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Neuroprotective effects of the ketogenic diet and its potential in psychiatric treatment- A review

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ABSTRACT

Introduction: Medical researchers have recently investigated new treatment methods for psychiatric disorders due to drug resistance in many patients. Clinical studies show that following different specific types of diets has a positive impact on health. According to existing literature, one of them is a ketogenic diet. This dietary restriction has a neuroprotective effect in response to reducing carbohydrates to 10%, with a shift in metabolism to fatty acids. The aim: This publication aims to present the theoretical mechanism of the ketogenic diet and its potential for application in medical conditions with an emphasis on psychiatric disorders. For this purpose, we analyzed clinical studies conducted in this area. Results: Evidence suggests that psychiatric disorders may be associated with disturbance in neurotransmitter balance, inflammation, mitochondrial and energy metabolism dysfunction, oxidative stress, and gene expression changes. Moreover, the ketogenic diet may affect the regulation of these pathological processes. While most studies have shown a potential positive impact, the current evidence remains insufficient to use it as a standardized therapeutic option. Conclusion: There is a close relationship between the use of the ketogenic diet and its impact on pathological mechanisms in individuals with psychiatric conditions. However, the results remain more theoretical, and studies with an extended observation period and more participants are required.

Keywords: ketogenic diet, drug resistance, psychiatric disorders, neurological disorders, nervous system, mitochondrial dysfunction

1. INTRODUCTION

New therapeutic approaches for psychiatric disorders have received increasing attention due to the high prevalence of these conditions in recent years. Unfortunately, long-term remission still cannot be sustained in many individuals, and they are treatment-resistant. To identify the problem, we must start by making a good psychiatric diagnosis. The patient should receive proper treatment but fails to respond as expected. However, it is good to point out that there is a difference in

resistance criteria for each psychiatric condition (Howes et al., 2022). Unfortunately, the side effects of pharmaceutical agents impact the quality of life and sometimes lead to treatment discontinuation.

Furthermore, these undesirable effects of antidepressant medication can affect up to 60-75% of these patients (Campos et al., 2021). Psychiatric disorders are often directly associated with metabolic dysfunction, such as obesity, overweight, and risk of cardiovascular disorders. Moreover, the use of antipsychotic drugs can additionally lead to increased body mass and BMI. Regrettably, this effect can apply to typical and atypical forms of these pharmacological agents (Bak et al., 2014). Therefore, it has become essential to search for a new method that would reduce the metabolic effects and regulate symptoms of psychiatric conditions.

The primary assumption of the ketogenic diet is to use the appropriate proportions of carbohydrates, fats, and proteins. This intervention creates a state of ketosis. In this case, we have to reduce carbohydrates to 10%. After applying these conditions, metabolic processes primarily use fatty acids. It enables the production of ketone bodies, serving as an energy substrate. Recent literature shows that the ketogenic diet has multiple positive effects on our brains, which will be presented below (Ułamek-Kozioł et al., 2019). These potential mechanisms of the ketogenic diet's impact on the nervous system have opened up the possibility of discussing its use also in psychiatric diseases.

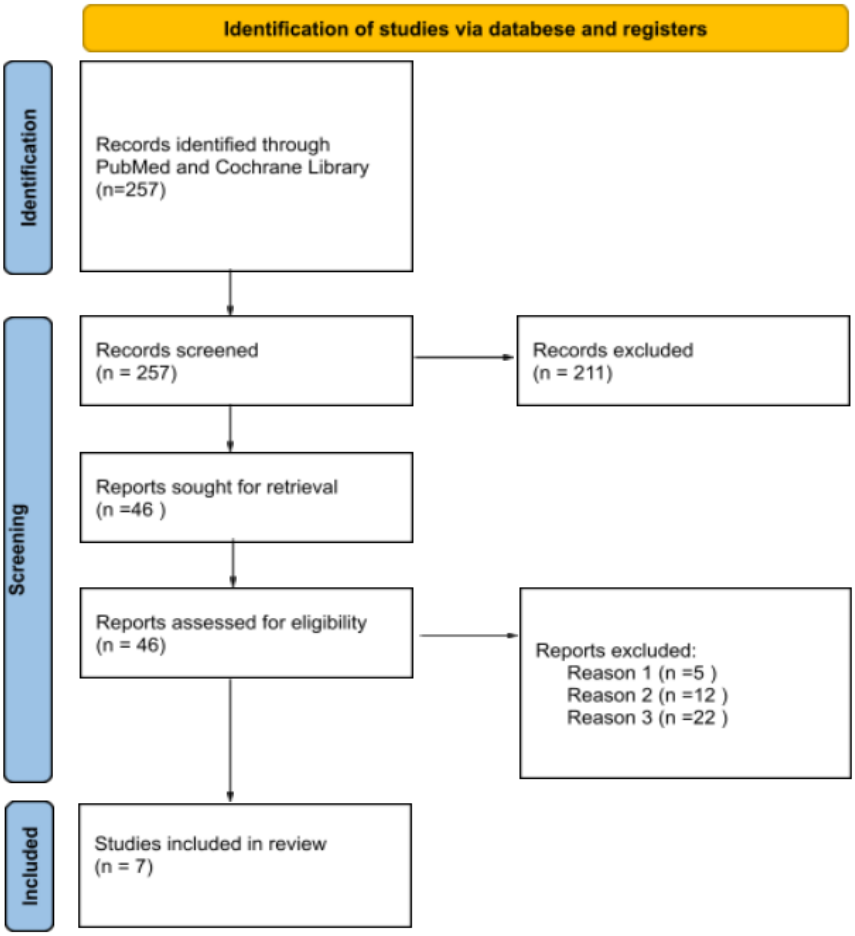

Figure 1: PRISMA flowchart

2. REVIEW METHODS

This review article was based on an analysis of medical literature using PubMed and Cochrane Library. For this purpose, basic keywords related to the topic were used, such as: "ketogenic diet" AND "psychiatric disorders". The search covered medical studies published from 2009 up to May 2025, with a larger focus on the last few years. The review aimed to present the potential mechanism of the ketogenic diet, pathophysiological changes in individuals suffering from mental disorders, and the possible use of this diet as a treatment method, and, in conclusion, summarize the recent findings. The inclusion criteria contained relevant peer-reviewed articles-systematic reviews, narrative reviews, meta-analyses, clinical trials, and case reports. The included literature focuses on the

mechanisms of the ketogenic diet and psychiatric disorders, as well as connections between this dietary intervention and its impact on the nervous system. Exclusion criteria contained non-English articles (Reason 1), articles without full-text access (Reason 2), and articles with missing data related to the topic(Reason 3). We took into consideration only articles we assessed as high-quality. A total of 7 articles met all criteria (Figure 1).

3. RESULTS AND DISCUSSION

What is the ketogenic diet, and the state of ketosis?

Researchers observe several mechanisms by which the ketogenic diet influences health outcomes. Firstly, the ketogenic diet has a different composition of fundamental dietary components. The basic assumption is to reduce the number of calories and increase fat levels while maintaining adequate protein and low carbohydrate levels. The standard ketogenic diet contains 70% fat, 20% protein, and carbohydrates limited to 10% (Zhou et al., 2022). As a consequence of its application, we can achieve a state of ketosis. The energy supply is usually glucose. However, in this case, it is ketone bodies. Moreover, fat levels in this diet must reach 70-80% (Dyńka et al., 2023). We can identify the following types of ketogenic diet: a medium-chain triglyceride diet (MCT), a modified Atkins diet (MAD), and a low-glycemic index treatment (LGIT). These forms differ in the proportion of components (Borowicz-Reutt et al., 2024). Returning to a key point, we can distinguish three central forms of the ketone bodies: β-hydroxybutyrate, acetoacetate, and acetone (Dyńka et al., 2022). The accumulation of ketone bodies can cause pathology, but under appropriate conditions, we can use them as a source of energy. It is also crucial to point out that this dietary approach reduces glycolysis processes compared to the increase of ketogenesis in this situation (Malinowska & Żendzian-Piotrowska, 2024). In normal conditions, the energy source is glucose (Dyńka et al., 2022). The state of ketosis can also occur when fasting and reducing the amount of calories because it also initiates the synthesis of ketone bodies. β-hydroxybutyrate can pass the blood-brain barrier and step the Krebs cycle promptly. It is a more effective energy supply than glucose (Cannataro, 2023).

The impact of the ketogenic diet on other medical conditions as a potential treatment method

The use of the ketogenic diet as a therapeutic approach originated from research focused on drug-resistant epilepsy. Studies have shown its therapeutic benefits on other medical conditions: metabolic and neurological disorders and cancer (Malinowska & Żendzian-Piotrowska, 2024).

Metabolic effect

It is good to point out that a positive metabolic effect is also significant when considering its use in psychiatric disorders due to the strong connection between them. Maintaining an appropriate lipid profile is crucial. Inappropriate values of LDL, HDL, triglycerides (TG), and total cholesterol (TC) may become risk factors for the development of many medical conditions, such as cardiovascular disease. In clinical cases, there is a significant relationship between the application of the ketogenic diet and its influence on body weight, glycemia, and lipid profile. Moreover, there is still discussion about whether this diet has a better effect than other dietary interventions. In a meta-analysis of randomized controlled trials, Zhou et al., (2022) assessed the relationship between the ketogenic diet and its impact on lipid fractions. The study group was overweight patients with T2DM and carbohydrate intake of less than 50g. Results showed a greater reduction in body weight compared to other applied diets. Moreover, it showed changes in lipid profile: higher reduction in triglyceride level and an increase in HDL level, with no significant change in LDL and total cholesterol compared to other applied diets. It also showed a greater reduction in HbA1c with no significant difference in fasting glucose and HOMA-IR.

In a systematic review and meta-analysis, Giovanna Muscogiuri et al. assessed the impact of a very low-calorie ketogenic diet on weight changes. The meta-analysis included controlled studies with patients using VLCKD. VLCKD maintained the level of carbohydrates at 30–50 g/day with ≤800 kcal. It also showed that the VLCKD diet had a bigger influence on weight loss than other body loss interventions. Muscogiuri et al., (2021) also noted changes in lipid profile. These results showed bigger reductions in triglyceride and total cholesterol than other interventions. It showed LDL reduction, but not more significant than other therapeutic methods, with no change in HDL. In addition, it revealed positive changes in fasting glycemia, HbA1c, and HOMA-IR. HOMA-IR changes were more significant after the VLCKD than in other analyzed groups.

In summary, the metabolic effect of the ketogenic diet is visible in patients with obesity and diabetes. Compared to other analyzed interventions, the results regarding changes in some individual parameters are more significant. Unfortunately, it is challenging to reach a clear conclusion because the different results in the attached meta-analysis may be due to the inclusion criteria. We haven't

found a meta-analysis of metabolic effects for psychiatric patients. The next section of this review presents the results of this correlation in the context of individual studies.

Neurological disorders

However, the primary area of application of the ketogenic diet is neurological disorders. Although many therapeutic options for epilepsy, such as medications, deep brain stimulation, or surgery, are available, the disorder is still often drug-resistant. Regrettably, inadequate control of the disease may lead to adverse effects such as decreased quality of life or increased risk of sudden death. It is essential to highlight that a new generation of anti-epileptic medications can reduce side effects and interactions with other medications without significant changes in effectiveness (Borowicz-Reutt et al., 2024). Significantly, numerous clinical studies with the application of the ketogenic diet have demonstrated a reduction in the frequency of seizures, mostly in children and adolescents. Most showed visible improvement in a treatment (Faheem et al., 2024). After noticing these positive results, subsequent research explored its use in neurodegenerative disorders. Dementia is one of the symptoms of these conditions. Later studies on the impact of this diet also included Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (Rusek et al., 2019).

The main pathway of action in the neurological system

However, there are many possible hypotheses about the mechanisms of action by which this dietary restriction can affect biological pathways in the nervous system. The search for these connections was the beginning of creating assumptions about the similarities to psychiatric conditions. One perspective holds that diet can affect the level of neurotransmitters, which seems most relevant to the topic. The observed changes may include a decrease in glutamate and an increase in GABA (gamma-aminobutyric acid) (Dyńka et al., 2022). The ketogenic diet also affects the functioning of mitochondria. It is the organelle responsible for energy production during the Krebs Cycle and the place for oxidative phosphorylation (Paoli & Cerullo, 2023).

The positive impact of this diet on neurodegenerative diseases is associated with the regulation of mitochondrial function. It can influence the respiratory mitochondrial complex and the level of antioxidants. Furthermore, the level of reactive oxygen species decreases. Additionally, in neurodegenerative diseases, stimulation of neuroinflammatory pathways increases (Tao et al., 2022). Ketogenic diet and its potential impact on psychiatric disorders. Researchers are considering new therapeutic methods because neuroleptics prescribed for psychiatric conditions may induce a range of unbeneficial side effects, such as negative metabolic impact, which may often result in discontinuation of the treatment (Pillinger et al., 2020).

What's more, the link between epilepsy and bipolar disorder is evident in the pharmacological treatment used for both conditions. It can support the hypothesis that both disorders can share underlying mechanisms because, in bipolar disorder, we can use several anti-epileptics. In both cases, neurological and psychiatric disorders may occur, among others, biochemical disturbances in neurotransmitter levels, neuroinflammation, oxidative stress, and mitochondrial impairment (Danan et al., 2022). To discover the potential effect of a ketogenic diet on psychiatric disorders, it is necessary to consider the pathway of their origin. It is worth mentioning that the etiology of these conditions may be multifactorial.

One hypothesis is that mitochondrial dysfunction occurs in these conditions. In a meta-analysis, Pinto Payares et al., (2024) analyzed the relationship between mitochondrial dysfunction and mental disorders. The presented results suggest that this correlation may occur among others in individuals with schizophrenia, bipolar disorder, anxiety, major depression, and ADHD. Mitochondrial dysfunction can appear in a different perspective, e.g., as a shift in gene transcription, gene mutation, structural abnormality, disturbance in oxidative phosphorylation, and ATP formation. The function of mitochondria is primarily energy production. Moreover, it also plays an important role in other cell processes, such as calcium buffering and apoptosis (Toker & Agam, 2015). Furthermore, mitochondria also control ion and redox reactions. Moreover, it regulates the growth of cells and their signaling (Javadov et al., 2020).

Researchers have tested the mitochondrial dysfunction hypothesis on individuals. Studies in patients with bipolar disorder have shown that there are observable changes in this subject. Changes appear in the mitochondrial dynamics. Results suggested an increased fission process (Scaini et al. 2017). The process of fusion and fission regulates the number of mitochondria and their quality. Mitochondria with damaged morphology reduce fusion, which enables the destruction of proper organelles (Kornmann, 2014). Studies show that the ketogenic diet may prevent mitochondrial fission and regulate mitochondrial dynamics (Guo et al., 2020). Moreover, studies showed that mitophagy dysfunction can occur in individuals with neuropsychiatric conditions (Jiang et al., 2024). Mitophagy is a special form of autophagy that causes degradation of impaired mitochondria. It is essential for cellular metabolism and maintaining proper mitochondrial condition (Liu et al., 2023).

A study on mice showed that the level of mitophagy regulator BNIP3 increased in individuals with a ketogenic diet, which may suggest that this diet has a potential impact on this process (Newell et al., 2016). Mitochondrial dysfunction may also be indirectly related to gene changes in the electron transport chain. Moreover, studies showed mutations in the mtDNA. Consequently, another potential cause of psychiatric disease is oxidative stress. Increased oxidative stress may cause numerous damages (Madireddy & Madireddy, 2022). An increased production of reactive oxygen species can cause a disturbance in cell physiology. Studies showed changes in proteins, DNA, lipids, and other macromolecules. It is good to point out that oxidative stress is a significant factor in degenerative disease, which induces neuronal damage (Hajam et al., 2022). The ketogenic diet reduces the production of reactive oxygen species. Moreover, we can observe a higher level of antioxidants (Tao et al., 2022). These processes enable us to keep up high-quality mitochondria. Another important aspect is the creation of new organelles. It is possible thanks to mitochondrial biogenesis. During this process, new mitochondria can arise from old ones. The correlation between biogenesis and mitophagy creates a state of homeostasis (Popov, 2020).

The ketogenic diet can potentially induce biogenesis. It may be possible due to increased transcription of the electron transport chain subunit messenger ribonucleic acids. It can improve ATP production (Paleologou et al., 2017). Studies on animals and humans showed that there is a correlation between depression and neuroinflammation. In microglia, we can find expression of NLRP3 inflammasome signaling, which is responsible for the P2X7-NLRP3 cascade. It is a key factor in the pathophysiology of depression (Wu & Zhang, 2023). One of the hypotheses on the beneficial effect of the ketogenic diet is its neuroinflammatory effect. There are a lot of potential pathways associated with this effect. One is the influence on the activation of NLRP3-induced inflammation and then interleukin. Beta-hydroxybutyrate can inhibit this mechanism (Di Majo et al., 2022). Mitochondrial dysfunction can be associated with disturbances in calcium homeostasis, which play crucial roles in neuroplasticity and neurotransmission. These organelles can also influence the time and level of neurotransmitter release from the presynaptic space. Disturbances in these processes can lead to psychiatric disorders. Basal Ca2+ levels are lower in the intracellular space, and their changes can result in mitochondrial depolarization. Additionally, Ca2+ levels in the mitochondria can influence ATP production (Bansal & Kuhad, 2016).

Another hypothesis related to the connection between psychiatric disorders and the ketogenic diet is associated with neurotransmitter levels. Clinical studies showed that neurotransmitter levels are disturbed in individuals with psychiatric disorders. Mostly, disturbance in neurotransmitters regarding GABA and glutamate. Glutamate has an excitatory effect, while GABA has an inhibitory one. The brain requires both at a good level for proper functioning. The key method to determine the level of these neurotransmitters is 1H magnetic resonance spectroscopy (MRS) (Sarawagi et al., 2021). An additional prospective benefit of the ketogenic diet may be its epigenetic regulation. This dietary intervention can influence gene expression through different processes. There are assumptions that ketone bodies can also act as histone deacetylase inhibitors (Dąbek et al., 2020).

Current evidence on the use of the ketogenic diet

Current research on the ketogenic diet remains limited. Researchers conducted only a few clinical studies showing an evident effect. Unfortunately, most of them are still case reports. More randomized clinical trials are still needed. Initially, the research started on animals. It focused on various conditions: anxiety, depression, schizophrenia, autism spectrum disorder, and attention deficit hyperactivity disorder. However, it is essential to point out that tests conducted on animals cannot be the sole determinant. Research on humans is necessary to use the ketogenic diet as a form of therapy (Bostock et al., 2017).

Scientists have described only a few case reports and have conducted limited clinical studies. It is essential to highlight that some individuals with schizophrenia and bipolar disorder experienced a beneficial impact after the ketogenic diet. In one case report, Kraft and Westman (2009) presented a case of a 70-year-old woman with a diagnosis of schizophrenia. Her symptoms, such as auditory and visual hallucinations, had persisted almost daily since the onset of the disease. In this article, we can observe that despite the use of various drug combinations, there was no improvement. Symptoms disappeared after starting a low-carbohydrate ketogenic diet with a maximum carbohydrate intake of 20g/day. Moreover, during the 12-month observation, patients maintained an improvement in symptoms. Additionally, these individuals experienced weight loss.

In a clinical study conducted with adult patients diagnosed with schizophrenia and bipolar disorder, Sethi et al., (2024) investigated the potential effects of using a ketogenic diet on these conditions. Each person was taking a psychotropic drug and was obese or had gained weight during therapy or had at least one metabolic problem. Patients used a diet with carbohydrate reduction to a maximum of 20g per day. Patients showed an improvement in disease severity of 31% on average. There was an increase from 33% to 75% in individuals who were in recovery. At the beginning of the study, 29% of patients met the criteria for metabolic syndrome,

whereas at the end, none did. In addition, a pilot study conducted by Needham et al., (2023) with a patient with bipolar disorder showed the result of using a modified ketogenic diet. They checked the recruitment and feasibility of staying on this diet. Of 26 individuals, 20 completed the intervention. The side effects observed during the observation period were mild, e.g., hypoglycemia, fatigue, constipation, drowsiness, or diarrhea. One individual using SGLT2 inhibitors experienced one adverse effect - ketone levels of 7.1 mmol/L.

This dietary intervention also improved the symptoms of depression, anxiety, and schizoaffective disorder. In a retrospective clinical study, Albert Danan et al. examined the effect of the ketogenic diet on individuals with major depression, bipolar disorder, and schizoaffective disorder. Most of the patients were taking a psychotropic (25 of 28). After the intervention, 64% of patients taking psychotropic medication had their dose or number reduced. In patients taking non-psychotropic, it was 71%. At the end of the study, researchers assessed the results using questionnaires: Hamilton Depression Rating Scale, Montgomery-Åsberg Depression Rating Scale, and Positive and Negative Syndrome Scale (PANSS) for schizoaffective patients. There was a visible improvement after the intervention (Danan et al., 2022). Moreover, in a case report, a patient with bipolar disorder using a strict ketogenic diet observed an improvement in mood, cognitive functions, concentration, and sleep.

In addition, they experienced a decrease in anxiety and a shortening of episodes of depression. They also extended remission periods after the application of a restrictive diet. There was no hypomania, and patients could reduce the doses of medications. The last modification that led to complete remission involved the introduction of the ketogenic diet with a cyclical one-day fast every 7-10 days (Chmiel, 2022). A case study presented by Melanie Tidman showed a 68-year-old individual with Parkinson's disease and additional anxiety and depression symptoms. She also experienced positive changes after the application of the ketogenic diet. Scores decreased from 42 to 34 points in the Center for Epidemiologic Studies Depression Scale and from 23 to 17 points in the Parkinson's Anxiety Scale in a 24-week (Tidman, 2022).

While all studies showed a positive impact, the evidence is insufficient to establish the diet as a standard treatment. Table 1 summarizes the articles discussed in this section.

Table 1. Summary of research on the use of the ketogenic diet in psychiatric disorders

Authors	Year	Study group	Intervention	Results/ Conclusions
Bostock et al.,	2017	Animal models (anxiety, depression, schizophrenia, ASD, ADHD)	ketogenic diet	Further human studies are necessary.
Kraft & Westman	2009	A 70-year-old woman with schizophrenia	low-carbohydrate ketogenic diet (max carbohydrate intake 20g/day)	Hallucinations disappeared after the intervention.
Sethi et al.,	2024	Patients taking psychotropic medications with bipolar disorder or schizophrenia + metabolic problems	ketogenic diet (max carbohydrate intake 20g/day)	Improvement in disease severity of 31% on average. Recovery rates increased from 33% to 75%. In the end, 0% met the criteria of metabolic syndrome.
Needham et al.,	2023	Patients with bipolar disorder	modified ketogenic diet	20 patients from a group of 26 completed the intervention. Mild side effects, one adverse.
Danan et al.,	2022	Patients with major depressive disorder, bipolar disorder, and schizoaffective	ketogenic diet	64% of psychotropic users reduced dose or number of medications. In non-psychotropic 71%.

		disorder		Improvement on HDRS, MADRS, PANSS.
Chmiel	2022	Patient with bipolar disorder	ketogenic diet + cyclic 1-day fasting every 7-10 days	Improvement in mood, cognitive function, concentration, and sleep. Decreased anxiety and shortening of the episode of depression, and then complete remission.
Tidman	2022	Patient with Parkinson's disease and additional depression and anxiety symptoms	ketogenic diet	CES-D reduction from 42 to 34, PAS reduction from 23 to 17.

4. CONCLUSION

Unquestionably, we can find in the medical literature the mechanisms by which the ketogenic diet may influence psychiatric disorders. We can observe a positive impact on the nervous system. Moreover, this dietary intervention can regulate neurotransmitter levels, mitochondrial function, and gene expression processes. It reduces inflammation and oxidative stress reactions, which are significant in the etiology of mental illness. Therefore, clinical trials mostly focused on individuals with epilepsy and then on neurodegenerative disease. Regrettably, results regarding patients with psychiatric disorders are still insufficient. Most studies are case reports or observational trials with a limited sample size, which is not satisfactory to use as a standardized therapeutic option. We should introduce this intervention with caution in the subsequent clinical trials. Undoubtedly, studies showed a reduction in psychiatric symptoms, but a more extensive analysis is needed. The potential is visible, but further RCTs must include a larger group of individuals and a more extended period.

Author's Contributions

Agnieszka Czernecka- Conceptualization, review and editing, investigation, methodology
Karolina Jałocha - Methodology, investigation, visualization, supervision
Kinga Świtała - Conceptualization, visualization, resources,
Kinga Erazmus - Review, data curation, investigation
Marek Borecki - Resources, writing- rough preparation, data curation
Patrycja Pysz - Visualization, data curation, investigation
Maria Mroczka - Review, visualization, formal analis
Justyna Kuciel - Supervision, writing- rough preparation, data curation
Dominik Tomczak - Review and editing, formal analis, supervision
Roksana Hrapkowicz - Resources, writing- rough preparation, formal analis
Project administration - Agnieszka Czernecka

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Informed consent

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Ethical approval

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Conflict of interest
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Data and materials availability
All data associated with this study will be available based on the reasonable request to corresponding author.

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