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Review Article

Behavioral strategies to prevent and mitigate COVID-19 infection

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ABSTRACT

The single stranded RNA virus SARS-CoV-2 has caused a massive addition to the already leading global cause of mortality, viral respiratory tract infections. Characterized by and associated with early and deleteriously enhanced production of pro-inflammatory cytokines by respiratory epithelial cells, severe COVID-19 illness has the potential to inflict acute respiratory distress syndrome and even death. Due to the fast spreading nature of COVID-19 and the current lack of a vaccine or specific pharmaceutical treatments, understanding of viral pathogenesis, behavioral prophylaxis, and mitigation tactics are of great public health concern. This review article outlines the immune response to viral pathogens, and due to the novelty of COVID-19 and the large body of evidence suggesting the respiratory and immune benefits from regular moderate intensity exercise, provides observational and mechanistic evidence from research on other viral infections that suggests strategically planned exercise regimens may help reduce susceptibility to infection, while also mitigating severe immune responses to infection commonly associated with poor COVID-19 prognosis. We propose that regular moderate intensity exercise should be considered as part of a combinatorial approach including widespread hygiene initiatives, properly planned and well-executed social distancing policies, and use of efficacious facial coverings like N95 respirators. Studies discerning COVID-19 pathogenesis mechanisms, transfer dynamics, and individual responses to pharmaceutical and adjunct treatments are needed to reduce viral transmission and bring an end to the COVID-19 pandemic.

Introduction

Viral infections of the respiratory tract are the leading cause of mortality,[1] representing the most prevalent and pathogenic form of infectious disease in the world. There is a wide variety of respiratory viruses including rhinovirus (the common cold), the more pathogenic influenza virus, and the recently discovered and relatively unknown SARS-CoV-2. The virus was discovered in December of 2019 and the World Health Organization (WHO) characterized COVID-19 as a pandemic in March 2, 020.[2] According to the Worldometer, a free website dedicated to accurate reporting of statistics, as of September 1, 2020, it has infected 25,695,457 people, with 855,968 confirmed deaths.[3] Models from the University of Washington project it to take another 60, 000 lives in the next four months in the U.S.[4] Infection occurs when a person is exposed to infected aerosolized droplets or contaminated surfaces, following which the virus invades and infects the upper and/or lower respiratory mucosal tissues through interaction with the angiotensin converting enzyme 2 (ACE2) receptor on host respiratory epithelial cells.

COVID-19 seems to have a much longer duration (2–6 weeks) than typical respiratory infections[5,6] like influenza, which generally have a duration of 7–14 days. Symptomology in mild COVID-19 cases presents as traditional respiratory virus symptoms such as cough, nasal congestion, fever, body aches, sore throat, and malaise. However, certain cases present with diarrhea, difficult or labored breathing, chest pain, and in more severe cases acute cardiac injury, acute respiratory distress syndrome, pneumonia, and death.[5,6] Populations at high risk include those with, hypertension, diabetes, preexisting cardiorespiratory conditions, asthma, autoimmune conditions, and those above the age of 70.[7]The current situation is unpredictable, as our knowledge of the virus changes daily. COVID-19, on top of all other seasonally occurring infections, creates a potential overload of the limited resources in healthcare

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systems worldwide.[4]

In the absence of a vaccine and specific pharmaceutical treatments, the COVID-19 pandemic necessitates refinement in prophylactic strategies of the general population to reduce the spread and improve individual resilience to infection. Cross sectional and longitudinal data suggest that individuals who engage in regular moderate intensity exercise maintain a reduced risk of self-reported respiratory symptoms[8–10] and show improvements in mucosal immunity biomarkers[8,11,12] associated with lower risk of infection.[8,11,13,14] Animal models from our group[15] and others[16,17] have demonstrated that moderate intensity exercise performed before infection[15,16] or infectious symptoms,[17] can reduce respiratory virus-associated mortality and severity of symptoms. However, the "dose" of exercise is important, as prolonged and unusually high intensity exercise before or during infection has been associated with increased morbidity and mortality,[18–20] especially in those naïve to such exercise. Although controversial,[21,22], according to the J curve hypothesis, while optimal doses of exercise lower the risk of respiratory infections, prolonged/intense exercise may significantly increase the risk of infections (Fig. 1).

The goals of this review are to discuss host immune defense against respiratory viral infections and highlight non-pharmaceutical prophylactic and health maintenance guidelines for the general population. We will provide observational and mechanistic evidence suggesting strategic amounts of exercise may be a valuable addition by aiding in prevention and strengthening immune defense against viral respiratory pathogens. Due to the recency of SARS-CoV-2 discovery, research cited in this review will not be specific to that pathogenic strain, but generalized to known viral respiratory infections.

Human Respiratory Viruses

Most acute respiratory infections are caused by RNA viruses belonging to the families *Picornaviridae*, *Coronaviridae*, *Paramyxoviridae*, and *Orthomyxoviridae*. Representative viruses belonging to these families are depicted in Table 1. Infection of otherwise healthy individuals by these viruses occurs early and often during life and is characterized by relatively minor symptoms that are perceived mostly as inconvenient. However, respiratory viral pathogens are capable of causing high morbidity and mortality in susceptible populations such as children, the elderly, or those with pre-existing conditions and SARS-CoV-2 is no exception.

Members of the viral family *Coronaviridae* contain large positive sense single-stranded RNA genomes (~30–32 kb) and possess a characteristic crown-like appearance when viewed by electron microscopy. Infection of

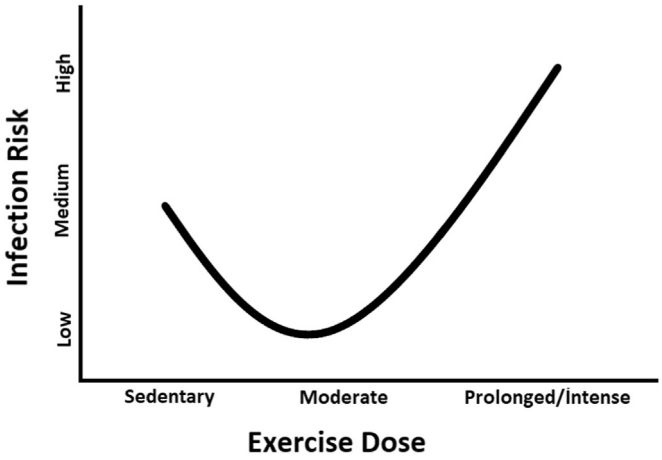

Fig. 1. The J-shaped model depicting the dose-dependent effect of exercise on risk of developing upper respiratory tract infections (Nieman DC, and Wentz LM. The compelling link between physical activity and the body's defense system. *J Sport Health Sci* 2019; 8:201–217).

Table 1
Common viral causes of respiratory infection.

Family	Strain/Type
Picornaviridae	Enterovirus D68
	Enterovirus D71
	Rhinovirus
Coronaviridae	HCoV-OC43
	HCoV-229E
	HCoV-NL63
	HCoV-HKU1
	SARS-CoV
	SARS-CoV-2
	MERS-CoV
Paramyoxoviridae	RSV
Orthomyxoviridae	Influenza A
	Influenza B

Human coronavirus (HCoV).
Severe acute respiratory syndrome (SARS).
Middle east respiratory syndrom (MERS).
Respiratory syncytial virus (RSV).

non-immunosuppressed people by seasonal human coronavirus (HCoV) strains HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoV-HKU1 causes relatively mild upper-respiratory illness. In fact, it is estimated that these HCoVs account for approximately 15–30% of 'common cold' illnesses.[23] However, during the last few decades three highly pathogenic novel strains of coronavirus have emerged that represent a serious threat to global health. In particular, severe acute respiratory syndrome (SARS)-CoV, SARS-CoV-2 (the virus responsible for COVID-19), and Middle East respiratory syndrome virus (MERS)-CoV are highly infectious diseases capable of causing high mortality.

Aside from respiratory illness, HCoV-OC43, HCoV229E, SARS-CoV, MERS and SARS-CoV-2 are also capable of invading the central nervous system and potentially infecting neuronal cell populations.[24,25] Neurological manifestations have been associated with each of these strains, and are more prevalent amongst the more virulent SARS and MERS strains.[26] The neuroinvasive potential of HCoVs is not entirely surprising since other CoV strains have been known to do so for decades. In particular, the murine betacoronavirus mouse hepatitis virus (MHV) strains A59 and JHM are neurotropic and are established models for the human disease multiple sclerosis.[27] Indeed, mounting evidence suggest that infections by both SARS-CoV and SARS-CoV-2 are associated with the occurrence of encephalopathy, para-/postinfectious inflammatory CNS/PNS syndromes (i.e. acute disseminated encephalomyelitis and Gillian Bare syndrome), (meningo-)encephalitis, and neuropsychiatric complications. Additionally SARS-CoV and SARS-CoV-2 infections are also linked to the development of cardiovascular disease.[26]

There are only a limited number of FDA-approved drug targets against RNA viruses and they are only prescribed after the onset of symptoms. No vaccines are currently approved for rhinovirus, HCoV, or RSV. Therefore, these is a need to discover and explore alternative strategies that can be implemented to control morbidity and mortality. Such strategies would be beneficial if: 1) similar mechanisms control the generation of immunity towards respiratory viral infection, and 2) the strategy could bolster beneficial immune responses or enhance viral clearance without increasing morbidity.

Viral pathogen recognition and early innate immune responses

Fig. 2 depicts the immune response to respiratory viruses. The respiratory tract is constantly exposed to environmental (dust, pollution) and pathogenic (bacteria, viral, fungal) insults, yet under normal circumstance is remarkably able to maintain homeostasis. This feat is attributable, in part, to ciliated epithelial cell barriers, but also to the presence of an elaborate mucosal immune system comprised of numerous cells including: resident alveolar macrophages (AM), interstitial macrophages (IM), nerve and airway associated macrophages (NAM),

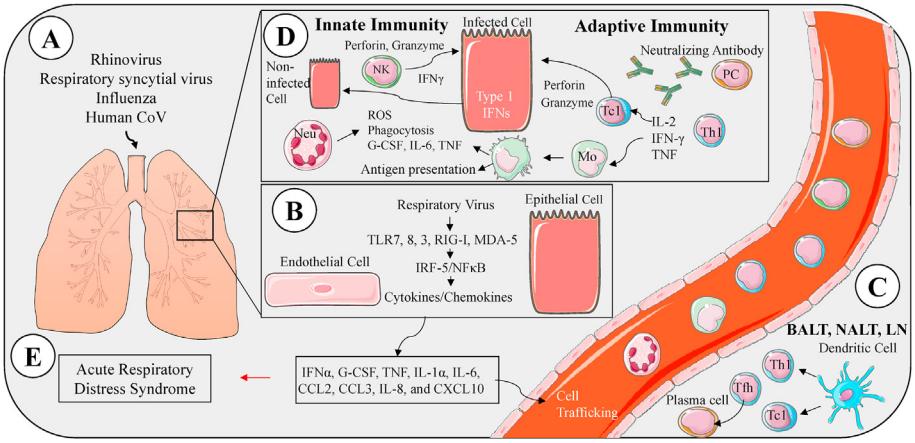

Fig. 2. Immune Response to Respiratory Viruses. **A.** Rhinovirus, respiratory syncytial virus, influenza virus and human coronaviruses are capable of establishing respiratory tract infection. **B.** Viruses are detected by PRRs (TLR7, TLR8, TLR3, RIG-I and MDA-5) which activate IRF-5 and NFκB to produce cytokines and chemokines (box below). These cytokines induce fever, loosen tight junctions on endothelial cells, and promote cell trafficking of immune cells to the site of infection. **C.** Dendritic cells transfer antigen to the regional lymphoid tissue where they expand virus-specific T and B cell clones and polarize T cell responses. Tfh cells promote B cell maturation to antibody producing plasma cells. **D.** Summary of innate and adaptive immune responses that promote viral clearance of infected cells. **E.** Sustained or dysregulated immune activation can cause acute respiratory distress syndrome, loss of function, and increase risk of mortality.

plasmacytoid dendritic cells (pDCs), conventional dendritic cells (cDC), conventional natural killer (NK) cells, innate lymphoid cell subsets (ILC1, ILC2, ILC3), and tissue resident memory T and B cells. Several excellent reviews on the specific functions of these cells have recently been published.[28,29] Of importance here is that these cells are able to perceive the threat of viral infection and to respond appropriately.

Viral RNA is recognized by the cytosolic pathogen recognition receptors (PRRs) retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA-5) as well as the endosomal toll-like receptors (TLR) TLR3, TLR7, TLR8 and TLR9. Importantly, these PRRs are not only expressed by macrophages and dendritic cells, but are also expressed in lung epithelial cells and memory lymphocyte cell populations.[30] Activation of these receptors by viral pathogen associated molecular patterns culminates in the production of the pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and IL-12, the chemokines C–C motif ligand (CCL)2, CCL5, C-X-C motif ligand (CXCL)10, and type I (IFNα, IFNβ) and III (IFNλ) interferons, which are critical for interfering with viral replication. Lung macrophages and DCs function to phagocytose debris and dying cells as well as facilitate immune response generation by means of antigen processing and presentation to adaptive T and B lymphocytes. Dendritic cells from the respiratory tract present antigens to lymphocytes within the nasal-associated lymphoid tissue (NALT), bronchus-associated lymphoid tissue (BALT), and mediastinal lymph nodes. In cDC's, PRR activation induces cell maturation characterized by upregulation of surface co-receptors CD80 and CD86. Binding of these co-receptors to CD28 on T cells and is required for efficient priming.

Data generated from animal and human studies indicates that MDA-5 and TLR3 are essential for recognizing rhinoviruses.[31–34] Studies using murine hepatitis virus, the prototypical β-coronavirus, indicate MDA-5 and TLR7 are important for IFN production and protection against infection.[35–37] In contrast, TLR2/6 and TLR3 are needed for cytokine and chemokine production following RSV infection.[38–40] Finally, influenza viral RNA is recognized by TLR7, TLR8 and RIG-I.[41–45] Activation of different PRRs is needed for the recognition of pneumotropic viruses. It is notable that stimulation by each ultimately culminates in a global transcriptional response that is shared. Recently, an integrated transcriptomic analysis of multiple patient cohorts derived from controls or patients infected by rhinovirus, RSV, and influenza viruses identified 396 genes distinctive genes, termed the meta-virus signature (MVS) that is shared between respiratory viral infections. The MVS was also found to be specific in predicting respiratory viral infection resulting from SARS-CoV, and was able to distinguish between infections caused by bacteria. While responses are not identical between different viruses, these data do indicate that conserved immune responses occur in response to respiratory infection by RNA viruses that may be exploited for therapeutic benefit.[46] For instance, the requirement of TLR7 in the recognition of SARS-CoV-2 in humans is reinforced by the finding that single nucleotide polymorphisms in *TLR7* are predictive of poor prognosis and mortality.[47] As such, interferon treatment of patients harboring inborn errors in *TLR7* might be efficacious in preventing morbidity and mortality.

Innate lymphoid cells are derived from a common lymphocyte progenitor and are divided into subsets that are based on type-specific effector functions. The ILC1 subset includes both conventional natural killer cells (cNK) as well as non-NK cell helper-like ILC1. Both cNK cells and innate lymphoid cells (ILC1s) are important in slowing viral replication and spread during acute respiratory infection. Like conventional NK cells, ILC1 cells are capable of quickly generating robust production of IFNγ, particularly in response to stimulation by IL-12 and IL-18[48] and are thought to limit viral infection in a STAT1-dependent manner prior to the arrival of circulating conventional NK cells.[49,50] However, unlike cNK cells, ILC1s lack perforin and granzyme B and therefore lack the capacity to lyse target cells.[50] The ability for NK cells to lyse virally infected targets is conveyed by through the recognition of activation receptors expressed targets during cellular stress, suppression of inhibitory receptor signaling and by IgG1 or IgG3 activation of FcRVIII (antibody dependent cell mediated cytotoxicity; ADCC).[51] Regarding the latter, a recent longitudinal study showed that increased levels of antibodies capable of facilitating ADCC decreases susceptibility to influenza infection.[52] There is optimism that the same might hold true during infection with SARS-CoV-2[53]. Moreover, Bongen et al. found that the presence of killer cell lectin-like receptor subfamily D, member 1 (KLRD1)-expressing NK cells were negatively associated with symptom severity in IAV and HRV infection.[54] Furthermore, patients with primary NK cell deficiency have increased risk for viral infection[55] including those of the respiratory tract.[56] Current evidence suggests that NK cells might be dysfunctional in SARS-CoV-2 patients and that this may contribute to disease exacerbation.[53] Specifically, NK cells are reduced in the circulation of persons infected with SARS-CoV-2 and that their effector function might be impaired.[57,58]

Adaptive immune responses to respiratory infection and generation of immunological memory

The polarization of naïve $CD4^+$ helper T cells toward specific subsets, namely Th1, Th2, Th17, Treg and Tfh, is essential for directing immune responses against specific pathogens. Of these subsets, Th1 and Tfh cells are important for the generation of efficient viral immunity.[59] Virus-specific $CD4^+$ Th1 cells are generated from naïve T cells following T cell receptor recognition of MHC class II presented antigens, co-stimulation by activated APCs as well as stimulation by IL-12. These cells are characterized by the production IFNγ, TNF and IL-2, which aid in viral clearance and provide help to cytotoxic $CD8^+$ T cells (CTLs). Cytotoxic T cells recognize foreign epitopes presented by MHC class I

molecules and play an important role in viral clearance through the production of cytokines such as IFNγ as well as by directly lysing infected targets.[59] Not only do these cells participate in viral clearance, but pre-existing virus-specific cells have been shown to correlate with protection from infection.[60,61] The Tfh cell subset is a specialized cell subset that is generated in the presence of high levels IL-6 and IL-21. Tfh cells are required for germinal center formation and function and thus have a major role in the processes of affinity maturation and class switching in B cells.[62] While Tfh cells are important, it is notable that, in mouse studies, IFNγ production by Th1 cells can also promote class switching and the generation of neutralizing antibodies to IAV in the absence of Tfh cells, indicating some compensatory mechanisms exist.[63]

The generation of high affinity antibody of the correct isotype is important for immunity to respiratory viral infections as they act to directly neutralize virus receptor interactions, promote opsonization and antigen presentation, facilitate antibody dependent cell mediated cytotoxicity and complement mediated cell lysis. Interestingly, Heinonen et al. examined differences between immune cell profiles and leukocyte transcriptomes between age-matched healthy control infants, RSV infected infants with a mild infection, and infected infants requiring hospitalization. Their results suggest that the phenotypic and transcriptomic signature of mild RSV infection was characterized by an increase in IFN and plasma cell genes compared with patients with severe infection.[64] Moreover, the therapeutic efficacy of monoclonal antibodies with paratopes specific for G and F to minimize symptoms of disease in passively immunized children also provides support.[65–67] Antibodies specific for the influenza lipid membrane protein haemagglutinin (HA) are directly neutralizing, but antibodies with specificity to neuraminidase (NA) and matrix (M)2 protein also confer protection. In humans, influenza-specific antibody responses are dominated by IgG1 isotypes but also present are virus-specific IgG2 and mucosal IgA1. The latter confers protection in the upper-respiratory tract, whereas IgG1 is dominant in the lower respiratory tract.[68] Infection by HRV also induces anatomically dichotomous antibody responses. Specifically, Eccles et al. found that experimental HRV infection increased a subtype of memory B cells, characterized by the expression of the transcription factor T-bet and absence of the chemokine receptor CXCR5, which was cross-reactive for different HRV strains within the nose. These cells respond rapidly to HRV infection and exclusively produced IgG. In contrast, systemic B cell responses were mono-specific and produced virus-specific IgA, IgG and IgM.[69] The functional significance of these cells has not yet been clearly defined, but opens the door to new avenues of investigation across respiratory infections. Finally, antibody responses directed towards the spike protein of SARS-CoV, and MERS-CoV are neutralizing and associated with recovery from infection.[70–72] These data provide hope for the successful development of a vaccine against SARS-CoV-2.

Cytokine storm and mortality

Severe respiratory viral infections caused by influenza, SARS or MERS can be lethal. Mortality is influenced by virus-intrinsic factors such as virulence, and genetic factors of the host, but may also be attributable to dysregulated immune activation. For instance, Cynomolgus macaques infected with the influenza strain responsible for the 1918 pandemic exhibited increased viral replication, enhanced viral dissemination, increased lung pathology and aberrant changes to innate immune responses compared to a monkey infected with a conventional influenza virus (A/Kawasaki/173/01; K173).[73] The dysregulated immune response is predictive of disease severity and death,[73–76] is characterized by early and enhanced production of the pro-inflammatory cytokines IFNα, G-CSF, TNF, IL-1α, IL-6, CCL2, CCL3, IL-8, and CXCL10 and has been termed the "cytokine storm". Cytokine storm is also observed in SARS-CoV, MERS-CoV and SARS-CoV-2 infected patients and is associated with poor prognosis.[77–79] In fact, SARS-CoV-2 patients on ventilation or oxygen therapy had reduced percentage of death after receiving treatment with dexamethasone, a synthetic glucocorticoid and potent immunosuppressive molecule.[80] The consistent correlation between overt inflammation and clinical outcome has sparked interest into the molecular events and cellular sources responsible for initiating and perpetuating the cytokine storm, as these may prove to be clinically relevant. Studies utilizing mouse-adapted and never-adapted strains of human influenza virus indicate that the cytokine storm is initiated by endothelial cells and can be suppressed by activation of sphingosine 1 phosphate ($S1P_1$) receptor signaling. In this study, leukocyte accumulation in the lung was dependent on cytokine and chemokine production and mortality was mitigated following treatment with S1P analogs.[81–84] Recent experimentation using influenza has implicated interferon regulatory factor-5 (IRF-5) as essential for the generation of the cytokine storm.[85] It is notable that TLR7 can directly activate MyD88 and that IRF5 signaling is a downstream target of MyD88. The transcription factor IRF-5 appears to be crucial for cytokines storm generation as *Irf5* knockout mice are resistant to uncontrolled cytokine/chemokine production and virus induced mortality.[85] Interestingly, activation of hexosamine biosynthesis pathway by excessive glucosamine enhanced cytokine production from influenza infected cells by a mechanism that was dependent on O-linked β-N-acetylglucosmine (O-GluNAc) transferase mediated O-GlcNAcylation of IRF-5.[86] These results might partially explain why patients with diabetes are at risk for mortality following SARS-CoV-2 infection and imply that management of in blood glucose by exercise may act decrease risk of serious complications during respiratory infection. Thus, TLR7 may play Janus-face role in the pathogenesis of COVID-19, in that it is required for efficient viral recognition and initial IFN production, but aberrant activation may prove detrimental.

Exercise as a Prophylactic and Adjunct Treatment Strategy

Epidemiologic Studies. The exercise immunology community has reached a consensus belief that regular bouts of moderate to vigorous intensity physical activity about an hour or less in duration is beneficial for the functioning of the immune system, and is probable to reduce risk of viral respiratory infections in the general population.[21,87] A recent review article by Nieman and Wentz[20] compiled evidence from four recent epidemiological studies with sample sizes of 547 or greater. These studies demonstrated a 29% decreased illness risk when comparing upper versus lowest quartiles of physical activity,[88] an 18% decreased illness risk in high activity versus low activity groups,[9] a 43% decrease in total illness days in high vs lowest fitness tertiles,[89] and a 26% decreased risk of developing the common cold in high activity groups.[90] Epidemiologic evidence to this point supports the consensus belief that physically active individuals are at lower risk of developing respiratory infection.

Randomized Controlled Trials. Three meta-analyses of available randomized controlled trials have been conducted on the incidence of respiratory infections[91,92] including the common cold.[93] Lee et al.[93] analyzed four randomized controlled trials encompassing 281 participants and found that the exercise groups had a relative risk of 0.73 compared to sedentary controls in developing the common cold. Interestingly, this number increased (but not significantly) to 0.79 in groups with interventions shorter than 16 weeks. They also saw a reduction in reported mean illness days in the three studies that reported it.

Rocco et al.[92] conducted a meta-analysis of four systematic reviews and included data from five randomized trials on 311 healthy 25–85 year olds of both sexes, with most treatments being 30–45 min of moderate intensity exercise 5 days a week. The authors calculated a 16% decrease in incidence of respiratory infections in the exercise group, but graded the certainty of the evidence as very low.

Grande et al.[92] conducted a systematic review of 14 randomized or quasi-randomized (participant selection based on birth date or medical record number) from 1990 to 2018 with 473 participants of both sexes with ages 18 to 55. Interventions were three or more days a week, usually 30–45 min in duration. A mixed effects model revealed no significant exercise effect in number of reported ARI illness episodes per person per

year, proportion of participants who experienced at least one ARI illness episode over the trial period, or number of symptom days per episode. Some trials in the analysis measured biomarkers such as serum lymphocytes, IgA, and neutrophils, none of which demonstrated exercise-induced changes. However, symptom severity and amount of symptom days in the follow-up period were significantly lower in the exercise intervention groups, supporting a beneficial effect of exercise.

The authors of all three above reports noted that certainty of the evidence was either low or very low due to variations in study design and insufficient sample size. Additionally, some included interventions contained exercise bouts longer than the generally recommended duration. For example, Barrett et al.[94] included weekly group sessions two and a half hours long and Silva et al.[95] included three 90 min sessions per week (in participants over 60 years of age). Such high levels of exercise may increase infectious disease risk according to the J curve hypothesis. Some studies were of shorter length. For example, Manzaneque et al.[96] only included an intervention period of 1 month, Weidner et al. 1998[97] only 10 days, and Weidner et al. 2003[98] only 7 days. These results indicate a need for more randomized controlled trials with larger sample sizes and more refined and homogeneous exercise intervention strategies to discern the capacity of strategic intensities, durations, and frequencies of regular exercise training in the prevention of viral respiratory tract infections.

Definitive studies where exact dosages of respiratory viruses are given to exercised trained or acutely exercised participants are difficult to perform due to ethical reasons. However, one group at Ball State University has published such a study. Weidner et al., 1998[97] randomized 34 young adults of moderate fitness to a 10 day moderate exercise intervention (70% of heart rate reserve, 40 min/d) or control (n = 16) treatment and then administered rhinovirus 16 intra-nasally. There were no differences in self-reported respiratory infection symptoms or mucus weights (collected from facial tissues) indicating that moderate exercise during an upper respiratory tract infection with rhinovirus 16 did not alter severity or duration of illness. Unfortunately, definitive assessment of viral load was not performed and the duration of the intervention was quite short.

Effects of Exercise on Biomarkers of Anti-viral immune defense

Due to the difficulties of performing ethical human studies, many investigators have examined the effects of exercise on immune measures important in anti-viral defenses. Using this approach, some information about the effects of exercise on baseline host defense and susceptibility to viral infection can be gained. However, without tracking immune responses and outcomes to an actual viral infection, the approach provides only correlational data.

Along these lines, the important role of salivary immunoglobulin A (SIgA) in mucosal immunity have led to its investigation in relationship with respiratory infection and exercise; as it functions as a neutralizer and opsonin for antigens the host has previously been exposed. Intensified periods of exercise training are associated with a decrease in the concentration and secretion of SIgA,[20,21,99] while regular moderate intensity exercise has been found to increase these markers.[8,12,100] SIgA and salivary flow rates have been negatively correlated with occurrence of respiratory infection symptoms in some cases,[13,101,102] but other groups have failed to make this association.[103–105] Campbell and Turner[22] suggest periodontal diseases as a potential uninvestigated confounder, as they are common in athletes and have been shown to cause large fluctuations in SIgA and saliva levels. Currently, evidence does not exist examining the relationship between SIgA levels and infection rates among sedentary or non-athletic populations. One criticism of these studies has been that many of the symptoms and infections in the majority of these studies are self-reported and not physician diagnosed or laboratory confirmed.

Spence et al.[106] tested for pathogens in athletes presenting upper respiratory infection symptoms and found that confirmed viral infections were only present in 30% of athletes reporting symptoms. These results suggest many symptoms indicative of an infection could be due to allergy or some other non-specific inflammatory stimuli. Evidence has revealed that only a small percentage of athletes experience recurrent infection symptoms,[107] an observation that has led to a search for common traits among susceptible individuals. Colbey et al.[108] found that athletes who reported symptoms for two or more days a month were high expressors of interferon alpha inducible protein 27 (IFI27). Cox et al.[109] found that athletes who self-reported three or more episodes of upper respiratory symptoms (URS) within a 12 month observation period were much more likely to be high expressers of IL-6 and low expressers of IL-4 (though not as robustly) than those who reported fewer than three episodes. IL-2 high expression genotype was also associated with decreased likelihood of frequent URS. Researchers noted they could not adjust for training volume. Zehsaz et al.[110] found that male athletes with the IL-10-1082 high expression genotype were more likely to experience frequent URTI. Interestingly, Gleeson et al.[101] found that antigen-stimulated whole blood culture of illness prone subjects produced IL-10 and IL-4 at rates 2.5 fold higher than the healthy group. At a $p = 0.06$, they also found higher production of IFN-γ and IL-2 in the illness-prone group. However, the production of IL-10 was significantly positively correlated with number of weeks with infection symptoms. These findings suggest the phenomena of increased rate of URTI incidence among athletes with high training loads to be a complicated issue that warrants further investigation using genomic and transcriptomic approaches. More robust data and homogenous study designs are needed on salivary biomarkers in the general population and cytokine centered investigation to determine their relevance moving forward. The clinical relevance of exercise-induced changes in alpha amylase and lysozyme are also under investigated now.[111] Currently, the anti-inflammatory properties of Treg cells and IL-10 stand out as interesting targets of investigation.

Another strategy to address the actual immune response to a challenge in people involves assessing the impact of exercise on the immune response to a vaccination. While closer to addressing exercise's impact on a natural infection and informative, it is important to note that most vaccinations are administered intra-muscularly, which is not the route of infection for respiratory viruses. A study from our lab demonstrated that older adults engaged in moderate endurance exercise realized a longer lasting protective effect of the annual influenza vaccine such that they had protective antibody titers into March and April, whereas the control group did not.[112] A systematic review by Grande et al.[113] using a random effects model of six randomized trials totaling 599 participants revealed exercising immediately before influenza vaccination to be neither helpful nor harmful in the general adult population, but also noted that the analyzed data was of low quantity and quality with many design limitations. A flaw in this review was that it did not distinguish between regular and acute exercise before vaccination, which is often differentiated in other exercise immunology research. A recent observational study published by Lim Wong et al.[114] of 56 elderly Singaporean Chinese women showed that those who were in the highest quartile of steps taken on an Actical wrist-worn device displayed greater post vaccination expansion of monocytes and plasmablasts in peripheral blood. They also presented lower baseline levels of IP-10 and Eotaxin, but upregulation of genes associated with monocyte/macrophage phagocytotic activity. Researchers also found positive correlations between monocyte response and post vaccination H1N1 antibody titers, and higher induction of antibodies against Flu B in 18 month s vaccination follow up. These findings display potential importance in measures of monocyte activity, which could be an interesting target for future investigation.

In support of the J curve hypothesis, athletes who regularly partake in prolonged endurance exercise (<90 min/session) may be at a higher risk of experiencing URS.[20] However, defining prolonged exercise as causative in this trend is a contentious topic among the exercise immunology community.[21] There is reason to believe that physiological states frequently associated with prolonged bouts of high intensity exercise (i.e. psychological stress, sleep deprivation, physical exhaustion, potential

carbohydrate inadequacy) during competition periods cause transient immunosuppression, which may increase risk for respiratory infection.[21] While evidence attributing immunosuppression to prolonged exercise is equivocal, there is evidence in animal models (see more below) animals subjected to exhaustive exercise exhibit increased mortality rates in response to viral infection.[18] Of note, many of these studies utilized animals naïve to exercise (i.e. not trained). While animal models are limited in their interpretation, data of this nature presents the potential risk of unfamiliar and/or exhaustive exercise as exacerbating viral infection symptoms or risk of contraction in vertebrates. It is recommended to err on the safe side during a pandemic when the chance of becoming infected is abnormally high and the risk is relatively unknown, especially in those unaccustomed to intense, prolonged exercise. If one does partake in prolonged exhaustive exercise, the recommendation has been to maintain adequate consumption of carbohydrates as NK cell, T cell, and neutrophil functions have been reported to decline to a greater extent following exercise in a glycogen depleted state.[20,99] This is thought to be due to the larger stress response, causing greater cortisol, catecholamine, and IL-6 release.[99] Consumption of polyphenols has also been shown to attenuate some aspects of potential resultant immune suppression.[20]

Animal models

Due to the obvious ethical concerns associated with properly controlled studies examining responses to specific pathogens in humans, we turn to animal models for the bulk of evidence regarding the role of exercise in viral infection illness severity and potential molecular mechanisms. Findings from work by our group[17,115] and Davis et al.[18] on viral infections in untrained mice demonstrated that 1) a single bout of high intensity treadmill exercise to volitional fatigue mice before inoculation with herpes simplex virus 1 increased mortality rate by 25%,[18] 2) four days of moderate exercise after infection with laboratory influenza strain A/Puerto Rico/8/34 at a dose designed to induce 50% mortality reduced mortality by 38%,[17] and 3) in a follow-up study,[115] resulted in a twofold reduction in Th1 type cytokines and chemokines including IFN-γ, IL-17, IL-13, IFN-inducible T-cell alpha chemoattractant, leptin, stromal cell derived factor 1, lipopolysaccharide-inducible CXC chemokine, and IL-12 in the lungs. This led to speculation that exercise may skew the immune response to influenza away from an inflammatory Th1 phenotype and more towards an anti-inflammatory Th2 phenotype that results in less lung pathology and symptom severity, and that this may happen to a detrimental amount in prolonged exhaustive exercise.[116]

Warren et al.[16] put mice on a traditional or obesogenic diet, then randomized them into sedentary or daily treadmill running (started at 10 min/day but gradually increased to 45 min/day) groups for eight weeks in a 2 × 2 design. Mice were infected with influenza A/PR/8/34 24 h after the last exercise session. Exercised mice lost less weight, indicating reduced severity of illness, and had greater food intake during the duration of infection (although all groups showed reduced food intake in comparison to non-infected control mice). Interestingly, caloric intake in obese mice was half that of non-obese mice when totaled during the weight loss phase and they also experienced longer times associated with weight loss. Lean exercised mice had decreased viral load in comparison to sedentary mice, increased early infection expression of type-1-IFN-related genes, decreased BAL cytokines (IL-5, IFNγ, IL-1β, IL12p70, TNFα, IL-13, IL-6, IL-15 and IL-17) and chemokines (CCL11, CCL2, CCL3, G-CSF, CCL5, and CXCL10) production, of which only CCL11, CCL2, CCL3, G-CSF, CCL5, IL-13 and TNFα, remained at day 8 while IL-10 became significantly reduced by exercise at that point. Vastly different effects were observed in the immune biomarkers of obese mice, as exercise reversed delay in bronchoalveolar-lavage (BAL) cell infiltration, increased or "restored" BAL cytokine (IL-1β, IL-4, IL-5, IL-6, IFNγ, IL-10, IL-12p70 IL-13, IL-15, IL-17, TNFα and IFNα) and chemokine (CCL11, CCL2, CCL3, G-CSF, CCL5, and CCL10) production from an apparent deficit when compared to non-obese mice, and increased ciliary beat frequency and IFNα related gene expression. In both body types, exercise increased serum anti-influenza virus specific antibodies, percentage of BAL cytotoxic T cells, and reduced production of TNFα by influenza viral NP-peptide-responding $CD8^+$ T cells. The results in the lean mice are relatively like our 2006 data and display the ability of regular exercise to reduce severity of inflammatory responses in the lungs to an appropriate degree. In short, regular exercise reduced illness severity via decreased immune activity in lean mice, and via increased immune activity in obese mice. Exercise may help prevent the "cytokine storm" responsible for the excessive inflammatory response to Sars-CoV-2 infection, but human data are needed to make this conclusion.

Mechanisms

There is a growing list of potential mechanisms potentially responsible for the effects exercise has on the immune system. Five recent review articles have compiled available experimental data that have found regular moderate intensity exercise can alter many immune biomarkers including reductions in senescent T-cells, increased T-cell proliferation and mobilization, lower systemic levels of pro-inflammatory cytokines preventing chronic inflammation, increased neutrophil phagocytosis leading to greater pathogen clearance, lowered inflammatory response to bacterial challenge, greater NK cell cytotoxicity indicating more effective clearance of MHC 1 presenting infected cells, increased IL-2 and IL-7 production,[10,22,99,117] upregulated expression of CD28 on Th cells, muscular production of IL-6,[118] shifting the Th1/Th2 balance more towards Th2 dominance potentially reducing excessive inflammatory responses,[117] increasing antioxidant capacity leading to less free radical damage,[119] altered adipokine production to a less inflammatory profile[120] and increased leukocyte telomere length indicating increased proliferative capacity.[20] Additionally, there are some potential indirect mechanisms[99] due to resultant reductions in white adipose tissue[120,121] chronic psychological stress,[122] and chronic inflammation,[121] all of which are regarded as immunosuppressive in some aspect.[123–126]

Other prophylactic measures

Face Coverings. The CDC is currently recommending that individuals who go out in public where other people may be present wear face coverings acting as a physical barrier to prevent complete release of viral particulates present in saliva. These particles may infect others or be inhaled with the air, potentially resulting in infection. N95 respirators are currently believed to be the gold standard for prevention of respiratory viral spread among people, however there may not always be adequate supply for the general public. This has caused many individuals to turn to making masks out of cloth or using medical masks for affordability or availability reasons. A cluster of randomized controlled trials in the health care setting by MacIntyre et al.[127] showed that cloth masks contribute to a higher rate of influenza like infection than both workers wearing medical masks at all times and those who follow institutional standard practice, which may or may not include mask use. Authors noted that the ineffectiveness may have been due to moisture retention and poor filtration, but could also possibly be due to reuse without proper cleaning. While evidence suggests cloth masks may not be effective in the prevention of infection of individuals in the healthcare setting, data are needed on their efficacy in preventing infected individuals from spreading the infection in the public setting in general to make public health guidelines regarding their use. In health care settings, the wearing of medical masks at all times reduced relative risk of Ebola virus contraction among healthcare workers.[128] However, when it comes to laboratory confirmed viral respiratory infections in healthcare workers, they show an insignificant reduction in relative risk (0.78 of control), where continuous N95 respirators show greater, significant reduction.[129,130] There is currently a paucity of data on medical mask use in community settings. Per a review by Macintyre and Chughtai 2015,[131] RCTs on data collected during SARS and influenza outbreaks

demonstrate that wearing facemasks have potential efficacy in reducing transmission dependent on compliance and early use. However, due to mixed interventions in all available RCT data and meta-analyses, consensus conclusions are not currently available. Early evidence for COVID-19 indicates that many people can transmit the virus asymptomatically or with very mild symptoms. It will be important to understand if wearing a mask in a community setting helps to reduce viral spread.

Personal and Workspace Hygiene. Following workplace promotion of alcohol-based sanitizers and wipes, Arbogast et al. found a 24.3% lower incidence of healthcare insurance claims for hand-hygiene preventable illnesses (like flu and cold).[132] Distribution of a hand hygiene bundle, weekly reminder emails, strategically placed signage, and staff disinfection of tracer infection seeded fomites 3.5 h after colonization demonstrated an 85% reduction in viral presence per surface area on hands and fomites. This reduction was reduced to 42% when hand hygiene bundles and reminders were not provided.[133] Similar results have been attained with the implementation of a healthy workplace project, involving hand sanitizers, promotional signs, disinfecting wipes, facial tissues, and use instructions/information.[134] Viable particles of the SARS-CoV-2 virus can be detected for up to 72 h following colonization of plastic or stainless steel surfaces, 4 h on copper, and 8 h on cardboard.[135] While proper hygiene can mitigate many fomite contact transmission risks, the virus may also remain viable in aerosols for up to 3 h.[135] This indicates a need for further protective measures to completely halt spread of the virus.

Social Distancing. According to a systematic review by Ahmed et al.,[136] non-healthcare workplace social distancing primarily modeled by a 50% reduction in workplace contacts for the duration of an influenza outbreak resulted in a median reduction of 23% in the cumulative attack rate. When combined with other non-pharmaceutical interventions such as respiratory etiquette and hygiene initiatives, this number jumped to 75%. Addition of pharmaceutical antiviral treatment and prophylaxis further raised it to a 90% reduction. This effect was higher in workplaces than in the general population, with the effectiveness decreasing with higher virus R_0. They also discovered a reduction in the peak daily attack rate in the five studies that reported it. The peaks were a median of 6 days later than a control group, although the variability was quite high. Fong et al. updated this with three additional published studies and found similar results but added that paid sick leave could improve compliance with regards to isolation of infected individuals.[137] A 16-month study of over 230 adult office workers demonstrated that employees exposed to individuals with symptoms of a respiratory tract infection were 5 times more likely to report a similar infection during the same week than those not exposed.[138] These findings suggest the importance of social distancing and avoiding unessential proximity in the workplace during viral outbreak periods, especially in those presenting symptoms of infection.

Randomized controlled trials in the public community setting are logistically very difficult to complete and thus do not currently exist, so evidence in a community setting is primarily based on observational and simulation studies. Investigation of an outbreak of COVID-19 on a cruise ship demonstrated the importance of individual responsibility in isolating oneself after close proximity to a confirmed case.[139] Fong et al. found through systematic review that the evidence supporting quarantine of exposed persons on a community level is "weak" because being able to identify infected individuals and their close contacts in a timely manner can be very laborious during early phases, and close to impossible during later phases of a pandemic.[137] School closings are efficacious, but timing and programming to ensure availability of non-academic resources are important. Closings should be done before the spread reaches its peak, and certain school associated resources, such as counseling and meals, need to be made available remotely to ensure proper physical and psychosocial development of children.[140] It is also important that school closings occur simultaneously with workplace measures allowing working from home, as this allows employees to take care of children.[137] Timely implementation and high levels of compliance were shown to be critical concerning social distancing policies combating influenza outbreaks.[137] There is also the potential for quarantine to have negative psychological effects on quarantined children and adults such as post-traumatic stress symptoms, confusion, and anger, illustrating an importance for assuring proper length, supplies, rationale, support systems, and information to those it affects.[141] Additional information on vehicle and airline travel and dynamics of transfer of respective viruses can further inform the most practical and efficacious methods of social distancing in outbreak situations for both the community and workplace.

Other Lifestyle Factors. Various other lifestyle choices have an impact on susceptibility to SARS-CoV-2 and COVID-19 disease. Importantly, poor lifestyle choices have been found to be exacerbated during the pandemic and subsequent lock down, perhaps due to the stress and isolation associated with the pandemic. In one study, 46% of respondents self-reported an increase in caloric intake and weight gain during confinement.[142] While primary data is scarce, there is also public health concern regarding the increased consumption of alcohol during the pandemic[143] to the extent that some countries have limited bans on alcohol sales.[144] There is little information on the risk for COVID-19 disease and alcohol use and underlying liver disease. In one study, COVID-19 mortality was higher in patients with concomitant cirrhosis compared to controls, but the numbers of patients in the study were small.[146] In a systematic review and meta-analysis of 12 studies representing 2794 patients, of whom 596 had severe disease, Del Sole et al. found that smoking was associated with an overall higher risk level of 1.54 (95% CI 1.07–2.22) for severe COVID-19 disease.[145] More studies are needed, but most believe that there will be higher disease burden in smokers and alcoholics. As with most infectious diseases, malnutrition is both exacerbated by infection and a risk factor for poor outcomes.[147] Given that the pandemic started recently, there is little data on the role of poor diet on SARS-CoV-2 outcomes. Several dietary micronutrients, notably Vitamin A, Vitamin D, Vitamin E, Zinc and Selenium have shown significant influences on viral immune biomarkers,[148] making it important to ensure their regular and adequate consumption. An important caveat is that vitamin E supplementation has displayed deleterious effects in some populations.[149] More specifically, COVID-19 mortality rates have been linked to low levels of Vitamin D[150] and Selenium,[151,152] and multiple associations have been drawn between vitamin D levels (or biomarkers thereof) and other outcomes like infection rates[150] and illness severity.[153] Additionally, multiple clinical case reports have used zinc supplementation on admitted COVID-19 patients,[154,155] with seemingly positive results, though more controlled and mechanistic evidence is needed to make specific conclusions.[156] Using evidence from other viral pathogens and candidate biomarkers, a review by Jayawardena et al.[148] Supports the notion that supplementation of vitamin D, zinc, and selenium may be beneficial in the prevention and treatment of COVID-19 infection. The authors further stated that supplementation of Vitamin A may help with COVID-19 prevention and treatment, and supplementation vitamin C may help with treatment alone. Supplementation of certain micronutrients may prove beneficial for COVID-19 outcomes, but further investigation is needed to assure this and determine appropriate doses. For maintenance of overall health, including protection from infectious diseases like COVID-19, it is always prudent to stop smoking, consume alcohol in moderation, and eat a healthy diet. It is also important to be aware that the response to the pandemic (i.e. confinement, stress) and the virus itself likely changes our behaviors in ways that might increase our susceptibility.

Overall, combinations of the above strategies have proved to be the most effective in terms of behavioral prophylaxis with the goal of delaying spread, reducing total number of cases, and delaying and reducing peak attack rate.[136,137,157] It may take an individual plan designed for each virus and time period/place to identify the most effective public health policies. Such policies should take into account infectious properties of the virus, current infection rates among the respective population, general economic and public health needs, and

availability of resources. Additionally, increasing production of effective equipment such as N95 respirators and disinfecting agents could prevent the use of potentially ineffective alternatives.

Conclusion

This article has provided evidence to support the claim that multidisciplinary prophylactic approaches can aid in handling the COVID-19 pandemic. We believe it is advisable to enact widespread hygiene initiatives in all settings, carefully planned public social distancing policies, and extensive production and use of N95 respirators or other effective alternatives in addition to regular moderate intensity exercise. We hypothesize that many of the exercise-induced benefits observed in viral respiratory infection outcomes will display external validity with respect to COVID-19, though the exact magnitude remains to be seen. Moderate intensity exercise training has shown merit in producing cytokine profiles indicative more appropriate inflammatory responses after viral respiratory infection. While unfamiliar and exhaustive exercise may not be unequivocally causative in the development of URTI, animal models suggest it may reduce individual resilience to infection and may be a high risk activity in light of the highly infectious nature of COVID-19. New technologies and research techniques will allow us to better characterize genetic components associated with frequent symptoms of URTI. Until there is more evidence on COVID-19 infected individuals specifically, more exact conclusions cannot be made.

Submission statement

The articles and studies cited in this interview are cited honestly and represented without fabrication or data manipulation. The manuscript has not been published and is not in review elsewhere.

Authors' contributions

All members contributed to literature review. NTH drafted the abstract, introduction, behavioral prophylaxis, Exercise as a Prophylactic and Adjunct Treatment Strategy, Effects of Exercise on Biomarkers of Anti-viral Immune Defense, animal models, mechanisms and conclusion. AS drafted the Human Respiratory Viruses section. JAW edited and contributed to all sections, and worked with NTH to assemble the manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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