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Authors' Affiliation:
University Clinical Hospital in Poznan, Przybyszewskiego 49, 60-355 Poznan, Poland

***Corresponding author:**
Agnieszka Mariowska,
University Clinical Hospital in Poznan, Przybyszewskiego 49, 60-355 Poznan, Poland; e-mail: agnieszkamariowska18@gmail.com
Phone number: (+48) 733 211 463

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The Impact of Obesity on the Development and Progression of Selected Autoimmune Diseases: Interplay Between Inflammation and Immune Dysregulation – A Review

Agnieszka Mariowska*, Paulina Horwat, Anita Szymańska, Weronika Pierudzka, Marta Dzieciątkowska

ABSTRACT

Background: Obesity is a metabolic disorder and an immunomodulatory factor that may play an essential role in the pathogenesis of autoimmune diseases. Chronic low-grade inflammation associated with excess body fat can lead to impaired immune tolerance and activation of autoimmune responses. Aim: The aim of our systematic review focused on assessing the impact of obesity on selected autoimmune diseases. Materials and Methods: The databases Pubmed and Google Scholar were searched for the years from 2000 to 2024. Researchers searched using the keywords: "obesity and autoimmunity", "adipokines and inflammation" , "obesity and type 1 diabetes" , "obesity and Hashimoto's thyroiditis", "obesity and rheumatoid arthritis", and "obesity and psoriasis". This review includes original studies, reviews, and meta-analyses on the relationship between obesity and autoimmunity. Results: The article describes the impact of obesity on the immune system, taking into account the role of leptin and adiponectin, among others. Furthermore, it highlights the correlation between obesity and autoimmune diseases, particularly type 1 diabetes, Hashimoto's disease, psoriasis, and rheumatoid arthritis. Research shows that obesity can exacerbate disease symptoms, worsen response to treatment, and increase the risk of complications. Conclusions: Obesity has multiple effects on the course of autoimmune diseases. Weight reduction may provide therapeutic benefits by reducing inflammation and improving response to treatment.

Keywords: obesity, autoimmune diseases, adipokines, inflammation, immune system

1. INTRODUCTION

Obesity is becoming an increasingly serious health problem due to the growing prevalence of this condition (Busebee et al., 2023). According to the World Health Organization (WHO), obesity affects 603 million adults and 107 million children

globally. The marker used to define excess weight such as overweight and obesity is body mass index (BMI). Being overweight is diagnosed when BMI is between 25 and 29,9 while being obesity when the marker is over 30 (Koliaki et al., 2023). Epidemiological estimates indicate that by 2030, 30% of the world's population may be overweight and 20% obese (Hruby and Hu, 2014). In addition, there is an increasing incidence of autoimmune diseases, which are characterized by abnormal functioning of the immune system and attacks on the body's own tissues (Miller, 2023). The most common autoimmune diseases include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), Hashimoto's autoimmune thyroiditis, and psoriasis (Gremese et al., 2014; Verbeeten et al., 2010; Hedström et al., 2012). These entities present with a variety of clinical manifestations, follow a chronic course, and have a partially unrecognized etiopathogenesis. Obesity is not only a metabolic disorder, but also affects the functioning of other systems, including the immune system, by modifying the function of this system. As a result, activated lymphocytes may contribute to the onset or progression of autoimmune diseases (Milano et al., 2022).

The aim of this systematic review is to summarize the relationship between obesity and selected autoimmune diseases, with particular emphasis on the role of adipokines in the pathogenesis and course of these diseases.

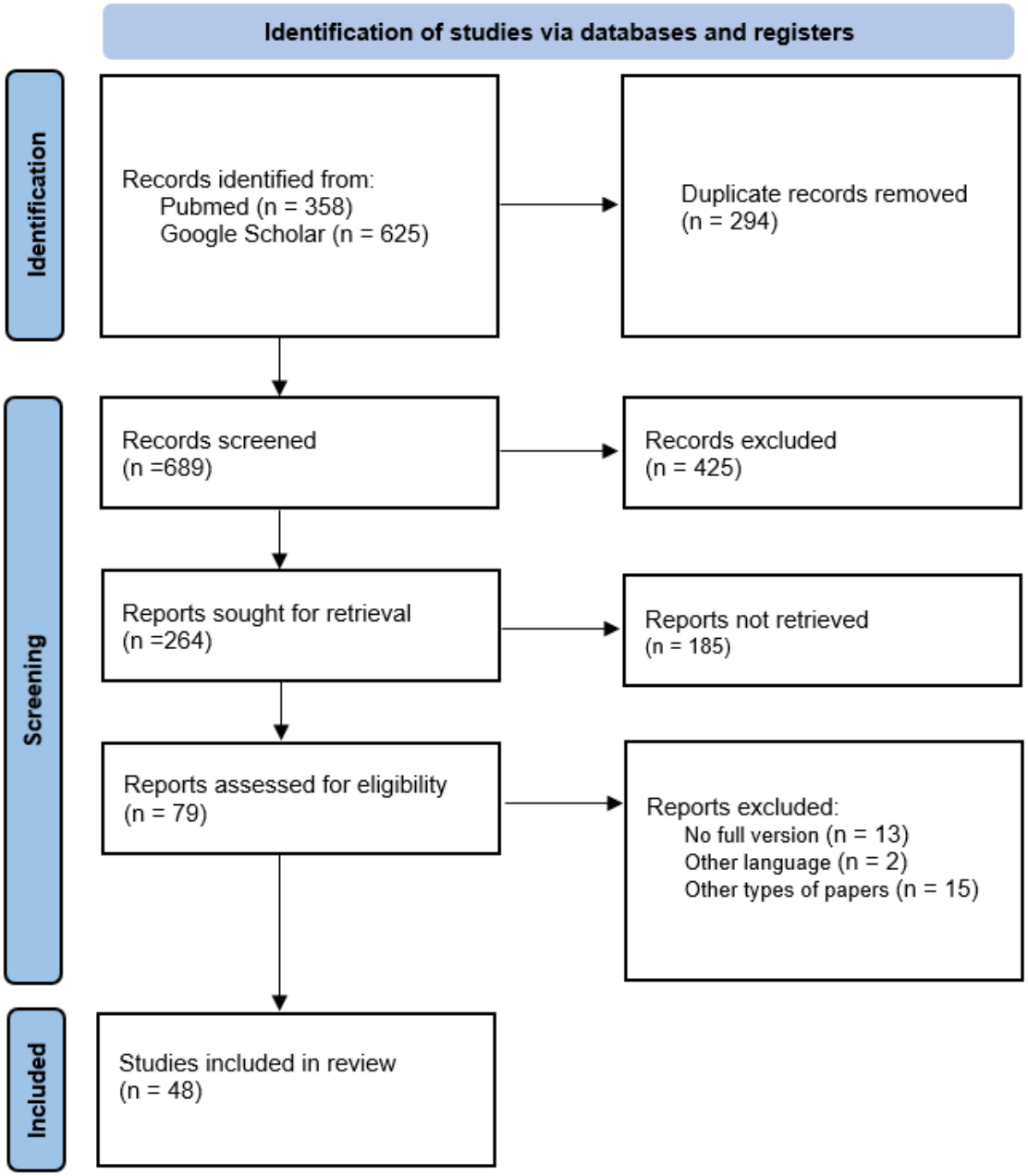

Figure 1. PRISMA diagram with search criteria

2. REVIEW METHODS

The systematic review is based on a literature search using keywords related to the impact of the obesity on the course of autoimmune diseases. The search covered publications from 2000 to 2024, with particular attention to research from the last five years. The authors used two databases for the literature search: PubMed and Google Scholar. This study employed the following keywords in various combinations: "obesity and autoimmunity", "adipokines and inflammation", "obesity and type 1 diabetes", "obesity and Hashimoto's thyroiditis", "obesity and rheumatoid arthritis", "obesity and psoriasis". The authors include original research articles, reviews, systematic reviews, and meta-analyses published in peer-reviewed journals. The authors selected articles based on their relevance to the topic, availability in English or Polish, and focus on the pathophysiological links between excess adipose tissue and immune dysregulation. The authors also screened reference lists of selected publications to identify additional relevant sources. The exclusion criteria included editorials and publications that did not contain a link between obesity and autoimmune disease. This review also does not include descriptions of clinical cases. A PRISMA flow diagram illustrating the selection process and applied inclusion and exclusion criteria is presented in Figure 1.

3. RESULTS & DISCUSSION

3.1. Adipose tissue as an endocrine organ

Adipose tissue servers not only as a storage site for lipids but also has a crucial role as an active endocrine organ. Such tissue secretes numerous biologically active protein compounds, collectively referred to as adipokines, which exert autocrine, paracrine and endocrine effects, modulate metabolic, immune and inflammatory processes in the body (Adamczak and Wiecek, 2013). Under physiological conditions, adipokines are involved in regulating energy, lipid, and carbohydrate metabolism, glucose homeostatis, blood pressure, and coagulation. However, in the course of obesity, excess body fat leads to dysregulation of the adipokine profile, promoting chronic inflammation and immune dysfunction, which may play an essential role in the pathogenesis of autoimmune diseases (Ouchi et al., 2011). Leptin, one of the best-studied adipokines, produced mainly by WAT adipocytes, exhibits pleiotropic effects - influencing appetite, metabolism, and immune response. Hyperleptinemia accompanying obesity correlates with an increased IL-6, TNF-α levels, and with activation of T lymphocytes particularly Th1 cells, leading to an enhanced cell-mediated immune response and promoting the development of chronic inflammation (Paz-Filho et al., 2012).

Leptin encourages Th1 lymphocytes to differentiate while dampening the regulatory function of Treg cells, which can disturb immune tolerance (Ouchi et al., 2011). On the other hand, adiponectin has properties that reduce inflammation and support cardiovascular health. Higher body fat is often linked to lower levels of this hormone in obese individuals. Moreover, adiponectin inhibits the expression of pro-inflammatory cytokines, especially IL-5 and TNF-α. Decreasing these cytokines activates various pathways in the body that reduce insulin response sensitivity (Galic et al., 2009). Problems with its secretion can increase the likelihood of developing insulin resistance as well as autoimmune conditions such as systemic lupus erythematosus (SLE) (Dini et al., 2017). Resistin and wisfatin are additional adipokines involved in the development of immune disorders. Resistin, mainly produced by by macrophages, boots pro-inflammatory factors by activating the NF-κB pathway. Elevated resistin levels in obese patients are associated with both insulin resistance and worsening inflammation (Ouchi et al., 2011). Wisfatin serves as both an enzyme and an adipokine and enhances inflammation by upregulating IL-6, TNF-α, ICAM-1, and VCAM-1. As a result, it can activate the immune system and potentially contribute to the development of autoimmune conditions (Park and Ahima, 2014). Adipose tissue contributes to the metabolic-immune axis through the hormones, called adipokines, that it secretes. Its dysfunction in the course of obesity leads to chronic inflammation and modulation of the immune response, which can promote the onset and progression of autoimmune diseases.

3.2. Obesity and psoriasis

The incidence of psoriasis in the obese population is significantly higher than among normal-weight individuals. Barros and Setty show in their research that obesity increases the risk of developing psoriasis by around 50 do 100%, with the risk rising as BMI goes up (Barros et al., 2022; Setty, 2007). Population studies have shown that both overweight and obesity independently raise the risk of developing psoriasis (Armstrong et al., 2012). Moreover, people with pre-existing psoriasis are more likely to have abdominal obesity and metabolic syndrome, which worsens prognosis and increases the risk of cardiovascular complications (Love et al., 2010). On a molecular level, excess fat tissue, particularly visceral fat, triggers chronic inflammation. This happens through the accumulation of pro-inflammatory cells (Th1, Th17) and elevated levels of cytokines like IL-17, IL-22, and IFN-y. These mediators amplify inflammation in the skin. In addition, adipokines by fat tissue can directly promote inflammation in the skin and immune system, which in turn

worsens disease progression (Scala et al., 2024). Excess weight can also limit the success of psoriasis therapies, especially biologic ones. Studies have shown that patients with a high BMI have a significantly lower clinical response to the treatments used, compared to normal-weight patients (Enos et al., 2021). Reduced treatment efficacy may result from pharmacokinetic alterations such as increased clearance in individuals with obesity, as well as from heightened systemic inflammation (Paroutoglou et al., 2020). Clinicians typically evaluate the effectiveness of psoriasis treatments using the special marker - Psoriasis Area and Severity Index (PASI), which assesses skin lesion severity based on erythema, scaling, thickness, and the extent of the affected area. Patients with obesity are significantly less likely to achieve a reduction in lesions of ≥75% (referred to as PASI 75) or ≥90% (PASI 90) relative to people with a normal body mass index (BMI) (Pirro et al., 2021). Studies indicate that reducing body weight by diet, exercise, or surgery can improve how well patients respond to biologic therapy. This approach can also help decrease psoriasis severity (Vata et al., 2023; Gisondi et al., 2008).

3.3. Obesity and Diabetes Type 1

Increasing attention is focusing on the prevalence of overweight and obesity among with the type 1 diabetes (T1D) and the resulting health consequences for their future development. Obesity not only affects the course and treatment of T1D but may also be involved in its pathogenesis. Environmental, genetic, and immunological factors interact in complicated way, and obesity increases the risk of developing and worsening autoimmune diseases (Buzzetti et al., 2020).

Excessive body weight promotes insulin resistance, resulting increased insulin demand. It also leads to stress on pancreatic β-cells and their faster destruction. This endoplasmic reticulum stress may trigger the production of altered β-cell antigens (neoantigens), potentially triggering an autoimmune response (Nitecki et al., 2023; Marré et al., 2015). In addition, a higher BMI in children promotes early destruction of pancreatic β-cells and consequently a faster onset of T1D (Marré et al., 2015; Richardson et al., 2022). A meta-analysis found similar results, showing that children with obesity are more likely to develop T1D than their healthy peers (Verbeeten et al., 2010). High energy intake, especially from sucrose, proteins and fats, during childhood may further accelerate this process (PundziuTė-Lyckaů et al., 2004). Obese patients with concomitant T1D have higher HbA1C levels, which shows the difficulty in maintaining good metabolic control, even with insulin therapy. As a result, this leads to an increased demand for insulin and the use of gradually higher doses. In contrast, insulin resistance increases weight gain, which fuels a vicious cycle of disorders (Wellens et al., 2021; Dubose et al., 2015).

Obesity in patients with T1D significantly increases the risk of developing both microvascular (retinopathy, nephropathy) and macrovascular (atherosclerosis, hypertension) complications (Merger et al., 2016). Data from European and US registries unequivocally show a correlation between high BMI and a higher incidence of severe hypoglycemia and higher HbA1c values. The mechanisms may include reduced sensitivity to hypoglycemic cues, impaired glycemic perception, and increased glycemic variability, among others (Lee et al., 2016). In addition, children with T1D and overweight are more likely to have lipid abnormalities, hypertension, and increased liver enzymes, suggesting the possibility of developing non-alcoholic fatty liver disease (NAFLD) in this population. Obesity may therefore modify the classic course of T1D, making it more similar to the picture of type 2 diabetes mellitus (Mottalib et al., 2017). Insulin therapy remains the mainstay of treatment for T1D, but its use can promote weight gain. Consequently, researchers and clinicians are actively exploring strategies to simultaneously control blood glucose levels and body weight. Researchers are investigating the use of T2D medications, such as metformin, GLP-1 receptor agonists and SGLT-2 inhibitors in T1D. However, more research is needed to confirm their safety and effectiveness in children and adolescents (Ciężki et al., 2022).

3.4. Obesity and Hashimoto's disease

Obesity affects thyroid function on many levels, from changes in the hypothalamic-pituitary-thyroid axis through the thyroid parenchyma, and also leads to the development and worsening of the course of Hashimoto's autoimmune disease (HT). Individuals with elevated BMI often have elevated TSH levels with normal FT4, suggesting pituitary resistance to negative feedback of thyroid hormones. Leptin may drive this mechanism, as its concentration increases in proportion to fat mass. Leptin stimulates secretion of hormones secreted by the hypothalamus and pituitary gland (thyrotropin-releasing hormone, thyrotropin), leading to disturbances in the functioning of the hypothalamus-pituitary-thyroid axis (Biondi, 2023; Song et al., 2019). In addition, obesity reduces the conversion of active thyroid hormones thyroxine to triiodothyronine. This increases the deficiency of hormones responsible for metabolism, leading to its decline (Biondi, 2023). It has been shown that there is a correlation between obesity and thyroid autoimmunity. The levels of TPOAb and TgAb antibodies more likely to exceed normal ranges in obese people. Leptin, as a pro-inflammatory adipokine,

modulates the balance between Th1 and Th2 lymphocyte subpopulations. At the same time, it enhances the Th1-type immune response and suppresses the activity of regulatory T cells, increasing the risk of immune reactions. (Marzullo et al., 2010).

In their meta-analysis, Song et al., (2019) demonstrated that obesity significantly increases the risk of Hashimoto's disease. In addition, a Chinese cohort study involving more than 12,000 people found that the risk of hyperthyrotropinemia doubled among overweight or obese individuals when antithyroid autoantibodies were present (Guo et al., 2020). In addition, obesity affects the tissue structure of the thyroid gland. Patients with severe obesity often show thyroid enlargement and decreased parenchymal echogenicity on ultrasound. These changes may be a result of capillary dilation, increased vascular permeability, and inflammation within the gland (Longhi and Radetti, 2012; Fontenelle et al., 2016). Obesity also affects the effectiveness of hypothyroidism treatment in HT. Overweight and obese patients often require higher doses of levothyroxine due to increased drug volume of distribution, reduced bioavailability, and abnormal hormonal regulation caused by inflammation and leptin resistance. Research indicates that tailoring L-T4 dosage according to lean body mass rather than total body weight yields better results (Michalaki et al., 2011).

3.5. Obesity and Rheumatoid arthritis

In recent decades, the incidence of rheumatoid arthritis (RA) has risen among overweight people. Findings from the Nurses' Health Study show that individuals who are overweight before age 55 have a higher developing RA compared to those with a normal weight (Lu et al., 2014). A population-based study conducted in Olmsted County supported these findings, revealing an association between obesity and rheumatoid arthritis diagnosis before age of 60 (Crowson et al., 2012). Furthermore, a BMI of 25 kg/m² or more at the age of 18 has been identified as an independent predictor for the subsequent development of RA (Lu et al., 2014). Based on meta-analyses, a dose-response relationship between body mass index and risk of RA has also been demonstrated, which is particularly relevant for seronegative forms of the disease and in the female population (Qin et al., 2015; Ohno et al., 2020; Feng et al., 2016). Despite some inconsistent results, the general evidence supports a strong influence of excess body weight on the occurrence of RA. The metabolic activity of adipose tissue may partly explain this relationship.

Visceral fat is not only an energy reservoir, but also performs endocrine functions. It releases inflammatory cytokines and adipokines such as leptin and FGF-21 (Landecho et al., 2019; Rohm et al., 2022). These molecules intensify local and systemic inflammation. Also, they promote the occurrence of RA and worsen its course. Li et al., (2019) showed that adiposin plays a crucial function in activating the complement system, which may exacerbate arthritis. Furthermore, mice with excessive adipose tissue had higher neutrophil counts and increased infiltration in their joints (Gremese et al., 2012). Obesity has an essential impact on the development and course of the disease, as well as the response to the treatment. Overweight patients have a lower chance of achieving remission in RA and respond less effectively to biologic therapies, particularly TNF-α inhibitors (González-Gay and González-Juanatey, 2012; Gremese et al., 2012). These observations suggest that excessive body weight may reduce the efficacy of treatment as a result of drug dilution, changes in pharmacodynamics, and the production of inflammatory factors. Furthermore, a higher BMI is also associated with a poorer response to treatment with synthetic disease-modifying drugs (DMARDs), which complicates the delivery of effective therapy (Heimans et al., 2013).

3.6. Weight reduction – a component of autoimmune diseases therapy

Reducing excess body weight promotes well-being, but what is more important improves the effectiveness of treatment autoimmune diseases. In patients who lost a few kilograms, an improvement in the efficiency of biological therapy was observed (Tournadre and Beauger, 2023). Obesity may adversely affect the clinical response to applied biologic treatment, particularly for interleukin-targeted drugs, which show greater sensitivity to changes in BMI compared to therapies based on tumor necrosis factor-alpha (TNF-α) inhibitors (Pirro et al., 2021). Decreasing visceral fat results in lower levels of pro-inflammatory cytokines like TNF-α and interleukin-6 (IL-6), helping to mitigate chronic inflammation (Lira et al., 2010). In the context of autoimmune diseases such as systemic lupus erythematosus (SLE) or chronic autoimmune thyroiditis (Hashimoto's disease), regular physical activity has been shown to promote immune homeostasis by, among other things, reducing the expression of inflammatory pathways and improving the role of regulatory T cells, which may contribute to alleviating the course of the disease and increasing the effectiveness of therapy (Luo et al., 2024). Table 1 summarizes the impact of obesity on the development of selected autoimmune diseases.

Table 1. Summary of the impact of obesity and adipokines on autoimmune diseases

Autoimmune/Inflammatory Disease	Association with Obesity	Key Mechanisms	Clinical Consequences	Treatment Considerations
Psoriasis	Obesity increases risk by 50–100%; higher BMI worsens prognosis	Chronic inflammation via Th1/Th17 cells, cytokines (IL-17, IL-22, IFN-γ), adipokine-mediated immune activation	Reduced response to biologics, higher PASI scores	Weight reduction improves biologic therapy response and disease severity
Type 1 Diabetes (T1D)	Overweight children have higher risk and faster onset	Insulin resistance → β-cell stress → neoantigen formation → autoimmune response	Higher HbA1C, increased insulin requirement, greater risk of micro- and macrovascular complications	Careful weight management; experimental use of T2D medications (metformin, GLP-1 agonists, SGLT2 inhibitors) under research
Hashimoto's Thyroiditis	Higher BMI increases risk; obesity alters thyroid hormone regulation	Leptin-driven Th1/Th2 imbalance, Treg suppression; altered deiodinase activity	Elevated TSH, thyroid enlargement, higher levothyroxine requirements	Adjust L-T4 dose based on lean body mass; weight loss may improve thyroid function and immune balance
Rheumatoid Arthritis (RA)	Overweight increases risk, especially in women and seronegative forms	Visceral fat secretes adipokines (leptin, FGF-21), adiposin → complement activation → systemic inflammation	Lower likelihood of remission, worse response to biologics and DMARDs	Weight loss reduces inflammation and improves treatment outcomes
General Inflammatory Conditions	Obesity contributes to chronic inflammation and immune dysregulation	Dysregulated adipokines (leptin ↑, adiponectin ↓, resistin, visfatin) → pro-inflammatory cytokines, impaired Treg function	Increased disease activity, progression of autoimmune disorders	Lifestyle interventions: diet, exercise, bariatric surgery; reduce visceral fat to lower pro-inflammatory cytokines and improve therapy response

4. CONCLUSION

Obesity is a compound disease that promotes inflammation in the body, which mediates the pathogenesis of autoimmune diseases. Considered an endocrine organ, adipose tissue secretes adipokines that modulate the immune response, promoting autoimmunity. Excessive body weight has been associated with an increased risk of developing diseases such as type 1 diabetes, Hashimoto's disease, rheumatoid arthritis, and psoriasis, as well as with a more severe disease course and poorer response to treatment. Leptin, resistin, and visfatin promote pro-inflammatory responses, whereas obesity reduces the beneficial effects of adiponectin. Weight reduction can improve disease control, increase treatment efficacy, and reduce inflammatory activity. Interventions, including weight reduction, should therefore be an integral part of therapy for patients with autoimmune diseases who are overweight.

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Author contributions

Agnieszka Mariowska: Conceptualisation, Formal analysis, Project administration, Writing - review and editing
Paulina Horwat: Software, Investigation
Anita Szymańska: Methodology, Check
Marta Dzieciątkowska: Resources, Writing - rough preparation
Weronika Pierudzka: Data curation, Visualisation
All authors have read and agreed with the published version of the manuscript.

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Not applicable.

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Not applicable.

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Conflict of interest
The authors declare that there is no conflict of interest.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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