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Review

Demystifying roles of exercise in immune response regulation against acute respiratory infections: A narrative review

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ABSTRACT

The benefits of physical activity and exercise, especially those classified as moderate-to-vigorous activity (MVPA), have been well-established in preventing non-communicable diseases and mental health problems in healthy adults. However, the relationship between physical activity and exercise and the prevention and management of acute respiratory infection (ARI), a global high-burden disease, has been inconclusive. There have been debates and disagreements among scientific publications regarding the relationship between exercise and immune response against the causative agents of ARI. This narrative review aims to explore the theory that sufficiently explains the correlation between exercise, immune response, and ARI. The potential root causes of discrepancies come from research associated with the "open window" hypothesis. The studies have several limitations, and future improvements to address them are urgently needed in the study design, data collection, exercise intervention, subject recruitment, biomarkers for infection and inflammation, nutritional and metabolism status, and in addressing confounding variables. In conclusion, data support the clinical advantages of exercise have a regulatory contribution toward improving the immune response, which in turn potentially protects humans fromARI. However, the hypothesis related to its negative effect must be adopted cautiously.

1. Introduction

In recent decades, especially progressively after the coronavirus disease 2019 (COVID-19) pandemic, an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), recommendations and guidelines have been developed to carry out physical activity and motivate behavior change. Lack of physical activity in adults is influenced by several environmental, social, and psychological factors.[1] Physical activity is fundamental in preventing non-communicable diseases such as diabetes mellitus and cardiovascular disease. The risk of developing these chronic diseases can be reduced by regular physical activity and minimizing sedentary lifestyle.[2] Moreover, physical activity helps relieve stress and promote general well-being by increasing energy levels.[3]

In 2018, the World Health Organization (WHO) launched a global action plan to reduce physical inactivity and sedentary lifestyle up to approximately 10% by 2025 and 15% by 2030.[4] According to WHO recommendations, adults performing moderate-intensity physical activity for fewer than 150 minutes (min) and children and young adults performing Moderate to Vigorous Activity (MVPA) for fewer than 60 min daily are classified as physically inactive. Physical activity should become an integral part of healthy living because physical inactivity is a major contributor to global mortality.[5,6]

The benefits of physical activity in healthy adults, especially those that conform with the MVPA guidelines, for preventing non-communicable diseases and mental health problems, have been widely reviewed.[5,7–9] However, no guidelines have been established regarding physical activity as a prevention modality for infectious diseases. Accumulated evidence indicates that physical inactivity should be considered a risk factor for acute respiratory infections (ARI). Physical activity can prevent and reduce the severity of ARI symptoms, which were prominently highlighted in the COVID-19 pandemic era.[10] Furthermore, studies have proven the long-term beneficial effects of exercise on the respiratory system. These effects include increased mechanical work due to increased respiratory muscle strength, increased efficiency of pulmonary gas exchange, increased oxygen delivery to body organs, and increased activity of oxidative enzymes in muscles.[11] Exercise also has advantageous effects on the air-pollutant-induced damage to the respiratory system. It has been reported to reduce pro-inflammatory markers

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List of abbreviations:

ADP	Adenosine diphosphate
ALRs	Absent in melanoma-2 (AIM2)-like receptors
APC	Antigen presenting cells
ARI	Acute respiratory infections
ATP	Adenosine triphosphate
BMI	Body mass index
CAP	Community acquired pneumonia
CCL2	Chemokine (C–C Motif) ligand 2
CD	Clusters of differentiation
CLRs	C-type lectin receptors
COVID-19	Coronavirus disease 2019
DALDA	Daily analysis of life demands of athletes
DC	Dendritic cells
DNA	Deoxyribonucleic acid
FITT	Frequency intensity time and type
HBcAg	Hepatitis B virus core antigen
HIIT	High intensity interval trainning
IFNs	Interferons
Ig	Immunoglobulin
IL	Interleukins
IL-1RA	Interleukin-1 receptor antagonist
ISG	Interferon-stimulated genes
iTRAQ	Isobaric tags for relative or absolute quantitation
LRTI	Lower respiratory tract infections
LSD	Long-slow distance training
MCP-1	Monocyte chemoattractant protein-1
METs	Metabolic equivalents
mRNA	messenger RNA
miRNA	microRNA
MVPA	Moderate to vigorous activity
MyD88	Myeloid differentiation primary response 88
NF-κB	Nuclear factor kappa B
NO	Nitric oxide
NK	Natural killer cells
NLRs	Nucleotide oligomerization domain (NOD)-like receptors
O_2^-	Superoxide anion
PAMPs	Pathogen-associated molecular patterns
PBMC	Peripheral blood mononuclear cell
PRRs	Pattern recognition receptors
RCT	Randomized controlled trial
RLRs	Retinoic acid-inducible gene-I (RIG-I)-like receptors
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RSV	Respiratory syncytial virus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
$TCD4^+$	T lymphocytes $CD4^+$
$TCD8^+$	T lymphocytes $CD8^+$
TLRs	Toll-like receptors
TNF	Tumor necrosis factor
URTI	Upper respiratory tract infections
VO_{2max}	Maximal oxygen consumption
VO_{2peak}	Peak oxygen uptake
WHO	World Health Organization
WURSS	Wisconsin upper respiratory symptom survey

and increase anti-inflammatory markers. Still, these reductions are insufficient to prevent lung function damage in animals exposed to air pollution.[12]

ARIs are a group of diseases that involve respiratory organs. It covers many diseases that have mild to severe symptoms and can be fatal, though dominantly it is mild and is relieved without medical intervention. There are several updates on the case definition of ARI affecting the sensitivity of the case definition.[13] Based on the anatomical area of the organ involved, ARIs are conventionally divided into two groups of illnesses: Upper respiratory tract infections (URTIs) involving the nose, sinuses, middle ear, larynx, and pharynx; and lower respiratory tract infections (LRTIs) affecting the trachea, bronchi, and lungs.[14,15]

ARI was documented as a high burden disease with substantial morbidity and mortality, that affects all ages.[16,17] Data on ARIs are scattered, partial, and mostly focus on the prevalence of ARIs in infants and children. Data from Nepal showed that 60.8% of children suffer from ARI, and almost 20% have severe or very severe pneumonia.[18] In Yogyakarta province in Indonesia, almost 96% of infants had at least one episode of non-pneumonia ARI. The highest incidence rate of ARI and pneumonia was documented in children who were 9 to < 12 months old whereas the lowest incidence rate was documented in infants less than 3 months old.[19] Patients suffering from URTI are frequently admitted to outpatient clinics with less risk of fatality[20] whereas LRTIs are the most frequent cause of illness and are responsible for 4.4% of deaths globally.[16]

ARI is caused by several pathogens, including viruses, bacteria, fungi, and protozoa. However, confirmatory laboratory procedures were not available in low-middle-income countries, which may affect the accuracy of the ARI etiological diagnosis.[21] The following viruses have been reported as causative agents of ARI in children < 5 years of age: respiratory syncytial virus (RSV), adenovirus, rhinovirus, influenza virus, human metapneumovirus, human bocavirus, parainfluenza virus, human coronavirus 43, and enterovirus.[22–24] The bacteria responsible for ARIs are *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Hemophilus influenzae*, *Pseudomonas aeruginosa*, and Group A *Streptococcus*. Mixed pathogens of viruses and bacteria are commonly found in patients with ARI.[23]

The causative agents responsible for ARI in adults are similar to those in children and infants; viruses dominate the cases and influenza was reportedly the common virus isolated among adults.[25] A study in Korea showed that there were differences in the frequency of each virus between the two age groups. The influenza virus and the human rhinovirus were found to be dominant in adults and in children, respectively.[26]

This review aims to explore the potential theory that sufficiently explains the correlation between exercise and ARIs. The debate that exercise will increase immune response and eventually protect humans from infection was opposed by contradictory arguments. Therefore, this narrative review proportionally highlights publications that correlated exercise and ARI.

2. Method

To conduct this narrative review, a literature search was completed using Medline/PubMed and Scopus databases to identify relevant publications using a combination of the following keywords: physical activity, exercise, immune responses, innate immune, adaptive immune, acute respiratory infection, bacterial infection, and viral infection. Relevant articles were retrieved and used to identify additional sources by cross-referencing and manually checking reference lists. Relevant publications reporting the association between exercise, immune response, and the risk of acute respiratory infection are reviewed. A short list of publications concerning the open window hypothesis is presented in Table 1.

3. Immune response against acute respiratory viral infection

The innate immune response against viral infections is initiated when viral components are recognized by Pattern Recognition Receptors

Table 1
Contradictive publications related to the open window hypothesis.

Authors	Subjects and sample size	Physical activities	Research design	Parameters	Key findings	Possible limitation/s
Kakanis et al. (2010)[155]	Ten elite "A" grade club level male cyclists were recruited from various cycling and triathlon clubs	2 h of cycling at 90% of the second participant's ventilatory threshold (T_{V2})	Non-randomized non-controlled experimental study	Numbers of blood cells, NK Cytotoxic Activity Assay, Oxidative Burst Assay, Phagocytic Function Assay	• Immediate post-exercise increases were observed for the blood counts of total neutrophils and lymphocytes. • A decrease in neutrophil phagocytic function was observed from 2 h post-exercise to 6 h and 24 h post-exercise; neutrophil oxidative burst activity was not changed. • Confirmed the presence of lower immune cell numbers and function following an acute bout of endurance exercise.	• Very limited sample size, only 10 male athletes • There is no data of URTI observed.
Mårtensson et al. (2014)[156]	Male ($n = 4$) and female ($n = 3$) cross-country (XC) skiers, male biathletes ($n = 2$) and male long-distance runners ($n = 2$), who were accepted as elite athletes	Unspecified	Retrospective self-reported sickness	Training volume (km or hours), the number of sick days and the number of days injured	• High training load was associated with low incidence of training days lost due to self-reported days of sickness. • The number of training hours per year was inversely correlated with the number and variation in exercise-constrained sick days.	• Very limited sample size, only 8 male and 3 female elite athletes • Self-reported day of sickness without illness confirmatory diagnosis procedures • There were no interventional physical activities specified. • There was no data of immune response. • There was no confounding variable control, such as diet and athletes' performance
Fahlman et al. (2017)[157]	22 students of cross-country team member and 23 physically active students (minimum 30 min, 3 times per weeks) as controls	Intense acute exercise and exercise across a training season in highly competitive athletes.	Non-randomized, controlled, quasi-experimental study.	Salivary IgA concentration and secretion rate of Salivary IgA. Self-report of upper respiratory syndrome	• An acute bout of high-intensity exercise resulted in decreased salivary IgA concentration and secretion rate. The decreased state was documented within the 1st month of prolonged training and remained low throughout the season. • The decrease in the secretion rate of salivary IgA did not result in the increased frequency of upper respiratory syndrome (cough, runny nose, and nasal congestion).	• Self-reported symptoms and sign of ARI among the subject, without illness confirmatory diagnosis procedures • Only Salivary IgA was measure for immunological parameter.
Schlagheck et al. (2020)[158]	24 healthy men (aged 20–35 years)	Endurance exercise and resistance exercise using cycle ergometer.	Randomized crossover study design	Counts and measure the proportions. of leukocytes, neutrophils, lymphocytes, lymphocytes subsets, CD4/CD8 ratio, and systemic immune inflammation index.	• An acute bout of endurance exercise showed more immune response disturbance than resistance exercise. • A single bout of endurance exercise resulted stronger alterations of cellular immune response than resistance exercise.	• Subjects were homogenous in characteristic and men only. • There was no data for the susceptibility to ARI among subjects. • Resistance exercise and endurance exercise interventions were performed using cycling ergometer, which may differ with a predominantly upper body workout as a resistance exercise.
Isaev et al. (2018)[159]	147 athletes with highest mastery level of cyclic (swimming, skiing) and acyclic sports (wrestlers and boxers)	Unspecified	Non-randomized, non-controlled experimental study	Neutrophil secretory activity and ability to produce reactive oxygen intermediate; lysosomal activity; and the concentration IgA, IgM, and IgG.	• Athletes of acyclic sports (wrestlers and boxers) experienced a significant double increase in the level of secretory immunoglobulin IgA. • A variety of immune response were observed	• There was no interventional exercise applied to the subjects. • The aim is to describe the immunological response to the persons physical activity habits in different types of exercises.

(*continued on next page*)

Table 1 (*continued*)

Authors	Subjects and sample size	Physical activities	Research design	Parameters	Key findings	Possible limitation/s
					among the athletes from different sports. The highest lysosomal activity was recorded for skiers. Boxers, wrestlers, and swimmers had a decrease in lysosomal activity level. The maximum and minimum phagocytic numbers were recorded in wrestlers and boxers, respectively.	
Tanner and Day (2017)[109]	Ten female synchronized swimmers: age (16.8 ± 0.8) years; body mass index (19.2 ± 1.7) $kg{\cdot}m^{-2}$	4 weeks of training and competition	Repeated measure design	Salivary Secretory Ig A, salivary testosterone, salivary cortisol, Questionnaire: URTI symptoms; DALDA	• A short period of intensified training and competition did not have a detrimental effect on mucosal immunity in elite synchronized swimmers. • Salivary IgA concentration and secretion increased during and throughout the international competition period • No correlation was found among URTI symptom scores and IgA concentration, and secretion rate nor DALDA scores	• Small sample size, i.e., 10 female only elite athletes. • Self-reported symptoms and signs of ARI among the subjects without illness confirmatory diagnosis procedures • There were no interventional physical activities specified.
Monje et al. (2020)[160]	10 male and 10 female long-distance national level runners	10 sessions of acute high intensity interval session (HIIT)	Non-randomized, non-controlled pre- and post- test experimental studies	Salivary IgA, cortisol, testosterone	• After an acute session of HIIT, the catabolic/anabolic balance was maintained; cortisol levels increased in both gender, and testosterone concentration was unchanged. • One session of HIIT increased salivary IgA levels in both genders. • HIIT session did not cause immune risk and the anabolic/catabolic balance was maintained.	• Very limited sample size: 10 male and 10 female athletes • There was no prohibition from consuming tobacco, alcohol and caffeine in the 12 h prior to the HIIT session
Born et al. (2017)[161]	28 recreational endurance runners	High-intensity interval training (HIIT) for nine sessions or long-slow distance (LSD) training for 60–80 min for 3 weeks	Non-randomized, pre- and post-test control groups	Salivary sIgA secretion rate, cortisol	• No compromised mucosal immune function was observed for the groups. HIIT increased the sIgA secretion rate throughout the entire training period • Functional adaptation of the mucosal immune system was observed in response to the increased stress and training load of HIIT	• Limited sample size: 16 subjects underwent HIIT and 12 subjects underwent LSD training. • There was no information about controlling the confounding variable, such as gender and nutrition. • No data collection regarding the infection
Barrett et al. (2012)[162]	154 adults 50 years old and above from the community	8-week moderate-intensity continues exercise, 8-week mindfulness meditation, control	Balance, randomized control design	Interleukin-8 (IL-8), neutrophil count, and viral nucleic acid. ARI illness with Wisconsin Upper Respiratory Symptom Survey (WURSS)	• Decreased scores of ARI illnesses were observed among the participants randomly allocated to the exercise training group. • Viruses were identified in 54% of samples from meditation, 42% from exercise, and 54% from control groups. • The total days of illness (duration) was low for the exercise group. • Neutrophil count and interleukin-8 levels were similar among the intervention groups.	• A blinded study was not achieved for behavioural interventions.

Notes. NK, natural killer cells; URTI, upper respiratory tract infections; *n*, number; XC, cross country; IgA, immunoglobulin A; IgM, immunoglobulin M; IgG, immunoglobulin G; ARI, acute respiratory infections; CD4, clusters of differentiation 4; CD8, clusters of differentiation 8; DALDA, daily analysis of life demands of athletes; HIIT: high intensity interval session; LSD, long-slow distance; WURSS, Wisconsin upper respiratory symptom survey; h, hours.

(PRRs) which detect the viral antigens or genetic material (deoxyribonucleic acid/DNA or ribonucleic acid/RNA) of the viruses acting as Pathogen-Associated Molecular Patterns (PAMPs).[27,28] Because the viral components are synthesized by host cells, the main PAMPs of viruses are their nucleic acids. There are many PRRs in vertebrates that were classified as Toll-Like Receptors (TLRs), Nucleotide Oligomerization Domain (NOD)-Like Receptors (NLRs), Retinoic Acid-Inducible Gene-I (RIG-I)--Like Receptors (RLRs), C-type Lectin Receptors (CLRs), and Absent In Melanoma-2 (AIM2)-Like Receptors (ALRs).[27]

Type I and type III interferons (IFNs), chemokines and proinflammatory cytokines are produced to initiate inflammation response following PRRs' recognition of PAMPs.[29] IFN I and IFN III stimulate the Interferon-Stimulated Genes (ISG) which eventually express many proteins with antiviral properties by inhibiting viral entry, replication, and release.[30] However, many data demonstrate that ISG not only encodes proteins through mRNA transcription-translation processes. The IFN I and IFN III induce plenty of noncoding RNAs, including long noncoding RNAs and microRNAs (miRNAs) that are known to exhibit gene regulation and silencing properties.[31,32]

It is noteworthy that various cells, namely, macrophages, neutrophils, natural killer (NK) cells, and dendritic cells (DC), play important roles in the innate immune response against viruses. Upon the virus-induced macrophage activation, the antiviral response and inflammation start to eliminate the virus. The macrophage activation results in cytokine and chemokine secretion.[33] The NK cells are recruited from the circulation to the site of viral infections. This is the pivotal step for the innate response and viral containment.[34] DCs are identified as the source of IFN during the innate immune response. DCs, with their various subsets, are of great relevance in the clearance of viruses.[35]

Proinflammatory cytokines production is important in recruiting immune cells to the infection site. They activate immune cells including professional antigen presenting cells (APCs), thereby activating the adaptive immune response.[28,29]

Adaptive immunity is important for virus clearance and the establishment of long-term immune memory to combat future viral infections.[36] The adaptive immune response is initiated by the activation of naïve T lymphocytes with antigen presentation. The DCs, macrophages, and B lymphocytes engulf virus particles, process them intracellularly, and present them as antigens bound to major histocompatibility complex (MHC) class II molecules on the surface of APCs to the naïve clusters of differentiation 4^+ ($CD4^+$) T lymphocytes. When a viral infection occurs, the viral specific $CD4^+$ and $CD8^+$ T lymphocytes are activated, proliferated, and differentiated to become effector memory cells. Furthermore, the $CD4^+$ T lymphocytes serve as a helper for B lymphocytes and $CD8^+$ T lymphocytes clonal expansion via cytokines. The activated $CD8^+$ T lymphocytes serve as the effector cells of the cellular immune response following its proliferation and differentiation.[37] Whereas the B lymphocytes mediated humoral immune response is an adaptive immune response that inhibits and eradicates respiratory viral infection through the secretion of neutralizing antibodies.[36]

4. Immune response against acute respiratory bacterial infection

The innate immune response against bacteria initially recognizes the bacterial PAMPs that are mostly part of the cell wall, such as lipopolysaccharide, peptidoglycan, lipoteichoic acids, and cell wall lipoproteins. The main properties of the innate immune response against bacterial infection are the activation of the complement system, phagocytosis, and inflammatory response.[38]

The complement system comprises plasma proteins that need to be activated. After activation, they facilitate the cells' mobilization from the immune system to the site of bacterial infection to eradicate the bacteria through opsonization or, in many cases, direct destruction. The macrophages, neutrophils, and DCs serve as main phagocytes in the innate immune response against bacteria. The DCs are a class of professional APCs whose primary function is to present antigens to the immune system. Immature DCs have a higher capability of phagocytosis, than mature DCs. The phagocytosis mechanisms clear bacteria by destroying them inside the phagocytic cells.[39]

Adaptive immune response against bacterial infections by the humoral immune response pathway includes the complement activation that results in the production of antibodies. The antibodies, immunoglobulin M (IgM) and later immunoglobulin G (IgG), work together with complement cells for efficient functioning. The humoral adaptive immune response is the primary protection from extracellular bacteria; by blocking these bacteria using neutralization antibodies.[38] Some bacterial antigens activate the cellular adaptive immune response mediated by $CD4^+$ T lymphocytes, which produce cytokines to induce inflammation, increase phagocytosis, and anti-microbicidal properties of neutrophils and macrophages. Moreover, the $CD4^+$ T lymphocytes induce cytotoxic and memory $CD8^+$ T cell responses.[40]

5. Exercise intervention for disease management

Physical activity is any bodily movement that is caused by the conscious contraction of the skeletal muscles accompanied by increased energy expenditure. It covers a wide range of physical activities that are conducted on a regular or irregular basis in a relatively unstructured and unplanned manner.[41] Compared with physical activity, exercise is more specific and has measurable goals. It is a physical activity that is planned, structured, and repetitive. It aims to improve or maintain any component of fitness for health or sport.[42]

Although the importance of physical activity as a means of promoting health and wellbeing is not a new concept, research developments have increased the understanding of the impact of physical activity on several chronic diseases, such as obesity, hypertension, cardiovascular disease, diabetes mellitus, and cancer. The epidemiological evidence supports it as a dose-response relationship because the greater physical activity levels were associated with reduced risks of developing chronic conditions.[42]

The precision exercise medicine has been developed because every human is unique, including his/her response to physical activity or exercise. Heterogeneity is observed in the response to the same acute and/or chronic physical exercise and the adaptation to the same physical exercise, either within an individual (intraindividual) or between individuals (interindividual).[43,44] The variation in the response to exercise can be explained by many factors such as genetic, biological, behavioral factors, and measurement error. The interindividual responsiveness to exercises and, in turn, interindividual heterogeneity in outcomes, are caused by several factors, categorized as nonmodifiable (e.g., sex or genotypes) and modifiable (e.g., nutrition, social or cognitive activities, and exercise prescription).[45] Adjusting the prescribed exercise dosage is warranted to achieve adequate exercise outcomes in nonresponsive individuals.

It is also necessary to consider acute and chronic effects to assess responsiveness. The acute effects of physical activity refer to the health-related changes that occur during and after several hours of physical activity. The chronic effects of physical activity occur from time to time due to changes in the structure or function of various body systems. In addition, the recurring effects, acute, low-intensity, physical activity can result in small changes that may not have been detected in clinical studies but still have a visible effect when adopted by a large population.

Although several systematic reviews have described that the dose-response relationship of exercise is not a determinant of outcomes, it is important to pay attention to the exercise dose to gain optimal health benefits. The dosage influences budgeting, space allocation, adherence, and results. It is necessary to consider the dosage when translating exercises into clinical practice to account for the influence of the complexity and resources of the clinical setting to obtain the intended health benefits.[46]

Ideally, the essential components of exercise include several measured parameters i.e., the frequency, duration (time), and intensity

(absolute and relative), depending on the type of exercise. These parameters calculate the exercise's dose (or volume).[7] Unfortunately, many studies do not specify the intensity, duration, and frequency measures but use subjective judgments such as "little, moderate, and severe". The exercise dose represents the energy expended and is one of the potential mediators of the health benefits of physical activity.

It is important to determine the intensity and duration of the type of physical activity to decide the dose-response relationship and obtain optimal health benefits. This is problematic because some studies relied on self-report approaches (questionnaires, physical activity logs, and diaries) to predict the intensity of physical activity. The results based on such perceptions may not reflect the absolute intensity for all age groups, genders, or special conditions required to convert to metabolic equivalents (METs). The METs are commonly used units to estimate the metabolic cost (oxygen consumption) of a physical activity. The physical activity intensity recommendations typically focus on achieving MVPA either continuously, such as a 30 min run, or divided into short bouts performed throughout the day (i.e., three 10 min bouts). The evidence shows that people can engage in MVPA if it aligns with their physical abilities and personal preferences. The MVPA accumulated in bouts of $<$ 10 min is associated with favorable health-related outcomes.[47]

The intensity and duration of physical activity are important because of their known effects on physical fitness. Physical fitness is usually assessed as a measure of Maximal Oxygen Consumption (VO_{2max}). Oxygen consumption in physical activity is higher at high than low intensity. Many studies have shown that fitness is an intermediate factor between physical activity and health benefits, thus, VO_{2max} has been used to determine the "dose" of physical activity.[48] The relationship between duration and intensity is that less strenuous activities require a long time to obtain comparable health benefits. However, the greater the intensity and volume of the exercise, the greater the risk of injury and harmful effects; especially musculoskeletal injury for most individuals and cardiovascular injury for those with underlying diseases.[49]

6. Evidence on the close relationship between immune response and exercise

Regular exercise has been reported to enhance immune cell activation in response to induction by the heat-inactivated *S. pyogenes* or hepatitis B core antigen (HBcAg), resulting in increased cytokine production mediated by the TLR signalling pathways. The expression levels of TLR2, TLR7, and myeloid differentiation primary response 88 (MyD88) were significantly increased after HBcAg stimulation in the regular exercise group compared with those in the sedentary control group. However, only TLR2 and MyD88 were upregulated in the presence of the heat-inactivated *S. pyogenes*. Consequently, the levels of IFN-γ, tumor Necrosis Factor Alpha (TNF-α), and IL-6 produced by the Peripheral Blood Mononuclear Cell (PBMC) were elevated in the regular exercise group after HBcAg and *S. pyogenes* stimulation.[50]

Several studies showed the correlation between exercise and the cellular components of the human immune system, such as neutrophils, NK cells, cytotoxic T lymphocytes, and B lymphocytes.[51] A recent research on adolescence showed the difference between low and high-intensity exercise training on the human cellular immune response and inflammatory biomarkers. All participants were enrolled in aerobic training on a treadmill three times a week. The high-intensity exercise reduced the number of neutrophils and monocytes, while low-intensity exercise did not reduce the monocytes but increased the number of neutrophils. No change was observed in the number of leucocytes. Interestingly, IL-6 and TNF-α levels were decreased under high-intensity exercise but increased under low-intensity exercise.[52] A study on women enrolled in an acute bout of moderate aerobic exercise on the cycle ergometer at a workload comparable to 60% of the participant's peak oxygen uptake (VO_{2peak}) for 30 min reported that the NK cell count significantly increased immediately after exercise compared with that at baseline pre-exercise but decreased to the baseline during recovery.[53] An investigation on the adults cycling for 30 min at 115% of their lactate threshold power showed that exercise enhances NK cell cytotoxic activity by lowering cortisol and increasing IFN-γ levels.[54]

As part of the innate immune response against infectious agents, the inflammation induced by the pathogen's infection is an essential broad-spectrum protection against the microbial infection. However, cytokine production can be modified by oxidative stress or muscle contraction during physical exercise. Muscle contraction increases the release of anti-inflammatory and proinflammatory cytokines at varying levels according to the volume of contractile mass involved, duration, and intensity of the exercise. Exercise induces the release of cortisol into circulation, influencing the release of neutrophils from the bone marrow. Proinflammatory cytokines, namely TNF-α and IL-1β, attract neutrophils to the site of inflammation. Approximately 24 hours (h) after the aerobic physical exercise, a significant decrease was observed in neutrophil chemotaxis without compromising the bactericidal activity. This decrease is reversed within 48 h after physical activity, the point at which the opportunistic activity of infectious microorganisms may occur.[55] A recent systematic review of the effect of regular exercise on inflammatory cytokines response showed that regular exercise affects inflammation by decreasing the levels of IL-1β and IL-18. Moreover, aerobic exercise is the most effective training where low-to-moderate and mixed intensity are better than high-intensity to regulate the inflammasome.[39] When contracting and requiring nutrition, muscles synthesize glutamine in an adenosine triphosphate (ATP)-dependent reaction. It is released into the plasma via a bidirectional Nm transport system. Energy requirements are very high in strenuous and prolonged exercise causing muscle catabolism and reduced glutamine concentrations. Lymphocytes, neutrophils, and macrophages also need glutamine as a nutrient to maintain immunological performance, including the synthesis of pro-inflammatory cytokines.[56]

It is currently recognized that exercise may be involved in regulating inflammation. An appropriate inflammatory response allows protection against infections and can act as an integral part of muscle repair and regeneration. Conversely, chronic and uncontrolled inflammation may produce tissue damage.[57]

Further concern was raised on immune response dysfunction because of high-intensity exercise. Numerous cells and biomarkers corresponding to the deterioration of immune response have been correlated with prolonged and intensive endurance exercise. These phenomena have been recognized as transient immune dysfunctions after heavy exertion.[51,58]

Evidence that acute and chronic exercise can leverage the immunological parameters such as the number of leukocytes, lymphocytes, lymphocyte subpopulations, NK cells, and various cells with $CD3^+$, $CD4^+$, $CD8^+$, $CD16^+$, $CD18^+$, $CD19^+$, $CD20^+$, $CD22^+$, $CD44^+$, $CD45^+$, $CD56^+$, and $CD95^+$ markers were documented. In addition, many studies evaluated the production of cytokines, interleukins IL-1, IL-2, IL-6, IL-8, IL-10, and IL12; TNF-α, interferon-gamma (IFN-Ɣ), and immunoglobulins.[59–61] A systematic review showed that acute exercise does not alter immunoglobulin A (IgA) levels in untrained subjects, in contrast with conditions wherein acute exercise is performed by trained subjects, particularly after a strenuous exercise. In addition, there was a negative correlation between the ARI incidence with IgA level.[62] However, these analyses failed to include many variables, such as gender, contraceptive pill use by women, individual physical capacity of the participants, environment where the study was performed, type and intensity of the exercises, and appropriate time for blood collection and serum preparation. Moreover, these variables may alter the biomarkers measured in the studies. Further investigation is strongly recommended to reach a firm conclusion.[59–61] In summary, the immune response indeed is significantly affected by exercise (Fig. 1). However, the frequency, intensity, duration, and type should necessarily be considered to discuss the modulation of the immune response associated with exercise. The dose-response relationship for the effect of physical activity on the immune system requires further research to understand the mechanism.[63]

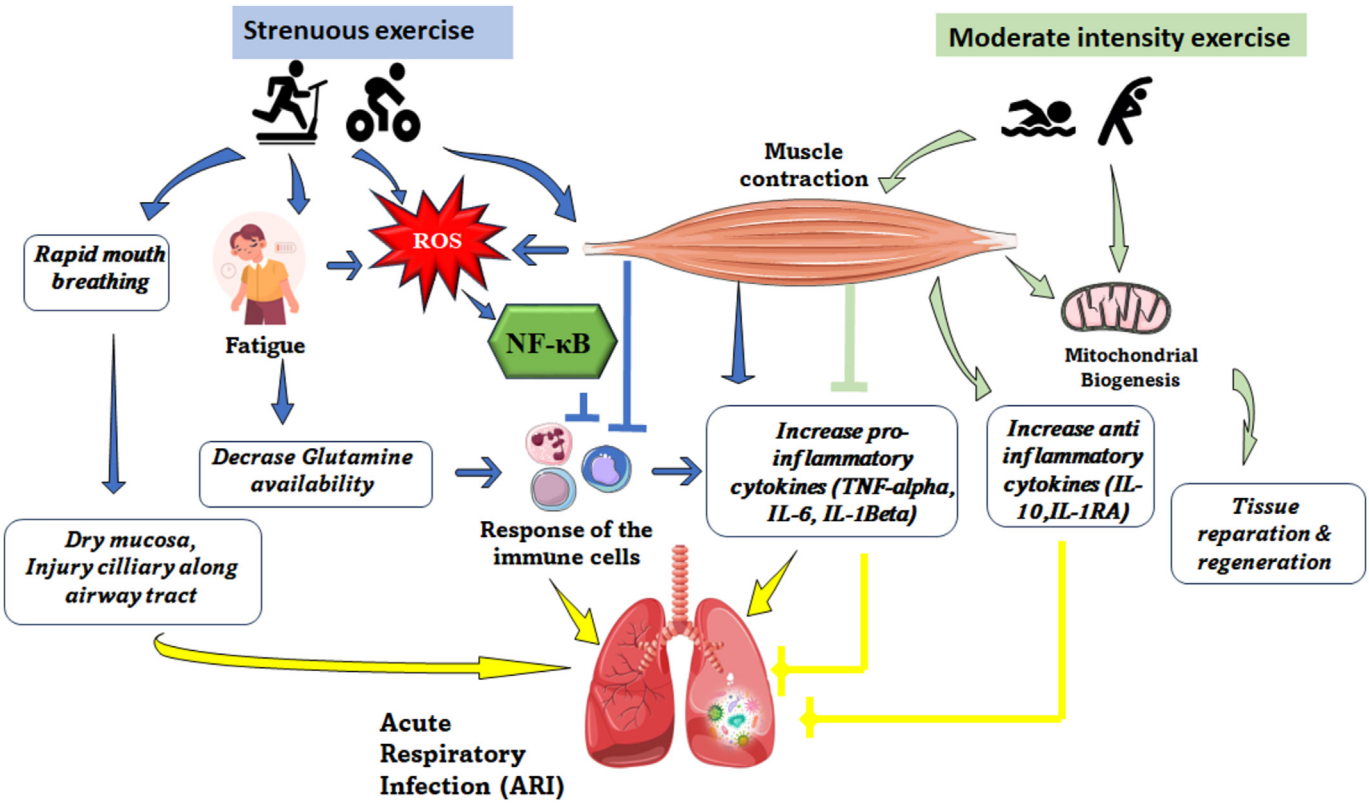

Fig. 1. Associations of exercise, immune response, and ARI.
Exercise influences various functions of human tissues, including skeletal muscle. The intensity of exercises may induce different responses to the human immune system. Moderate intensity exercise will not result in the increase of proinflammatory cytokines; instead it will increase anti-inflammatory cytokines (green arrows). Contrary, strenuous exercise may increase the number of immune cells and proinflammatory cytokines (blue arrows). These mechanisms are hypothesized to affect the susceptibility to ARI although the direct effect of the regulation of the immune system by exercise to ARI incidence has not been conclusive yet (yellow arrows). Part of the figure was prepared using pictures modified from https://www.freepik.com and Servier Medical Art (https://smart.servier.com). Notes. ROS, reactive oxygen species; NF-κB, Nuclear Factor Kappa B; TNF-alpha, tumor necrosis factor-alpha; IL-6, interleukin-6; IL-10, interleukin-10; IL-1Beta, interleukin-1Beta; IL-1RA, interleukin-1 receptor antagonist; ARI: acute respiratory infections.

7. Exercise regulates the expression of immune response associated genes

The effects of exercise are associated with alterations of gene expression which are involved in several critical functions, i.e., inflammation, cellular communication, signal transduction, cellular protection, growth, and repair.[64] Studies have shown the effect of exercise to the expression of genes related to immune response. A 20-week exercise intervention was performed in the male and female prepubertal individual (8–11 years old) with overweight/obesity. The intervention altered the transcriptome profile of whole blood. Enrichment of genes related to immune response expression were detected after exercise, with significantly different genes profiles between male and female.[65]

Since exercise evokes inflammatory-like responses of the immune system, studies concerning gene expression dynamics are therefore important. A study using only unfractionated peripheral blood leukocytes, showed that there was a time bound regulation of the gene expression in response to the exercise. It was shown that the level of messenger RNA (mRNA) expression peaked after 4 h of exercise and remained similar with the baseline within 20 h after exercise.[66] The effect of acute bouts of high-load strength exercise to the gene expression was regulated differently in skeletal muscle and circulating immune cells. The mRNA level of IL-6, TNF, and chemokine (C–C motif) ligand 2 (CCL2) in skeletal muscle increased significantly compared with smaller or no response in PBMCs after exercise. However, the mRNA level of IL-1RN, IL-8, and IL-10 increased significantly both in skeletal muscle and PBMCs.[67]

The alteration of immune response in relation to exercise was linked with epigenetic regulation of gene expression. Exercise acts as an environmental inducer for epigenetics that in turn regulates the gene's expression (Fig. 2). The cross talks between exercise and epigenetics were through various mechanisms, i.e., histone modification, DNA/RNA methylation, and microRNAs (miRNAs).[68,69] There have been reviews stating that exercise influences the epigenetic regulation of the immune response which involve various immune cells and cytokines, skeletal muscle, adipose tissues, cardiac muscles, brain, pancreas, and other tissues.[70–72]

Histone modification occurs through several mechanisms, such as acetylation, methylation, adenosine diphosphate (ADP) ribosylation, and others. Histone modifications will change the physical interaction between the histone and the DNA encoded gene targets, which in turn render the accessibility of genes for transcription machines.[73,74] A single bout of resistance exercise induces histone modifications and alters gene expression in the human skeletal muscle. It was noted that up-regulation of gene expressions after resistance training was via enhancement of histone acetylation.[75] Indeed, there were few reports regarding histone modification regulated by exercise, though the evidence mainly came from animal experiments.[76]

DNA methylations affect the DNA through the addition of a methyl group at the 5th C of the cytosine base nucleic acid (5 mC), the 6th C of the adenine base nucleic acid to form N6-methyladenine (6 mA), and the 7th C of guanine base nucleic acid to form 7-methylguanine (7 mG). Exercise induces DNA methylation alterations in various tissues, such as blood cells, skeletal cells, and adipose tissue.[70] The effect of exercise to genome wide DNA methylation is represented by studies using blood cells. Genes with methylation level changes caused by 8 weeks of supervised

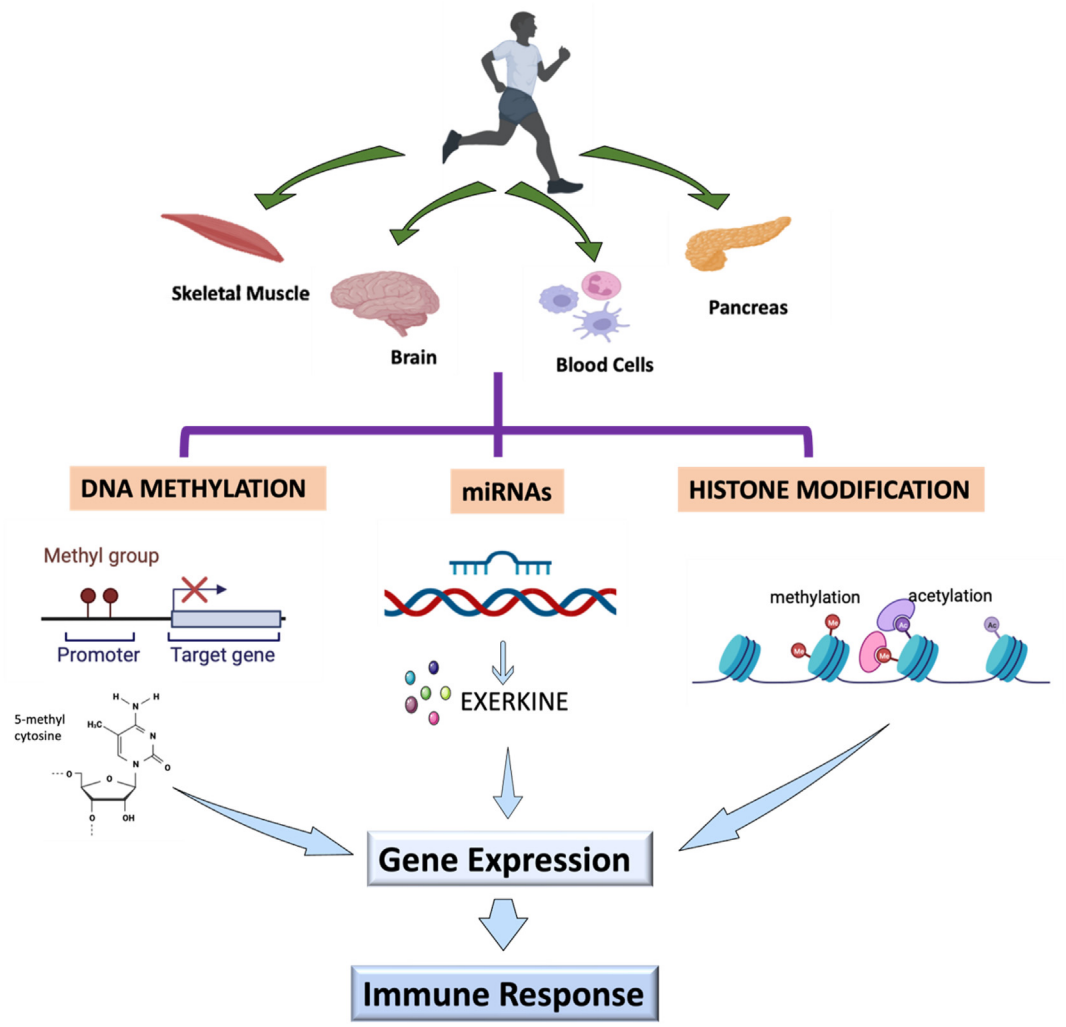

Fig. 2. Exercise regulates immune response associated genes expression.
Exercise influences the epigenetic regulation of the immune response which involve various immune cells and cytokines, skeletal muscle, adipose tissues, cardiac muscles, brain, pancreas, and other tissues. The cross talks between exercise and epigenetics were through various mechanisms, i.e., histone modification, DNA/RNA methylation, and microRNAs (miRNAs). Part of the figure was prepared using pictures modified from bio RENDER (https://www.biorender.com/).

resistance exercise training were associated with various pathways of immune response in leukocytes.[77] However, more conclusive data of gene expression regulation by DNA methylation were obtained in tissue specific gene expression, such as in skeletal muscle.[78,79] For example, well known pro-inflammatory markers, Nuclear Factor Kappa B Subunit 1 (NFKB1) and Nuclear Factor Kappa B Subunit 2 (NFKB2) encoded genes were hypermethylated in its promoter region after five months of interval aerobic training in elderly people.[80]

miRNAs are about 22 nucleotides short non-coding RNA molecules. miRNA is able to bind to mRNA leading to degradation and eventually prevent translation of genes.[81] Various exercises (acute resistance, acute endurance, cycling, and others) have been reviewed to have a direct effect on the expression of various miRNA. There are hundreds of miRNA that are altered in response to exercise. Many of them are responsible for immune response regulation, such as miR-21, miR-27b, miR-124, miR-146a, miR-155, miR-223, and miR-326. Indeed, studying to identify miRNA that work as up regulators or down regulators in response to exercise for every gene needs a lot of work.[69,72] miRNA with other non-coding RNAs are secreted from multiple tissues acting as exerkines, which are shuttled by exosomes. Exerkines are signalling moieties released in response to acute and/or chronic exercise. which include cytokines, lipids, metabolites, and nucleic acids (miRNA, mRNA, and mitochondrial DNA).[70,82] Immune systems produce and are influenced by exerkines, which are related with the pleiotropic and variable response to exercise.[82]

The NF-κB, a well-known transcription factor, played fundamental roles in the gene expression alteration after exercise.[64] NF-κB regulates the expression of inflammatory myokines IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) after resistance exercise intervention.[83] Exercise to exhaustion both in normoxia and severe hypoxia conditions were able to activate NF-κB in comparable levels.[84] NF-κB may become a checkpoint to activate or not activate the inflammatory condition, in response to the exercise modality. Excessive physical exercise may upregulate NF-κB through TLR2 and TLR4 stimulation. A high mitochondrial oxidative stress induced by strenuous aerobic exercise may increase Reactive Oxygen Species (ROS) formation and stimulate the NF-κB expression. Both mechanisms of the NF-κB stimulations result in the increase of pro-inflammatory cytokines. On the other hand, regular physical exercise of moderate intensity reduces TLR2, TLR4, and NF-κB expression which will trigger the opposite anti-inflammatory pathway.[85] Most components of the NF-κB signalling pathway return to baseline levels very fast, within 1 min after exercise, when the muscles recover with a free circulation.[84]

8. Clinical advantages of exercise to prevent and manage ARI

Regular physical activity is associated with low likelihood of adverse COVID-19 outcomes. A study shows the protective effects of engaging in sufficient regular physical activity against SARS-COV-2 infection, hospitalization, severe COVID-19, and death.[86] A randomized controlled trial (RCT) involving patients with COVID-19 and utilizing 2 weeks of 30 min moderate-intensity aerobic exercise as the main intervention showed that the intervention groups had advantages of decreased severity and progression of COVID-19-associated conditions as well as quality of life. In addition, their laboratory examinations showed increase in the number of leucocytes, lymphocytes, and IgA.[87] A study on the subjective wellbeing of patients with COVID-19 who were isolated, reported that physical activity can give advantage when performed habitually from the pre isolated period and not just during periods of social isolation.[88] The supervised 8 weeks low-and moderate-intensity multicomponent exercise is effective to improve the post-COVID-19 conditions, including health markers for quality of life and fatigue, psychological condition, cardiovascular fitness, and muscular strength.[89]

An association was reported between regular physical activity and lowered risk of pneumonia and associated mortality in physically active individuals compared with those who were least or not physically active.[90] A daily walking habit of $>$ 1 h per day has been shown to decrease the mortality rate of pneumonia in the elderly.[91] Exercise intervention in adult patients with community acquired pneumonia (CAP) who were hospitalized have shown great advantages in improving the life quality, dyspnea, and peripheral muscle strength but not in lung function, C-reactive protein, and length of hospitalization.[92]

Physical activity is an immunological function acting as an adjuvant to enhance immunity post-antiviral vaccination and increase its potency.[93] Interestingly, exercise can regulate the immune response against influenza that ensues after exercise. A report showed that aerobic exercise with light-to-moderate-intensity and long duration (90 min but not 45 min of exercise) enhances the antibody response to H1N1 influenza, seasonal flu, and COVID-19 vaccine. Exercise can boost the protective effects of vaccine, whether performed before or after vaccination.[94–96] Regular physical activity boosted the COVID-19 vaccine's effectiveness to prevent hospitalization.[97] An interaction was found between acute exercise and physically active lifestyle; where less active persons benefit less from acute exercise as an adjuvant to influenza vaccination compared with the active participants.[98] However, performing an eccentric upper arm exercise immediately prior to influenza vaccination administration did not show any effect on the antibody titers or cell mediated immune responses in a group of older adult participants.[99] There was a report stated that the resistance, flexibility and balance exercise with the same duration as aerobic exercise did not show significant improvement in seroprotective levels.[96]

9. Is there direct association between exercise with ARI incidence?

Strenuous exercise is hypothesized to be responsible for the increase of ARI incidence. This hypothesis needs to be clarified based on the research that directly measures the increase in ARI incidence related to the exercise. A systematic review was performed and included studies reported from 1990 to 2020. The recruited athletes in these studies were included in this meta-analysis. The overall ARI incidence in athletes is 4.9/1 000 athlete days, which corresponds with approximately 1.8 ARI per athlete per year. Acute respiratory illness is the most common illness experienced by athletes, and these are presumed mostly ARI. However, the reason for the assumption is not clear. It could be due to the diagnosis of ARI but this was not supported by enough clinical and laboratory evidence. Furthermore, a higher incidence of ARI was found in non-elite athletes than in elite athletes.[100]

One of the strategies to analyse the effect of exercise to the ARI incidence is to obtain data of ARI incidence among athletes, who are presumed to have regular and heavier physical activity, and then compared to the common population. However, this strategy has many pitfalls which prevent it from serving a solid conclusion.[101] A Cochrane systematic review analysed data of 473 subjects aged 18–85 years from 14 trials including RCTs and quasi-RCTs. The result showed that there was no observed difference between exercise and no exercise in the number of ARI episodes per person per year with risk ratio (RR) 1.00, 95% confidence interval.[102] This is indicative that exercise has no effect on ARI incidence both in athletes and the common population. Indeed, exercise did not cause more exercise-related injury including ARI. The evidence supporting the association remains of low certainty (Fig. 1).[103]

10. Pros and cons in the association of exercise with immune response against ARIs

Several studies showed discrepancies in the effect of acute physical activities on IgA levels and URTI symptoms.[104] Some works reported a decrease in salivary IgA among young and elite athletes[105,106] that is not associated with the URTI incidence.[106,107] Another report showed that the decrease in IgA was parallel with the increase in URTI incidence.[108] A study reported an increase in salivary IgA concentration with no consequence on increased documented URTI symptoms.[109] Another research reported no significant association between Ig A and exercise.[110]

These discrepancies may be related to the knowledge gap regarding the direct association between exercise and health outcomes measured by observing signs and symptoms of URTI. In addition, the immune response which may bridge the two variables, was measured only by single parameter, salivary IgA.

One systematic review comparing exercise and no exercise in association with the occurrence, severity, and duration of ARIs indicated the lack of difference between the two groups in the number of ARI episodes per person per year and the quality-of-life outcome. In addition, exercise reduced the severity of the ARI symptoms but did not alter the laboratory parameters including blood lymphocytes, salivary secretory immunoglobulin, and neutrophils.[102] However, a recent meta-analysis of RCTs and prospective studies showed that regular MVPA is associated with a decrease in the risk of community acquired infectious diseases and infectious disease mortality.[93] The different outcomes of these two works added to the contradiction in this field.

The potential effect of a physically active lifestyle to protect from infectious diseases has long been accepted. However, the correlation between acute exercise and ARI is still subject to debate. The effect of acute exercise on individual susceptibility to infectious diseases closely related to the “open window” hypothesis. It was Nieman in 1994 who proposed the “J shaped” relationship between risk of having URTI and exercise intensity,[111] while Pederson and Ullman further described the period for athletes to become at high risk of infection, as called “open window”. The “J Shaped” relationship was formulated mainly based on the epidemiology data, while the open window was formulated after observing the NK cells dynamic during exercise.[112] The three principles of this hypothesis are as follows: the risk of suffering from infection increases after an acute bout of prolonged and vigorous aerobic exercises; acute bouts of vigorous exercise may result to short-term reduction in salivary IgA, making individuals prone to opportunistic infection; and the number of cellular components of immune response temporarily decreases during the hours following extensive exercise, leading to immunocompromised conditions.[51,113,114]

The notion that an acute bout of prolonged and vigorous aerobic infection may increase the risk of acquiring URTI is not completely accepted by scholars. Some criticized that this hypothesis may hinder the public enthusiasm to be physically active and demanded for further critical review of this hypothesis. They also pointed out several aspects to be reconsidered as limitation of the open window hypothesis.[113,115,116]

The relationship between exercise workload and the risk of suffering from URTI was also described using the J-shape model which is useful to explain the decrease in the risk of URTI when a person engages acute

moderate exercise, and its eventual increase when the person undergoes heavy exertion.[51] Later, new doubt was pointed to this modelling because it was developed mainly with athletes as the subject and thus may not be applicable to other populations.[61] The situation is also unsuitable to elite athletes on the highest level, which can be more precisely described as a S-shaped model. The increase in workload will no longer be a concern related to an increased the risk of illness.[117]

11. Where did the controversial evidence come from?

The debate on the validity of the open window hypothesis originated from the accuracy of the premise used to develop the hypothesis itself. The open window hypothesis was established after several studies were conducted separately with different settings and methodological approaches. It became debatable since it was declared. Selected reports are summarized in Table 1 to illustrate recent studies supporting or contradicting the open window hypotheses. The application of this hypothetical theory as a framework for development of exercise as a potential approach for ARI prevention and management should be adopted with caution. The open window hypothesis appears to simplify the multidimensional factors influencing the association of exercise with ARI.

Several propositions were offered to explain the discrepancies. The following factors make the studies heterogenous and unable to reach a comprehensive conclusion: (1) Study design, such as cross sectional, longitudinal, observational, or randomized control trial; (2) Exercise intervention and modalities applied to the subjects, including acute or chronic exercise, intensity and duration; (3) Training status of the subjects, such as sedentary, habitual physically active, athletes, and elite athletes; (4) Measured parameter of immune systems; (5) Nutritional status and medication administered during the study; (6) Environment setting of the study; (7) Genetic makeup and other individual characteristics of the subjects; (8) General fitness of the subject[118,119]; and (9) Other potential immune response modifiers, such as increased energy expenditure, sleep deprivation, and psychological stress following intense training.[118]

11.1. Study design

Study design is important in measuring the extent of conclusions and generalization of a research. Studies use various study design and data collection methods. Observational studies, such as case control studies and prospective cohorts are less powerful than randomized control trials, which are considered as gold standard for studying certain exposures. Retrospective studies using self-reporting questionnaires are completely different from cohort prospective data collection. Though a retrospective study is easy and less expensive, its main challenge is recall bias. Several reports pointed out this potential limitation of a self-reported retrospective data collection.[120–122] In addition, self-reported ARI symptoms may lead to over-reporting by health-conscious individuals.[123] Although ARIs are a common community disease, the symptoms and signs are not specific and may be experienced by people that suffer from allergic conditions, drugs eruption, intolerance with ambient condition, and other systemic diseases. Meanwhile, the confirmatory laboratory tests for ARI were not performed in several studies.[113] This situation is the main pitfall of self-reported ARI procedure in the studies correlating exercise with ARI frequency.

11.2. Exercise intervention

The exercise intervention discussed in many experiments and observations in relation with the risk of people suffering from ARI after exercise is apparently not homogeneous. Studies used many kinds of exercises in terms of frequency, intensity, type, time, and duration. Diverse operational definitions were applied in publications reporting the association of exercise with ARI. The most highlighted difference is the exercise dose and modalities based on the self-reported data from the participants that may result in perceptual bias.[60,86,93] The interpretation of the results may be ambiguous because of heterogeneity interventions. In addition, the findings on the direct dose-response relationship between exercise load and URTI risk are inconsistent. The main URTI risk determinants are subject-dependent, including fitness condition, sleep deprivation, nutritional status and psychological stressor; the effect is not solely attributed to exercise dose.[124]

11.3. Selection of subjects

Publications concerning the open window hypothesis were based on observational and experimental studies involving selected subjects, athletes. Thus, the measurements of infection rates in elite athletes show potential selection bias. The immune response alteration after exercise in athletes versus non-athletes is also controversial. No agreement has been reached on whether a difference in immune response alteration occurs between the two groups.[125,126] The conclusion may not be suitable for the general population, especially for promoting exercise to cope with ARI, which is common in the community.

11.4. Measured parameter of immune systems

Saliva IgA was used as a proxy parameter to measure the effect of prolonged vigorous exercise on the immune response depletion that facilitates the opportunistic infection and ARI.[110] A recent studies revealed that approximately 20%–30% of patients with IgA deficiency develop severe respiratory illness.[127] As mentioned above, the human immune response against ARI includes innate and adaptive immune responses working together for infection control. A decrease in a single response (i.e., IgA) may not reflect the whole immune system. Further discussion regarding the significance roles of other respiratory tract mucosal antimicrobial properties in the exercise-induced modifications of the immune response is warranted.

11.5. Other potential ARI susceptibility modifiers

Susceptibility to infection, including ARI, is multifactorial. Determinants such as genetics,[119,128] nutritional status,[129,130] sleep quality,[131,132] concurrent illness,[133] smoking,[134] alcohol consumption,[135] psychological stress,[136] and environmental condition[137] may simultaneously contribute to an individual's susceptibility to infection. Susceptibility to infection is related to the balance between the virulence factor of the pathogens and the protective measure of the host. Any condition contributing to the deterioration of the host condition also contributes to the host's susceptibility to infection.

12. What are the future evidence and research improvement needed?

Based on inconsistent findings from the 1990s until recently, further sophisticated research is urgently needed to gain solid data on the relation of exercise with immune response against ARI. Several key points are identified to improve the data. The establishment of solid methodologies to address confusing results on the relationship between exercise and ARI is urgently demanded. The improvement should cover study design, data collection, exercise intervention, subject recruitments, biomarkers for infection and inflammation, nutritional and metabolism status, body composition, cardiovascular endurance, and hydration, as well as consider confounding variables (Fig. 3).

Data collection using the self-report method for exercise, must be performed using a standardized questionnaire that can properly record the intensity and duration of exercise or a smartwatch or other electronic devices that objectively record the exercises.[138] The ARI symptom and sign data collection should not rely on self-reporting. Laboratory confirmatory tests must be imposed. The demand for confirmatory laboratory tests for ARI has been challenging because of the limited

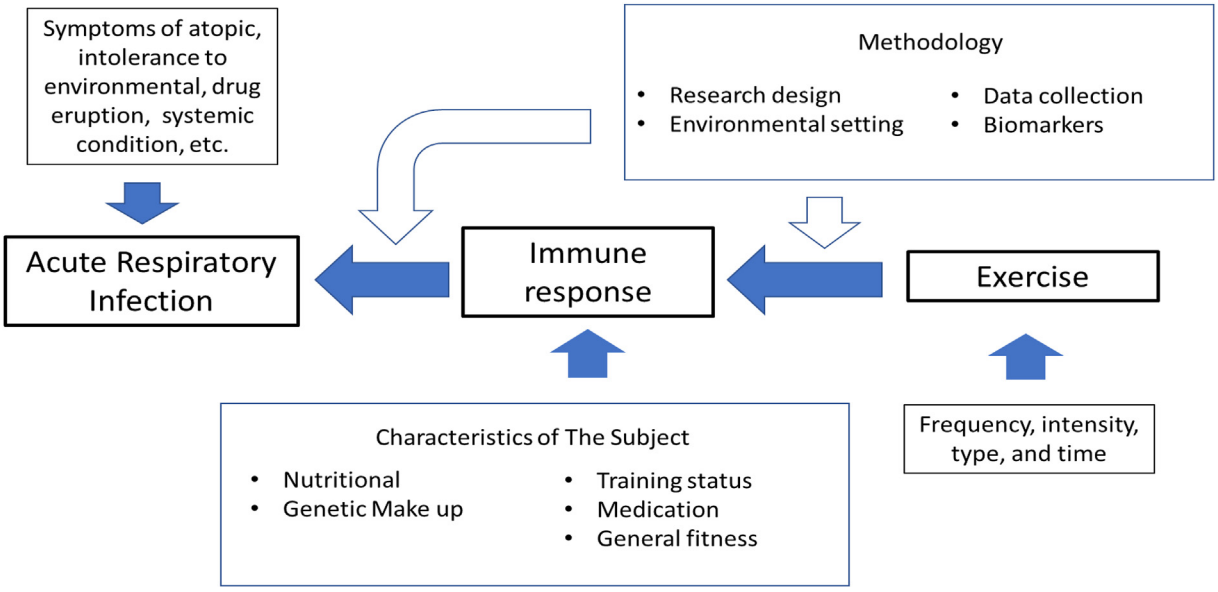

Fig. 3. Conceptual framework.
The scheme depicts variables to be considered for future research in the association of exercise with acute respiratory infections (ARI) through immune response regulation. The proposed improvement should be based on the methodological aspect that will affect the whole interpretation of links among exercise, immune response, and ARI. In detail, the research must concentrate on the characteristics and modalities of exercise, recruited subjects, and recognize other factors related with ARI symptoms.

knowledge to differentiate among endogenous microbes, colonization, and pathogens in the respiratory tracts.[139] The importance of respiratory tract microbiome must also be elucidated to explain the mechanisms of immune response against ARIs. The interaction of immune response microbiota environments is the key factor to be studied.[140]

Some studies use self-reported physical activity methods, either in the form of logbooks or questionnaires. While it is not completely wrong, there are some limitations. The results of measuring physical activity using self-reported tools may not be as accurate as objective tools because it is difficult for individuals to accurately estimate the amount and type of physical activity completed in the time surveyed or precisely report the intensity of physical activity. Studies have obtained inconsistent results because the correlation between self-reported and objective measures of physical activity differs based on the intensity of activity, body mass index (BMI), age, gender, marital status, and chronic disease.[141] Individual differences such as gender, fitness, perceived activity, and past physical activity experiences may contribute to errors in self-reported physical activity, contributing to the observed differences between measures.[142] Therefore, more research is needed to clarify these findings. The self-reported method has difficulty recalling activities of low intensity and short duration (e.g., walking to get coffee, active transportation) than activities with vigorous intensity. However, it is important to observe the contribution of light-intensity physical activity to health outcomes. The weak correlation between measurements was paralleled by significant absolute differences between measurements at most intensities, with a tendency to be underreported. This underreporting means that the number of individuals achieving the recommended physical activity guideline of at least 150 min of MVPA per week differs by up to 18%, depending on the measuring method. Only 22%–32% of total physical activity, expressed in MET: min·week^{-1}, measured with physical activity trackers, is typically reported using self-reports, indicating that a large proportion of total physical activity is unaccounted for when using self-reports.[143]

Objective measures of physical activity, such as the use of accelerometers, global positioning systems, heart rate monitoring, and movement sensors, can solve the problem of recall bias that arises in retrospective subjective questionnaires. However, objective efforts can be expensive, and logistically difficult to implement across populations.[144] Although there are many similarities between instruments, differences in operationalizing algorithms of sedentary behavior and exercise result in substantive differences in reporting of physical activity. A systematic review and meta-analysis showed that evidence of the effect of physical activity monitors is low for physical activity interventions but moderate for moderate to vigorous physical activity and sedentary time. Physical activity monitor-based interventions safely and effectively increase physical activity to moderate to vigorous intensity.[145]

Exercise as an interventional or observational variable must be standardized. Frequency, intensity, time, and type (FITT) must be considered in every research. Though challenging, FITT is important in appraising the results and interpretation. This principle is useful for researchers and healthcare professionals in recommending the right exercise regimen for subjects.[146]

Data collection for immunological biomarkers should not be performed as one measurement at a time. Multiple point measurement provides high accuracy to determine the dynamic of immune response according to stressors. The use of salivary IgA as a biomarker of immune response against ARI should be further validated. As highlighted above, saliva is a potential source of specimen for analyzing the body's response to exercise.[147] However, biomarker identification must be intensified for immune response dynamic measurements corresponding to exercise. There are several candidates of immunological biomarkers related to exercise, such as immune cell concentrations, immunoglobulin,[60] cytokines,[148] and circulating MicroRNAs[149] which need blood specimens. Whereas, isobaric tags for relative or absolute quantitation (iTRAQ) proteomics technology is used to identify differential proteins and their characteristics in urine.[150] All biomarker candidates offer different accuracies and advantages. Accuracy improvement of these biomarkers may boost the understanding of exercise's role in the prevention and management of ARI and may help monitor the risk of infection related to the exercise.

Future research regarding the regulation of immune response by exercise should address inter and intra individual variation.[151] Inter individual variability can be mitigated with sampling and sample size. Whereas, intra individual variability can be alleviated using measurement technology and timing as for example to deal with circadian immune

response variation. Moreover, genetic variation is a factor that is responsible for individual variation of the immune system besides intrinsic factors such as age and gender, as well as environmental determinants e.g., microbiota, cohabitation and chronic viral infections. It was estimated that genetic variation accounts for 20%–40% of immunological variation.[152] Since genetic variation is also associated with the ARI susceptibility,[128] taking account of genetic variation in the future research is unavoidable. Genetics and intrinsic factors should be the drivers of personalized exercise programs in interventional exercise studies.

Confounding variables intervene in the association between exercise and the risk of ARI may work together to modify the balance between pathogen virulence and host immune response. Traditionally, to exclude or control confounding variables, researchers need to do randomization, restriction and matching.[153] However, if this is impractical in the research design, researchers may rely on statistical modelling.[154] For future research addressing the open window hypothesis, we need to identify the confounding factors and control it from the very beginning of the research.

The WHO recommends that people should embrace physical activity as a lifestyle, which requires solid scientific evidence to convince everybody.[4] Studies involving non-athletes or sedentary individuals, subjects of different ages, and genders may give broad insight into maximizing the generalization of the conclusion. The findings will help in the promotion of physical activity for improved health. Involving diverse groups will also reduce the selection bias of research subjects. Learning the basic concept of the open window hypothesis is not completely acceptable, it is better to hold the information of the negative effect of exercise to the community for several reasons: (1) The negative effect was hypothesized in conditions wherein vigorous exercise is occur, that is not in the range of recommend physical activity to leverage healthy life; (2) Promotion of physical activities in safe and acceptable doses will not do any harm to the community.

In conclusion, exercise has a regulatory contribution towards improving the immune response, which in turn potentially protects humans from ARI. However, the hypothesis related to its negative effect must be adopted cautiously. New data from comprehensive researches are warranted.

Submission statement

We declare that the work described has not been published previously and is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

Authors' contributions

Denny Agustiningsih: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Data curation, Conceptualization. **Tri Wibawa:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Data curation, Conceptualization.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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