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Meditation and Yoga Practices as Potential Adjunctive Treatment of SARS-CoV-2 Infection and COVID-19: A Brief Overview of Key Subjects

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Editor's Note: As an acute condition quickly associated with multiple chronic susceptibilities, COVID-19 has rekindled interest in, and controversy about, the potential role of the host in disease processes. While hundreds of millions of research dollars have been funneled into drug and vaccine solutions that target the external agent, integrative practitioners tuned to enhancing immunity faced a familiar mostly unfunded task. First, go to school on the virus. Then draw from the global array of natural therapies and practices with host-enhancing or anti-viral capabilities to suggest integrative treatment strategies. The near null-set of conventional treatment options propels this investigation. In this paper, researchers from the Massachusetts Institute of Technology, University of California-San Diego, Chopra Library for Integrative Studies, and Harvard University share one such exploration. Their conclusion, that ''certain meditation, yoga asana (postures), and pranayama (breathing) practices may possibly be effective adjunctive means of treating and/or preventing SARS-CoV-2 infection'' underscores the importance of this rekindling. At JACM, we are pleased to have the opportunity to publish this work. We hope that it might help diminish in medicine and health the polarization that, like so much in the broader culture, seems to be an obstacle to healing. —*John Weeks, Editor-in-Chief*, JACM

Potential Adjunctive Therapies for SARS-CoV-2 Infection and COVID-19 Disease

There is an urgent need to identify strategies to help prevent and treat SARS-CoV-2 infection and COVID-19 disease.[1–4] Included among the intensive search for novel and effective therapeutic approaches are considerations of those therapies derived from integrative and complementary medicine,[5–8] including from traditional whole medicine systems such as Chinese Medicine and Ayurvedic medicine.[6–8] In this article, the authors present a selective narrative review of the literature with a primary focus on certain complementary practices of seated meditation, yoga asanas (postures), and pranayama (breathing) with relevance to immune function for consideration for SARS-CoV-2 infection and COVID19 treatment and/or prevention.

The authors propose that certain complementary practices may be helpful *adjunctive* means of treating and/or preventing SARS-CoV-2 infection[1,9] and helping to reduce severity of COVID-19 disease, including its collateral effects and sequelae. Despite being speculative for the present situation, there is a body of literature relevant to the anti-stress and anti-inflammatory effects of certain seated meditation, yoga asanas, and pranayama practices. Such studies include demonstrating promising immune effects relevant to improving lung health[10,11] and reducing viral susceptibility and improving acute respiratory infections.[12–14] The potential benefits of these practices extend to broader neuroimmune systems, an advantage when dealing with a systemically dysregulating disease such as SARS-CoV-2.[15] Such complementary practices have been found to act as a regulating influence on a number of key inflammatory functions that SARS-CoV-2 disrupts.[16]

The use of certain complementary practices as potentially effective adjunctive means of treating and/or preventing SARS-CoV-2 infection must be put to rigorous scientific

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investigation. During this time, however, when there are numerous exploratory pathways being urgently probed,[1,2,6,8] it is important to look to ''evidence-based principles that emphasize the practical application of the findings of the best available current research'' (see ''implementation of evidence-based interventions'' defined and advocated by NIH/CDC).[17] With this consideration in mind, best available research reasonably advocates that the utilization of certain forms of some complementary practices be examined as potential adjunctive interventions to help prevent and treat SARS-CoV-2 infection and potential future pandemics.

Theoretical frameworks as models have been put forth seeking to explain how complementary practices such as seated meditation, yoga asanas, and pranayama work, which have examined multiple psychologic, emotional, epigenetic, neural, and behavioral processes, as well as shifts in self-awareness.[18–24] An in-depth model proposed by Holzel et al., for example, focuses on mindfulness meditation practice-induced changes in attention regulation, body awareness, emotion regulation, and perspective of self, citing supportive underlying neuroplastic changes.[18] Gard et al. examine the effects of yoga practices on cognition, emotional, and behavioral regulation, and autonomic output under stress with an emphasis on interoceptive processes and self-regulation.[19]

The current state of the rapidly evolving field of Integrative Medicine research intersects with the intensive search for successful treatments for this pandemic viral infection. When considering complementary practices, the National Academy of Science's Institute of Medicine stated that the field of ''behavioral medicine'' should be considered in the evolving standard model of fundamental life science research and should be advocated on the front line of serious medical and health-optimizing treatment and intervention.[25] With this in mind, in 2009, one of the authors (W.B.), with the collaboration of Neil Theise MD (then of the Albert Einstein College of Medicine), began to review the scattered and disparately emerging body of research on the inflammatory cytokine-based pathogenesis of many virulent infectious diseases (bacterial, viral, other) and ''cytokine storms,''[26] following the pioneering work of Clark et al.[27] and others. This was connected with research into the potential anti-inflammatory, antistress, and anti-infectious properties of meditation and yoga practices, thereby beginning the development of a scientific model in behavioral health.[26,28] This developing scholarly territory needs to be fully explored with scientific rigor and open minds due to both its inherent value and the urgency of the present situation.[29,30]

Anti-Inflammatory Effects Associated with Meditation and Yoga Practices

An extended runaway hyperinflammatory host response to SARS-CoV-2 infection is the primary pathway to COVID-19 disease morbidity and mortality.[31] Spread of the virus through the body leads to widespread and intensive activation of the inflammatory defenses, although originally intended to combat the pathogen, but instead resulting in widespread tissue damage to the host, to acute respiratory distress syndrome (ARDS); the virus itself plays a much lesser role in the tissue damage that can ultimately produce extreme critical disease states (pulmonary aspiration, septic shock), and potentially death.[15,32]

Beginning in the mid-1990s and developing up to the present, increases in scientific knowledge about the immune system and the inflammatory dimension of it led to the recognition that many infectious diseases caused their damage to a large extent through the host's own inflammatory responses.[27] Around the same time, research by Kevin Tracey and colleagues[33] (and see Bushell, Olivo, Theise, 2009)[34] led to the discovery that inflammation could be brought under control through stimulation of the vagal nerve complex, a major component of the central and peripheral nervous system, which also controls responses to psychosocial stress, and stimulation of which can reverse the ''fight or flight'' response through replacing it with the ''relaxation response,''[35] in simplified schematic terms.

Starting in the early 2000s, Bushell and colleagues proposed that intensive forms of meditation and yoga could potentially be effective as adjunctive interventions against serious forms of infectious diseases, including malaria, HIV/AIDS, and SARS, among others. These authors were at the time demonstrating an appreciation of the key significance of the common denominator of the inflammatory-driven pathogenesis of the spectrum of such virulent infectious diseases and the potentially important relevance of the antistress and anti-inflammatory properties of these behavioral health practices for possible forms of adjunctive preventative or treatment therapies.[27,36–38]

It had also been found that meditation, as well as yoga practices, is capable of significantly increasing vagal tone and therefore could not only be effective against psychologic stress-based issues, including trauma,[35,36] but inflammatory-based diseases as well.[16,41–46] Included in this consideration are studies documenting effects of a diverse range of meditative and yoga practices to promote anti-inflammatory and typically reduce proinflammatory cytokine activity, incuding natural killer (NK) cell activity and NK and T cell cytokine production,[45–50] which has been a topic of two systematic reviews.[51,52] For example, Bower et al.[49] showed that 6 weeks of 20-min daily mindfulness meditation resulted in a significant downregulation of a 19-transcript composite of proinflammatory genes and a significant reduction of activity of the proinflammatory transcription factor nuclear factor kappa B (NF-κB). In parallel, they observed an increase of anti-inflammatory glucocorticoid receptor activity and increased type I interferon signaling, a transcription factor linked to SARS-CoV-2 treatment.

Other studies show decreases in the circulating levels of the proinflammatory cytokine interleukin (IL)-12 and increases of the anti-inflammatory cytokine IL-10.[47,48,50] In specific patient groups or obese individuals, other studies document reductions in circulating levels of C-reactive protein (CRP) and IL-6,[49,50,53] although these findings were not replicated by some investigators.[48] Some of the cytokine-related effects of seated meditation, breathing practices, and yoga asana practices are related to a reduction in sympathetic nervous system activation, as evidenced by parallel reductions in levels of the catecholamines epinephrine and norepinephrine.[47,52,54] Studies also suggest differential effects of meditation practices on immune cell subsets, including NK and T cells, of relevance to the innate and adaptive immune systems.[55,56]

The benefits of yoga therapies on the health of the innate immune system have also been demonstrated in a study showing that 90 min of yogic asana stretching is able to increase expression of the two important antimicrobial peptides, β-defensin and HBD-2 expression.[57] Importantly, with regard to COVID-19, both of these antimicrobial peptides are expressed in respiratory epithelial cells.[58] Yoga therapy has also been shown to downregulate the cytokine receptors tumor necrosis factor (TNF)-RII and IL-1RA, and stress-related CRP.[59] Epel et al. showed that combined mantra-based meditation and yoga asana practices regulated levels of the proinflammatory cytokine TNF-α and metabolism of the Alzheimer's disease-associated amyloid-β protein,[60] and also reported reduced expression of proinflammatory genes in association with a meditation practice.

Table 1 presents cytokine effect sizes from practices of meditation, yoga asana, and pranayama, reviewed in this article, paired with findings to date from COVID-19 studies reporting cytokine values. Figure 1 presents effect sizes from Table 1. It is evident that effect sizes are larger with COVID-19. The significance of the presentation, however, is to show the relevant overlap and general directions of effects on cytokines and that these practices can provide systemic regulatory effects on a range of cytokines. It is important to note that the reviewed studies were on more short-term practitioners of the modalities where such cytokine data are available. There is a fairly large literature, although comparing the effects of longer term compared with more novice practitioners, that shows significantly larger effects with longer practice in domains, for example, of autonomic, neurohormonal, and brain functioning.[61–63] Needed are studies of immune function in longer term practitioners directly compared with novice practitioners, although some studies have examined immune-related profiles in longer term meditators compared with nonpractitioner controls.[64–66]

Furthermore, according to a small but relevant body of research, certain meditation and yoga practices bring another set of key neuroendocrine factors into the picture, in particular melatonin, which in addition to its systemic health-promoting properties has beneficial effects on mood, affect, emotion, and mental state and functioning.[26,27,67,68] Studies provide insight into the epigenetic and microbiome pathways of complementary practices relevant to inflammatory processes.[24,64–66,69]

Meditation and Yoga May Potentially Enhance the Activity of Melatonin, One of the Most Beneficial Pleiotropic Natural Substances Known

The functions of melatonin are extensive. In the words of leading melatonin researcher Russell Reiter of the University of Texas, writing in the life sciences journal, *Physiology*, and referring to thousands of published scientific studies[70]: ''Melatonin has a bewildering array of functions and employs a variety of means to carry them out…These actions likely impact every cell in every organism throughout the plant and animal kingdoms. Its discovered actions are uniformly beneficial, although not all the specific mechanisms have been described. In addition to its multiple positive physiologic actions, melatonin has an uncommonly high safety profile.'' As cited in Bushell,[68] these include a wide array of anti-inflammatory, antioxidant, anti-infectious immune-enhancing actions on most of the cells and organs of the body that have been investigated, including the brain, heart, visceral organs, bone, muscle, and skin. In addition, there are beneficial effects on the mitochondria and nucleus of cells, including DNA repair. Melatonin has also been demonstrated to possess significant antiviral properties, including relevance to respiratory diseases.[71,72]

Of particular relevance, researchers have specifically identified melatonin as a substance that should be investigated for possible treatment against COVID-19.[73,74] Furthermore, melatonin is protective against ventilator-induced lung injury in animal models.[75,76] Studies in animals and humans have found beneficial effects of melatonin against serious viral infections, including herpes, HIV/AIDS, influenza A-H1N1, West Nile virus, coxsackievirus (the virus that

Table 1. Cytokine Effect Sizes (Cohen *d*) from Complementary Studies Paired with Findings from COVID-19 Studies Reporting Cytokine Values

Study	*COVID-19* d	*Median* d	*Marker*	*Median* d	*Meditation* d	*Study*
Chen et al.[3]	−1.651	−1.651	IFN-λ	−0.783	−1.235	Carlson et al.[40]
					−0.330	Carlson et al.[42]
Qin et al.[29]	0.493	0.493	IL-10	0.118	−0.073	Carlson et al.[40]
					0.309	Witek-Janusek et al.[41]
Chen et al.[3]	−1.578	−1.578	IL-10	−0.375	−0.375	Carlson et al.[42]
			IL-4	−0.889	−1.014	Carlson et al.[40]2007
					−1.007	Carlson et al.[42]
					−0.459	Witek-Janusek et al.[41]
Qin et al.[29]	2.911	2.722	IL-6	−0.386	−0.571	Witek-Janusek et al.[41]
Wang et al.[4]	2.533				0.582	Cahn et al.[44]
					−0.941176471	Shete et al.[55]
					−0.2	Bower et al.[45]
Qin et al.[29]	−1.452	−1.452	IL-8			
Qin et al.[29]	−3.077	−3.077	NK activity	0.472	0.472	Witek-Janusek et al.[41]
Qin et al.[29]	3.008	3.008	TNF-α	−1.064	−1.064	Carlson et al.[40]
					−1.407	Epel et al.[56]
					−1.043	Shete et al.[55]

IFN-λ, interferon-λ; IL, interleukin; NK, natural killer; TNF-α, tumor necrosis factor alpha.

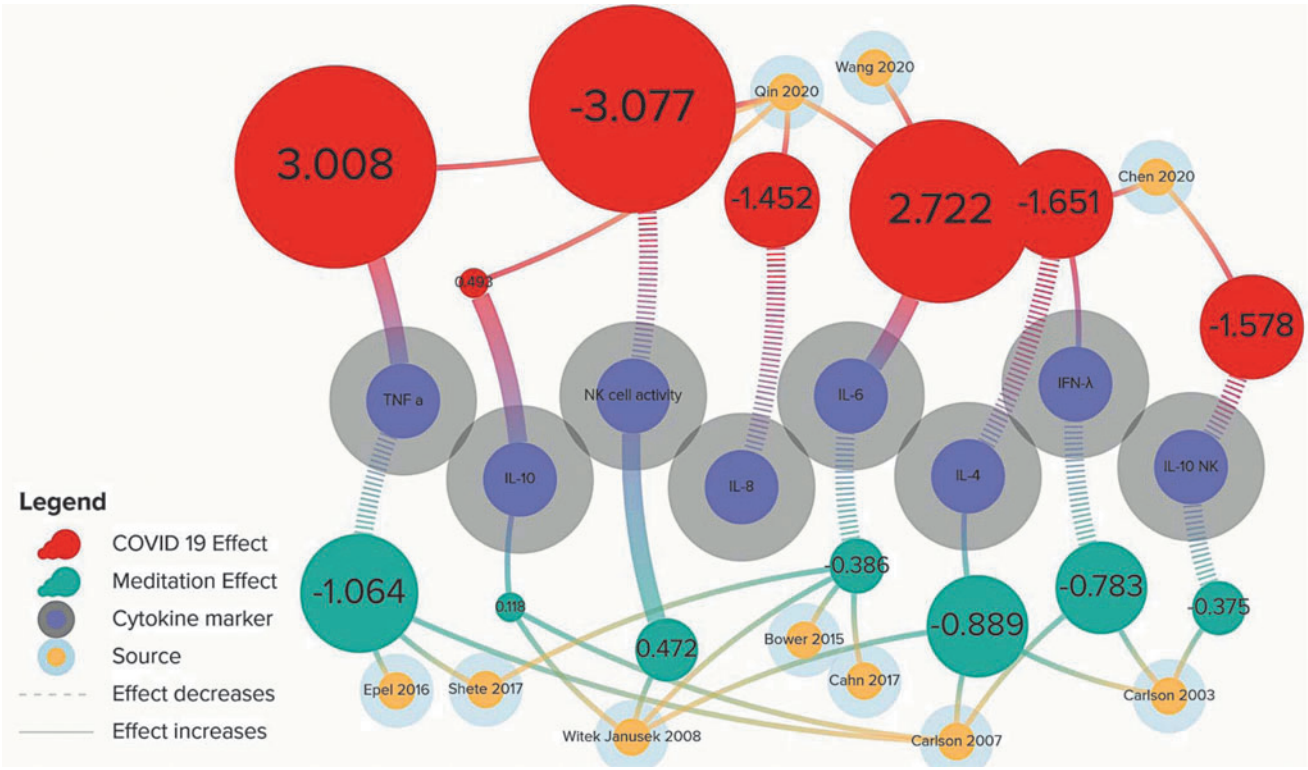

FIG. 1. Graphics of effect sizes (Cohen *d*) presented in Table 1. It is evident that effect sizes are larger with COVID-19. The significance of the graphics is the relevant overlap and general direction of effects on cytokines and that these practices can provide broad systemic regulatory effects on a range of cytokines. Note too that the reviewed studies were from more short-term practitioners of the modalities, where such cytokine data are available. There is a fairly large literature comparing the effects of longer term with more novice practitioners, which shows significantly larger effects with longer practice in domains of autonomic, neurohormonal, and brain functioning. Needed are studies of immune function in longer term practitioners compared wiht novices. The median effect sizes of complementary practices tracked here include small ($d \sim 0.2$), moderate ($d \sim 0.4$), and large ($d \sim 0.80$).

causes Venezuelan equine encephalomyelitis [VEE]), Semliki Forest virus, and encephalomyocarditis virus.[73,77–86] Melatonin has also been hypothesized to contribute to heretofore unexplained seasonality of certain infectious diseases.[8] Mechanisms through which melatonin exerts its protective and antiviral effects include protective antioxidant and free radical-scavenging properties (e.g., HIV/AIDS, other retroviruses),[17,88] including with respect to the potential development of septic shock (e.g., VEE; some forms of ARDS of viral origin)[71,89]; immunomodulatory effects, which can include initial acute upregulation of inflammatory responses followed by well-timed downregulation, including through key influences on gene expression of NF-kB and specific inflammatory cytokine-regulating genes (e.g., respiratory syncytial virus; viral encephalitis)[77,80]; and through melatonin's recently discovered modulation of autophagic and apoptotic processes (e.g., coxsackievirus-B3, some forms of herpes virus disease).[78,81]

While not an area of intensive research, a small yet compelling body of studies show that regular practice of meditation and/or yoga is associated with elevations in melatonin.[87,90–95] Studies report that while during the practices of seated meditation and pranayama, levels of melatonin can decrease,[91,96] longer term practice leads to elevations in levels.[90,92,96] Solberg et al., for example, reported that more experienced meditators had 150% higher resting levels of melatonin (4.9 pg/mL) compared with an age-, gender-, and physical fitness level-matched reference group (3.1 pg/mL).[87]

Melatonin appears to possess the capacity to selectively up- and downregulate its antiviral/immune-enhancing and its anti-inflammatory effects according to the state of the milieu or environment in which it is present.[78,97–100] In other words, melatonin biochemically ''senses'' the inflammatory and/or viral (or more generally infectious) nature of its *milieu interieur*, and then appears to generate the necessary effects to fit the situation, from its wide-ranging pleiotropic repertoire of potential effects. This is a growing field that needs further development. Whether or not it can do so successfully in the case of COVID-19 is a matter for further research,[73,74] but presently there is research being conducted by institutions worldwide, which seek to find medicines and/or medicine regimens that possess simultaneous capacities for antiviral and anti-inflammatory actions, in line with such principles.[73,101,102]

Meditation and Yoga for Well-Being During the Social Distancing Intervention for Ending the COVID-19 Global Pandemic: A Program That Goes Beyond Homeostasis

Relevant to the COVID-19 pandemic are the documented effects of some complementary practices, even potentially for novice practitioners, on reducing the severity of

psychosocial stressors, including social isolation. While it is recognized that certain levels of stress can be beneficial for the development of resilience,[103] the emerging stress landscape of the COVID-19 pandemic is extreme, involving not only threats to health and physical survival, but also to economic survival, housing, adequate nutrition, personal relationships, the very fabric of society and ''normal life'' itself, ranging from the local to global scale. The prospect of being a patient in an overwhelmed health system is among the most extreme stressors possible to experience, owing to the heightened sense of vulnerability.

These kinds of extreme chronic stressors are known to be capable of leading to an overwhelmed immune system, compromising the ability to mount an effective immune response to infectious challenge and leaving the individual susceptible to severe medical consequences.[104,105] Scientific research shows that psychosocial stress can not only substantially reduce immune defenses against infectious challenges but also overstimulate host inflammatory responses to such a level that it can lead to tissue damage and even death.[24,26,106,107] In addition, studies show in the elderly, a population of particular susceptibility to SARS-CoV-2, that stressors such as caregiving, chronic stress, bereavement stress, and social isolation are associated with increased inflammation, including elevated circulating cytokine levels.[108–113]

Epidemiologic and historical epidemiologic evidence, from the 1918–19 influenza pandemic to more recent epidemics and pandemics involving SARS and H1N1, demonstrates that social distancing can serve a vital function[114,115] in restricting further transmission of viral and other pathogens. Nevertheless, it is clear that such social distancing can also lead to intensified social isolation stress,[116,117] which is in fact utilized as a standard immunity-compromising challenge in animal studies of viral infection and immune response. In addition to the social isolation stress, other pandemic-associated stressors, as listed above, can amount in many cases to pandemic-based PTSD.[118,119] Because of the likely ongoing nature of the pandemic, it would perhaps make sense in this context to speak of *Ongoing* Traumatic Stress Disorder (OTSD), rather than *Post* Traumatic Stress Disorder. Bruce McEwen and colleagues developed the concepts of allostatic load and overload as quantifiable constructs for ongoing states of chronic stress—as is implied in the label OTSD—and underscored the complex pathophysiologic synergisms between psychosocial stressors and inflammation, including through epigenetic pathways, and have advocated the use of meditation techniques as treatments.[120,121]

Germane to these current pandemic-associated psychosocial stressors, there is evidence that diverse meditation and yoga practices provide beneficial effects on mental health. For example, systematic reviews of the effects of a variety of meditation techniques on depressed mood, anxiety, and quality of life show promising findings in diverse populations, including clinical populations.[122–124] Systematic and more qualitative reviews examining the effects of yoga practices on these same endpoints also report evidence of beneficial effects, although this literature is somewhat less consistent.[125–127]

Regarding different forms of meditation practice, given the current social stressors, the authors posit that loving kindness and compassion meditation practices could possibly be utilized to not only counteract the inherent negatives of the developing situation—from the perspectives of individual physical and emotional health—but socially as well.[128–130] Certain forms of stress can synergize to produce greater negative consequences, but the converse may also be true that such forms of loving kindness/compassion meditation lead to a ''broadening and building'' of social connectedness through the generation of positive psychologic states,[130,131] which are further associated with enhanced vagal tone[132] and even reduced viral replication and function (e.g., in HIV-infected women),[133] thereby leading to a range of associated positive outcomes.

Recent articles in the scientific[134] and popular press[135] show that the COVID-19 pandemic is beginning to reveal social isolation-based negative effects on mental health, including depression and anxiety, which typically exert subsequent negative health outcomes. These considerations may be particularly relevant to the elderly who are more prone to both social isolation and its adverse psychologic effects, as well as to higher levels of chronic inflammation (recently dubbed ''inflammaging'').[136]

Mediation/Yoga-Based Behavioral Health Interventions for Disease Survivors and Their Progeny: The Important Role of the Lingering Effects of Infection and the "Inflammatory Load"

It is crucial to include in this brief overview a larger perspective on the potentially devastating effects of the pandemic relating to the risk of overwhelming the health care system. Modeling and projections of international health care systems show that while highly developed nations are able to absorb the extreme patient load from SARS-CoV-2 without disrupting their core functions, they will not be able to do so in the face of a sustained pandemic.[137] The strain on the system is exacerbated by the lengthy and intensive care required to combat the cytokine storms.[32] Here the authors consider the potential and likely *aftereffects* of infection, from both individual and societal perspectives. A particular key term is that of inflammatory load which the life science biologist and historical epidemiologist, Caleb E Finch, developed as a major operational construct in all fields of human biologic science.[138] Inflammatory load in individuals and populations represents chronic elevated levels of inflammatory substances in the blood and tissues due to lingering subclinical levels of infectious pathogens, bacterial, viral, and otherwise. According to this body of research, the persistence of pathogens in environments contributes to increased risk and occurrence of most chronic diseases through transmission of subclinical infection, including cardiovascular, neurodegenerative, and other major forms of chronic inflammation-based diseases.

While in contemporary times a higher burden of chronic systemic inflammation has resulted from noninfectious environmental factors, including pollution,[139,140] infectious pandemics and large-scale epidemics increase infectious cohort-wide inflammatory damage in populations, as Finch and colleagues demonstrated for the 1918 influenza pandemic and other widespread infectious disease situations.[138] As they conclude in a key article, ''a 'cohort morbidity phenotype' represents inflammatory processes that persist from early age into adult life''.[138] These contribute to

increased risk and incidence of cardiovascular diseases, neurodegenerative diseases such as Alzheimer's, and a range of other diseases that are, in large part, pathogenically based on extended durations of chronically elevated levels of inflammatory substances in the body.[141,142]

According to the above-cited work on the 1918 influenza pandemic, such conditions resulting from heightened inflammation also significantly affect future generations, as Finch and colleagues[138] reported, that those born to mothers infected during the pandemic had heightened vulnerability to cardiovascular disease (males particularly) and growth retardation, and that ''prenatal exposure to even uncomplicated maternal influenza may have lasting consequences later in life''.[143] This research is to be further considered in the context of psychosocial stress-associated influences that may extend over generations, via epigenetic and possibly other mechanisms—and especially with respect to the pathophysiologic connections between psychosocial stress and inflammation.[144,145]

Conclusion and Further Recommendations

The authors find themselves in the midst of a pandemic, the extent of which is not yet clear, and it is a time to enlist all manner of assistance in resisting and combating the multiple threats associated with it. As they have reviewed, there is evidence of stress and inflammation modulation, and also preliminary evidence for possible forms of immune system enhancement, accompanying the practice of certain forms of meditation, yoga, and pranayama, along with potential implications for counteracting some forms of infectious challenges. Their apparent association with enhanced melatonin activity also implies another pathway by which the beneficial properties of these modalities may be effective, especially with respect to aspects of viral challenges of various forms.

The points discussed in this article suggest potential initial short-term acute interventional and long-term benefits focusing on these practices as well as in the reduction of future sequelae to pandemic-associated negative inflammatory and psychosocial stress factors.

The authors readily acknowledge that in the context of the SARS-CoV-2 pandemic, the ideas put forth in this article must be put to further rigorous scientific investigation. During this time of urgency, however, when numerous novel approaches are being explored for their potential therapeutic efficacy, based on the existing evidence base for certain complementary practices as here briefly reviewed, the authors advocate for such consideration and further research.

Authors' Contributions

All authors contributed to this work.

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