by S. Hasan et al. indicates that bone growth is mediated through several mechanisms including macro- and micronutrients, and endocrine and paracrine hormones. These mechanisms can be affected by childhood obesity as excess adiposity may affect signaling pathways, place undue stress on the body, and affect normal physiology [29]. Thus, pediatric bones require adequate levels of minerals, vitamins, amino acids, and a base caloric supply for energy. Therefore, recommendations should focus on a nutrient-dense dietary approach rather than restrictive caloric diets to maintain optimal health [29].

Correction of nutritional status in obese children should also be accompanied using special sets of exercises [16]. A randomized clinical trial has proven the positive effect of changes in diet and physical activity on changes in mineral content and bone density in obese adolescents undergoing a weight loss program [30].

Conclusions. A narrative review of publications over the past three years suggests that obesity in children and adolescents contributes more often to an increase than to a decrease in bone mineral density. But there is a certain level of BMI saturation, after which its direct dependence with BMD can become inverse. In addition, in the case of the metabolically unhealthy type of obesity, this dependence is also more often inverse. This then leads to an increased risk of osteopenia and osteoporosis, whether in childhood or later in adulthood. Therefore, measures to normalize body weight are necessary already in childhood and serve, among other things, to prevent osteoporosis in the future. It is necessary not only to correct the nutritional status, but also to use special sets of exercises for overweight and obese children and adolescents.

BIBLIOGRAPHY

1. López JM. Bone Development and Growth. *Int J Mol Sci*. 2024; 25(12): 6767. doi: 10.3390/ijms25126767.
2. Gordon RJ, Misra M, Mitchell DM. Osteoporosis and Bone Fragility in Children. 2023. In: Feingold KR, Anawalt B, Blackman MR et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. PMID: 37490575. NBK593436.
3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet.* 2024; 403(10431): 1027–1050. doi: 10.1016/S0140-6736(23)02750-2.
4. WHO. Malnutrition. 2024. Available at: https://www.who.int/news-room/fact-sheets/detail/malnutrition/.
5. Formosa MM, Christou MA, Mäkitie O. Bone fragility and osteoporosis in children and young adults. *J Endocrinol Invest*. 2024; 47(2): 285–298. doi: 10.1007/s40618-023-02179-0.
6. Gruneisen E, Kremer R, Duque G. Fat as a Friend or Foe of the Bone. *Curr Osteoporos Rep.* 2024; 22(2): 245–256. doi: 10.1007/s11914-024-00864-4.
7. Report on the fifth round of data collection, 2018–2020: WHO European Childhood Obesity Surveillance Initiative (COSI). Copenhagen: WHO Regional Office for Europe; 2022. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/europe/publications/i/item/WHO-EURO-2022-6594-46360-67071.
8. World Obesity Atlas 2024. London: World Obesity Federation, 2024. https://data.worldobesity.org/publications/?cat=22.
9. Lopes KG, Rodrigues EL, da Silva Lopes MR et al. Adiposity Metabolic Consequences for Adolescent Bone Health. *Nutrients*. 2022; 14(16): 3260. doi: 10.3390/nu14163260.
10. Ouyang Y, Quan Y, Guo C et al. Saturation Effect of Body Mass Index on Bone Mineral Density in Adolescents of Different Ages: A Population-Based Study. *Front Endocrinol (Lausanne)*. 2022; 13: 922903. doi: 10.3389/fendo.2022.922903.
11. Zierle-Ghosh A, Jan A. Physiology, Body Mass Index. 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. https://pubmed.ncbi.nlm.nih.gov/30571077/.
12. Wang GX, Fang ZB, Li HL, Liu DL, Chu SF, Zhao HX. Effect of obesity status on adolescent bone mineral density and saturation effect: A cross-sectional study. *Front Endocrinol (Lausanne)*. 2022; 13: 994406. doi: 10.3389/fendo.2022.994406.
13. Velychko VI, Khatsko VE, Lahoda DO, Bazhora YaI, Pencho GO. Modern views on metabolic syndrome in children and adolescents. *The Odesa Medical Journal*. 2024; 2(187); 57–64. (In Ukrainian). Available from: https://doi.org/10.32782/2226-2008-2024-2-10.
14. Aniśko B, Siatkowski I, Wójcik M. Body mass composition analysis as a predictor of overweight and obesity in children and adolescents. *Front Public Health*. 2024; 12: 1371420. doi: 10.3389/fpubh.2024.1371420.

15. Cristi-Montero C, Peña-Jorquera H, Landaeta-Díaz L et al. The inverse relationship between fatness and bone mineral content is mediated by the adolescent appendicular skeletal muscle mass index: The Cogni-Action Project. *Front Nutr.* 2022; 9: 1040116. doi: 10.3389/fnut.2022.1040116.
16. Gil-Cosano JJ, Ubago-Guisado E, Migueles JH et al. A 20-week exercise program improved total body and legs bone mineral density in children with overweight or obesity: The ActiveBrains randomized controlled trial. *J Sci Med Sport*. 2024; 27(1): 3–9. doi: 10.1016/j.jsams.2023.10.005.
17. Franceschi R, Radetti G, Soffiati M, Maines E. Forearm Fractures in Overweight-Obese Children and Adolescents: A Matter of Bone Density, Bone Geometry or Body Composition? *Calcif Tissue Int.* 2022; 111(2): 107–115. doi: 10.1007/s00223-022-00971-3.
18. Khwanchuea R. Predictive factors of bone strength variation in adolescent girls according to body composition. *Ann Pediatr Endocrinol Metab*. 2024; 29(2): 119–129. doi: 10.6065/apem.2346122.061.
19. Lin R, Tao Y, Li C et al. Central obesity may affect bone development in adolescents: association between abdominal obesity index ABSI and adolescent bone mineral density. *BMC Endocr Disord*. 2024; 24(1): 81. doi: 10.1186/s12902-024-01600-w.
20. Ma G, Xu B, Zhang D et al. Association between weight-adjusted waist index and bone mineral density in adolescents. *Sci Rep.* 2024; 14(1): 16509. doi: 10.1038/s41598-024-66565-1.
21. Labayen I, Cadenas-Sánchez C, Idoate F et al. Liver Fat, Bone Marrow Adipose Tissue, and Bone Mineral Density in Children With Overweight. *J Clin Endocrinol Metab.* 2023; 109(1): e253–e258. doi: 10.1210/clinem/dgad429.
22. Pludowski P, Marcinowska-Suchowierska E, Togizbayev G et al. Daily and Weekly "High Doses" of Cholecalciferol for the Prevention and Treatment of Vitamin D Deficiency for Obese or Multi-Morbidity and Multi-Treatment Patients Requiring Multi-Drugs – A Narrative Review. *Nutrients*. 2024; 16(15): 2541. doi: 10.3390/nu16152541.
23. Boucher BJ. Comment on Lopes et al. Adiposity Metabolic Consequences for Adolescent Bone Health. Nutrients 2022, 14, 3260. *Nutrients*. 2023; 15(23): 4952. doi: 10.3390/nu15234952.
24. Demay MB, Pittas AG, Bikle DD et al. Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2024; 109(8): 1907–1947. doi: 10.1210/clinem/dgae290.
25. O'Sullivan B, Ounpraseuth S, James L et al. Vitamin D Oral Replacement in Children With Obesity Related Asthma: VDORA1 Randomized Clinical Trial. *Clin Pharmacol Ther*. 2024; 115(2): 231–238. doi: 10.1002/cpt.3086.
26. Bleizgys A. Zinc, Magnesium and Vitamin K Supplementation in Vitamin D Deficiency: Pathophysiological Background and Implications for Clinical Practice. *Nutrients*. 2024; 16(6): 834. doi: 10.3390/nu16060834.
27. Alzahrani BA, Badri ZA, Aljuhani JA, Alshamrani RM, Ahmed ME, Jari Alshumrani M. A Comparison of Magnesium Levels in Obese Versus Normal-Weight Children. *Cureus*. 2023; 15(8): e44053. doi: 10.7759/cureus.44053.
28. Qi H, Hu C, Zhang J et al. Early-life famine exposure, adulthood obesity patterns, and risk of low-energy fracture. *Front Med*. 2024; 18(1): 192–203. doi: 10.1007/s11684-023-1023-9.
29. Hasan S, Naseer S, Zamzam M et al. Nutrient and Hormonal Effects on Long Bone Growth in Healthy and Obese Children: A Literature Review. *Children (Basel)*. 2024; 11(7): 817. doi: 10.3390/children11070817.
30. Videira-Silva A, Santos I, Freaza D, Gameiro M, Sardinha LB, Fonseca H. Dietary content and combined training, but not daily physical activity, are associated with 6-month bone mineral changes in adolescents with obesity: A Secondary analysis of the PAC-MAnO trial. *Eur J Pediatr*. 2024; 183(9): 3969–3978. doi: 10.1007/s00431-024-05659-4.

Надійшла до редакції 10.07.2024 р.
Прийнята до друку 30.01.2025 р.
Електронна адреса для листування nata3567501@gmail.com