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Effect of exposure to disinfection by-products during swimming exercise on asthma-related immune responses

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ABSTRACT

Swimming is a widely practiced exercise in modern society, where there is a heightened interest in health. The exceptional benefits of swimming are well-known, yet the issue of water quality management inevitably arises due to its nature as an aquatic exercise. Several studies reported that chlorine disinfectants commonly used in swimming pool water disinfection could degrade into toxic disinfection by-products (DBPs) and suggested that the DBPs might induce respiratory disorders, including asthma. Conversely, there were also reports that the DBPs had no significant effects on respiratory conditions. In this study, we investigated the influence of swimming exercise and DBPs on asthma. The decomposition products had little effect on the number of T cells in various immune organs. However, swimming exercise was found to increase the cell count in proportion to the exercise duration. Nevertheless, there were no significant changes in other immune cells and the secretion of asthma-related cytokines. These findings indicate that the effects of swimming pool DBPs on respiratory conditions during swimming exercise are either negligible or absent, and instead, the immunological benefits gained through consistent swimming exercise outweigh any potential drawbacks.

Key words: asthma, disinfection by-products, immune response, indoor swimming pool, swimming, swimming pool environment

HIGHLIGHTS

- Disinfection by-product (DBP) exposure did not cause lung damage in this model.
- Inflammatory cytokine levels were unchanged due to DBP exposure, except IL-6.
- There were no significant changes in asthma-related blood cell type distribution.
- These results suggest that swimming exercise does not have an effect on asthma and may have a positive long-term effect on the immune system.

INTRODUCTION

Recently, due to the increasing interest in leisure and health, the number of indoor swimming pool users is increasing along with the increase in the social sport population (Jo *et al.* 2023). Swimming, a representative exercise in water, consumes more energy than aerobic exercise performed on land because it uses the four characteristics of water: buoyancy, water temperature, water pressure, and resistance. Compared to exercise on land, it reduces the burden of body load and puts less strain on joints. Therefore, it is a full-body exercise where patients can experience the effects of exercise without much difficulty (Park *et al.* 2021). Furthermore, it is evident that swimming exerts a positive influence not only on diseases but also on immune function (Lee *et al.* 2019a, 2019b). Specifically, it has been reported to reduce cough perception, enhance respiratory muscle strength, and decrease the likelihood of exercise-induced asthma (Chandratilleke *et al.* 2012). Swimming exercise has been documented as a safe and primarily recommended rehabilitation method for patients with asthma (Beggs *et al.* 2013).

However, recent reports on the potential adverse effects of disinfection by-products (DBPs) generated during the disinfection process, which can harm the health of swimming pool users through skin contact or respiratory exposure, have sparked increased interest in the quality of swimming pool water (Jo *et al.* 2015). Just as with drinking water, chlorine disinfectants, used essentially for the prevention of infectious diseases, are the most commonly employed oxidizing and disinfecting agents in swimming pools due to their cost-effectiveness, efficient bacterial eradication capabilities, and convenient application

(Kim *et al.* 2017; Sun *et al.* 2019). However, the use of disinfectants generates DBPs, such as total trihalomethanes, haloacetic acids, haloacetonitriles, and chloral hydrate, and the highly oxidizing sodium hypochlorite, produced during the disinfectant manufacturing process, may also be introduced (You 2020). In particular, DBPs that have been shown to have a higher risk of exposure in swimming pool water than in drinking water are also found to be significantly involved in the risk of association with respiratory symptoms such as allergies and asthma and in causing inflammation (Villanueva *et al.* 2004; Caro & Gallego 2007; Kaydos-Daniels *et al.* 2008; Florentin *et al.* 2011; Del Giacco *et al.* 2015).

Some studies showed that an increase in the number of patients with asthma had been reported to be associated with exposure to chlorinated irritants in swimming pools (Varraso *et al.* 2002; Kohlhammer *et al.* 2006), and the association between the duration spent in indoor swimming pools and adverse health outcomes, including asthma, has also been reported (Zheng *et al.* 2020, 2021). However, these reports have limited data to detect harmful associations (Del Giacco *et al.* 2015), and scientific evidence regarding inhalation of DBPs and changes in the immune system has not been clearly established to date (Lee 2023).

In this study, we sought to determine how factors such as DBPs, asthma, and inhalation time of DBPs to swimming exercise affect the immune system.

MATERIALS AND METHODS

Animals

Six-week-old male C57BL/6 mice (Dongnam Institute of Radiological and Medical Sciences Animal Inc., Busan, Korea) were used after a 1-week quarantine and acclimatization period. The mice were housed in a room maintained at 23 ± 2 °C, with a relative humidity of 50 ± 5%. The lighting schedule consisted of artificial light from 08:00 to 20:00; the air within the room underwent 13–18 air changes per hour. The mice were provided a standard laboratory diet and had unlimited access to water. All experimental procedures adhered to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals and were performed according to a protocol approved by the Institutional Animal Care and Use Committee of the Dongnam Institute of Radiological and Medical Sciences (Permit Number: DI-2023-010). Animal welfare was ensured in compliance with the regulations stipulated by the National Animal Welfare Law of Korea.

Induction of allergic airway inflammation

Sensitization and challenge were modified based on a previous study (Lee *et al.* 2019a, 2019b). As shown in Figure 1, all mice were sensitized intraperitoneally with 2 mg of aluminum hydroxide (alum; InvivoGen, San Diego, CA, USA) dissolved in 200 μL of phosphate-buffered saline (PBS) containing 100 μg of ovalbumin (OVA; Hyglos GmbH, Regensburg, Germany) on days 0, 7, and 14. The mice were anesthetized with isoflurane (2% induction and 1.5% maintenance, 80% N_2O and 20% O_2), and 50 μg of OVA in PBS was administered intranasally three times a week for 4 weeks. Control mice were sensitized and challenged with PBS at the time of OVA challenge. Pulmonary function measurements were conducted within 24 h after the final challenge, and all mice were sacrificed for analysis within 2 days of the last OVA challenge. The mice were randomly divided into 12 groups ($n = 15$–20): challenge with PBS and non-exercise (control), challenge with OVA and non-exercise (asthma), challenge with PBS and inhalation of DBPs for 30 min (swim 30 m control), challenge with PBS and inhalation of DBPs for 60 min (swim 60 m control), challenge with PBS and swimming for 30 min (swim 30 m test), challenge with PBS and swimming for 60 min (swim 60 m test), and the same 6 group settings after pre-induced asthma. The pre-asthma large group was entered into the experiment after implementing the OVA-induced asthma schedule.

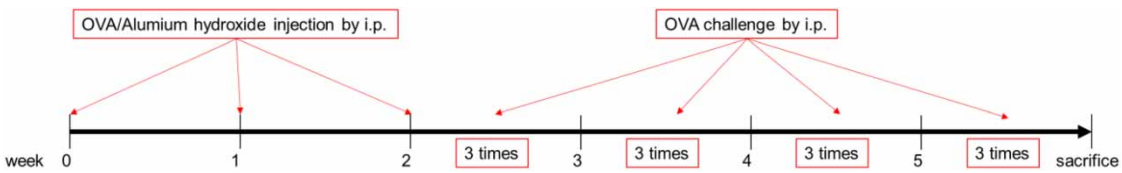

Figure 1 | Schedule of OVA challenges for the induction of asthma in mice.

Modeling of the animal swimming pool environment for DBP gas inhalation

We experimented with inhalation of DBPs and the indoor swimming environment by applying the indoor swimming pool environment model created in a previous paper (Lee 2023). The experimental method was the same as in the previous paper. Briefly, the mice were exposed to the DBP gas using the previous setup. To induce the generation of DBPs, sodium hypochlorite and the synthesized bodily fluid mimicry solution were reacted in a constant-temperature stirrer and a reaction tank. Chlorine concentration following chlorination was measured in the reactor tank using a residual chlorine analyzer, and an initial residual chlorine concentration of 5 mg/mL or higher was ensured. After the reaction, the final residual chlorine concentration was maintained at 1 mg/mL or less. The synthesized solution was loaded into a syringe for usage.

Aquatic exercise

Aquatic exercise was performed in a constant-temperature water bath (width × length × height; 90 × 30 × 30 cm) filled with water to a height of 13 cm and temperature at 29 °C for 30 or 60 min. All mice were made to swim for 4 s at a speed of 10 cm/s with 4-s intervals between swims, and the backs of the mice were tapped with a soft brush at every 4 s to maintain the swimming intervals. This process was repeated five times a week for a total duration of 4 weeks (Lee *et al.* 2019a, 2019b).

Inflammatory cell count in bronchoalveolar lavage fluid

The mice were euthanized 48 h after the final challenge through intraperitoneal injection of Alfaxan (0.5 mg/kg; Australia), and a tracheostomy was performed. To obtain the bronchoalveolar lavage fluid (BALF), ice-cold phosphate buffered saline (PBS) (0.5 mL) was infused into the lungs thrice and withdrawn each time through tracheal cannulation, resulting in a total volume of 1.5 mL. The total number of inflammatory cells was determined by counting the cells in at least five squares of a hemocytometer after excluding dead cells using trypan blue staining. Differential cell counts in BALF were determined using Systemex ADVIA 2120 (Siemens Healthcare Diagnostic Inc., IL, USA) following the manufacturer's instructions. The numbers of macrophages, neutrophils, and lymphocytes were calculated by multiplying the percentages obtained from the total yield. The slides were imaged using a digital camera attached to a microscope (Nikon Eclipse 80i; Nikon Corporation, Tokyo, Japan).

Enzyme-linked immunosorbent assay

The amounts of interleukin (IL)-2, IL-4, IL-6, IL-10, and interferon (IFN)-γ secreted in the serum of the controlled mice were quantitatively measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (BD OptEIA™ Mouse IL-2 (#555148), IL-4 (#555232), IL-6 (#555240), IL-10 (#555252), and IFN-γ (#555138) ELISA KitII), according to the manufacturer's instructions (BD Biosciences, San Diego, CA, USA).

Flow cytometry analysis

The isolated cells were resuspended in 100 μL of 1% fetal bovine serum (FBS) solution in PBS and incubated with anti-CD3 (PE-Cy7-conjugated, BD Ms T Lym Subset Ab Cktl, #558391), anti-CD4 (PE-conjugated, BD Ms T Lym Subset Ab Cktl, #558391), anti-CD8 (FITC-conjugated, BD Ms T Lym Subset Ab Cktl, #558391), and anti-CD25 (APC-conjugated, BD MS CD25 APC, #558643) antibodies. The cell pellets were resuspended in 400 μL of 1% FBS solution in PBS and analyzed using flow cytometry (FACS) (FACSAria II cell sorter, BD Biosciences, USA).

Statistical analysis

Statistical differences between groups were analyzed using Student's two-tailed *t*-test for comparisons between two groups and one-way analysis of variance for comparisons between more than two groups. All calculations were performed using GraphPad Prism software (version 5.0). Significance was set at $p < 0.05$.

RESULTS

Changes of immune cells by swimming exercise condition

To know the roles of swimming exercise on immune cells associated with asthma, blood cells were harvested (Figure 2). Analyses of isolated cells revealed a significant increase in eosinophils in the asthma-induced group, while no significant changes were observed in the remaining groups (Figure 2(d)). Also, changes in the other cell types were not observed in the groups. These findings suggest that DBPs do not exert any significant influence on immune cells associated with asthma.

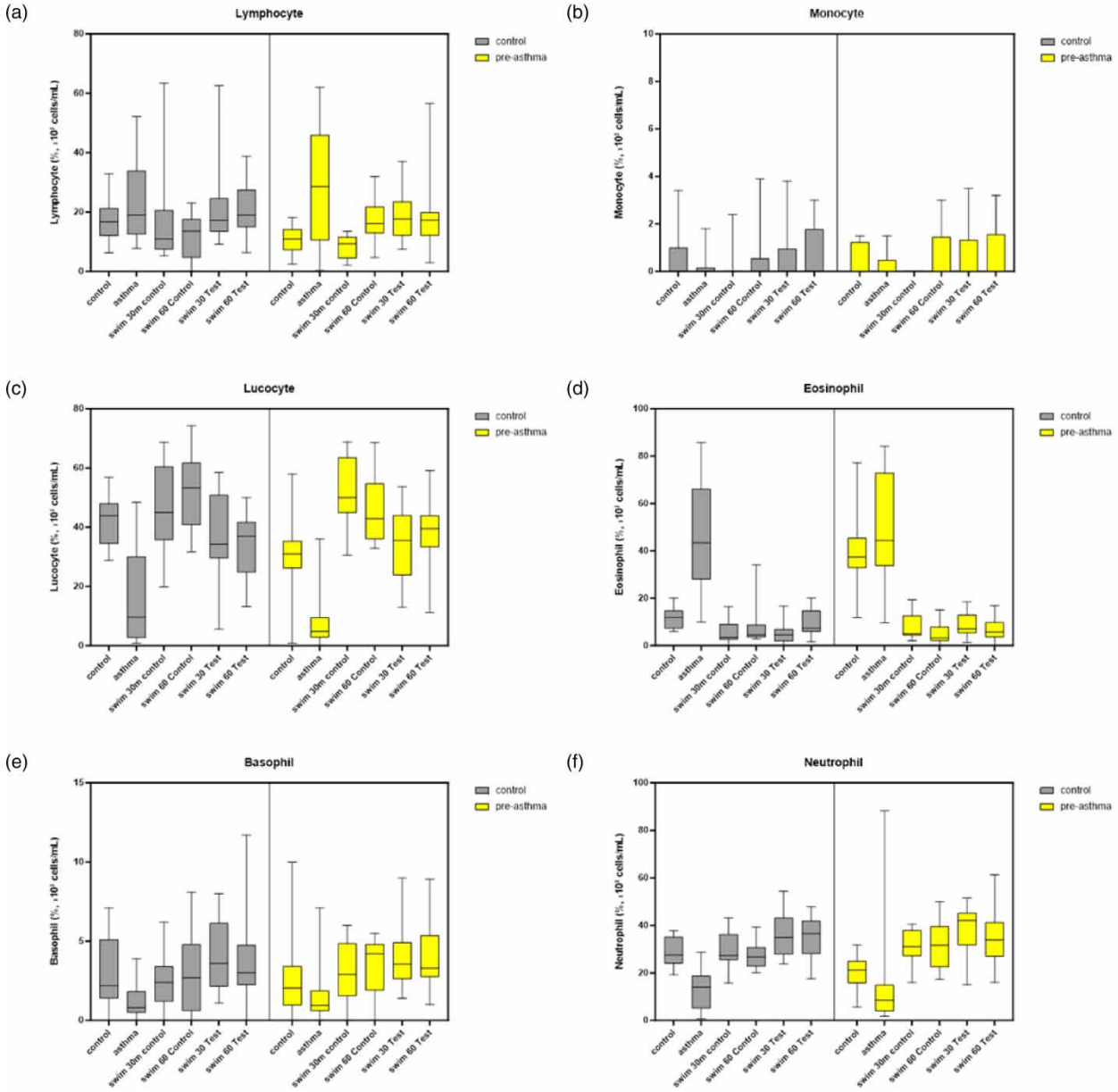

Figure 2 | Changes in immune cells by the inhalation of DBPs and swimming exercise. Immune cells were harvested from the mice under the specified conditions outlined in the 'Materials and Methods' section. The cells were analyzed with the FACS system, and the data are expressed in the bar graph: (a) Lymphocytes, (b) monocytes, (c) leukocytes, (d) eosinophils, (e) basophils, and (f) neutrophils. Data are expressed as the mean ± SD ($n = 15$–20 for each group).

Changes of T-cell subsets by swimming exercise condition

To determine the effects of swimming exercise on the immune system of asthmatic murine models, we examined the distribution of T cells in BALF, lymph nodes, spleen, and thymus. Analysis of T-cell distribution isolated from BALF revealed that in the control group, there was no significant difference in cell numbers. However, in the pre-asthmatic group, there was a noticeable decrease in cell numbers in the group induced with asthma. Notably, in both groups, there was an increase in cell numbers in the group subjected to swimming exercise (Figure 3(a)). This pattern was similarly observed in lymph nodes, with a more pronounced increase in cell numbers due to swimming exercise (Figure 3(b)). However, in T cells isolated from the spleen, no significant results were observed (Figure 3(c)). In the thymus, an increase in cell numbers was observed in

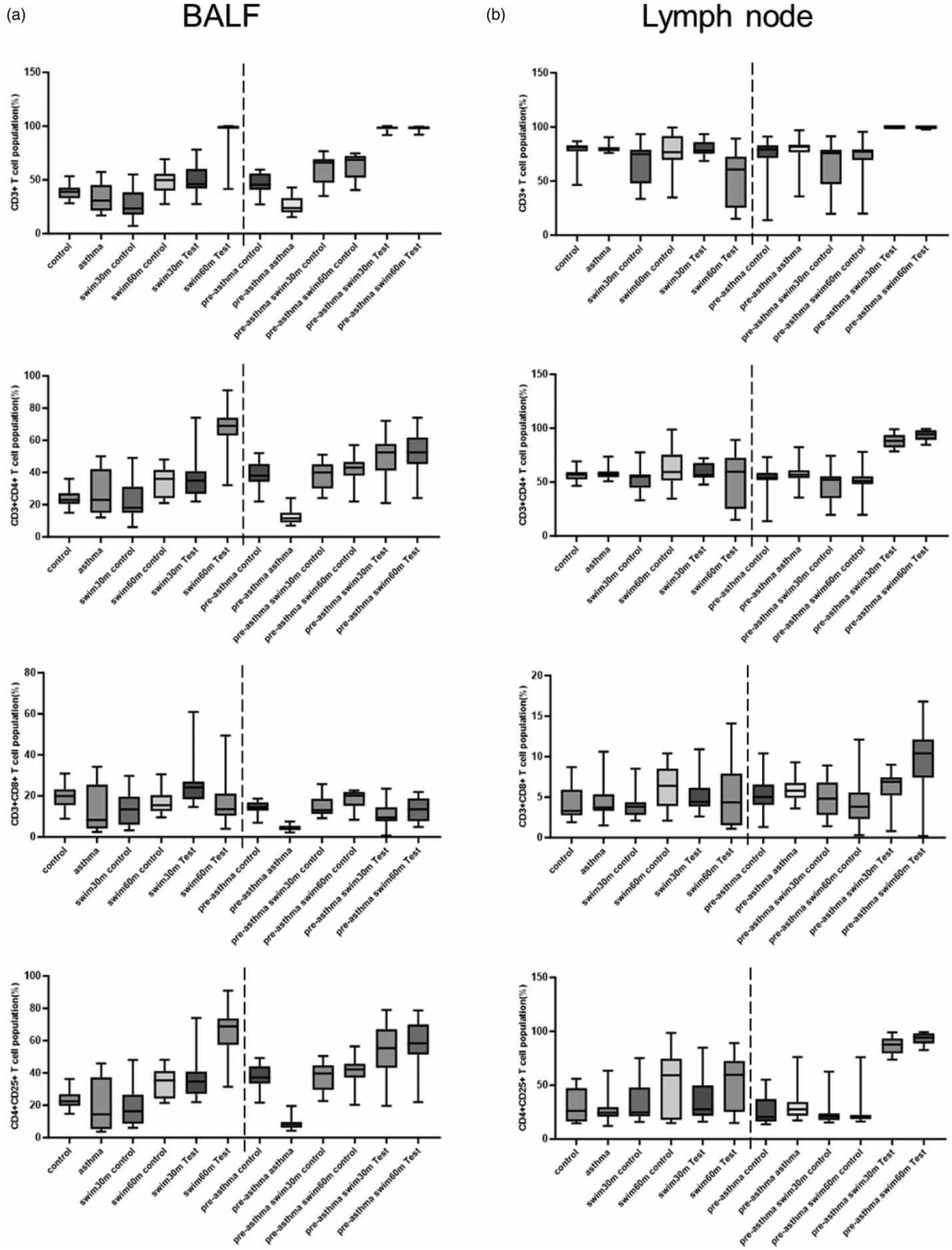

Figure 3 | Changes in T-cell populations by the inhalation of DBPs and swimming exercise. T cells harvested from each tissue of the investigated mice were analyzed with the FACS system: (a) BALF, (b) lymph node, (c) spleen, and (d) thymus. Data are expressed as the mean ± SD ($n = 15$–20 for each group). (*continued.*).

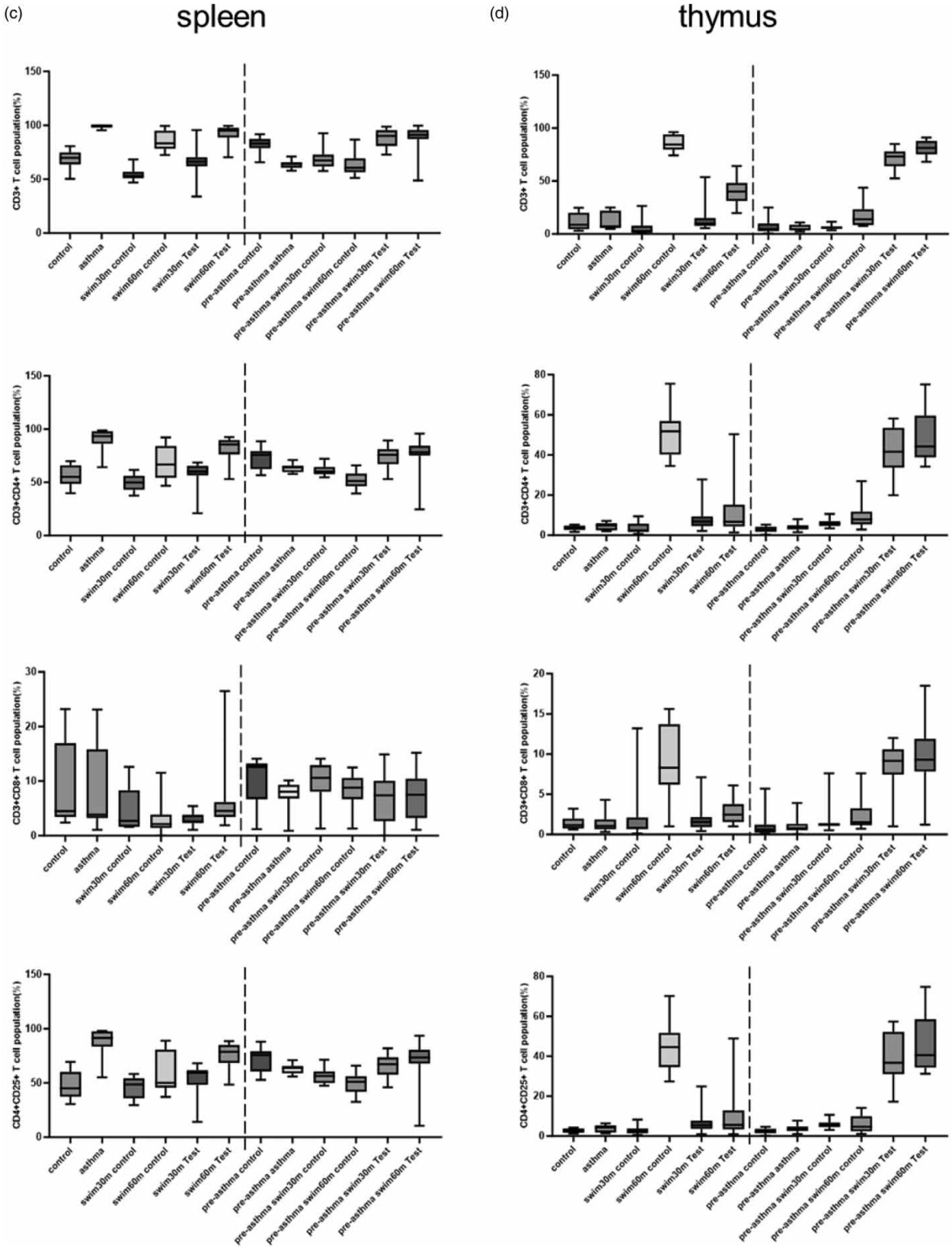

Figure 3 | Continued.

the control group that inhaled only DBPs without swimming exercise. Furthermore, in the asthmatic group subjected to swimming exercise, a noticeable increase in cell numbers was also observed (Figure 3(d)). These results suggest that inhalation of DBPs does not significantly affect the increase in immune cell numbers, while swimming exercise exerts a substantial influence on the composition of these T cells.

Changes of cytokine involved in asthma by swimming exercise condition

To study the effects of DBPs and swimming exercise on cytokines involved in asthma, cytokine levels in BALF and blood were measured using ELISA (Figure 4). In the results, the levels of IFN-γ, IL-2, IL-4, IL-6, and IL-10 in BALF and blood did not show significant changes. These data indicate that neither DBPs nor swimming exercise exerts a discernible influence on cytokines associated with asthma.

DISCUSSION

Swimming exercise is an important recreational activity for many people around the world and is often recommended by doctors for improving lung function. However, many studies have raised concerns about potential adverse health effects from exposure to chemically disinfected swimming pool water (Zwiener *et al.* 2007; Chowdhury *et al.* 2014; Valeriani *et al.* 2017; Lee 2023); in recent years, the association between the frequency of exposure in swimming pools and asthma has not been proven, and the results are often conflicting (Weisel *et al.* 2009; Font-Ribera *et al.* 2014; Voisin *et al.* 2014). Therefore, because the use of disinfectants in swimming pools has an important impact on public health in any country around the world (Voisin *et al.* 2010; Dehghani *et al.* 2018), this study examined the inhalation of DBPs in indoor swimming pools and swimming exercise. We would like to discuss the results of confirming the relationship and progression of asthma and analyzing changes in immune response. Asthma is a chronic inflammatory disease of the respiratory system that releases various chemical mediators that are closely related to inflammatory cells (Lee *et al.* 2019a, 2019b).

Studies looking at the effects of these mediators on asthma have found no significant changes. According to a study that compared and analyzed the frequency of DBP inhalation according to swimming pool attendance in 5,738 people, lung function and risk of asthma symptoms were not significantly related to the frequency of DBP inhalation (Font-Ribera *et al.* 2011), and there was no significant association between respiratory disease and the frequency of environmental exposure during swimming pool exercise among 3,223 participants (Font-Ribera *et al.* 2009). These reports supported our results that DBPs had a minimal effect on the expression of asthma-related factors. In other words, it could be seen that inhalation of DBPs in the swimming pool during swimming exercise had no or minimal effect on respiratory diseases, and the causal relationship was uncertain (Goodman & Hays 2008; Weisel *et al.* 2009; Villanueva & Font-Ribera 2012; Font-Ribera *et al.* 2014; Voisin *et al.* 2014).

Exercise is an important physical stress factor, and it has been reported that inflammation is induced and differentiated changes in T-cell distribution occur depending on the type and intensity of exercise. It means that exercise affects various immunological processes by affecting the concentration of catecholamines, a stress hormone, in blood and lymphocyte population (Krüger *et al.* 2008). That is, exercise promotes an intensity-dependent increase in sympathetic activity as well as activation of the hypothalamic–pituitary axis, leading to systemic secretion of catecholamines. In this study, the inhalation of DBPs did not statistically significantly show changes in T cells and cytokines, but changes in T cells were observed in all mice that underwent swimming exercise. These results are supported by studies showing that continuous swimming exercise has a positive effect on the body's immunity due to an increase in the number of T cells (Liu *et al.* 2011; Kang *et al.* 2021) and that swimming exercise is an important non-pharmacological intervention for chronic inflammation or T cells (Xie *et al.* 2019). Therefore, it can be seen that the change in lymphocytes through swimming exercise is safe for the efficiency of the immune system, and the increase in T cells through exercise is also effective in promoting the secretion of cytokines (Lee 2023).

Cytokines, which are signaling molecules secreted by immune cells, play an important role in maintaining homeostasis between cell-mediated and humoral immune responses and regulating inflammatory processes (Zuo *et al.* 2014; Couto *et al.* 2021). In particular, Th2 cytokines are considered the main cause for asthma because they promote the infiltration of eosinophils (Krüger & Mooren 2014). IFN-γ, IL-2, IL-4, IL-6, and IL-10 cytokines are said to be affected by physical activities such as swimming (Lee *et al.* 2019a, 2019b; Lee 2023). Many researchers have reported that although adequate exercise clearly promotes immune parameters, the effect is closely related to training parameters such as the type, intensity, and duration of exercise (Hillman *et al.* 2008; Font-Ribera *et al.* 2009; Radak *et al.* 2010; Walsh *et al.* 2011; Krüger & Mooren 2014).

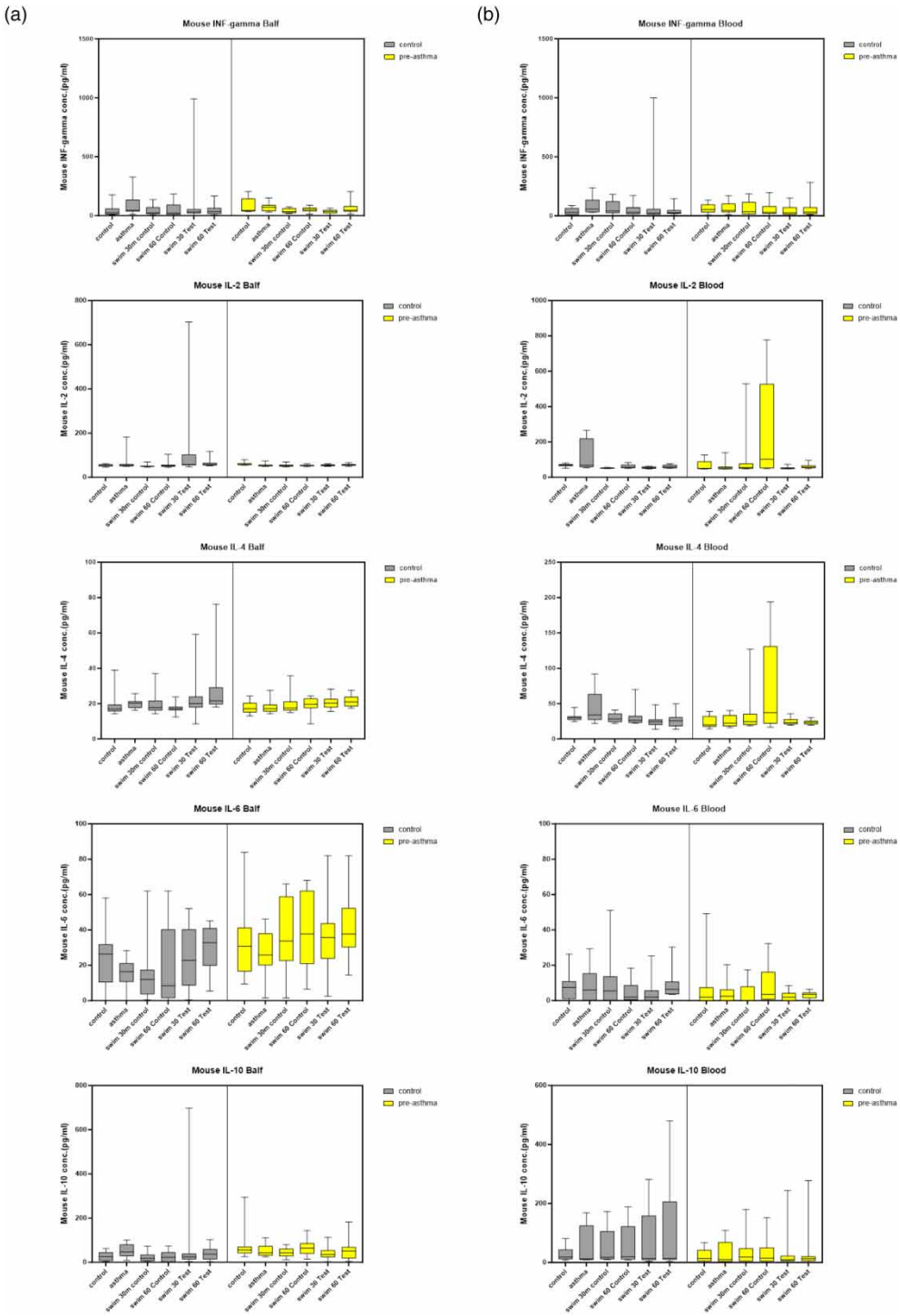

Figure 4 | Analysis of cytokines involved in asthma by the inhalation of DBPs and swimming. Secreted cytokines in indicated fluids were analyzed with ELISA: (a) BALF and (b) blood. Data are expressed as the mean ± SD ($n = 15–20$ for each group).

Therefore, long-term vigorous exercise may actually cause a higher incidence of upper respiratory tract infections, and immunological loss cannot be ruled out. Therefore, the positive effects of swimming and the suppression and improvement of asthma triggers are dependent on the individual's physical fitness level. Exercise should be encouraged.

CONCLUSIONS

This study analyzed how the inhalation of DBPs during swimming exercise affects asthma-related immune responses and drew the following conclusions. Factors such as inhalation of DBPs, asthma, and exposure time to swimming exercise did not appear to affect the immune system related to respiratory diseases. Therefore, considering that swimming is a recommended sport for individuals with asthma and respiratory diseases and that the immunological benefits gained from regular swimming exercise are greater, swimming is considered to be a safe and beneficial exercise for respiratory diseases. However, swimming pools are aggressive environments with high levels of DBPs in water and air due to constant disinfection and organic load from swimmers, so special attention to immune management is always required.

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AUTHOR CONTRIBUTIONS

B-A. Lee did all the work in this study. The author has read and agreed to the published version of the manuscript.

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INSTITUTIONAL REVIEW BOARD STATEMENT

The animal study protocol was approved by the Institutional Review Board of the Institutional Animal Care and Use Committee of the Dongnam Institute of Radiological and Medical Sciences (Permit Number: DI-2023-010), and all experimental procedures adhered to the National Institute of Health Guidelines for the Care and Use of Laboratory Animals. Animal welfare was ensured in compliance with the regulations stipulated by the National Animal Welfare Law of Korea.

DATA AVAILABILITY STATEMENT

All relevant data are included in the paper or its Supplementary Information.

CONFLICT OF INTEREST

The author declares there is no conflict.

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