THE EFFECT OF EXERGAMES ON IMMUNE RESPONSE AMONG SECONDARY SCHOOL STUDENTS IN PULAU PINANG, MALAYSIA

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by

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LIST OF ABBREVIATIONS

WHO	World Health Organization
ISEI	International Society for Exercise and Immunology
NK	Natural Killer Cells
H1N1	Swine Flu
URTI	Upper Respiratory Tract Infection
HS-CRP	High-Sensitivity C-reactive Protein
TNF	Tumor Necrosis Factor
TNF-α	Tumor Necrosis FactorAlpha
IGF	Insulin Growth Factor
IGFBP	IGF Binding Protein
TGF-b	Transforming Growth Factor-beta
IgA	Immunoglobulin A
IgG	Immunoglobulin G
COVID-19	Coronavirus Disease 2019
HIV	Human Immunodeficiency Virus
EBV	Epstein-Barr Virus
VZV	Varicella-Zoster Virus
KAP	Knowledge, Attitude, Practice
PRRs	Pattern Recognition Receptors
PAMPs	Pathogen-Associated Molecular Patterns
RNA	Ribonucleic Acid
LPS	Lipopolysaccharides
APCs	Antigen-Presenting Cells
MHC	Major Histocompatibility Complex
BCRs	B-Cell Receptors
Tregs	T Regulatory Cells
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-10	Interleukin-10
WBCs	White Blood Cells
NES	Nintendo Entertainment System

ANOVA	Analysis of Variance
MANOVA	Multivariate Analysis of Variance
CVI	Content Validity Index
I-CVI	Content Validity of Individual Items
S-CVI	Content Validity of Overall Scale
SPSS	Statistical Package for the Social Sciences
SD	Standard Deviation
SEM	Standard Error of Measurement
SDC	Smallest Detectable Change
SDCind	Smallest Detectable Change for Individual Subjects
SDCgroup	Smallest Detectable Change for Groups
ICC	Intraclass Correlation Coefficient
IC	Confidence Interval
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
NHMS	National Health and Morbidity Survey, Malaysia
PALMS	Physical Activity and Leisure Motivation Scale
VAS	Visual Analogue Scale
EDTA	Ethylenediaminetetraacetic Acid
RCTs	Randomized Controlled Trials

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KESAN EXERGAMES TERHADAP TINDAKBALAS IMUN DI KALANGAN PELAJAR SEKOLAH MENENGAH DI PULAU PINANG, MALAYSIA

ABSTRAK

Terdapat beberapa bukti bahawa bermain exergames boleh meningkatkan aktiviti fizikal secara berkesan, terutamanya di kalangan orang yang lebih muda (kanak-kanak dan remaja). Walaupun beberapa kajian telah dijalankan untuk menyiasat beberapa hasil fisiologi yang dikaitkan dengan mengambil bahagian dalam exergames. Walau bagaimanapun, masih tidak jelas sama ada exergames, satu bentuk aktiviti fizikal yang popular, boleh menjejaskan tindak balas imun dalam kalangan kanak-kanak dan remaja. Sepanjang pengetahuan kami, tiada penyelidikan telah dilakukan di Malaysia yang menyiasat kesan exergames terhadap tindak balas imunologi pelajar sekolah menengah. Oleh itu, kami telah menjalankan dua kajian untuk menyiasat kesan exergames terhadap tindak balas imun pelajar sekolah menengah di Malaysia. Kajian pertama dibahagikan kepada dua bahagian yang berbeza. Fasa pertama projek ini bertujuan untuk membangunkan dan mengesahkan instrumen kajian dalam bentuk soal selidik yang secara khusus mengukur tahap pengetahuan, sikap, dan amalan latihan dalam kalangan pelajar sekolah menengah, serta pengalaman mereka dengan bermain exergames. Dalam Fasa 2, kami menggunakan soal selidik yang telah disahkan sebelum ini. Dapatan kajian pertama mencadangkan bahawa soal selidik kami yang baru dibangunkan mempunyai tahap kesahan dan kebolehpercayaan yang tinggi. Di samping itu, dapatan kajian menunjukkan bahawa pelajar sekolah menengah mempunyai pemahaman yang kukuh tentang senaman dan sikap yang menggalakkan terhadap mereka. Garis panduan

Pertubuhan Kesihatan Dunia, bagaimanapun, menyatakan bahawa kanak-kanak dan remaja (umur 5 hingga 17) harus melibatkan diri dalam aktiviti fizikal sederhana hingga sengit selama 60 minit setiap hari. Oleh itu, berbanding cadangan organisasi kesihatan dunia, kadar penglibatan mereka masih rendah. Kajian kedua menyiasat kesan exergames terhadap tindak balas imunologi dan membandingkan tahap keberkesanan antara exergames dan jenis senaman tradisional dalam meningkatkan imuniti pelajar sekolah menengah. Penemuan kajian kedua mendedahkan bahawa peningkatan ketara dalam WBC, neutrofil, dan basofil dan penurunan ketara dalam kiraan mutlak NK dalam kumpulan senaman tradisional. Kumpulan Exergame menunjukkan peningkatan ketara dalam kiraan basofil dan penurunan ketara nisbah CD3+CD8+ diperhatikan. Walau bagaimanapun, selepas sesi exergame, terdapat peningkatan dalam leukosit, neutrofil, monosit, eosinofil, imunoglobulin A dan kiraan dan nisbah NK ($p > 0.05$). Perbandingan Anova antara kumpulan menunjukkan perbezaan yang signifikan secara statistik dalam kiraan mutlak CD16+56+ antara kumpulan kajian. Peningkatan yang lebih ketara dalam kiraan CD16+56+ telah diperhatikan dalam kumpulan Exergames berbanding kumpulan lain dengan nilai separa eta kuasa dua 0.264, yang menunjukkan kesan ketara intervensi exergame. Secara umum, Dapatan kajian ini menekankan kepentingan meningkatkan kesedaran terhadap exergameas sebagai strategi canggih untuk meningkatkan tahap aktiviti fizikal dan meningkatkan imuniti dalam kalangan kanak-kanak dan remaja.

THE EFFECT OF EXERGAMES ON IMMUNE RESPONSE AMONG SECONDARY SCHOOL STUDENTS IN PULAU PINANG, MALAYSIA

ABSTRACT

There is some evidence that playing exergames can effectively enhance physical activity, particularly among younger people (children and adolescents). Although several studies have been conducted to investigate a number of the physiological outcomes that are associated with participating in exergames. However, it is still unclear if exergames, a popular form of physical activity, can affect the immune response among children and adolescents. To the best of our knowledge, no research has been done in Malaysia that investigates the impact of exergames on the immunological response of secondary school students. Therefore, we have conducted two studies to investigate the effect of exergames on the immune response of secondary school students in Malaysia. The first study was divided into two distinct parts. The first phase of the project intended to develop and validate a research instrument in the form of a questionnaire that would specifically measure the knowledge, attitudes, and practice levels of exercise among secondary school students, as well as their experiences with playing exergames. In Phase 2, we utilised the previously validated questionnaire. The first study's findings suggested that our newly developed questionnaire possesses high levels of validity and reliability. In addition, the study's findings demonstrated that secondary school students had a solid understanding of workouts and a favourable attitude toward them. World Health Organization guidelines, however, state that children and adolescents (ages 5 to 17) should engage in moderate-to-intense physical activity for 60 minutes daily.

Therefore, compared to World Health Organization recommendations, their involvement rate is still low. The second study investigated the impact of exergames on immunological responses and compared the level of effectiveness between exergames and traditional types of exercise in increasing the immunity of secondary school students. The second study's findings revealed a significant increase in WBCs, neutrophils, and basophils and a significant decrease in NK absolute count in the traditional exercise group. The Exergame group showed a significant increase in basophil count, and a significant decrease in the CD3+CD8+ ratio was observed. However, after the exergame session, there was an increase in leukocytes, neutrophils, monocytes, eosinophils, immunoglobulin A and NK count and ratio ($p > 0.05$). ANOVA between-group comparisons showed statistically significant differences in CD16+56+ absolute count between the study groups. A more substantial increase in CD16+56+ count was observed in the Exergames group than in other groups with 0.264 partial eta squared value, which indicates a significant effect of exergame intervention. In general, the findings of this study highlighted the importance of raising awareness towards exergames as a cutting-edge strategy for increasing physical activity levels and boosting immunity in kids and teenagers.

CHAPTER 1
INTRODUCTION

1.1 Background and Scope of the Research

Any skeletal muscle movement that involves energy expenditure and raises the heart rate to boost the body's calorie output and maintain physical fitness is called physical exercise (World Health Organization/ Europe, 2011). Exercise is any regularly occurring, repeated physical activity planned and organized (World Health Organization/ Europe, 2011; Buford et al., 2014). The World Health Organization (WHO) recommends engaging in sustainable and health-promoting lifestyle activities to increase physical activity and exercise (Bull et al., 2020). Physical activity and exercise are crucial for individuals' growth throughout their lifespan and have benefits on people's health and well-being concerning all-cause mortality rates, cancer, musculoskeletal health, cardiovascular health, neurocognitive health, and metabolic health (Malm et al., 2019; Miko et al., 2020; Roychowdhury, 2020; Da Silveira et al., 2021). Exercise and physical activity can also help to fight infections by strengthening the immune system's defense mechanisms (Da Silveira et al., 2021).

The human immune system is orchestrated by a complex, intricate network of molecules and cells (Hao Shi et al., 2020). Their prime function involves protecting the human body from microbial attacks and preventing diseases (Warrington et al., 2011). The human immune system comprises two parts: innate immunity (the nonspecific and natural immune systems) and adaptive immunity, which is specific and can produce memory cells and antibodies to provide lifelong protection against many pathogens (Warrington et al., 2011). These two essential immune systems provide a complete immunological response for humans (Gasteiger and Rudensky, 2014; Iwasaki and Medzhitov, 2015).

The significant impact of exercise on the human immune system has been comprehensively documented (Simpson et al., 2015; Nieman and Wentz, 2019; Burtscher et al., 2020). It has been acknowledged in previous studies that acute and chronic exercise can influence the immune system (Gonçalves et al., 2020; Jee, 2020; Da Silveira et al., 2021). Previous research has shown that several influential factors, such as frequency, duration, intensity, and effort type of exercise, influence the modulation of the human immune system (Simpson and Katsanis, 2020; Laddu et al., 2021). Moderate-intensity physical activity helps to improve cellular immunity (Da Silveira et al., 2021). However, prolonged or high-intensity exercise without enough rest may reduce cellular immunity and increase vulnerability to infectious diseases (Da Silveira et al., 2021). The International Society for Exercise and Immunology (ISEI) states that the immune system declines with extended periods of physical activity, in other words, following 90 minutes of moderate- to high-intensity exercise (Da Silveira et al., 2021). The moderate-intensity activity is 'immuno-enhancing' and has been used successfully to boost vaccine responses (Simpson et al., 2015). Regular moderate-intensity exercise has been connected to enhanced T-cell proliferation, decreased levels of circulating inflammatory cytokines, higher neutrophil phagocytic activity, increased NK-cell cytotoxic activity and lower numbers of exhausted or senescent T-cells (Simpson et al., 2015).

Increased epidemiological data following the H1N1 influenza pandemic revealed that physically active people had shorter-lasting and less severe URTI than sedentary people (Matthews et al., 2002; Wong et al., 2008; Fondell et al., 2011;

Nieman et al., 2011; Siu et al., 2012). Further studies revealed that regular participation in a moderate-to-high physical activity level, as compared with a lower physical activity level, is associated with a reduced rate of URTI (a weighted mean reduction of 28%) (Matthews et al., 2002; Fondell et al., 2011; Zhou et al., 2018). However, randomized clinical trials supported a reverse relationship between moderate-intensity physical activity and URTI incidence (Nieman and Wentz, 2019). Moreover, epidemiologic studies suggested that regular exercise can be linked to reducing mortality rates, pneumonia, and influenza (Campbell and Turner, 2018). According to previous studies, increased immunosurveillance seems to be the primary mechanism behind these immunological adaptations to physical activity (Nieman and Wentz, 2019; Laddu et al., 2021). In a nutshell, a single session of a moderate-intensity exercise can inspire an increase in the activity of macrophages, temporary rises in the recirculation of the immune cells, immunoglobins and anti-inflammatory cytokines in the human blood (Da Silveira et al., 2021; Laddu et al., 2021). Such a combined effect can decrease the inflammatory cells' influx into the human lungs, thereby lowering the load of a pathogen (Davison et al., 2016; Nieman and Wentz, 2019).

An exercise session (i.e., a moderate-to-intense aerobic workout lasting less than 60 minutes) can stimulate the redeployment of immune cells between the blood circulation and tissues, increased immunoglobulin recirculation secreted by B cell, neutrophils, anti-inflammatory cytokines such as IL-6, and a significant inflow of natural killer (NK) cells and CD8+T cells (Campbell et al., 2009; Campbell and Turner, 2018; Nieman and Wentz, 2019). Physical exercise can impact different lymphocyte subpopulations in the blood (Graff et al., 2022). T cells (CD3+, CD4+, CD8+) and NK cells (CD16+/CD56+) rose considerably in young persons following a vigorous exercise session (Gonçalves et al., 2020). A previous study found increased CD4+ and CD8+ after moderate exercise in healthy males (Gonçalves et al., 2020). Additionally, studies have indicated that older adults who exercise regularly for longer than six months are less likely to develop age-associated immunosenescence, immunological dysfunction, or chronic low-grade inflammation and are more likely to benefit from the flu shot (Cao Dinh et al., 2017).

Exergames, also called 'active video games,' require the player to engage in physical activity while playing. It has also been suggested as a potentially helpful sort of at-home exercise, notably during the coronavirus epidemic. Exergaming is a relatively recent intervention in which players make physical gestures to play a game. Exergaming effectively combines training and gaming (Barry et al., 2014). Exergames can sometimes be played with portable controllers (Nintendo Wii), certain physical motions that are captured through a video camera (Microsoft Xbox Kinect & Sony EyeToy), and platforms of weight-sensing (Nintendo Wii Fit & DDR or Dance Dance Revolution) (Barry et al., 2016). (Barry et al., 2016). The results of several studies substantiated that practising exergames have improved cardiorespiratory capacity and controlled blood pressure, enhancing people's health (Wiles et al., 2017; Babu et al., 2019). Improvements in cardiorespiratory function, a reduction in fatigue, and a lessening of adjuvant therapy side effects were also observed in breast cancer survivors, according to a meta-analysis of a randomized controlled study reported by Cornette et al. (2016). Another study in a sedentary group found that participants' metabolic profiles improved after 24 weeks of playing exergames. These improvements included a lower level of fasting blood glucose, total cholesterol, glycated haemoglobin, and triglycerides, as well as a lower level of fat tissues and lower blood pressure, in addition to the proinflammatory marker High-sensitivity C-reactive Protein (hs-CRP) serum (Di Raimondo et al., 2013). Likewise, the results of systematic reviews reported that exergames were reported to increase mobility, balance, and muscle strength in older people and reduce falls and sarcopenia, delaying dementia and cognitive decline (Hill et al., 2015; De Almeida et al., 2020).

In addition, exergames may also strengthen the human body's immune system based on previous research (Takatori et al., 2016; Amorim et al., 2018; Kim et al., 2018). In the incidence of pneumonia in weak, older adults, exergames have greatly enhanced the peak cough flow and physical function, thereby inhibiting aspiration pneumonia (Takatori et al., 2016). In patients with thyroid cancer, 12 weeks of the exergames training session was reported to have considerably enhanced the NK cells' number (Kim et al., 2018). Moreover, a randomized controlled trial showed a significant decrease in the levels of the TNF serum in the wake of a 12-week practice of exergames among cancer patients (D. H. Lee et al., 2013; M. K. Lee et al., 2017). A Previous study reported that exergames had increased the levels of IGF binding protein (IGFBP)-3, insulin-like growth factor-1 (IGF-1), and adiponectin in the survivors of colorectal cancer, stage II and III (D. H. Lee et al., 2013).

It is worth mentioning that only a few studies were conducted to assess healthy people (Pell, 2011; Amorim et al., 2018). A previous study showed a significant decrease in adipokine levels in healthy women after a one-month dance using the Xbox 360 Kinect console (Amorim et al., 2018). No substantial changes in Salivary Immunoglobulin A (s-IgA) and a significant increase in cortisol were found following the exercise in the fair fitness group after participants had attended three times per week of 30-minute exercise sessions for a total of four weeks of exercise sessions using Nintendo Wii (Pell, 2011). However, it is still unknown whether exergames impact the immune response among children. To the researcher's knowledge, no pertinent studies have investigated how exercise games affect Malaysian secondary school students' immune response status.

1.2 Problem Statement

Because of the game-oriented features of exergaming, such games may be preferable to other forms of exercise. Video game enjoyment is a frequent feeling and a primary motivator for bodily exercise. As a result, techniques and components that improve the gaming experience, such as aesthetic considerations, gameplay mechanics, and narrative elements, are crucial and warranted to be studied (Rüth and Kaspar, 2021). Although several studies have investigated some physiological outcomes associated with participating in exergames and that exergames may improve adolescents' immunity over a sedentary lifestyle, it is unclear whether exergames are protective against infection and illness among children, as suggested for adults. The delivery mode of exercise may impact an individual immune response to exercise, thus moderating the body's ability to reap the benefits of a given intervention.

Therefore, more comprehensive studies on the effect of exergames on the immune response among healthy people are needed. To our knowledge, no study has investigated the effect of exergames on the immune response of secondary school students in Malaysia. If such a study can find something beneficial in humans from a young age, we can plan an early intervention. This study was expected to demonstrate that the exercise intervention facilitated by exergames is more effective in increasing the immune level of secondary school students in Malaysia than a conventional exercise intervention.

1.3 Aims of the Research

This research aimed to determine whether using exergames can increase the immune response of secondary school students in Pulau Pinang, Malaysia.

The specific objectives of this research are as follows:

(i) To develop and validate a questionnaire assessing knowledge, attitude, and practice (KAP) regarding exercise and exergames experiences among secondary school students.

(ii) To determine the level of KAP regarding exercise among secondary school students and the level of experience towards exergames among secondary school students.

(iii) To compare the level of effectiveness between exergames and conventional exercise in increasing the immunity of secondary school students in Pulau Pinang, Malaysia.

1.4 Significance of the Research

The outcome of this study will provide essential knowledge to support the potential advantage of exergames in increasing immunity, implying that they may be a joyful and convenient type of exercise for a broader range of children. Enhancing children's immune systems can help promote their general health and avoid disease and other illnesses. Exergames could be used as a preventive measure against infectious diseases and lower the incidence of infections among children if it is discovered that they have a good impact on immunity. Studies on exergames and immunity in kids can help schools, policymakers, and medical experts understand the potential advantages of adding exergames into physical activity programs. The findings of this research could serve as a guide for selecting an appropriate physical activity regimen for Malaysian children to improve their overall health and immunity, which is especially important during outbreaks of pandemic diseases.

1.5 Research Flow

This thesis includes two main studies. Chapter 2 of the literature review reviews the topic in great length. Chapter 3 summarises the research strategy, conceptual framework and the flowchart for this research project. The first study comprised two phases. Phase 1 was designed to develop and validate a research instrument, a questionnaire presented in Chapter 4. Phase 2 is a cross-sectional study to determine the KAP about exercise and experience towards exergames among Malaysian secondary school students in Pulau Pinang, presented in Chapter 5. The second study, in Chapter 6, was designed to examine the effect of exergames and conventional exercise on the immune response of secondary school students in Malaysia. Finally, Chapter 7 provides this doctoral research project's overall conclusion and recommendations.

1.6 Operational Definition

The list of operational definitions is shown in Table 1.1.

Table 1.1 Operational Definitions

Abbreviation	Operational Definition
Exergame	Exergame is a term used to describe an active video game that requires the player to engage in physical activity while playing. These games are available on various platforms, like Wii, Xbox, and PlayStation. In this study, we used the Nintendo Wii ring fit.
Conventional Exercise	Conventional exercise refers to basic movements of push and pull, squats, lunges, leaps and jumps, planks, etcetera, done through body weight management or exercise equipment in the gym.
Secondary school	Secondary education in Malaysia is a continuation of primary education. It comprises lower secondary (Form 1 – 3) and upper secondary (Form 4 & 5). Generally, a secondary school in Malaysia is equivalent to a high school in many countries.
Secondary School Student	Children who have completed primary school and enrolled in a secondary school.
Healthy population	Someone healthy is well and is not suffering from any illness.
Acute Exercise	Acute exercise is defined as a single session of exercise.
Chronic Exercise	Repeated amount of bouts of exercise during a short or long-term period.

CHAPTER 2
LITERATURE REVIEW

2.1 General Immunity

Immunity is the ability of an organism to resist infection or disease by defending against harmful pathogens, including bacteria, viruses, parasites, fungi, and abnormal or tumor cells like cancer cells (Marshall et al., 2018; McComb et al., 2019). An intricate network of immune cells, tissues, and organs collaborate in the immune system to identify and eliminate foreign antigens or other invaders. Innate immunity and adaptive immunity are the two main categories of immunity (Marshall et al., 2018). The first line of defence against pathogens is innate immunity, which offers a quick but generic response (Marshall et al., 2018). It includes various molecules and cells like neutrophils, macrophages, natural killer cells, cytokines like tumour necrosis factor-alpha (TNF-α), interleukin 1 (IL-1) and interleukin 6 (IL-6), and complement proteins that recognize and get rid of pathogens. Physical barriers like skin and mucous membranes protect against bacteria by preventing them from entering our bodies. Furthermore, innate immunity is also responsible for shaping and activating adaptive immunity. The actions of the innate immune system aid in the development of adaptive immunity, which is critical when innate immunity is ineffective in eliminating infectious agents (Marshall et al., 2018).

Adaptive immunity is more specific and can produce memory cells and antibodies to provide lifelong protection against many specific pathogens that enter bodies after surviving through innate immunity (Bonilla and Oettgen, 2010; Marshall et al., 2018). T and B lymphocytes are activated in this process (Bonilla and Oettgen, 2010; Marshall et al., 2018). B cell-produced antibodies recognize and attach to the surface of specific antigens, marking them for destruction by other immune cells (Bonilla and Oettgen, 2010; Marshall et al., 2018). On the other hand, T cells (CD8+) can identify and destroy abnormal cells like cancer and virally infected cells (Bonilla and Oettgen, 2010; Marshall et al., 2018). Adaptive immunity is an antigen-dependent ability to produce memory cells, which enables the host to mount a more effective and quick immune response upon reexposure to the antigen (Bonilla and Oettgen, 2010). Immunization involves the administration of a safe antigen to encourage the development of memory cells without the occurrence of a contagious disease. Adaptive immune responses are the foundation for effective immunization against infectious diseases (Bonilla and Oettgen, 2010; Marshall et al., 2018; McComb et al., 2019).

The immune system is tightly regulated to prevent excessive or inappropriate immune responses that can damage healthy tissues, such as autoimmune diseases. Numerous mechanisms, such as the release of pro-inflammatory cytokines (IL-2)and the activation of regulatory T cells, are involved in achieving this regulation (Rajendeeran and Tenbrock, 2021). Ongoing research in this field sheds light on the complex mechanisms underlying immune function and dysfunction. It may result in novel medicines and treatments for several ailments.

2.2 Immune System Structure

The immune system's structure and mechanism of action have been extensively studied in recent years, yielding a wealth of new information. The immune system comprises numerous cell types, such as lymphocytes, macrophages, and dendritic cells, which work together to detect and destroy foreign invaders (Marshall et al., 2018). These cells are organized into several lymphoid tissues and organs, such as the spleen, bone marrow, thymus, and lymph nodes. These tissues and organs are essential for the development, proliferation, and maturation of immune cells and the synthesis of antibodies and other immunological components. The organs involved in the immune system are shown in Figure 2.1.

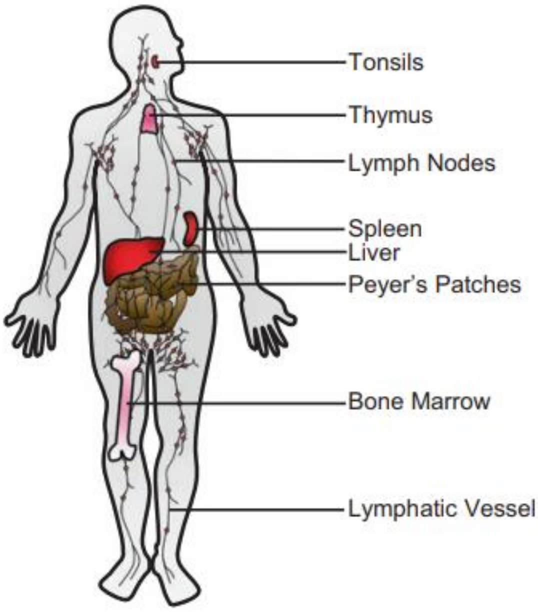

Figure 2.1 Immune system organs.

The picture was adapted from Smith (2014).

2.2.1 Innate Immunity

The innate immune system is essential for promptly recognizing and eliminating pathogens (Marshall et al., 2018). Four different forms of protective barriers can be regarded as being a part of innate immunity: endocytic and phagocytic, inflammatory, physiologic (temperature, low pH, and chemical mediators), and anatomic (skin and mucous membrane) (Marshall et al., 2018). The foundation of innate immunity against pathogens is pattern recognition receptors (PRRs), which allow immune cells to quickly detect and respond to a wide range of infections with similar structures or pathogen-associated molecular patterns (PAMPs). Examples include double-stranded RNA (RNA), which is created during viral infection, and lipopolysaccharides (LPS), which are found in bacterial cell walls (Marshall et al., 2018). Table 2.1 summarizes the innate immunity protective barriers adapted from the previous study (Marshall et al., 2018).

Table 2.1 Summary of Innate Immunity Protective Barriers

Barrier	**Mechanism**
Anatomic	
Skin	The barrier prevents access and microbial growth by maintaining an acidic environment (pH 3-5).
Mucous membrane	A membrane that has cilia on its surface that eject microorganisms from the body. A normal flora competing with bacteria for attachment sites is also a plus.
Physiologic	
Temperature	Some pathogens are prevented from growing by the body's fever reaction.
Low pH	Stomach acidity destroys the majority of undigested microorganisms.
Chemical mediators	Interferon triggers antiviral defenses in uninfected cells while Lysozyme breaks down the bacterial cell wall. Generally speaking, complement lyses microorganisms or promotes phagocytosis.
Phagocytic/endocytic	Various cells kill and digest entire creatures, internalize (endocytosis), and break down foreign macromolecules.
Inflammatory	Leakage of vascular fluid carrying serum protein with antibacterial activity is caused by tissue damage and

	infection, which causes an influx of phagocytic cells to the damaged area.

Innate immunity plays a critical role in quickly recruiting immune cells to regions of infection and inflammation by generating cytokines and chemokines (Marshall et al., 2018). Tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6) are critical inflammatory cytokines generated during the initial response to bacterial infection (Marshall et al., 2018). These cytokines are crucial for initiating cell recruitment and the local inflammation necessary to eliminate many conditions and aid in fever emergence. Inflammatory or autoimmune diseases are frequently linked to the dysregulated production of such inflammatory cytokines (Marshall et al., 2018).

2.2.1(a) Cells of the Innate Immune System

Phagocytes

Neutrophils or polymorphonuclear leukocytes are this system's initial responders. Neutrophils are short-lived cells in blood circulation and can react to invading pathogens in just a few minutes (Küppers, 2010). The majority of bactericidal reactive oxygen species are produced by these cells (Küppers, 2010). The mononuclear phagocyte is the second class of phagocytes to be activated. They develop from circulating monocytes into tissue cells. The process of phagocytosis, in which the phagocyte's plasma membrane engulfs the pathogen to create an endocytic vesicle known as a phagosome, is used by neutrophils and macrophages to ingest pathogens (Küppers, 2010). Local inflammation is the end outcome of these biological responses.

Macrophages are cells found in a variety of organs, including the skin. These local cells can produce cytokines and recruit immune cells to infection sites (Küppers, 2010).

Dendritic cells

A third kind of phagocytic cell, the dendritic cell, is crucial to antimicrobial responses. Like macrophages, these cells phagocytose antigens and eliminate infections, but in addition, they degrade the harmful proteins that have been broken down and display the peptides on the cell surface (Küppers, 2010). Dendritic cells migrate to lymph nodes after activation, interacting with T cells, presenting antigens, and initiating the adaptive immune response (Küppers, 2010). Hence, these cells serve as antigen-presenting cells, starting the adaptive immune response and as a crucial link between innate and adaptive immunity (Marshall et al., 2018).

Natural killer cells

Natural killer (NK) cells protect against intracellular infection (Marshall et al., 2018). Major Histocompatibility Complex (MHC) class I is typically downregulated by viral infections on the infected cell's surface (Marshall et al., 2018). NK cells only target cells with reduced or changed MHC (Marshall et al., 2018). The lack of MHC in the virus-infected cell activates the NK cell, causing it to produce cytotoxic granules that kill the infected cell when it contacts it (Marshall et al., 2018).

Mast cells and basophils

Mast cells and basophils have many distinguishing characteristics. Both play a vital role at the beginning of acute inflammatory reactions, such as allergies and asthma (Marshall et al., 2018). Mast cells play a crucial role in the immune system as ‘sentinel cells’, which are early makers of cytokines in response to infection or injury (Marshall et al., 2018). Basophils live in the circulation, unlike mast cells, which often live in the connective tissue surrounding blood vessels and are particularly prevalent near mucosal surfaces (Marshall et al., 2018). Eosinophils are granulocytes with phagocytic abilities that are crucial in eradicating parasites that are frequently too large to be phagocytosed. They also regulate the processes linked to allergies and asthma alongside mast cells and basophils (Küppers, 2010).

2.2.2 Adaptive Immunity

Adaptive immunity must occur when the innate immune system cannot effectively fight pathogenic microorganisms (Marshall et al., 2018). The identification of specific ‘non-self’ antigens and their differentiation from ‘self’ antigens, the creation of pathogen-specific immunologic effector pathways that kill particular pathogens or pathogen-infected cells, and the development of an immune memory with the ability to quickly wipe out a specific pathogen should recurrent infections occur are the three main functions of the adaptive immune response (Marshall et al., 2018). Effective vaccination against infectious illnesses is built on adaptive immune responses. T and B cells are the cells of the adaptive immune system (Marshall et al., 2018).

2.2.2(a) Cells of the Adaptive Immune System

B cells

A type of white blood cell called B cells, or B-lymphocytes, are a crucial component of adaptive immunity (Marshall et al., 2018). They produce protein molecules known as antibodies that recognize and neutralize foreign invaders such as viruses and toxins (Marshall et al., 2018). Due to the establishment of immunological memory, aided by B-lymphocytes, the immune system can remember all prior interactions with pathogens that enter the body to build a quicker and more efficient response upon repeat exposure (Marshall et al., 2018). B-lymphocytes develop through a complex process of maturation and selection before becoming fully functional. They are derived from bone marrow stem cells (Bonilla and Oettgen, 2010; McComb et al., 2019). They undergo a series of genetic changes during this process, which causes a vast array of various B-cell receptors (BCRs) to develop on their surface. Each BCR can recognize a specific molecular pattern, an antigen, present on a pathogen’s surface or a foreign substance (Bonilla and Oettgen, 2010; McComb et al., 2019). Upon encountering an antigen, B-lymphocytes can become activated and undergo clonal expansion, a process by which they proliferate and differentiate into memory B-cells and antibody-secreting plasma cells (Bonilla and Oettgen, 2010). Memory B-cells are long-lived cells that can persist for years and quickly react to subsequent exposures to the same antigen, in contrast to plasma cells, which are not only short-lived cells but are also able to secrete large amounts of antibodies into the bloodstream (Bonilla and Oettgen, 2010; Marshall et al., 2018).

T cells

T lymphocytes, or T cells, are white blood cells essential for the adaptive immune response (Smith, 2014; Marshall et al., 2018). These cells are produced in the bone marrow and differentiation in the thymus gland. There are different varieties of T cells, each with a specific function. Helper T cells, also known as CD4+ T cells, release cytokines and activate other immune cells, while cytotoxic T cells, also known as CD8+ T cells, are involved in the destruction of virus-infected cells and tumour cells (Smith, 2014; Marshall et al., 2018). T cells can identify particular antigens presented by MHC molecules on the surface of other cells (TCR) (Smith, 2014; Marshall et al., 2018).

2.3 Ontogeny of the Immune System in Pediatrics

Ontogeny refers to the development of the immune system from birth through childhood (Kloc et al., 2020). The altered immune response of the mother and fetus depends on several mechanisms, including the newly discovered function of T regulatory cells (Tregs) in developing and maintaining this tolerance (Kloc et al., 2020). The newborn is exposed to foreign antigens after delivery, demanding an immediate immune response (Simon et al., 2015). Yet, the immune system of infants is weak, fully developing during the first 7-8 years of life. Innate immune cells, including monocytes, macrophages, dendritic cells, and neutrophils, are the first-line immune responders in the fetus and infant (Simon et al., 2015; Kloc et al., 2020).

The fetus, baby, and growing child all have adaptive and innate immunity. The T cells are one of the cellular elements of adaptive immunity. Even though CD4 and CD8 T cells start to develop around the 15th week of pregnancy, quantitatively, T-cells are more prevalent at birth, grow during infancy, and then decline to adult levels in early childhood (Goenka and Kollmann, 2015; Simon et al., 2015; Kloc et al., 2020). Newborn T cells are more tolerogenic and hyporesponsive to antigens than adult T cells. The B cells are other adaptive immune system cells. Over 40% of the circulating B cells in the newborn and the first few months of life are low-affinity B1 cells (Simon et al., 2015). Later in life, these cells are replaced by typical B2 cells (Simon et al., 2015). Similar to T-cells, neonatal B-cells also have low numbers of memory B-cells, with about 95% having an immature character. The essential co-stimulatory molecules, such as the CD40 ligand, which promote communication between APCs, T cells, and B cells, are also expressed at low levels in newborn B cells (Simon et al., 2015; Kloc et al., 2020). Babies born before 32 weeks gestation are more susceptible to infection because transplacental antibody transfer allows foetal IgG levels to reach 50% of adult levels (Goenka and Kollmann, 2015).

Moreover, compared to adult antibody responses, neonatal antibody responses are delayed, reduced, and less lasting (Goenka and Kollmann, 2015). Serum antibody levels reach a physiological low point at around six months of age as newborn and infant (active) antibody production rises over the first year of life while transplacentally acquired (passive) antibody levels decline (Goenka and Kollmann, 2015). Only later in infancy does the IgG antibody repertoire begin to functionally diversify through somatic mutation (Goenka and Kollmann, 2015).

Immunization is essential for promoting immunity development and protecting against infectious diseases. However, the immune system of young infants may have a suboptimal response to vaccines due to their immaturity (Siegrist, 2018). Nutrition is another important factor in immune development because malnutrition can weaken immune function and increase the likelihood of infections (Fragkou et al., 2021). For optimal immune function in infants and children, it is crucial to consume sufficient amounts of nutrients such as vitamin D (Mailhot and White, 2020). The development of the immune system is also affected by infections and environmental exposures, with some directions leading to immune maturation while others impair it. For instance, early exposure to microbes and some environmental factors, such as farming and cowsheds, has been linked to a lower risk of developing allergic and autoimmune diseases (Okada et al., 2010). In contrast, exposure to other factors, such as pesticides, may increase the risk (Nino et al., 2021; Touil et al., 2023).

Elevations in circulating gonadal hormone levels are one feature of pubertal and adolescence (Brenhouse and Schwarz, 2016). Puberty is a sensitive stage for the organisation and activation of all actions of sex steroid hormones, such as oestrogens and androgens, because of the well-known modulatory effects that these hormones have on the brain and peripheral immune system during this time (Brenhouse and Schwarz, 2016). Lymphocytes and macrophages are impacted by sex hormones either directly through binding to surface hormone receptors or indirectly through their effects on other hormone-responsive target organs, including the hypothalamus-pituitary axis, which in turn alter immune responses (Brenhouse and Schwarz, 2016). As puberty begins, immune-related illnesses are frequently more common or severe in females (Brenhouse and Schwarz, 2016). In reality, testosterone can boost the amount of IL-10 that T-lymphocytes produce. This impact can be mediated directly by the androgen receptors on the T-lymphocytes themselves or indirectly by the receptors on innate immune cells like macrophages (Brenhouse and Schwarz, 2016). The consequence will make testosterone have an anti-inflammatory effect on peripheral immune function, which may be one reason why guys are less prone to immunological-related illnesses after puberty. While it is obvious that sex steroid hormones significantly impact peripheral immune function, it is still unclear how these pubertal hormones affect the complete maturation of the immune systems and how this may affect both physiological and behavioral outcomes during the adolescent period.

2.4 Influence of Exercise on Immune Response

Engaging in physical activity and regular exercise can positively impact the immune response in children and adolescents (Timmons, 2007). Physical activity promotes physical health and improves children's mental health and cognitive function (Bidzan-Bluma and Lipowska, 2018). Exercise is essential for boosting the immune system and preventing disease. A previous study showed that regular, as well as moderate-to-vigorous bodily exercises contribute to reducing risks of community-acquired contagious diseases, together with the mortalities of infectious diseases, boosting the first defence line of the human immune system and increasing vaccination potency (Chastin et al., 2021).

Regular exercise can help to reduce stress hormone levels, such as cortisol, which inhibits various critical functions of the human immune system, including the lymphocytes' capability of multiplying in response to infectious agents, the NK-cells functions, and the CD8+T-cells, which are all considered vital in the elimination and recognition of cancerous cells and virally infected cells (Duggal et al., 2019; Da

Silveira et al., 2021). Given exercise's beneficial effects, regular exercise can be a valuable tool in strengthening the immune system and maintaining optimal health.

2.4.1 Effect of Acute Exercise on the Immune System

Regular exercise has long been known to affect the immune system positively, but the effects of acute exercise, which is a single bout of physical activity, are less clear. Acute exercise can positively affect the immune system, which depends on several factors, including the intensity, duration, and type of exercise. Table 2.2 shows the summary of the effect of the exercise on immunological parameters.

Table 2.2 Summary of acute effects of exercise on immunological parameters in healthy individuals

Author	Population	Age	Intervention	Outcome
Sand et al. (2013)	Healthy adult (male and female)	19-44 y	One exercise session (running, cycling)	Significant increase in WBC, neutrophil, lymphocyte and monocyte.
Almada et al. (2013)	Healthy male	20.6 ± 2.1 y	One exercise session (Running)	IL-6 Increased from Pre to Post.
Davison et al. (2011)	Healthy male	27 ± 5 y	Cycling Wingate Test (4 × 30 s)	Neutrophil count Increased from Pre to Post
Huldani et al. (2021)	30 adolescents (15 athletic- 15 sedentary)	17 y	12 minutes running aerobic exercise	Increase the level of TNF alpha, leukocytes, neutrophils, and monocytes in sedentary populations.
Millard et al. (2013)	29 healthy adult (19 males, 10 females)	25–45 y	Running up and down 150 stair-steps	Significant increase in NK cells.
Eda et al. (2018)	23 Healthy females	60.4 ± 10.4 y	Yoga stretching for 90 min	IgA increased from pre- post.
Murase et al. (2016)	16 Sedentary young males	23.8 ± 1.5 y	Cycling for 59 min	IgA increased from pre to post.
Timmons et al. (2006)	22 healthy adolescents (11 boys, 11 girls)	14 y	Cycling for 60 min	Increased NK cells among both gender.
Timmons et al. (2006)	58 adolescents (33 boys, 25 girls)	12,14 y	Cycling for 60 min	WBC, neutrophil and CD3, CD4 increased from pre-post.

2.4.2 Mechanism of Changes in Immune Function during Exercise

The immune system's function is significantly impacted by exercise (Da Silveira et al., 2021). It is widely acknowledged that moderate-intensity exercise is good. In contrast, extended periods of intense exercise training can lower immunity (Simpson et al., 2015; Da Silveira et al., 2021). Single bouts of exercise increase the redistribution of leukocytes between the blood circulating and the lymphoid tissues (Simpson et al., 2015). This response is mediated by increased hemodynamics and the release of catecholamines and glucocorticoids after the sympathetic nervous system and hypothalamic-pituitary-adrenal axis are activated (Simpson et al., 2015).

Long-term exercise has been shown to change the balance of Type I such as IL-2 and Type II like IL-6 cytokines, decrease T-cell, NK-cell, and neutrophil function, and attenuate immunological responses to primary and recall antigens in vivo (Simpson et al., 2015). During intense training and competition, elite athletes frequently experience symptoms of upper respiratory tract infections (URTI), which changes in mucosal immunity may bring, specifically, decreases in secretory immunoglobulin A (Simpson et al., 2015). The 'immuno-enhancing' effects of brief, moderate-intensity exercise, on the other hand, have been successfully employed to boost vaccination responses in 'at-risk' patients. Regular moderate-intensity exercise can boost immunity by reducing inflammation, changing the makeup of 'older' and 'younger' immune cells, enhancing immunosurveillance, and reducing psychological stress (Simpson et al., 2015). Indeed, exercise is an effective behavioral intervention