ISSN 2221-2582

UDC 57.084.2+579.864.1+612.392.98+57.063.8+616.34-009.74-053.2
DOI: 10.56871/CmN-W.2023.75.34.002

PROBIOTIC PROPERTIES OF *LACTOBACILLUS REUTERI (L. REUTERI)* STRAINS

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For citation: Novikova VP, Magamedova DM. Probiotic properties of *Lactobacillus reuteri* (*L. reuteri*) strains. Children's medicine of the North-West (St. Petersburg). 2023; 11(3): 36-53. DOI: https://doi.org/10.56871/CmN-W.2023.75.34.002

Received: 07.06.2023 **Revised: 10.08.2023** **Accepted: 12.09.2023**

Abstract. Probiotic status is given to microorganisms that are considered safe and meet certain criteria. *Lactobacillus reuteri* DSM 17938 (*L. reuteri*) is a well-studied bacterium that can colonize various parts of the body in humans. The strain in use today, L. reuteri DSM 17938, recently renamed *Limosilactobacillus reuteri* (*L. reuteri*), is a probiotic well identified for its beneficial effects on several gastrointestinal diseases. The probiotic effect of *L. reuteri* is due to a whole range of special properties. *L. reuteri* is able to influence the biodiversity, composition and metabolic function of the gut, oral and vaginal microbiota. These effects are largely strain-specific. The main therapeutic target of *L. reuteri* is infantile colic. In infants, in addition to relieving colic and modulating the intestinal microbiota, *L. reuteri* is able to enhance the mucosal barrier function, which is necessary to block the entry of external antigens and toxins. Literature data indicate the effectiveness of *L. reuteri* in acute watery diarrhea, against *H. pylori* and other diseases: atopic dermatitis, obesity, caries, autism spectrum disorders, autoimmune diseases, incl. inflammatory bowel disease and systemic lupus erythematosus, etc. The safety and tolerability of *L. reuteri* has been proven by numerous clinical studies. There are several strains of *L. reuteri* with different origins and many of the probiotic functions of *L. reuteri* are strain dependent. Therefore, in the future, it may be advantageous to combine different strains of *L. reuteri* in order to maximize their beneficial effects.

Key words: *probiotic; L. reuteri; Limosilactobacillus reuteri; infant colic*

ПРОБИОТИЧЕСКИЕ СВОЙСТВА ШТАММОВ *LACTOBACILLUS REUTERI (L. REUTERI)*

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Для цитирования: Новикова В.П., Магамедова Д.М. Пробиотические свойства штаммов *Lactobacillus reuteri* (*L. reuteri*) // Children's medicine of the North-West. 2023. Т. 11. № 3. С. 36–53. DOI: https://doi.org/10.56871/CmN-W.2023.75.34.002

Поступила: 07.06.2023 **Одобрена: 10.08.2023** **Принята к печати: 12.09.2023**

Резюме. Статус «пробиотик» присваивается тем микроорганизмам, которые считаются безопасными и соответствуют определенным критериям. *Lactobacillus reuteri* DSM 17938 (*L. reuteri*) — хорошо изученная бактерия, способная колонизировать у людей различные участки тела. Штамм, который используется сегодня, *L. reuteri* DSM 17938, недавно переименованный в *Limosilactobacillus reuteri* (*L. reuteri*), является пробиотиком, хорошо идентифицированным по его благотворному влиянию на некоторые желудочно-кишечные заболевания. Пробиотический эффект *L. reuteri* обусловлен целым комплексом особенных свойств. *L. reuteri* способен влиять на биоразнообразие, состав и метаболическую функцию микробиоты кишечника, полости рта и влагалища. Эти эффекты в значительной степени штаммоспецифичны. Основной терапевтической мишенью воздействия *L. reuteri* являются младенческие колики. У младенцев, помимо купирования

колик и модуляции кишечной микробиоты, *L. reuteri* способны усиливать барьерную функцию слизистой оболочки, которая необходима для блокирования проникновения внешних антигенов и токсинов. Литературные данные свидетельствуют об эффективности *L. reuteri* при острой водянистой диарее, против *H. pylori* и при других заболеваниях: атопическом дерматите, ожирении, при кариесе, расстройствах аутистического спектра, аутоиммунных заболеваниях, в том числе воспалительных заболеваниях кишечника и системной красной волчанке и др. Безопасность и переносимость *L. reuteri* доказана многочисленными клиническими исследованиями. Существует несколько штаммов *L. reuteri* с различным происхождением, и многие из пробиотических функций *L. reuteri* зависят от штамма. И поэтому в будущем, возможно, может быть выгодно комбинировать различные штаммы *L. reuteri*, чтобы максимизировать их полезные эффекты.

***Ключевые слова*:** *пробиотик; L. reuteri; Limosilactobacillus reuteri; младенческие колики*

Lactobacillus reuteri DSM 17938 (*L. reuteri*) is a well-studied bacterium capable of colonising a wide range of vertebrates, including pigs, rodents and chickens. Evolution has adapted the bacterium to a large number of mammals [1]. In humans, *L. reuteri* is found in various body sites including the gastrointestinal tract, urinary tract, skin and breast milk [2, 3]. *L. reuteri* was first described in 1962 as a heterofermentative species that grows in oxygen-limited atmospheres and colonises the proximal gastrointestinal tract of humans and animals [17]. Around 1990, the probiotic properties of the parent strain of *L. reuteri*, ATCC 55730, were clinically proven [5]. After deletion of gene-bearing antibiotic resistance plasmids from *Lactobacillus reuteri* ATCC 55 730, the strain used today, *L. reuteri* DSM 17938, was generated [6]. It belongs to the genus *Lactobacillus*, which includes many other Gram-positive oxygen-resistant fermentative bacteria such as *L. acidophilus, L. bulgaricus, L. casei* and *L. rhamnosus* [7]. Lactobacillus reuteri DSM 17938, recently renamed Limosilactobacillus reuteri (*L. reuteri*), is a probiotic well identified for its beneficial effects on several gastrointestinal diseases [2, 4, 8–10].

The probiotic effect of *L. reuteri* is due to a whole complex of special properties. Due to its ability to form biofilms [4, 11], *L. reuteri* colonies are resistant to low pH values and bile salts [12]. *L. reuteri* has been shown to be able to attach to mucin, intestinal epithelium, and intestinal epithelial cells in a number of vertebrates [13]. The adhesion mechanism is thought to be due to the binding of bacterial surface molecules to the mucus layer. Mucus-binding proteins (MUBs) and MUB-like proteins encoded by *Lactobacillales*-specific clusters of protein encoding genes act as adhesins [14]. The considerable diversity of MUBs among *L. reuteri* strains and differences in the number of MUBs on the cell surface correlate with their ability to bind mucus [15]. The strain-specific role of MUBs in the recognition of mucus elements and/or their ability to stimulate aggregation may explain the contribution of MUBs to *L. reuteri* adhesion. Factors that mediate attachment to surfaces include many large surface proteins, MUB A, glucosyltransferase A (GtfA) and inulosucrase (Inu) and D-alanyl ester [2]. The relationship between bacterial adhesion to the epithelium of the host gastrointestinal tract and the ability of bacteria to form biofilms has been studied. Numerous experiments *in vitro* and on different animals, including microbe-free rodents, have shown that biofilm formation of *L. reuteri* strains depends on the origin of the host strains. For example, biofilm formation of *L. reuteri* TMW1.106 is associated with GtfA and Inu molecules [16]; *L. reuteri* 70902 and the secA2-SecY2 system were key factors regulating biofilm formation from L. reuteri 100–23 in germ-free mice [17]; the bfrKRT and cemAKR two-component systems are associated with biofilm formation of *L. reuteri* 100–23 [18]; *L. reuteri* RC-14 is able to penetrate into the mature biofilm of *E. coli* and become part of it [19].

The probiotic potential of *L. reuteri* is also associated with the production of their metabolites with antimicrobial and immunomodulatory effects [2]. The most studied is reuterin, which is a mixture of different forms of 3-hydroxypropionic aldehyde (3-HPA) [20]. Most strains of *L. reuteri* can metabolise glycerol to form reuterin in a glycerol dehydratase dependent reaction mediated by coenzyme B_{12} [21, 22]. Some other bacteria can also produce 3-HPA [23], but only *L. reuteri* is capable of secreting it in significant amounts above the bioenergetic requirement [24]. An important compound in the antimicrobial activity of reuterin is the acrolein-cytotoxic electrophile into which 3-HPA can be spontaneously converted. Conjugation of heterocyclic amines also depends on the formation of acrolein [25]. Reuterin can inhibit a wide range of microorganisms, mainly Gram-negative bacteria, while *L. reuteri* strains themselves show pronounced resistance to reuterin [26].

Some strains of *L. reuteri*, in addition to reuterin, produce other antimicrobial substances: a lactic acid, an acetic acid, an ethanol, and a reutericycline [21]. Due to the synthesis of these substances, *L. reuteri* is effective against various bacterial infections of the gastrointestinal tract: *Helicobacter pylori, E. coli, Clostridium difficile* and Salmonella [27–30]. In addition, due to metabolites having antiviral properties, *L. reuteri* is effective against pneumoviruses, circoviruses, rotaviruses, coxsackie viruses and papillomaviruses [31–34]. There are reports that *L. reuteri* also stops the growth and kills various *Candida* species [35].

Some strains of *L. reuteri* (for example, the human commensal bacterium *L . reuteri* 6475) convert the amino acid L-histidine into histamine [36], which suppresses tumour necrosis factor (TNF) production from stimulated human monocytes by activating histamine H_2-receptors, increasing intracellular cAMP and protein kinase A, and inhibiting MEK/ERK signal transduction [37]. Numerous experimental studies demonstrate the involvement of histamine in suppressing intestinal inflammation in mouse models of colitis [38, 39].

Tryptophan catabolites of *L. reuteri* have been recognised as ligands for the aryl hydrocarbon receptor (AhR). By activating AhR, *L. reuteri* can stimulate local production of IL-22 from innate lymphoid cells (ILCS) and induce the development of regulatory $CD4^+CD8aa^+$ double-positive intraepithelial lymphocytes [50, 51]. Given that AhR is expressed ubiquitously, *L. reuteri* and its metabolites may affect many other immune cell types besides ILCs and T cells [52].

Four strains of *L. reuteri* of different origins have been detected, among which the most studied are *L. reuteri* CRL1098 and *L. reuteri* JCM1112, which are capable of producing different types of vitamins, including vitamin B_{12} (cobalamin) and B_9 (folic acid). Vitamin B_{12} is vital for the production of reuterin, as a B_{12}-dependent coenzyme is required to reduce glycerol to 3 GPA [40–42].

L. reuteri can also produce gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the central nervous system [57]. It is possible that this accounts for the effect of the microorganism on visceral sensitisation [58].

The exopolysaccharide (EPS) synthesised by the *L. reuteri* is important for biofilm formation and adhesion of *L. reuteri* to epithelial surfaces [11]. Numerous experimental works on animals have shown that EPS can inhibit the adhesion of *E . coli* to epithelial cells [43, 44], inhibit gene expression of proinflammatory cytokines that are induced by *E. coli* infection, including IL-1β and IL-6, inhibit the binding of enterotoxigenic *E. coli* to animal erythrocytes [45], and induce Foxp3+ regulatory T cells (Treg) in the spleen [46].

The property of *L. reuteri* to induce Treg is highly strain dependent. *L. reuteri ATCC PTA, 6475, L. reuteri DSM 17938, L. reuteri 100–23, L. reuteri ATCC 23272, L. reuteri RC-14* have been described to mediate Treg cell induction in obesity, necrotising enterocolitis, inflammatory bowel disease (IBD), atopic dermatitis, systemic lupus erythematosus, wound healing and other conditions [2]. In addition to acting on Treg cells, L. reuteri can suppress Th1/Th2 responses in Treg-deficient mice [47]. Some strains of L. reuteri are able to reduce the production of many pro-inflammatory cytokines (MCP-1, TNF, IL-6, TNF, IL-22) [48, 49]. At the same time, studies investigating the effect of Lactobacillus reuteri on the levels of free secretory IgA (sIgA) in various tissues (blood, saliva, breast milk) give contradictory results, which is apparently due to the use of different strains [53–56].

The immune system of humans and animals is closely interrelated with the intestinal microbiota [59]. It has been shown that disturbances of the microbiota can contribute to the development of diseases, and restoration of the microbiota prevents or improves the course of some diseases [60]. *L. reuteri* is able to influence the biodiversity, composition and metabolic function of the gut, oral and vaginal microbiota. These effects are largely strain specific [18, 61, 62]. In rodent models, *L. reuteri* DSM17938 was demonstrated to increase the number of Firmicutes types and the genera *Lactobacillus* and *Oscilospira* in the gut [47], while reducing multi-organ inflammation; *L. reuteri* 6475 resulted in increased microbiota biodiversity in both jejunum and ileum [63]; *L. reuteri* C10–2-1 modulates the diversity of intestinal microbiota in ileum [53].

A number of researchers have studied the effect of *L. reuteri* DSM 17938 on the intestinal microbiota of infants. In one study, the administration of this strain to children aged 2 weeks to 4 months born by caesarean section reduced the number of enterobacteria and increased the number of bifidobacteria, that is, modulated the development of the intestinal microbiota in the direction of the composition of the microbiota found in infants born vaginally. At the same time, the structure of the intestinal microbiota of newborns born vaginally remained unchanged after taking *L. reuteri* supplements. [62]. In a study made by Savino et al. (2015) administration of the same *L. reuteri* strain to infants resulted in a decrease in the number of anaerobic gram-negative and an increase in the

number of gram-positive bacteria in the intestinal microbiota, while the content of enterobacteria and enterococci was significantly reduced [64]. The differences in the results of the two studies may be related to the different ages of the subjects, the duration of treatment, the method of administration and dosage.

The *L. reuteri* strain NCIMB 30242, which is administered as delayed-release capsules for 4 weeks, increased the ratio of *Firmicutes* to *Bacteroidetes* in healthy adults [65]. The mechanism of modulation of the intestinal microbiota in them is associated with the ability of this strain to activate the hydrolase of bile salts and increase the content of circulating bile acid in the blood [66]. Modulation of the intestinal microbiota using the *L. reuteri* DSM 17938 strain was also performed in patients with type 2 diabetes mellitus and cystic fibrosis [2].

In addition to modulating the intestinal microbiota, *L. reuteri* is able to enhance the barrier function of the mucous membrane, which is necessary to block the penetration of external antigens and toxins [67]. It has been demonstrated in animal models that *L. reuteri* can reduce the movement of bacteria from the gastrointestinal tract to mesenteric lymph nodes, increase the expression of dense compound proteins (TJ) in intestinal epithelial cells, which suppresses the translocation of proinflammatory molecules such as LPS [68–70]. *L. reuteri* is able to reduce intestinal permeability in children with atopic dermatitis; at the same time, the clinical picture of the disease is significantly improved [71].

In addition to influencing the gut microbiota and intestinal permeability, *L. reuteri* can influence the microbiota of other biotopes. The effects of two strains of *L. reuteri* — DSM 17938 and PTA 5289 — on the microbiota of the oral cavity have been most studied: changes in the composition of the microbiota, reduction in the number of periodontal pathogens in the sub-gingival microbiota [72]. There are studies demonstrating the positive effect of *L. reuteri* RC-14 on the vaginal microbiota in postmenopausal women and in patients with bacterial vaginosis [73, 74].

Due to its pronounced modulating effects on the host microbiota and immune responses, and its good safety profile, *L. reuteri* is a worthy candidate for the prevention and/or treatment of various diseases. The therapeutic potential of different strains of *L. reuteri* has been studied in various diseases and the results have been promising in many cases [2, 60].

The main therapeutic target of *L. reuteri* is infantile colic [75]. Colic in infants is characterised by restlessness or excessive crying; it occurs in 10–30% of cases. The exact cause and effective treatment of this condition remain unclear [76]. The clinical efficacy of *L. reuteri* DSM 17938 [77–81] and *L. reuteri* ATCC 55730 [86] in reducing restlessness and duration of crying has been demonstrated in a large number of clinical trials. There are reports that the use of *Lactobacillus reuteri* DSM 17938 has shown a positive therapeutic and preventive effect exclusively in breastfed infants (use for 21–28 days), whereas no positive result was obtained with artificial feeding [82, 83]. This may be due to the fact that *L. reuteri* is found in the breast milk of most women [87]. F. Savino et al. noted an increase in the number of lactobacilli and a decrease in *E. coli* in the faecal microbiota against the background of *L. reuteri* administration along with the clinical effect [81]. At the same time, there are studies that did not confirm the effect of *L. reuteri* on the gut microbiota [84] and on the duration of crying in infants [85]. Since most clinical studies were successful, experts consider the clinical efficacy of *L. reuteri* DSM 17938 proven [88, 89]. The failure of some studies may be explained by differences in the dosage of *L. reuteri* the age of the infants when the studies were initiated, or the basic structure of the microbiota of the subjects.

The use of *Lactobacillus reuteri* DSM 17938 was effective in the prevention and treatment of regurgitation in infants [77, 90], management of functional abdominal pain [91, 92], treatment of constipation in children and adults [10], and prevention and treatment of diarrhea [10].

A considerable amount of work has been devoted to the study of the effectiveness of *L. reuteri* in constipation. The mechanism of action of *L. reuteri* efficacy is associated with its ability to produce short-chain fatty acids (SCFA), reduce intraluminal intestinal pH level and also contribute to colonic peristalsis by affecting the frequency and speed of its myoelectric cells [93]. Current evidence suggests that *L. reuteri* improved defecation in patients (both children and adults) with chronic constipation [8, 9], but did not affect stool consistency [93]. Kubota et al. [8] reported that *L. reuteri* administered to children with chronic constipation, twice daily for four weeks, induced changes in the composition of the intestinal microbiota (reduction of *Clostridiales* genera such as *Oscillospira, Megasphaera* and *Ruminococcus*), increasing intestinal peristalsis and decreasing stool transit time, with significant results at week four *L. reuteri* improved stool frequency but not stool consistency [8]. *Coccorullo* et al. [94] proved that *L. reuteri* has a positive effect on functional constipation

in infants, improving the frequency of defecation at the 2nd, 4th and 8th weeks of administration. Indrio et al. [77] emphasised that *L. reuteri* reduced constipation during the first three months of life. A number of researchers have reported the efficacy of L. reuteri for constipation in adult patients [9, 95–97]; The mechanism of positive action is attributed to the reduction of methane (CH_4) production by intestinal microbiota (*Methanobrevibacter smithii*), modulation of serum levels of serotonin (5-HT) and brain-derived neurotrophic factor (BDNF) by this probiotic strain, activation of afferent sensory nerves affecting intestinal motility, and increase in excitability of myeenteric neurons due to the action on 5-HT pathways. At the same time, a number of studies have not observed a positive effect of *L. reuteri* in constipation in children [98] and adults [93], and no significant changes in the microbiota and its relationships with the dynamics of constipation have been found [98]. According to experts, to recommend the inclusion of *L. reuteri* in constipation therapy protocols, additional studies are needed to investigate the efficacy of probiotics in constipation and the mechanisms by which *L. reuteri* modulates intestinal motility with effects on constipation in children and adults [99–101].

Literature data indicate the effectiveness of *L. reuteri* in acute watery diarrhea [36, 102–107, 114, 115] and in the prevention of new episodes of diarrhea, including diarrhea after long-term antibiotic treatment [108, 109]. A.V. Shornikova et al. [110, 111] investigated the role of *L. reuteri* in acute watery diarrhea in children and in rotavirus gastroenteritis. In a randomised controlled clinical trial involving 86 children aged 6 to 36 months with rotavirus enteritis, *L. reuteri* administration was shown to reduce the duration of acute watery diarrhea with a dose-dependent effect. The mean duration of acute watery diarrhoea was 1,5 days in the group dosed with 10^{10} colony forming units (CFU) of *L. reuteri*, 1,9 days in the group dosed with107 CFU of *L. reuteri*, and 2,5 days in the group receiving placebo. By the second day of *L. reuteri* treatment, acute watery diarrhea persisted among 48% of people taking the high dose, 70% of people taking the low dose, and 80% of people treated with placebo. In another randomised placebo-controlled clinical trial [106], supplementation with *L. reuteri* at a dose of 4×10^8 CFU/day for 7 days was demonstrated to reduce the duration of acute watery diarrhoea in children aged 3 months to 3 years, with a maximum effect on the second and third day, with no reported side effects. Other studies [107, 112] found that administration of 5 drops containing 10^8 CFU of *L. reuteri* could reduce the duration of acute watery diarrhoea by up to 15 h in children aged 3 months to 5 years. A meta-analysis including 1229 children receiving *L. reuteri* at a dosage of 10^8 CFU daily for 5–7 days demonstrated a reduction in the duration of diarrhoea by 1 day with a maximum beneficial effect on the second day. Although the analysed studies were heterogeneous in duration and dosage of *L. reuteri* the authors confirmed the beneficial effect of this probiotic in the treatment and prevention of acute watery diarrhea [113]. Another review and meta-analysis [116] of 4 studies comparing the effects of L. reuteri at different doses with placebo or no treatment on the duration of diarrhea and stool volume, on the course of diarrhea, on the duration of diarrhea of 7 days or less and on the duration of hospitalisation. It was observed that L. reuteri reduced the duration of diarrhea by about 21 hours and the duration of hospitalisation in children by about 13 hours. Thus, most authors believe that *L. reuteri* may be a useful and safe, supportive measure for the treatment and prevention of diarrhea, reducing both its duration and intensity of symptoms [116].

L. reuteri strain DSM 17938 has been successfully used in preterm infants [117, 118]. Various authors have found a reduction in food intolerance and length of hospital stay in infants, but one study noted no effect on the incidence of necrotising enterocolitis (NEC) [118].

The use of *L. reuteri* strain DSM 122460 (from 19070–2) for 6 weeks [119] and *L. reuteri* strain ATCC 55730 for 8 weeks [120] was effective in atopic dermatitis. *L. reuteri* strain ATCC 55730 in infants with a family history of allergies was effective in preventing IgE-associated eczema, but did not provide protection against the common occurrence of eczema [121] and had no effect on the prevalence of asthma, eczema or other allergic diseases later in life [122].

The potential of *L. reuteri* in the treatment of obesity is actively debated. It has been shown in experimental and clinical studies that depending on the strain, *L. reuteri* can have different effects on body weight. For example, vancomycin-resistant *L. reuteri* in the intestinal microbiota has been identified as a predictor of increased body weight during vancomycin treatment [123]. In contrast, in a randomised, double-blind and placebo-controlled clinical trial, administration of *L. reuteri* JBD301 for 12 weeks significantly reduced body weight in overweight adults [124]. Experts of the European Paediatric Society of Gastroenterology, Hepatology and Nutrition (ESPGHAN), based on a review of a significant number of studies, con-

cluded that supplementation of infant formula with *L. reuteri* does not increase body weight in infants [125].

The clinical efficacy of *L. reuteri* against *H. pylori* has been described in a number of studies. It has been shown that adjuvant therapy with *L. reuteri* against antibiotics in eradication regimens can improve the tolerability of the regimens, reduce abdominal pain, diarrhoea, nausea, vomiting and abdominal bloating, restoring the balance of intestinal microflora [30, 126]. Dore et al. [127] showed that *L. reuteri* prevents *H. pylori* colonisation of human intestinal mucosa by inhibiting the binding of *H. pylori* to glycolipid receptors. It also increases the production of mucin, reuterin and antioxidant substances, stabilises the mucosal barrier and stimulates mucosal immunity [127, 128] with beneficial health effects in intestinal microbiota dysbiosis after the use of antibiotics and antisecretory treatments. A number of authors have noted that due to the above described properties, *L. reuteri* accelerates the eradication of *H. pylori* [129–131].

Experimental and clinical studies of *L. reuteri* efficacy in caries, autism spectrum disorders, autoimmune diseases including inflammatory bowel disease and systemic lupus erythematosus have been conducted [2].

In the last few decades, there has been a decline in *L. reuteri* in humans, probably caused by modern lifestyles (antibiotic use, western diet, improved hygiene). This decline coincides with an increase in inflammatory and autoimmune diseases over the same period. Although evidence is currently insufficient to establish a correlation, it is possible that increased colonisation of *L. reuteri* may be a new and relatively safe strategy against inflammatory diseases.

Conclusion. The safety and tolerability of *L. reuteri* has been proven by a large number of clinical studies. There are several strains of *L. reuteri* with different origins, and many of the probiotic functions of *L. reuteri* are strain dependent. And so in the future, it may be advantageous to combine different strains of *L. reuteri* to maximise their beneficial effects.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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