DOI: https://doi.org/10.17816/brmma630664

Pathogenetic aspects of dementia in patients with type 2 diabetes mellitus

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ABSTRACT

This review presents data from current Russian and international scientific studies on the causes and pathogenetic mechanisms of dementia in patients with type 2 diabetes mellitus (T2DM). Currently, T2DM is regarded as an independent risk factor for cognitive impairment and various dementia types, including vascular, mixed, and Alzheimer disease-related dementia. Dementia is a polyetiologic syndrome, and Alzheimer's disease and cerebrovascular pathology are considered the predominant causes in the elderly. Several studies reported an association between diabetes mellitus and neurodegenerative processes in the central nervous system. Cognitive impairments caused by suboptimal neurogenesis, brain tissue insulin resistance, dysglycemia, oxidative stress, chronic systemic inflammation, β-amyloid peptide accumulation, and structural and functional changes in the cerebral vasculature are prevalent in the elderly, who are more frequently diagnosed with both dementia and T2DM. Key contributors to dementia include genetic predisposition, environmental factors, lifestyle, and diet. However, growing evidence indicates additional risk factors such as insulin resistance, hypertension, obesity, dyslipidemia, amylin metabolism disorders, and gut microbiota imbalance. Brain tissue insulin resistance, often called "type 3 diabetes mellitus" and closely associated with cognitive impairment, is particularly significant. Moreover, poor glycemic control and recurrent hypoglycemic episodes play a role in cognitive deficits in patients with diabetes mellitus. Nevertheless, the molecular and cellular mechanisms underlying dementia in T2DM remain unclear.

Keywords: type 2 diabetes mellitus; cognitive impairment; Alzheimer's disease; cerebrovascular pathology; dementia; insulin resistance; dysglycemia; hypoglycemic episodes.

To cite this article

Romashevskiy BV, Salukhov VV, Maksim OV, Duganova AV. Pathogenetic aspects of dementia in patients with type 2 diabetes mellitus. *Bulletin of the Russian Military Medical Academy.* 2025;27(1):105–114. DOI: https://doi.org/10.17816/brmma630664

Received: 22.04.2024 **Accepted:** 03.02.2025 **Published online:** 28.03.2025

УДК 616.379-008.64-092:616.892.32
DOI: https://doi.org/10.17816/brmma630664

Патогенетические аспекты развития деменции у больных сахарным диабетом 2-го типа

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АННОТАЦИЯ

Приведены данные современной отечественной и зарубежной научной литературы, посвященные причинам возникновения и патогенетическим механизмам развития деменции у больных сахарным диабетом. В настоящее время сахарный диабет признан независимым фактором риска развития когнитивных нарушений и различных вариантов деменции (сосудистой, смешанной, деменции при болезни Альцгеймера). Несмотря на то, что деменция является полиэтиологичным синдромом, преобладающей причиной ее развития у пожилых пациентов считают болезнь Альцгеймера и цереброваскулярную патологию. Многочисленные исследования подтверждают взаимосвязь между сахарным диабетом и нейродегенеративными процессами в центральной нервной системе. Когнитивные нарушения, обусловленные неоптимальным нейрогенезом, инсулинорезистентностью тканей головного мозга, дисгликемией, окислительным стрессом, системным хроническим воспалением, накоплением β-амилоидного пептида, структурными и функциональными изменениями сосудов головного мозга, становятся наиболее актуальными у пациентов пожилого возраста, у которых и деменция, и сахарный диабет 2-го типа выявляются значительно чаще. Принято считать, что наиболее важные условия для развития деменции — генетическая предрасположенность, особенности окружающей среды, образ жизни и питания. Однако появляется все больше доказательств того, что такие факторы, как инсулинорезистентность, артериальная гипертензия, ожирение, дислипидемия, нарушения метаболизма амилина и дисбаланс кишечной микробиоты повышают риск развития деменции. Особое значение придается именно инсулинорезистентности тканей головного мозга, которая сопровождается когнитивными нарушениями и рассматривается как «сахарный диабет 3-го типа». Неоспорима роль неудовлетворительного гликемического контроля, рецидивирующих гипогликемических состояний в развитии когнитивного дефицита у пациентов, страдающих сахарным диабетом. В то же время молекулярные и клеточные механизмы развития деменции при сахарном диабете 2-го типа не до конца изучены.

Ключевые слова: сахарный диабет 2-го типа; когнитивные нарушения; болезнь Альцгеймера; цереброваскулярная патология; деменция; инсулинорезистентность; дисгликемия; гипогликемические состояния.

Как цитировать

Ромашевский Б.В., Салухов В.В., Максим О.В., Дуганова А.В. Патогенетические аспекты развития деменции у больных сахарным диабетом 2-го типа // Вестник Российской военно-медицинской академии. 2025. Т. 27, № 1. С. 105–114. DOI: https://doi.org/10.17816/brmma630664

Рукопись получена: 22.04.2024 **Рукопись одобрена:** 03.02.2024 **Опубликована online:** 28.03.2025

INTRODUCTION

The aging population has led to an increase in the number of individuals with cognitive impairment, particularly dementia. This issue is crucial from medical and social perspectives. According to Shin [1], the global prevalence of dementia reached 50 million cases. Approximately 10 million new cases are reported annually, two-thirds of which are diagnosed as Alzheimer's disease (AD) [2, 3].

Diabetes mellitus (DM) is a risk factor for cognitive impairment (CI) and is associated with an increased risk of dementia. Dementia is mainly caused by AD and vascular dementia [1–3]. Recent studies have shown that type 2 diabetes mellitus (T2DM) accelerates brain aging and cognitive decline from moderate impairment to dementia due to insulin resistance (IR) and other mechanisms. Thus, the risk of developing dementia almost doubles. Epidemiological, neuroimaging, and autopsy studies revealed the presence of cerebrovascular and neurodegenerative mechanisms of brain damage in T2DM. Insufficient compensation of carbohydrate metabolism and long-term DM are associated with cognitive decline [3].

The main risk factors for dementia include genetic predisposition, environmental influences, lifestyle, and dietary habits. However, cerebrovascular diseases, DM, hypertension, obesity, and dyslipidemia increase the risk of developing cognitive disorders. Despite the large number of studies on the pathogenesis of CI in patients with T2DM, the causal relationship between these conditions remains unclear.

This review aimed to analyze the data of current Russian and foreign scientific studies on the etiology and pathogenetic mechanisms of dementia in patients with T2DM.

SEARCH FOR ORIGINAL SOURCES

Current Russian and foreign studies on the etiology and mechanisms of dementia in patients with T2DM were reviewed using the electronic scientific library eLibrary.Ru and the PubMed electronic search system. The following keywords were used: *сахарный диабет 2-го типа* (*type 2 diabetes mellitus*), *когнитивные нарушения* (*cognitive impairment*), *деменция* (*dementia*), and *инсулинорезистентность* (*insulin resistance*).

Diabetes Mellitus as an Independent Risk Factor for Dementia

DM is an independent risk factor for CI development and is associated with an increased incidence of dementia, the primary etiologies of which are AD and vascular dementia [3, 4]. According to Meta-analysis findings indicated that the risk of developing dementia in individuals with DM exceeds 25% [4].

Various large-scale prospective studies [5–7] reported that the risk of developing dementia in patients with T2DM is nearly twofold higher, whereas the risk of developing AD is approximately 1.5-fold increased. Several studies [4, 6, 8] found that T2DM is characterized by combined vascular and AD-related dementia. The increasing number of patients with T2DM and the aging population further increase these rates [9, 10]. Evidently, moderate CI (45%–50%), which represents the preclinical stage of dementia, is prevalent among patients with T2DM [11, 12].

According to the 2023 American Diabetes Association guidelines for the care of patients with DM, older patients with DM are at a higher risk of developing CIs, which may range from mild executive dysfunction to memory loss and dementia [13]. Moreover, prediabetes increases the risk of cognitive decline. Women with prediabetes are more susceptible to these disorders and experience an earlier onset of dementia and metabolic disturbances in the cerebral cortex [4, 14].

A study using the UK Biobank database, which contains genetic and health information on over 500,000 UK residents [15, 16], showed that T2DM accelerates brain aging and cognitive decline. A mechanism wherein structural and functional changes develop in the brains of patients with DM is a chronic energy deficit caused by decreased IR and glucose utilization by neurons. Furthermore, IR in neurons may result in significant damage before T2DM symptoms occur.

Notably, CI in DM hinders patient adaptation and negatively affects adherence to treatment, such as those involving sugar-reducing medications or insulin therapy. Additionally, CI decreases glycemic self-control and compliance with dietary recommendations. These factors prevent glycemic compensation and increase the risk of acute and chronic complications of DM. Furthermore, CI increases the risk of cardiovascular disease and mortality [17–19].

DM may trigger the development of dementia in elderly and middle-aged people, who are at a higher risk of AD. Studies have shown that patients who develop DM in middle age more possibly develop dementia than those who develop DM in old age [20–22]. Therefore, the most effective way to prevent dementia is early diagnosis, treatment, and prevention of CI [23].

Pathogenesis of Dementia in Diabetes Mellitus

The pathogenesis of dementia in DM depends on several factors, including hyperglycemia, hypoglycemia, brain tissue IR, hyperinsulinemia, accumulation of advanced

glycation end-products (AGEs), and competition of the insulin-degrading enzyme with inhibition of amyloid beta peptide (Abeta) degradation. Other factors include microvascular and macrovascular cerebral disorders, neuroinflammation, impaired neurogenesis, blood–brain barrier (BBB) permeability, and increased glucocorticoid levels (Fig. 1).

Numerous studies using neuroimaging techniques confirmed an association between DM and brain atrophy, particularly in the hippocampus and amygdala, and revealed an association between DM and ischemic strokes and cortical and subcortical microinfarcts [24].

Hyperinsulinemia and Insulin Resistance

Insulin is a crucial hormone found in high concentrations in brain tissue. It is involved in cerebral functions including learning and memory [25].

It was assumed that the biological effects of insulin primarily manifested in adipose, muscular, and liver tissues. However, research has revealed that insulin modulates cell activity in the central nervous system (CNS) by binding to tyrosine kinase receptors, insulin-like growth factor receptors, and insulin receptors (pIR). Moreover, insulin regulates the phosphorylation of most intracellular proteins involved in deoxyribonucleic acid replication, cell cycle, metabolism, and autophagy. pIRs are widely distributed in different parts of the brain, particularly in the olfactory bulb, cerebral cortex, hypothalamus, amygdala, striatum, and hippocampus, the latter of which is responsible for memory. The binding of insulin to the insulin receptor substrate leads to its autophosphorylation, which initiates phosphatidylinositol-3-kinase activation. This enzyme stimulates protein kinase B production and inhibits glycogen synthase kinase-3. This process provides a membrane-stabilizing effect by inhibiting the production of free radicals [25–27]. Studies have shown that insulin-stimulated glucose transport into neurons increases the activity of cholinergic synapses in the CNS and enables higher brain functions [3, 16, 18].

Another key intracellular signaling pathway activated by insulin is the mitogen-activated protein kinase module. This module controls the transcription, translation, and posttranslational modifications of critical proteins, including growth factors, receptor genes, and matrix-modifying proteins. Furthermore, it regulates cell proliferation and apoptosis [25, 27].

Insulin induce neuroprotective effects that prevent damage caused by ischemia, beta-amyloid toxicity, and oxidative stress [3, 27, 28]. With advancing age, the total concentration of insulin in the brain decreases, as well as the ability of insulin to bind to receptors. This is known to result in cognitive dysfunction.

Cognitive function has been found to negatively correlate with insulin concentration, C-peptide levels, and the IR index in patients with T2DM, indicating the critical role of IR in brain tissue in the development of dementia [29, 30]. Recent studies have shown that CI in DM may be associated with IR and chronic inflammation in brain tissue, leading to neurodegeneration. This has led to considering dementia as *type 3 DM* (Fig. 2).

This hypothesis is supported by the fact that insulin levels and the number of insulin receptors are significantly higher in patients with AD, particularly in brain regions linked with learning and memory, than in healthy individuals. As previously mentioned, insulin and its signaling pathways regulate glucose and energy metabolism, learning, and memory. Structures associated with learning, such as the hippocampus, have a high density of pIR; thus, it is hypothesized that they are capable of producing insulin independently. Disturbances in insulin signaling mechanisms may lead to cognitive dysfunction, which is manifested by decreased memory and attention and impaired executive functions [30]. This is supported by autopsy findings in patients with AD, which revealed decreased expression of genes encoding proteins of the insulin signaling system [31].

IR and hyperinsulinemia also contribute to the development of dyslipidemia, hypertension, and cerebral atherosclerosis. These conditions cause vascular dementia [3, 18, 25].

Thus, IR plays a key role in the development of severe CIs in patients with T2DM. Treatment strategies should aim to use medications that improve insulin sensitivity, provide effective and safe glycemic control, and have neuroprotective potential. Other factors contributing to the development of dyslipidemia, hypertension, and cerebral atherosclerosis include IR and hyperinsulinemia, which result in cerebral lesions [3, 18, 25].

Dysglycemia

Notably, chronic hyperglycemia and hypoglycemia cause neuronal damage, oxidative stress, necrosis of brain structures, neuroinflammation, disruption of neuroplasticity, and neurodegeneration. Thus, a relationship was observed between glycemia, glycated hemoglobin (HbA1c) levels, and disorders of higher brain function in patients with DM. Sherwani et al. demonstrated that increased HbA1c levels were positively correlated with CI in the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes study [32]. However, single episodes of increased glycemia were not associated with a decrease in psychodiagnostic test results. This indicates that

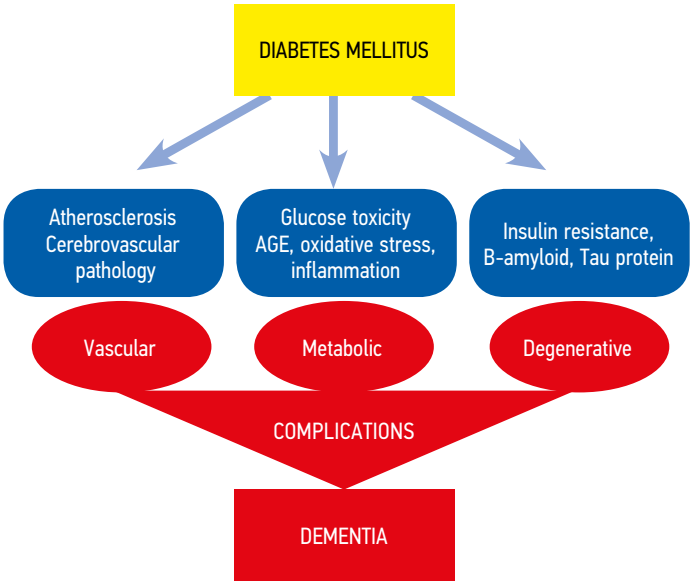

Fig. 1. General mechanisms of dementia development in patients with type 2 diabetes mellitus: AGE, advanced glycation end products
Рис. 1. Общие механизмы развития деменции у больных, страдающих сахарным диабетом 2-го типа: AGE — конечные продукты гликирования; Tau protein — тау-белок

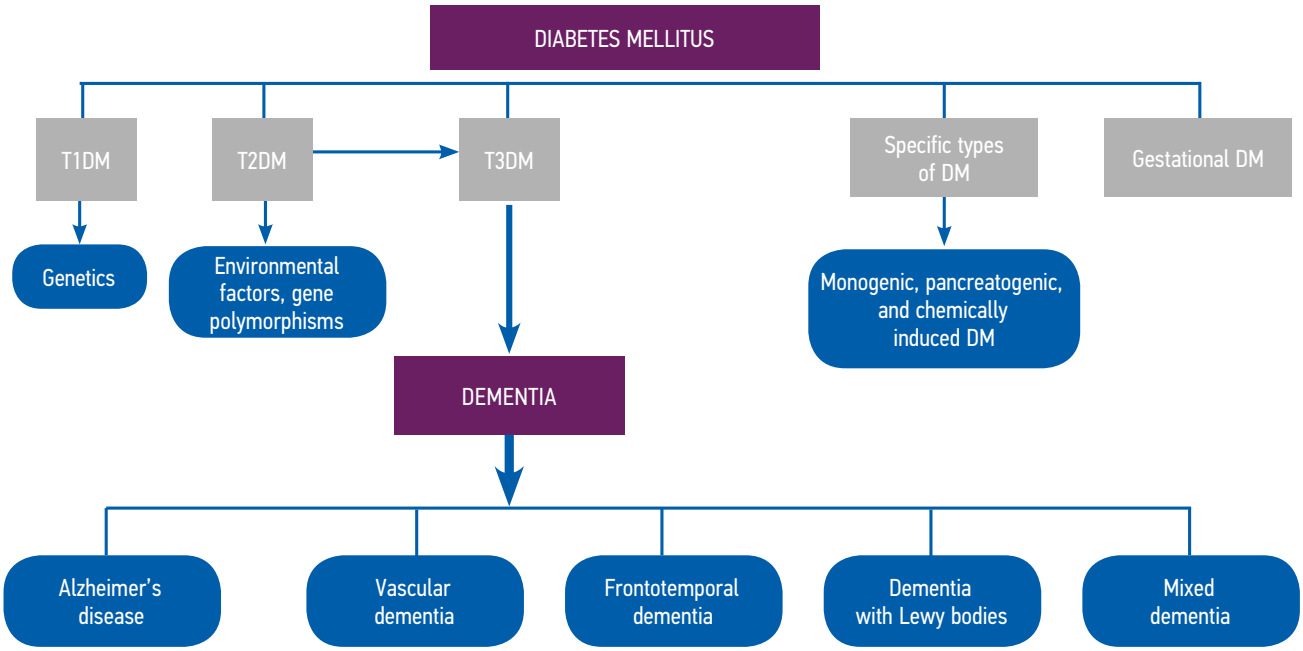

Fig. 2. Current perspectives on diabetes mellitus classification (adapted from [30] A. Selman et al., 2022. Distributed under the terms of the CC-BY 4.0 license)
Рис. 2. Современные представления о классификации сахарного диабета (адаптировано из [30] A. Selman и соавт., 2022. Распространяется на условиях лицензии CC-BY 4.0)

chronic hyperglycemia negatively impacts cognitive function. Other studies have reported that high average daily glycemic levels are linked with an increased risk of dementia [33]. In addition, a negative correlation was found between cognitive function and postprandial glycemic index [34, 35].

Several preclinical studies have demonstrated that hyperglycemia increases Abeta levels in the interstitial fluid, altering neuronal activity [36, 37]. Dysglycemia appears to alter the functioning of adenosine triphosphate-sensitive potassium channels, which correlates with changes in Abeta metabolism and the functional state of the CNS. Chronic hyperglycemia increases the binding of glucose to the amino groups of proteins, forming unstable and heterogeneous compounds, particularly AGEs, which modify neurofibrillary

tangles and beta-amyloid plaques, contributing to neurodegeneration progression in AD.

Hyperglycemia activates free-radical oxidation, nonenzymatic protein glycosylation, and the polyol pathway of glucose metabolism. These processes initiate the formation of AGEs, which cause endothelial dysfunction and hemorheological disorders, resulting in the development of cerebral microvascular lesions.

Hypoglycemia is another factor that affects structural and functional CNS disorders in patients with T2DM. Hypoglycemia has been found to play a critical role in the development and progression of CNS disorders, because normal brain function depends on glucose levels, which are the main source of energy for cerebral metabolism [38].

Short-term CIs may occur in mild hypoglycemia, causing symptoms such as confusion. Conversely, severe hypoglycemia may lead to disturbances in the brain, particularly in the cerebral cortex and hippocampus. For example, the Atherosclerosis Risk in Communities cohort study found that hypoglycemia was associated with decreased total brain volume [38]. Moreover, the Edinburgh Type 2 Diabetes Study found a correlation between hypoglycemic episodes and severe cognitive dysfunction [8]. In addition to neuroglycopenic reactions, acute hypoglycemia may lead to hypertensive crises, hemorheological disorders, sympathoadrenal system activation, and hormonal dysregulation. Furthermore, hemodynamic and hemorheological disorders that develop with endothelial dysfunction and oxidative stress, cytokine dysregulation, and activated apoptosis factors increase the risk of local tissue ischemia and vascular complications [25, 30].

Consequently, CI increases the risk of hypoglycemia because patients either fail to adhere to dietary recommendations or take excessive doses of sugar-lowering medications. Thus, the Action in Diabetes and Vascular Disease: PreterAx and DiamicroN-MR Controlled Evaluation study [13] revealed that severe cognitive dysfunction significantly increased the risk of hypoglycemia by over twofold [13]. Notably, CI impedes detection of hypoglycemia and timely and adequate medical care. Additionally, CI poses a danger of severe hypoglycemic episodes and fatal complications [10, 38]. The GERODIAB study, which examined the relationship between glycemic control and causes of death in patients with T2DM, found that mortality was twofold higher in patients with Mini-Mental State Examination scores <24 than in those with scores >24 after 2 years of follow-up [10].

Therefore, hypoglycemia plays a role in the development of severe CI. It increases the risk of dementia by reducing neuroplasticity and inducing neuronal death. Hypoglycemia contributes to increased platelet aggregation and fibrinogen formation, which may result in cerebral vascular thrombosis. Furthermore, it may lead to dysfunction in brain regions responsible for learning and memory [39–41].

Amylin

In recent years, the role of hyperamylinemia in the development of asthma has been discussed [40, 42]. Amylin, also called islet amyloid polypeptide, is a neuroendocrine hormone secreted by pancreatic beta cells with insulin. It interacts with brain nuclei to regulate satiety through central mechanisms, reduce appetite and gastric emptying rate, and suppress glucagon secretion, preventing postprandial hyperglycemia. Along with insulin and glucagon, amylin is one of the main pancreatic islet hormones involved in maintaining glucose homeostasis. Hyperamylinemia in patients with IR leads to increased amylin deposition in the pancreatic islets and decreased beta cells due to increased apoptosis and/or necrosis. Thus, hyperamylinemia contributes to the development of absolute insulin deficiency. Koenig et al. [40] showed that amylin gene polymorphism is associated with AD. The authors found that elderly patients with AD or moderate CI had lower plasma amylin concentrations than healthy individuals. Moreover, analysis of brain tissue from patients with T2DM and AD revealed a significant amount of amylin deposition in the gray matter of the brain and cerebral vessels. Additionally, studies have shown that amylin accumulation may increase Abeta aggregation, indicating a link between AD and T2DM. These substances have been detected in the brains of patients with AD and those without carbohydrate metabolism disorders [43]. The possibility of using an amylin analog (pramlintide) as a diagnostic test for AD is currently being studied [44, 45].

Gut Microbiota

Recent studies have demonstrated the role of gut microbiota disorders in the development of neuroinflammation and AD in patients with T2DM. Several studies [46, 47] have determined that the microbiome–gut–brain axis is a bidirectional system regulating nervous, immune, endocrine, and metabolic pathways. Increased BBB permeability with concurrent intestinal dysbiosis may influence the pathogenesis of AD and neurodegenerative changes. In addition, gut bacteria may produce significant amounts of amyloids and lipopolysaccharides that contribute to pro-inflammatory cytokine secretion and modulation of signaling pathways involved in AD pathogenesis. Moreover, gut dysbiosis may be a factor in chronic inflammation associated with the pathogenesis of obesity, T2DM, and AD.

DOI: https://doi.org/10.17816/brmma630664

CONCLUSION

Numerous studies confirmed the relationship between DM and neurodegenerative processes in the CNS. The links between the pathogenesis of T2DM and dementia include IR, dysglycemia, oxidative stress, chronic inflammation, macrovascular and endothelial dysfunction, Abeta accumulation, and CI. Notably, hyperinsulinemia and IR play a critical role in impaired insulin signaling and cognitive decline. The importance of IR of brain tissue, accompanied by CI, is significant, as it is considered *type 3 DM*. In some cases, IR in brain tissue results from impaired glucose metabolism in peripheral tissues. This leads to impaired glucose transport and increased Abeta levels, indicating the leading role of IR in the development of T2DM and dementia. Additionally, the macrovascular chronic complications of DM, hypertension, dyslipidemia, and intestinal dysbiosis are attributed to the development of dementia in patients with T2DM.

However, the molecular and cellular mechanisms of dementia progression in patients with T2DM remain unclear. Future studies are warranted to provide additional insight into the mechanisms of cognitive decline in patients with T2DM and methods to address these disorders.

ADDITIONAL INFORMATION

Authors' 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.

The contribution of each author. B.V. Romashevsky, development of a general concept, writing an article, data analysis; V.V. Salukhov, research design, data analysis; O.V. Maxim, literature review, writing an article; A.V. Duganova, literature review, data analysis.

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.

Вклад каждого автора. Б.В. Ромашевский — разработка общей концепции, написание статьи, анализ данных; В.В. Салухов — дизайн исследования, анализ данных; О.В. Максим — обзор литературы, написание статьи; А.В. Дуганова — обзор литературы, анализ данных.

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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