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Review

Coronavirus disease-2019: A tocsin to our aging, unfit, corpulent, and immunodeficient society

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Abstract

Acute and chronic respiratory illnesses cause widespread morbidity and mortality, and this class of illness now includes the novel coronavirus severe acute respiratory syndrome that is causing coronavirus disease-2019 (COVID-19). The world is experiencing a major demographic shift toward an older, obese, and physically inactive populace. Risk factor assessments based on pandemic data indicate that those at higher risk for severe illness from COVID-19 include older males, and people of all ages with obesity and related comorbidities such as hypertension and type 2 diabetes. Aging in and of itself leads to negative changes in innate and adaptive immunity, a process termed immunosenescence. Obesity causes systemic inflammation and adversely impacts immune function and host defense in a way that patterns immunosenescence. Two primary prevention strategies to reduce the risk for COVID-19 at both the community and individual levels include mitigation activities and the adoption of lifestyle practices consistent with good immune health. Animal and human studies support the idea that, in contrast to high exercise workloads, regular moderate-intensity physical activity improves immunosurveillance against pathogens and reduces morbidity and mortality from viral infection and respiratory illnesses including the common cold, pneumonia, and influenza. The odds are high that infectious disease pandemics spawned by novel pathogens will continue to inflict morbidity and mortality as the world's population becomes older and more obese. COVID-19 is indeed a wake-up call, a tocsin, to the world that primary prevention countermeasures focused on health behaviors and hygiene demand our full attention and support.

Keywords: COVID-19; Exercise; Immunology; Infection; Obesity

1. Introduction

Acute and chronic respiratory illnesses are the most common infectious diseases on earth and cause widespread morbidity and mortality. According to the World Health Organization, lower respiratory tract infections and pneumonia account for more than 4 million deaths annually.[1] The World Health Organization also estimates that influenza causes respiratory tract infections in 5%–15% of the world's population and severe illness in 3–5 million people.[1] The Global Burden of Diseases, Injuries, and Risk Factors Study ranks upper respiratory infections as the leading incident disease in the world (17.1 billion per year).[2]

There are many types of viruses that cause acute upper and lower respiratory illnesses in humans. Virus identification has improved by means of real-time reverse-transcription polymerase chain reaction testing. Multiplex polymerase chain reaction can detect multiple pathogens at the same time. Reverse-transcription polymerase chain reaction has shown that predominant viruses causing acute respiratory illnesses include human rhinoviruses, influenza A and B viruses, 4 types of parainfluenza viruses, respiratory syncytial virus, adenoviruses, and coronaviruses.[3,4]

Coronaviruses are enveloped RNA viruses with a zoonotic origin and include 4 types—229E, OC43, NL63, and HKU1—that typically cause common cold symptoms. Coronaviruses have a sharp seasonality, with high infection frequency during the winter and spring.[5] Three new types of coronaviruses have emerged. In 2003, a previously unrecognized coronavirus caused severe acute respiratory syndrome (SARS) before being stopped by rigorous infection control measures (8422 cases, with a case fatality rate of 11%).[6] Another novel coronavirus of animal origin appeared in 2012 as the causative agent of Middle East Respiratory Syndrome (MERS) (2519 cases, with a case fatality rate of 34%).[7]

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The impact of SARS and MERS was limited in comparison to the global disorder unleashed by the coronavirus SARS-CoV-2 that is causing coronavirus disease 2019 (COVID-19).[8,9] The causal virus was identified on January 7, 2020, with the genome sequence of SARS-CoV-2 released on January 10, allowing work on potential vaccines and therapeutics to commence.[8] Additional research showed that SARS-CoV-2 (1) is primarily transmitted through airborne droplets when infected individuals cough, sneeze, breathe deeply, or talk; (2) infects cells lining the air passageways by locking a spike (S) protein onto angiotensin-converting enzyme 2 receptors; and (3) typically causes modest symptoms such as coughing, fever/chills, shortness of breath, myalgia, and diarrhea before being eliminated by immune-generated neutralizing antibodies.[9–19] The SARS-CoV-2 can cause severe symptoms in some individuals when it infects the lungs, instigating an intense inflammatory response of the immune system and a cytokine storm.[17] This hyperinflammation state is characterized by increases in many cytokines, including those that are elevated after prolonged and intense exercise, such as interleukin-6, monocyte chemoattractant protein 1, and granulocyte-colony stimulating factor. SARS symptoms occur with SARS, MERS, and COVID-19, but the estimated case fatality rate of COVID-19 (2.3%) is substantially lower than SARS (11.0%) and MERS (34.0%).[20,21] When compared with SARS and MERS, COVID-19 has spread more rapidly, perhaps due to increased globalization and adaptation of the virus in nearly every environment.[20,21]

2. COVID-19 epidemiology: focus on age, obesity, and comorbidities

The SARS-CoV-2 is highly transmissible and may be spread by infected individuals prior to the development of symptoms. On average, each infected person spreads the infection to an additional 2 or 3 persons, and the virus has a mean incubation period of about 6 days.[18] SARS-CoV-2 RNA has been detected in upper and lower respiratory tract specimens and in blood and stool specimens.[22] The virulence of SARS-CoV-2 appears to lie between SARS-CoV and community-acquired human coronarviruses.[17] A vaccine should be developed soon, but may not be completely effective against COVID-19. The vaccine will be targeted initially to healthcare workers and vulnerable individuals.[23]

Within this context, the 2 most promising strategies to reduce the risk for COVID-19 at both the community and individual level are (1) mitigation activities and (2) the adoption of lifestyle practices consistent with good immune health. Mitigation approaches have been described extensively and adopted worldwide. They include personal protective measures (e.g., handwashing, cough etiquette, and face coverings), social distancing (e.g., maintaining physical distance between persons in community settings and staying at home), and environmental surface cleaning. This article provides an overview of the role of weight management and physical activity in improving immunosurveillance and viral defense.

Risk factor assessments based on data from China, Europe, and the United States indicate that those at greater risk for severe illness from COVID-19 include older males, and people of all ages with obesity and underlying medical conditions such as hypertension, cardiovascular disease, chronic lung disease, and chronic metabolic diseases such as type 2 diabetes.[10–21] Fig. 1, Fig. 2, and Fig. 3 summarize the effect of age, demographics, and comorbidities for patients hospitalized in March 2020 with laboratory-confirmed COVID-19 in the United States.[12,13] Among patients with data on underlying conditions, the most common

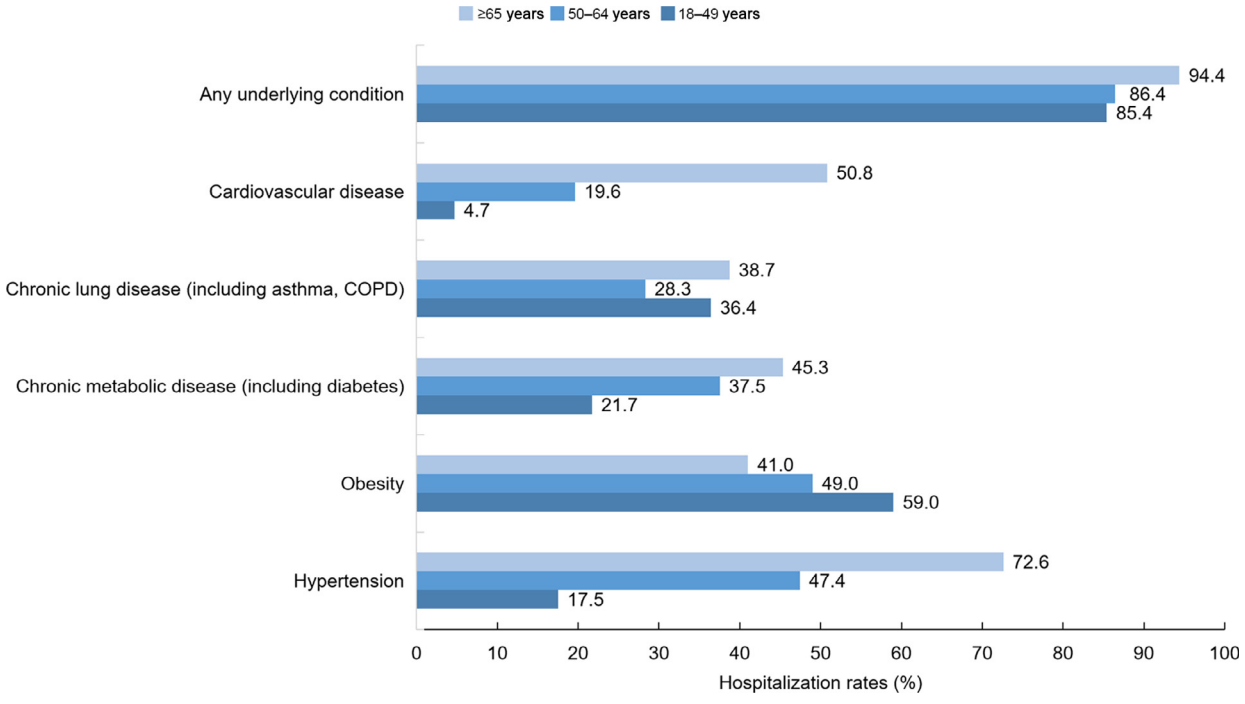

Fig. 1. Percentage of coronavirus disease-2019–associated hospitalizations, by age and comorbidity, in the United States (14 states) during March 2020.[12] COPD = chronic obstructive pulmonary disease.

were hypertension, obesity, chronic lung disease, diabetes mellitus, and cardiovascular disease. COVID-19 patients in hospitals tended to be older, non-white males. These findings underscore the importance of mitigation measures to protect older adults and those with underlying medical conditions. Additionally, this information supports the value of lifestyle approaches, such as physical activity, to reduce obesity prevalence in bolstering host antiviral, immune defense.[14]

3. Aging and obesity both impair host viral defense

The world is experiencing a major demographic shift toward an older, obese population. By 2050, the world's population aged 60 years and older is expected to total 2 billion, up from 900 million in 2015.[2] Aging in and of itself leads to negative changes in innate and adaptive immunity, a process termed immunosenescence.[24] The function of nearly every type of immune cell is negatively affected with increase in age, resulting in increased susceptibility to infectious diseases, reduced antibody responses to vaccinations, systemic inflammation, and decreased immune surveillance against cancer.[24–26] Influenza and COVID-19 infections are associated with high rates of complicated illness, including pneumonia, among the elderly.[10–16,27]

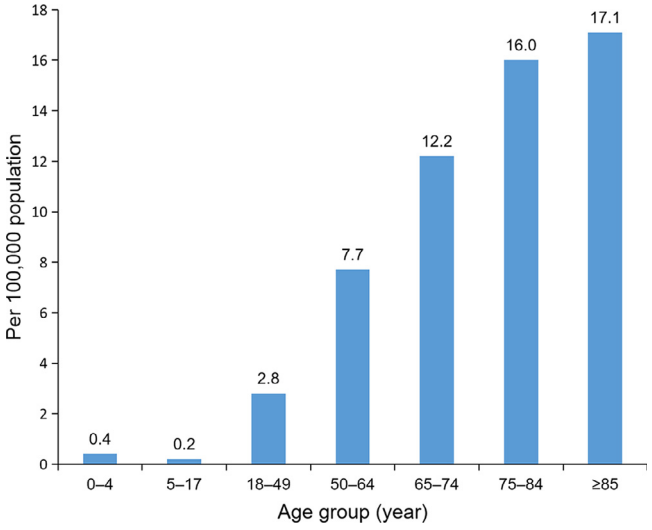

Fig. 2. Rates for age groups for coronavirus disease-2019–associated hospitalizations in the United States (14 states) during March 2020.[12]

If recent trends continue, nearly 50% of adults in the United States will be obese, and 60% of all adults worldwide will be overweight and obese, by 2030.[28,29] Obesity markedly increases the risk for hypertension, type 2 diabetes, and cardiovascular disease, three of the most important underlying conditions for COVID-19.[30,31] Obesity is a central component of the metabolic syndrome that undergirds many of the prevalent chronic diseases.[31]

Obesity also causes systemic inflammation and adversely impacts immune function and host defense in a way that patterns immunosenescence.[32,33] Obese patients have higher rates of nosocomial infections following surgery and experience altered pharmacokinetics of antimicrobial drugs.[32–36] Obesity emerged as an important risk factor for increased hospitalization and infection severity during both the 2009 influenza A virus H1N1 and COVID-19 pandemics.[14,37–42] The antibody response to the seasonal influenza vaccine is impaired in obese individuals, and virus shedding is prolonged during influenza illness.[43] Compared to vaccinated normal-weight adults, vaccinated obese adults have twice the risk of influenza or influenza-like illness.[33] Animal-based studies suggest that obesity increases the severity and duration of viral infections, increasing the potential for the evolution of pathogenic viral variants.[44]

The cytokine storm has been identified as the excessive immune response coupled with hyperinflammation in the lungs of the most severe COVID-19 cases.[45] Limited data suggest

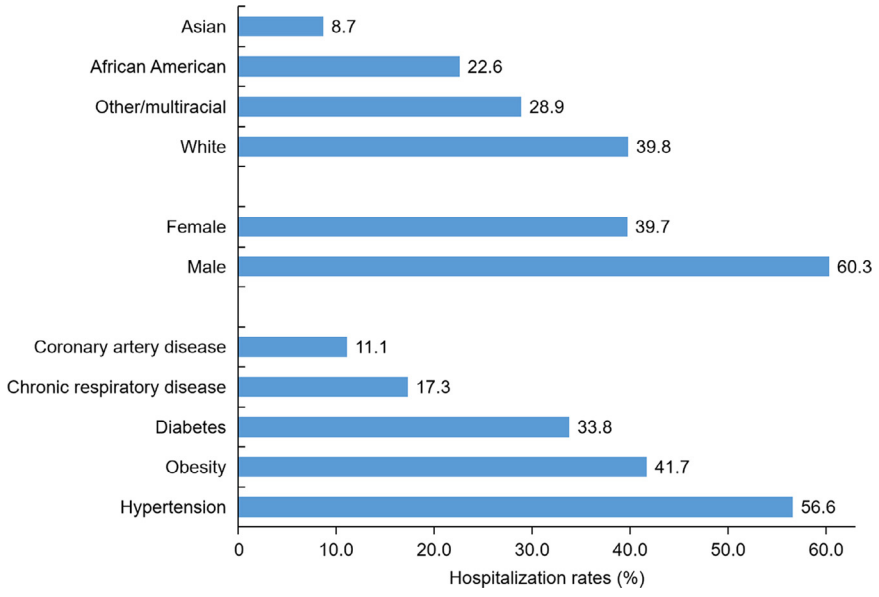

Fig. 3. Baseline comorbidities and demographics for 5700 coronavirus disease-2019 patients (median age, 63 years) admitted to 12 hospitals in the New York City area, USA, during March 1 to April 4, 2020.[13]

that obesity-induced systemic inflammation primes the immune system to generate an even more intense cytokine storm when elicited by infection.[46]

All projections indicate that the world's population will be older, more obese, and therefore increasingly more immunodeficient in the approaching decades. This shift is likely to increase the odds that infectious disease pandemics spawned by novel pathogens will continue to inflict widespread morbidity and mortality (Fig. 4).

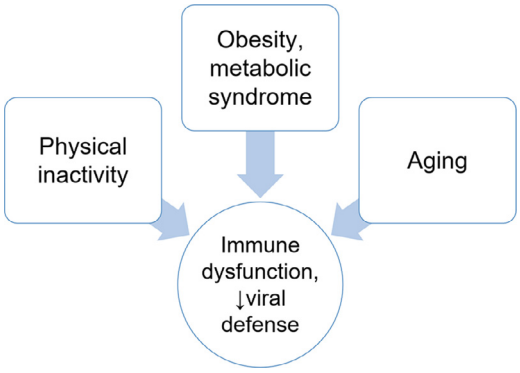

Fig. 4. Linkage between physical inactivity, aging, and obesity and the metabolic syndrome with immune dysfunction and diminished viral defense.

4. Viral illness and the exercise workload continuum

Patterns of physical activity vary widely in the general population, ranging from nearly complete inactivity to overtraining. Animal and human studies support a linkage between the range of physical activity behaviors and viral defense effectiveness (Fig. 5).[47]

4.1. Heavy exertion and decreased viral and immune defense

The earliest studies on heavy exertion and decreased viral and immune defense focused on muscular fatigue and pathogen resistance and were reviewed in 1932 by Baetjer,[48] who concluded that exhaustive exercise before or immediately following infection predisposed animals to a more rapid and fatal attack. This observation has been supported by numerous animal- and human-based studies conducted using a variety of pathogens.[49–75] The virulence of influenza, herpes simplex virus, and the Coxsackie virus, for example, is increased when mice are inoculated before or after being forced to swim or run to exhaustion.[52–65] Equine respiratory disease, especially from the influenza virus, is a common infection requiring veterinary medical attention, and intense exercise has been linked to increased susceptibility to influenza disease among horses.[71] Exhaustive exercise leading to increased morbidity and mortality from viral infection in animals has been linked to immune dysfunction, including a decrease in macrophage antiviral resistance and antigen presentation, natural killer cell cytotoxicity, and neutrophil oxidative burst activity.[54–65]

Clinicians since the 1940s have observed that certain patients with paralytic poliomyelitis gave a history of severe exertion immediately preceding or during the onset of paralysis.[49–51] The clinical data were strongest for polio patients who reported continuing physical activity after the onset of symptoms. This finding was confirmed in a study with infected rhesus monkeys that were subjected to exhausting exercise.[50]

These data imply that exercising heavily before or while infected with a systemic infection such as influenza or COVID-19 may lead to a more severe and prolonged illness and, in some instances, death. Numerous case reports have been published of protracted illness, fatigue, and death in young healthy people who engaged in vigorous-intensity exercise during an acute viral illness.[66–73] Acute respiratory infections are especially challenging in military settings because demanding physical training regimens are combined with crowded living conditions, physical and psychological stresses, and environmental challenges.[73] Military recruits often feel pressured to train even when they are sick. Clinical and autopsy records of 19 sudden cardiac deaths that occurred among Air Force recruits during basic training showed that the most frequent underlying etiology was myocarditis.[74] Viral illness is endemic in barrack-residing recruits, and exertion may have exacerbated viral-induced subclinical cases of myocarditis. A study of 20 male soldiers in the Israel Defense Forces who had died suddenly and unexpectedly within 24 h of strenuous exertion also reasoned that febrile disease might have been a cause of death in some of the subjects.[75]

Human epidemiologic studies indicate that the odds of acute respiratory illness following marathon or ultramarathon events climb sharply, especially when combined with mental stress, sleep disruption, and travel.[47] Intense acute and chronic exercise workloads cause varying levels of physiological, metabolic, and psychological stress leading to immune perturbations, inflammation, oxidative stress, muscle damage, and increased illness risk.[76–79] In particular, heavy exercise workloads result in an extensive downturn in the function of innate immune system cells including macrophages, neutrophils, and natural killer cells.[77–81] These data have been reviewed previously.[47]

Taken together, existing data support the viewpoints that (1) overtraining is not recommended in areas of the world where risk of COVID-19 transmission is high and (2) intense exercise should be avoided when the person is infected with COVID-19 or other systemic viruses.

4.2. Moderate-intensity physical activity and enhanced viral and immune defense

In contrast to high exercise workloads, animal and human data support the position that regular moderate-intensity

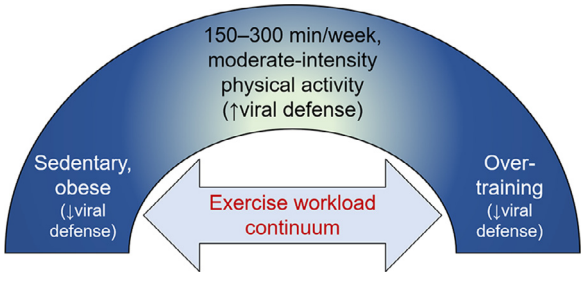

Fig. 5. The exercise workload benefit-risk continuum with viral defense.

physical activity improves immunosurveillance against pathogens and reduces morbidity and mortality from viral infection and acute respiratory illness.[47,78] As reviewed previously,[47] regular aerobic exercise similar to 30−60 min of near-daily brisk walking improves overall surveillance against pathogens by stimulating the ongoing exchange of important types of white blood cells between the circulation and tissues.[82−94] Stress hormones and inflammatory responses remain at low levels while neutrophils, natural killer cells, cytotoxic T cells, immature B cells, and monocytes circulate at a higher rate than normal during exercise and a few hours of recovery. When repeated in regular fashion, these transient, exercise-induced increases in antipathogenic leukocytes enhance immunosurveillance, reduce illness risk, and lower systemic inflammation. Thus, regular exercise training can be viewed as an immune system adjuvant and is of particular clinical value for obese individuals with comorbidities, as well as for older individuals.[95−103]

Cross-sectional studies comparing immune function in lean, fit individuals versus sedentary elderly individuals report that many aspects of immunosenescence are moderated.[24,87,88,101] Other data support the idea that habitual exercise improves regulation of the immune system in the elderly and delays the onset of immunosenescence because exercise provides a decrease in senescent T cells; an increase in neutrophils, natural killer cells, and T-cell function; and a reduction in systemic inflammation.[24,96−101] Exercise training has also been shown to improve vaccine efficacy for a variety of diseases, including influenza.[96,97]

Epidemiologic and randomized clinical trials support a 40%−45% reduction in illness days stemming from acute respiratory infections, such as the common cold, in younger and older adults who engage in near-daily aerobic activity compared to sedentary behavior.[47,104] A group of 1002 adults (aged 18−85 years) were monitored for acute respiratory illness symptoms and severity, using a validated survey, for 12 weeks during the winter and fall seasons.[104] The number of days with illness during the 12-week period was significantly reduced by 43% in those reporting 5 or more days per week of aerobic exercise compared to those who were largely sedentary. Illness severity and symptomatology were also reduced 32%−41% between high and low aerobic activity and physical fitness tertiles. These data indicate that physical fitness and frequency of aerobic exercise are important correlates of reduced days with acute respiratory illness and severity of symptoms during the winter and fall seasons, when common colds are more frequent. This study also showed that eating 3 or more servings of fruit per day was independently related to fewer days with respiratory illness.[104]

Physical fitness status and exercise training have also been linked to a reduced risk of stress-induced latent viral reactivation in astronauts.[85] Findings from other studies support a consistent and impressive reduction in pneumonia and influenza incidence and mortality with regular physical activity (Table 1).[105−115] The risk for severe influenza increased in communities reporting a high prevalence of physical inactivity and obesity, as well as for low intake of fruits and vegetables.[114] In contrast, regular exercise training was associated with reduced influenza mortality in elderly individuals.[110] Infectious disease mortality risk (primarily pneumonia and sepsis) was 40% lower in adults participating in physical activity more than 150 min per week compared to those who were inactive in a cohort of 97,844 men and women followed for more than 9 years.[113] Whether or not these data indicating reduced systemic infectious illnesses in physically active individuals are applicable to COVID-19 remains to be determined.

The robust reduction in mortality risk for community-acquired bloodstream infections has been reported by several other research groups.[116−118] A 15-year follow-up study of 64,027 individuals showed that bloodstream infections were nearly 5 times more likely in obese and physically inactive individuals who smoked tobacco compared to normal weight, physically active individuals who did not smoke.[116]

Animal studies support the linkage between physical exercise, augmented immunity, and reduced risk of influenza and pneumonia.[83,119−122] In one study using obese and lean mice, 8 weeks of exercise training followed by influenza viral infection decreased disease severity in both groups.[83] Chronic moderate exercise for 8−14 weeks followed by influenza infection in mice resulted in reduced symptoms coupled with lowered virus load and levels of inflammatory cytokines and chemokines.[83,95] Aerobic exercise training inhibited lipopolysaccharides-induced acute respiratory distress syndrome in mice by attenuating inflammatory cytokines and oxidative stress markers through inhibition of nuclear factor kappa B signaling, reduced neutrophil infiltration, and enhanced interleukin-10 production.[82,123] These data are of high interest for their potential relevance to COVID-19.

5. Physical activity, lifestyle habits, viral defense capacity, and COVID-19

Taken together, these studies support the viewpoint that regular physical activity and the avoidance of obesity maintain immune health while reducing the risk for several types of respiratory illnesses.[47] These primary prevention strategies against respiratory illnesses are particularly important in aging societies with a high prevalence of obesity and related comorbidities and are essential adjuvants to mitigation practices.

COVID-19 took just a few months to spread to nearly every nation on earth while causing widespread morbidity and mortality. The data support the belief that severe cases of COVID-19 are more likely in older and obese individuals. This is indeed a wake-up call, a tocsin, to the world that primary prevention countermeasures focused on health behaviors and hygiene demand our full attention and support. Secondary and tertiary prevention approaches centered on vaccine and therapeutics development will take time and may not be fully effective, giving even more urgency to staying fixated on primary prevention.

The relationship between varying exercise workloads and viral defense effectiveness can be placed on a continuum (Fig. 5).[47,78] Recommended amounts of moderate-intensity physical activity typically range between 150 and 300 min per week[124] and are consistent with enhanced immunosurveillance and lowered risk for respiratory illness. Physical inactivity, overtraining, and exercising while infected with a respiratory

Table 1
Epidemiologic research on the relationship between physical activity, influenza, and pneumonia.

Investigators, year published	Study population	Research design	Key findings
Baik et al., 2000[105]	26,429 men (40−79 years old), 78,062 women (27−44 years old)	290 new pneumonia cases in men (6-year follow-up), 305 in women (2-year follow-up), questionnaire responses entered into a Cox proportional hazards model	34% reduction in risk for developing pneumonia for women, but not men, in the highest *vs.* lowest quintile of physical activity
Inoue et al., 2007[106]	110,792 adults (40−79 years old)	1,112,747 person-years, 1246 pneumonia deaths, health screenings, questionnaire responses entered into a Cox proportional hazards model	Walking regularly for 0.5−1.0 h/day and more than 1.0 h/day decreased risk for pneumonia mortality by 20%−30% compared with 0.5 h/day
Wong et al., 2008[107]	24,656 adults (≥30 years old) who died in 1998 in Hong Kong, China	Families interviewed for lifestyle habits of deceased, sera influenza virus detection entered into multinomial logistic regression analysis	Excess risk of influenza-associated mortality reduced for low/moderate physical activity but not frequent physical activity
Neuman et al., 2010[108]	83,165 women (27−44 years old)	965,168 person-years, 1265 new cases of pneumonia, questionnaire responses entered into a Cox proportional hazards model	28% reduction in risk for developing pneumonia for women in the highest *vs.* lowest quintile of physical activity, but lowered to 16% reduction after adjustment for body mass index, smoking, and alcohol use
Williams, 2014[109]	109,352 runners, 40,798 walkers; age (mean ± SD), male runners (40.4 ± 10.9, walkers (61.2 ± 13.1); female runners (38.2 ± 10.1, walkers (50.4 ± 10.9)	11.4-year average follow-up for running and walking history, lifestyle habits entered into a Cox proportional hazards model	Risk for respiratory disease mortality decreased 7.9% and for pneumonia 13.1% per metabolic equivalent of task hours per day run or walked
Wong et al., 2014[110]	66,820 elderly adults (≥56 years old)	12-year follow-up, lifestyle habits entered into a time-dependent Cox proportional hazards model	Excess risk of influenza mortality was lower for frequent exercisers
Wu et al., 2016[111]	13,003 adults (≥18 years old)	Self-reported influenza-like illness and demographic data entered into a multivariate logistic regression model	Regular physical activity associated with a 20% reduction in likelihood of reporting influenza-like illness
Ukawa et al., 2019[112]	22,280 elderly adults (65−79 years old)	1203 pneumonia deaths, 11.9-year follow-up, health screenings, questionnaire responses entered into an inverse probability weighting Cox proportional hazards model	10%−35% reduction in risk for pneumonia mortality among elderly with or without underlying cardiovascular disease who walked regularly for ≥1.0 h/day compared with 0.5 h/day
Hamer et al., 2019[113]	97,844 adults (47.1 ± 17.7 years old)	9027 deaths from infectious disease, 9.4-year follow-up, questionnaire responses entered into a Cox proportional hazards regression model	40% reduced risk for infectious disease mortality with physical activity compared with physical inactivity
Charland et al., 2013[114]	Data records used from 274 counties with total population of 116,146,020. A total of 3,076,699 hospitalizations for influenza-like illness (all ages)	Data used to regress log-transformed age-sex influenza-related hospitalization rates with lifestyle factors after adjustment for covariates	A 5% increase in the prevalence of physical inactivity was associated with an 11% and 19% increase in influenza-related hospitalization rates for adults and children, respectively, after adjustment for potential confounders

pathogen, on the other hand, have been linked to immune dysfunction and elevated risk for respiratory illness. Until more is known, this model can be applied to COVID-19, with the high likelihood that risk of morbidity and mortality is moderated in lean, physically active individuals of all ages.

Competing interests

The author declares that he has no competing interests.

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