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Exploring the cellular and molecular mechanisms of exercise impact on autism health through meta-analysis

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ADMINISTRATIVE INFORMATION

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INTRODUCTION

Review question / Objective Objective: This meta-analysis aims to examine the effects of exercise interventions on the health of individuals with autism, providing a more accurate reference for interventions in autism.

Condition being studied Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that manifests in early childhood. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the diagnosis of autism is based on significant impairments in social communication and social interaction across multiple contexts, as well as restricted, repetitive patterns of behavior, interests, or activities. In recent years, the prevalence of autism has been rising steadily. In 2023, the Centers for Disease Control and Prevention (CDC) reported that the

latest ASD prevalence rate in the United States is 1 in 36. In China, the number of individuals with autism has exceeded 13 million, with an annual increase of nearly 200,000 people. The incidence of autism has become the leading type of mental disability. The core symptoms of autism not only limit the development of individuals with ASD but also severely impact the quality of life of their families, leading to significant economic burdens on society.

METHODS

Participant or population In conducting a meta-analysis related to Autism Spectrum Disorder (ASD), including both ASD patients and animal models is crucial. Including human ASD patients provides direct clinical relevance, revealing the real-world effects of exercise on their health. Meanwhile, animal models allow for detailed

studies of the biological impacts of exercise under controlled conditions, aiding in the exploration of potential molecular and cellular mechanisms. This multidimensional approach offers a more comprehensive understanding, helping to corroborate the benefits of exercise on ASD from different levels. The study subjects are individuals with a confirmed diagnosis of Autism Spectrum Disorder (ASD). The diagnostic interview includes self-reported diagnoses by physicians, registry data, or classification according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) indicating the presence of autism. Patients with comorbid conditions such as Attention Deficit Hyperactivity Disorder (ADHD), Down syndrome, and other neurodevelopmental disorders are excluded. Additionally, the study includes commonly used ASD models, and in the present study, only VPN-induced rat models of autism were included. Studies that do not use validated ASD animal models or fail to provide detailed descriptions of the exercise conditions are excluded. This inclusion and exclusion criteria are designed to ensure the integrity and specificity of the research findings.

Intervention In the screened studies, the experimental group received exclusively physical activity interventions, whereas the control group was subject to standard care or no intervention. Studies reporting only follow-up results were excluded. There were no restrictions placed on the types of physical activities involved.

Comparator In the screened studies, the experimental group received exclusively physical activity interventions, whereas the control group was subject to standard care or no intervention. Studies reporting only follow-up results were excluded. There were no restrictions placed on the types of physical activities involved.

Study designs to be included This investigation focuses on English or Chinese literature that has been publicly disseminated through peer-reviewed journals. Eligible studies include randomized controlled trials (RCTs) or non-randomized controlled trials, provided that they report sufficient statistical details such as means, standard deviations, participant numbers, etc. Exclusion criteria encompass literature reviews, case reports, conference abstracts, research proposals, as well as republished works, studies without accessible full texts, those from which valid data cannot be extracted, or those lacking raw data available.

Eligibility criteria In conducting a meta-analysis related to Autism Spectrum Disorder (ASD),

including both ASD patients and animal models is crucial. Including human ASD patients provides direct clinical relevance, revealing the real-world effects of exercise on their health. Meanwhile, animal models allow for detailed studies of the biological impacts of exercise under controlled conditions, aiding in the exploration of potential molecular and cellular mechanisms. This multidimensional approach offers a more comprehensive understanding, helping to corroborate the benefits of exercise on ASD from different levels. The study subjects are individuals with a confirmed diagnosis of Autism Spectrum Disorder (ASD). The diagnostic interview includes self-reported diagnoses by physicians, registry data, or classification according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) indicating the presence of autism. Patients with comorbid conditions such as Attention Deficit Hyperactivity Disorder (ADHD), Down syndrome, and other neurodevelopmental disorders are excluded. Additionally, the study includes commonly used ASD models, and in the present study, only VPN-induced rat models of autism were included. Studies that do not use validated ASD animal models or fail to provide detailed descriptions of the exercise conditions are excluded. This inclusion and exclusion criteria are designed to ensure the integrity and specificity of the research findings. In the screened studies, the experimental group received exclusively physical activity interventions, whereas the control group was subject to standard care or no intervention. Studies reporting only follow-up results were excluded. There were no restrictions placed on the types of physical activities involved. Study the molecular and cellular-level outcome indicators in the brain or blood of subjects with autism.

Information sources We searched for relevant documents in the following databases: CNKI, the Wanfang Data Knowledge Service Platform, Wikipedia, Web of Science, PubMed, Ebsco, Cochrane Library, ProQuest, Scopus. The retrieval period covered the period from the establishment of these databases until April 10, 2024.

Main outcome(s) Basic information of the included studies; Characteristics of the subjects (sample size, type); Exercise intervention measures (type of exercise, intervention period, frequency, duration); Control group intervention measures; Outcome measures and related data.

Quality assessment / Risk of bias analysis Two reviewers independently evaluated the methodological quality of all included studies. The Revised Cochrane risk-of-bias tool for randomized

trials (RoB2) was used to assess the risk of bias. The RoB2 includes five domains: (1) Risk of bias arising from the randomization process; (2) Risk of bias due to deviations from the intended interventions (effect of assignment to intervention); (3) Missing outcome data; (4) Risk of bias in the measurement of the outcome; (5) Risk of bias in the selection of the reported result. Each domain has several signaling questions which used to assess the quality of studies. The risk of bias can be assessed as “low risk of bias”, “some concerns” and “high risk of bias” in each domain.

Strategy of data synthesis All meta-analyses were performed using R studio Software. The outcome variables were continuous random variables and were assessed using different measurement methods, so the Standard Mean Difference (SMD) was used to combine the effect quantity. Data were extracted using WebPlotDigitizer 4.7 for some of the images in the literature; all data were transformed into mean \pm standard deviation for analysis. Due to varying characteristics of the selected papers, heterogeneity is anticipated. Consequently, the Q test and I^2 test are employed to assess the statistical heterogeneity of the included studies. If $p \geq 0.10$ and $I^2 \leq 50\%$, indicating no significant heterogeneity, a fixed effects model is used for the meta-analysis. Conversely, if $p > 0.05$, suggesting significant heterogeneity, the source of heterogeneity is analyzed, and a random effects model is adopted. Additionally, meta-regression and subgroup analyses were used to analyse sources of heterogeneity in each outcome indicator. Publication bias is assessed using the funnel plot and Egger's test, with $p > 0.05$ considered no significant publication bias. Finally, sensitivity analyses were performed on the studies to test the robustness of the results.

Subgroup analysis Three included papers (encompassing five studies) explored the effects of exercise interventions on BDNF expression in autistic rats, involving a total of 24 experimental subjects. The $I^2 = 84\%$ indicates heterogeneity among the studies; therefore, a random effects model was selected for analysis. The meta-analysis results reveal no significant differences in the impact of exercise interventions on BDNF expression, with an SMD of 3.05, 95% CI: -1.09 to 7.19, $P \geq 0.01$, suggesting similar levels of BDNF expression between the experimental and control groups of rats. Four included papers (comprising 17 studies) investigated the effects of exercise interventions on neuroinflammation in autistic rats, involving a total of 108 experimental subjects. The $I^2 = 92\%$ indicates significant heterogeneity among

the studies; therefore, a random effects model was chosen for analysis. The meta-analysis results demonstrated significant differences in the effects of exercise interventions on neuroinflammation in autistic rats, with an SMD of -1.10, 95% CI: -1.92 to -0.01, $P < 0.01$, indicating that exercise interventions significantly ameliorated neuroinflammation in the experimental group of autistic rats. Five included papers (comprising 18 studies) examined the effects of exercise interventions on hippocampal protein expression in autistic rats, involving a total of 122 experimental subjects. The $I^2 = 95\%$ indicates significant heterogeneity among the studies; therefore, a random effects model was employed for analysis. The meta-analysis results indicate significant differences in the effects of exercise interventions on hippocampal protein expression in autistic rats, with an SMD of 2.86, 95% CI: 0.38 to 5.35, $P < 0.01$, showing that exercise interventions significantly altered hippocampal protein expression in the experimental group of autistic rats.

Sensitivity analysis To investigate whether the heterogeneity was caused by individual studies, the stability of the results obtained was tested under hypothetical conditions. For studies with high levels of heterogeneity, a one-by-one exclusion method was used to analyze the combined effect size. The analysis revealed that the combined effect sizes, when individual studies were excluded, showed significant changes compared to the total combined effect size from all included studies. Overall, the meta-analysis results were not highly stable. Possible reasons for this instability may include small sample sizes and a high likelihood of methodological heterogeneity among the studies, leading to unstable outcomes.

Country(ies) involved China.

Keywords Cellular; Molecular Mechanisms; Autism Spectrum Disorder; Exercise; Meta-Analysis.

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