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Evaluating the Influence of Swimming Training on Memory Enhancement and Learning Skills in Mice

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YH Conceptualized the study and designed experiments. GD performed data preparation and analysis. XN wrote and edited the Manuscript

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ABSTRACT

Assessing the cognitive benefits of swimming exercise is extremely important for both public health and cognitive science. Our study seeks to examine the complex relationship between physical activity and cognitive improvement while suggesting practical methods for cognitive rehabilitation, proactive defenses against cognitive decline, and specialized techniques for cognitive augmentation. An exercise group of 30 male C57BL/6 mice and a sedentary group of 30 mice each were created. The sedentary group acted as the control group and underwent a long-term swimming exercise program. T-maze tests to determine brain-derived neurotrophic factor (BDNF) levels and Western blot analyses to assess learning and spatial memory were included in cognitive evaluations. A synaptic markers analysis was performed on the hippocampus. Our study showed that the exercise group showed greater learning potential and spatial memory retention. A western blot examination validated the exercise group's higher BDNF levels. In the hippocampus of the exercise group, synaptic markers were greater, indicating enhanced synaptic plasticity. The exercise group has better learning potential and spatial memory retention due to enhanced synaptic markers, brain network complexity, and BDNF levels. Thus, exercise has significant benefits for cognitive functions. In conclusion, swimming exercise promotes cognitive gains through synaptic plasticity and BDNF-related pathways. These findings have significance for programs that are specifically designed to improve cognition, prevent cognitive decline, and provide cognitive rehabilitation.

INTRODUCTION

An organism's cognitive ability and capacity for learning are key traits that substantially affect its overall well-being and adaptability (Babić *et al*., 2020). Investigations into the factors that might facilitate or impair particular cognitive processes have become increasingly important in recent years. According to Cabral *et al*. (2022), physical activity has a well-established positive effect on cognitive function and brain health in humans, and scientists are now investigating similar advantages in animal models to learn more about the underlying mechanisms. Among the several exercise options, swimming training has shown promise in improving mice's cognitive performance and capacity for learning (Charest and Grandner 2022; Park *et al*., 2018).

According to Bidzan-Bluma and Lipowska (2018), the relationship between physical activity and cognitive function has seen significant attention in recent years. Numerous studies have shown that physical activity can have a considerable impact on a variety of cognitive processes, including learning ability (Ahmadiasl *et al*., 2003). Findings have shown a positive correlation between regular physical activity and improved cognitive abilities, such as memory, attention, executive skills, and general cognitive performance (Podolski *et al*. 2017; Jia *et al*., 2019).

Neurological findings by Liu and Nusslock (2018) have alluded to the promotion of neurogenesis, which refers to the development of new neurons within the brain, as one important way that exercise affects cognitive ability. An increase in the production of new neurons inside the hippocampus can be caused by physical activity, such as swimming training (Radák *et al*., 2001; Kempermann, 2019). It is believed that this enhanced neurogenesis process plays a vital part in improving cognitive abilities, including learning and remembering. Previous studies have demonstrated a link between exercises such as swimming

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training to enhance synaptic plasticity (Kim *et al*., 2013).

Neurotrophic factors are crucial for stimulating the development, survival, and maintenance of neurons (Numakawa and Adachi, 2018). One such neurotrophic factor is brain-derived neurotrophic factor (BDNF) (Lima *et al*., 2019; Pietrelli *et al*., 2018). Exercise has been shown to increase the release of BDNF and other neurotrophic factors, creating an environment that is advantageous for the growth of neurons and the plasticity of synapses (Patil *et al*., 2009).

Swimming is regarded as a vigorous exercise that efficiently uses a number of muscle groups and helps to increase cardiovascular fitness (Crowley *et al*., 2018). In contrast to other forms of physical activity, the effect of swimming training on cognitive performance has gotten relatively little attention in the study. Several factors may have an impact on the ability of swimming exercise to improve cognition (Shoemaker *et al*., 2019). The duration, intensity of effort, and frequency of swimming workouts all have an impact on how much cognitive function is improved. Age, genetic factors, and pre-existing cognitive capacity can all affect how mice respond to swimming training (Patil *et al*., 2009).

Physical exercise has long been associated with cognitive benefits, particularly in the context of neurogenesis, synaptic plasticity, and the release of neurotrophic factors like BDNF (Wang and Holsinger, 2018; Mes *et al*., 2020). Our study aims to bridge this gap by thoroughly investigating the effects of swimming exercises on the cognitive function and learning abilities of mice. We seek to understand how swimming training influences neurogenesis, synaptic plasticity, and the release of BDNF. Additionally, we will explore the various factors, including exercise duration, intensity, and individual characteristics, that may affect the degree and longevity of cognitive improvements.

MATERIALS AND METHODS

Animals

Our study was conducted from January 2023 to August 2023. We carefully selected a cohort of 60 male C57BL/6 mice, aged between 8 and 10 weeks, in order to do a complete analysis. The mice utilized in this study ranged in weight from 150 to 180 g were housed in the Central Animal Facility's climate-controlled environment at 21±2 °C with managed light cycle from 6:00 to 18:00 h.

The mice were fed a laboratory diet (Amruth Feeds, India) that was nutritionally balanced and adequately stocked with essential vitamins, minerals, and nutrients. Plentiful quantity of pure tap water was made available without restrictions.

Experimental design

The exercise group (EGn=32) and the sedentary control group (SCn=32) were randomly chosen from the cohort of mice. The intervention group rigorously followed a properly designed long-term exercise activity program, while the control group maintained a sedentary lifestyle throughout the experiment. This exact allocation was made to make it easier to conduct a thorough examination of how swimming exercise affects mice's cognitive function and capacity for learning. This was carried out while taking into account potential variations in baseline characteristics and responses to the exercise program.

Exercise protocol

We have devised a precisely structured swimming protocol to give a systematic and effective swimming training program that is in accordance with our research goals. According to Anand *et al*. (2015), the swimming exercise training was carried out in a rectangular glass tank measuring 77 cm, 38 cm, and 39 cm. Water was added to the tank until it had a uniform height of 22 cm. With a tolerance of 1°C, the water temperature was carefully managed and kept constant at 32°C (Table I).

In order to maximize their participation and response, the mice underwent a graded swim training procedure. The mice were put through a training regimen where they had to carry a burden equal to 3% of their body weight during the first stage of the experiment (Zhang *et al*., 2022). To ensure stability and safety throughout the training procedure, this weight was properly fastened to their tails. The mice were given a chance to get used to the swimming activity by having the initial training session last 5 min each day. The length of the sessions increased gradually as the training program progressed, reaching a considerable duration of 30 min every day in the conclusion.

The 84 consecutive days of the rigorous swimming training regimen were carried out with excellent accuracy and attention to detail, with training sessions occurring six days each week. The constancy of the training sessions was of the highest importance, and ensuring the protocol's effectiveness was a critical component. The mice's capacity to adjust to longer and longer training sessions emphasizes the progressive nature of the program, which is intended to improve their athletic abilities without putting them under too much stress.

The sedentary control group (also known as SE-Cs) was only permitted to carry out activities inside their cages. By using this group as a comparison group, it was possible to assess the effects of swimming exercise in contrast to a typical level of physical activity. The use of this controlled methodology allowed for a thorough analysis of the impact of swimming training on the mice's cognitive function and learning capacity, increasing the thoroughness and validity of the inferences made from our study.

Assessment of the spatial working memory

After the swimming training procedure was completed, our study moved on to evaluate participants' spatial learning and memory skills using T-maze trials (Fig. 1), drawing on the methodology outlined (Jolitha *et al*., 2009). Our study's methodology included a rigorous approach with the goal of extensively analyzing the cognitive consequences of the swimming intervention in mice.

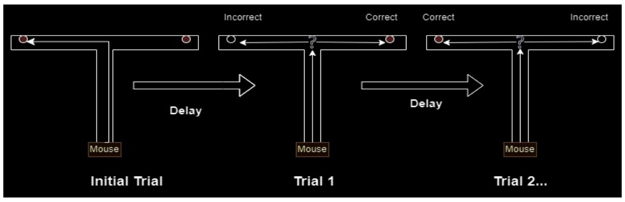

Fig. 1. Illustration of T-Maze trials.

The mice had to acclimate to the maze setting for many days before the T-maze trials could begin. The mice were allowed to freely explore the T-maze for 10 min as part of the experiment. Food pellets were placed as incentives in both arms of the maze to acclimate the mice to the maze layout. After that, a two-day habituation phase followed in which the mice were exposed to the start box for 60 sec before the sliding door was opened. The purpose of this activity was to familiarize the participants with the process of navigating the maze in order to collect food pellet incentives while attempting to create a cognitive link between particular areas and rewards.

The mice engaged in a set pattern of exercises designed expressly to stimulate spatial memory during the acquisition phase, which lasted for two weeks. A single labyrinth arm was specifically baited with a food pellet reward throughout each trial. To encourage the establishment of a learned tendency towards making the right choice, the mice were given the job of identifying the arm that led to a reward. The addition of a second component encouraged adaptability and cognitive flexibility by providing the mice with an incentive to resist returning to the arm they had previously inspected in exchange for a reward in order to assure the removal of any potential olfactory cues, a thorough cleaning procedure was carried out using a 70% ethanol solution in between each of the ten trials that were completed each day.

A series of memory retention tests were given every week for a total of 28 days after the initial two-week phase of acquisition. We were able to evaluate the mice's capacity for long-term spatial memory thanks to our longitudinal approach. A uniform and controlled setting for evaluation was created for the tests by adopting a standard inter-trial period of 60 sec. Based on a thorough analysis of the mice's precise decisions made throughout the ten trials, we evaluated their spatial working memory abilities.

Our study aims to evaluate the effect of swimming exercises on the spatial learning and memory capacities of mice through rigor and adherence to a painstakingly crafted procedure. The use of a systematic technique made it easier to identify small changes in cognitive function, which allowed for an evaluation of how much swimming training affected spatial working memory.

Western blot analysis

The rats were carefully exposed to CO_2 asphyxiation.

Cerebral cortex (CC), hippocampus (HC), and cerebellar (CB) regions of the brain were precisely identified, isolated and washed thoroughly using a cold saline solution. The weights of the various brain regions were precisely measured,.The tissue samples were homogenized using a high-speed centrifuge (Superspin-RV/FM, Plastocrafts) at 2000 g for 10 min at 4°C. The resultant homogenate was then centrifuged, to get a supernatant which will be used for estimation of the soluble components of the tissue as well as the targeted analyte (BDNF).

Table I. Exercise intervention protocol, including activities, duration, and training load during the 84 days.

Weeks	Activities	Water Temp.	Training load	Training duration	Increment	Weekly sessions
1-2	Acclimatization	32°C ± 1°C	3% BW	5min/day	-	6
3	Gradual increment	32°C ± 1°C	3% BW	10min/day	+5min/day	6
4-6	Progressive Inc.	32°C ± 1°C	3% BW	15min/day	+5min/day	6
7-9	Building endurance	32°C ± 1°C	3% BW	20min/day	+5min/day	6
10-12	Advancing intensity	32°C ± 1°C	3% BW	25min/day	+5min/day	6
13-14	Peak intensity	32°C ± 1°C	3% BW	30min/day	-	6

BW, body weight.

Sixty µg from each distinct area of the brain were electrophoresed on a gel with a 12% SDS-PAGE composition. After being isolated, the proteins were then transferred onto polyvinylidene fluoride (PVDF) membranes using a semi-dry blotting apparatus.

The membranes were incubated in a blocking solution containing 5% skimmed milk powder for 1 hour at room temperature (RT). Following blocking, primary antibodies specific for BDNF (1:1000, Santa Cruz Biotechnology, USA, molecular weight 14 kDa) and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (1:2000, Cell Signaling Technology, molecular weight 37 kDa, which was used as a loading control) were incubated with the membranes for an overnight period at 4°C. The membranes were subjected to a series of washing operations using Tris-buffered saline solution supplemented with 0.05% Tween 20 (TBS-T) after being incubated with the post-primary antibody. The subsequent steps involved the incubation of secondary antibodies, namely anti-mouse and anti-rabbit (1:2000, GE Healthcare, Buckinghamshire, UK) antibodies that were both conjugated with horseradish peroxidase (HRP).

The use of an Enhanced Chemiluminescence (ECL) solution (BIO-RAD) allowed chemiluminescence detection, allowing for the imaging of protein bands. With the help of a gel documentation system (Eastman Kodak, York) the bands' signal intensities were captured. The processed data was used to standardize the levels of protein expression by comparing them to the signal strengths of the GAPDH loading control.

Statistical analysis

Mean standard error was used to express the results. GraphPad Prism statistical software version 9.5.1 was used to perform a two-way analysis of variance on the data before performing a Tukey test. Statistics were deemed significant at $p < 0.05$.

RESULTS

Learning

Our study found that the learning potential showed significant improvements from the swimming training routine. Notably, as compared to their respective sedentary control peers, all experimental groups showed marked improvements in their ability to learn. Across all trial iterations, this improvement in learning capacity was consistent. The final trial results are shown in Figure 2 as an example of the significant improvement in learning outcomes. The SW-T group, which included people with swim training, demonstrated an amazing 96% correct choice rate in comparison to the sedentary at 62% ($p < .05$).

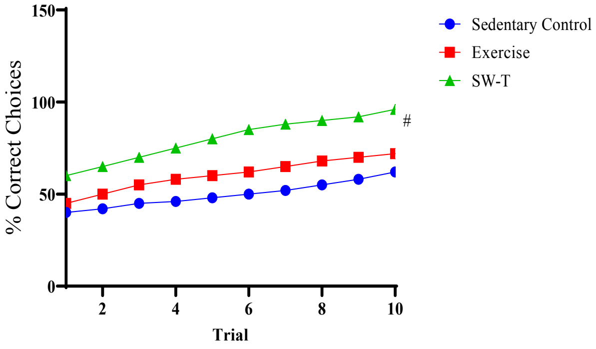

Fig. 2. Percentage of correct choices during learning. The comparison of sedentary control with experimental groups. The values are expressed as mean ± standard error of eight animals/group and were analyzed by two-way analysis of variance followed by Tukey's test. #p < 0.05 was considered statistically significant.

Memory

The results of our study on memory retention in terms of percentage latency are striking and highlight the strong influence of our swimming training program on cognitive outcomes. When compared to the sedentary control group (SE-C, N), a notable improvement in memory retention was seen across the experimental group even after 28 days. The role of the exercise protocol group, SW-T (N), in improving memory retention was significant ($p < .05$). When compared to the Sedentary group, this group showed tremendous improvements in memory recall, with improvements of 92%, 85%, 74%, and 66% at 7, 14, 21, and 28 days, respectively after the intervention regiment (Fig. 3).

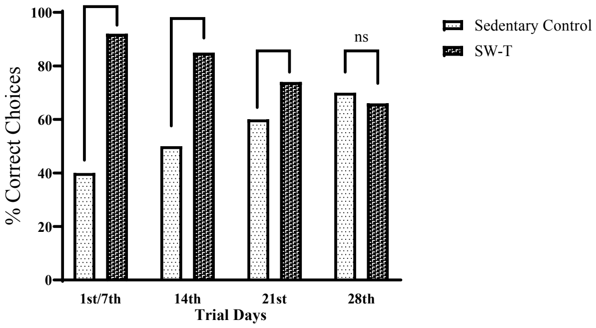

Fig. 3. Percentage of correct choices during memory retention. The comparison of the first trial/seventh day with other trials/days. The values are expressed as mean ± standard error of eight animals/group and were analyzed by two-way analysis of variance followed by Tukey's test. **p < 0.05 was considered statistically significant and ns, not significant.

BDNF levels

Through western blot analysis, the relative amounts of BDNF protein expression were compared (Figs. 4 and 5). Surprisingly, both the sedentary and trained groups showed increased BDNF expression levels when additional variables were present. Notably, compared to the CC and CB regions, the observed elevation was more pronounced in the HC region. According to Figure 4, sections A and B show the destruction of organoids and the visual cortices in the brain, while sections C and D show the neuronal response and the exit of axons from the brain. In sections E and F, BDNF reveals cerebral cortical cells such as astrocytes that were stained green and BDNF-positive cells stained red.

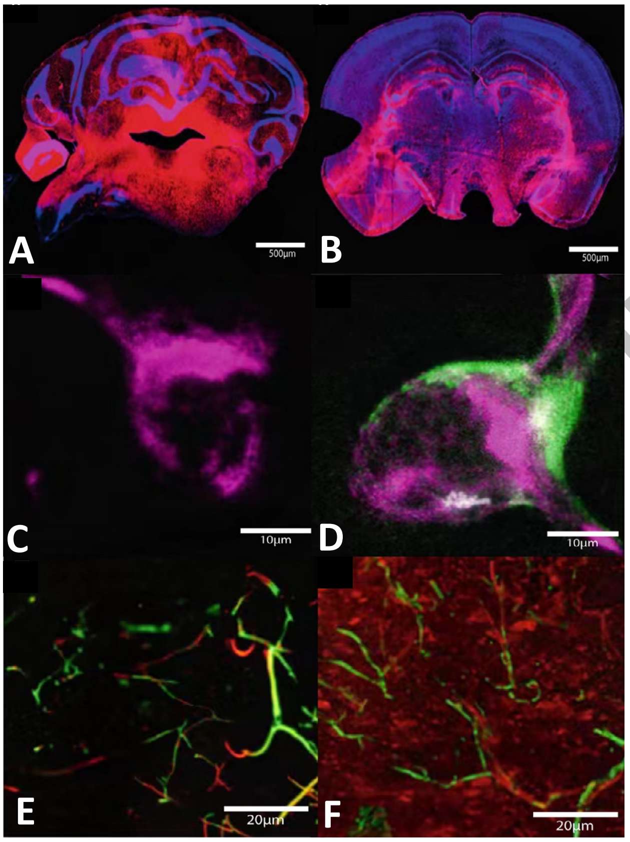

Fig. 4. Immunofluorescence staining imaging of brain sections.

Figure 5 shows an increase in the BDNF expression levels in the SW-T group compared to their respective sedentary control counterparts (SE-C, N) (p < 0.05). The expression levels were significantly increased in all the areas examined, including but not limited to the cerebral cortex (CC), hippocampus (HC), and cerebellum (CB) (p < 0.05).

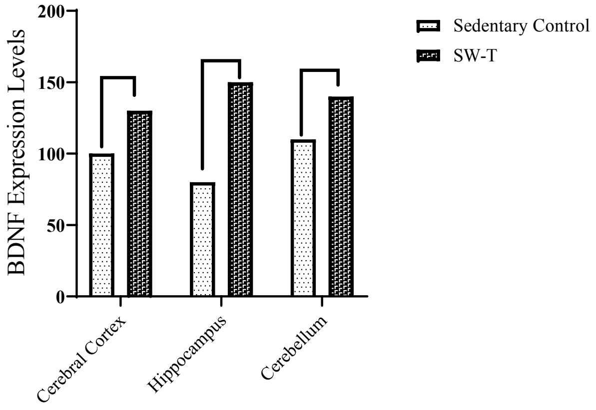

Fig. 5. Effect of exercise on the expression of brain-derived neurotrophic factor Immunoblot band densities in certain brain areas. Values were examined using a two-way analysis of variance, followed by Tukey's test, and are expressed as the mean standard error of eight animals/group. All the differences were statistically significant **p < 0.05.

DISCUSSION

Our study revealed complex mechanisms between swimming exercise, cognitive function, and neurological mechanisms. By focusing on the learning sequences, memory, and BDNF levels, we sought to enlighten the effect of swim exercise as an inducement on learning and how much memory is stored for long-term purposes. Our study found that gains in cognitive effects have effects in enhancing spatial awareness or memory. These findings were consistent with Mes *et al.* (2020), who showed that complex interaction between chemical mechanisms and neural circuitry provides insight into the many cognitive advantages of exercising. The many adaptations include a variety of neurobiological adjustments that collectively improve the brain's capacity for learning, memory, and cognitive flexibility. Similarly, Wang and Holsinger (2018) suggested that the short-term effects of exercise may lead to an improvement in performance on some cognitive tasks, and the underlying mechanisms of brain plasticity, neurotransmitter dynamics, and structural changes are key in facilitating longer-term cognitive gains. Our study reveals that sustained exercise over an extended time has the potential to improve cognitive function considerably, promote the development of new neurons, and increase synaptic plasticity.

Our study proposed that the dynamic trend denotes the exercise group's enhanced capacity for learning and memory consolidation. The striking increase in how frequently the SW-T made the correct choices during the probing exercise is the most compelling. This improvement shows not just a stronger memory recall but also the growth of a solid spatial cognitive map in the exercise group. Yao *et al*. (2023) suggested that the impact of exercise on memory consolidation and recall was studied using the T-maze test, a traditional method for assessing spatial memory, which results in astounding memory retention, even after 28 days. Therefore, it implies that swimming exercise not only improves spatial memory acquisition but also supports its long-term retention.

Our findings were consistent with Alomari *et al*. (2013), who demonstrated the potential of exercise to improve spatial learning tasks. These studies have indicated that exercise may enhance such tasks by affecting not only memory but also more sophisticated navigational strategies. In addition, the improved performance of the exercise group in the object identification task during the T-Maze test, as well as their ability to get accurate scores, serves as evidence for the significant impact of exercise on cognitive functions (Pimentel *et al*., 2022). Consequently, the process of associative learning is facilitated due to the presence of recognition memory, which plays a vital role in cognitive function and aids in the execution of daily cognitive tasks. The collaborative functioning of the hippocampus and prefrontal cortex facilitates the coordination of this cognitive skill. The alignment between the current study's results and previous research (Ahmadiasl *et al*., 2003) provides additional support for the proposition that prolonged aerobic exercise may enhance the enhancement of recognition memory by potentially promoting the growth of synaptic connections within these central regions of the brain.

Our findings suggest that the cognitive advantages lead to improvement of spatial awareness and memory retrieval. The intricate interplay between brain circuitry and chemical substrates underscores the diverse cognitive benefits associated with physical activity. Robbins and Gerszten (2023) and Khabour *et al*. (2013) showed that despite the initial, observable enhancements in cognitive task performance, the underlying mechanisms encompass a range of neurobiological alterations that collectively enhance the brain's ability to learn, remember, and withstand cognitive challenges. Moreover, our study aligned with Mandolesi *et al*. (2018) in showing that long-term exercise has been found to facilitate cognitive gains by virtue of its influence on brain plasticity, neurotransmitter dynamics, and structural alterations.

Our study provides support for the notion that the brain possesses a remarkable degree of plasticity and is capable of adapting to its environment in manners that go beyond the usual limitations imposed by age and circumstances, which was consistent with Alomari *et al*. (2013). Staudinger (2020) and Li *et al*. (2020) suggested that the concept of malleability, also known as neuroplasticity, underscores the capacity of therapies such as exercise to use the inherent capabilities of the brain and augment cognitive functioning. In order to maximize the utilization of cognitive developments, it is imperative to possess a comprehensive understanding of the fundamental mechanisms operating at the molecular, cellular, and network levels.

According to Ma *et al*. (2017), adding new neurons to neural circuits that already exist has the potential to improve brain connection, which makes it easier to comprehend and recall complicated information. The increased complexity enables the growth of many brain patterns necessary for complex cognitive processes like associative learning and pattern recognition, in addition to improving the capacity for storing information, as observed in the current study.

Gage (2004) proposed that the influx of new neurons has increased the hippocampus's plasticity, which enhances the capacity to adjust to various circumstances while boosting cognitive capacities. Additionally, exercise-induced neurogenesis is a significant phenomenon in the study of neurological disorders and cognitive aging. The need to promote neurogenesis is highlighted by the hippocampus' vulnerability to age-related deterioration and neurodegenerative diseases (Rodgers *et al*. 2013). Therefore, flexibility is the core characteristic of cognitive plasticity and is promoted by neurogenesis. The neurogenic capacity is the basis for functions including learning, memory enhancement, and the capacity to adapt and change in response to environmental and contextual cues.

CONCLUSION

The main findings reveal the transformative impact of swimming exercise on cognition. The research, which involved 60 male C57BL/6 mice subjected to a carefully planned long-term swimming exercise regimen, demonstrated significant cognitive benefits. These included improved learning potential across all experimental groups and exceptional spatial memory retention within the exercise group over 28 days. The study also confirmed an increase in BDNF levels, highlighting the neurobiological mechanisms behind cognitive enhancement.

Ethical statement

The Ethics Committee for Animal Research gave the study protocol its full clearance, indicating a consistent commitment to respecting ethical standards.

Statement of conflict of interest

The authors have declared no conflict of interest.

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