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REVIEW

Mindfulness Meditation Interventions for Long COVID: Biobehavioral Gene Expression and Neuroimmune Functioning

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Abstract: Some individuals infected with SARS CoV-2 have developed Post-Acute Sequelae of SARS CoV-2 infection (PASC) or what has been referred to as Long COVID. Efforts are underway to find effective treatment strategies for those with Long COVID. One possible approach involves alternative medical interventions, which have been widely used to treat and manage symptoms of a variety of medical problems including post-viral infections. Meditation has been found to reduce fatigue and unrefreshing sleep, and for those with post-viral infections, it has enhanced immunity, and reduced inflammatory-driven pathogenesis. Our article summarizes the literature on what is known about mindfulness meditation interventions, and reviews evidence on how it may apply to those with Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Evidence is reviewed suggesting effective and sustainable outcomes may be achieved for symptomatology and underlying pathology of post-viral fatigue (PASC and ME/CFS).

Keywords: long COVID, meditation, Myalgic Encephalomyelitis

Mindfulness Meditation Interventions for Long COVID

Biobehavioral Gene Expression and Neuroimmune Functioning

Although studies have shown that meditation can improve self-reported measures of disease symptomatology, the effect that meditation has on biological mechanisms underlying disease is less clear. The focus of this paper is to summarize the literature on mindfulness meditation interventions, and review evidence on its applicability to those with Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Evidence is reviewed suggesting effective and sustainable outcomes may be achieved for symptomatology and underlying pathology of post-viral fatigue (PASC and ME/CFS).[1–9] In a literature review, Islam, Cotler, and Jason[10] found some of patients affected by bacterial and viral epidemics developed persisting health complications. These types of post viral symptoms have also occurred with patients with Post-Acute Sequelae of SARS CoV-2 (PASC), which is also known as "Long-COVID".[11] Davis et al[12] found that six months following infection with SARS CoV-2, patients continued to have fatigue, post-exertional malaise, and cognitive dysfunction. Patients following infection with SARS CoV-2 have also developed Guillain-Barré syndrome,[13] lung scarring,[14] and heart damage,[15] including a higher risk of cardiac inflammation, especially in young males.[16]

Early on in the pandemic, the Body Politic COVID-19 support group[17] found 40 days after SARS CoV-2 infection, 91% of respondents had not recovered. In another study,[18] a longitudinal prospective cohort study involving individuals with confirmed SARS-Cov-2 infection, after 9 months, 30% of patients had recurring symptoms. Some have suggested that up 50–80% of PASC patients will continue to have symptoms 3 months post infection with SARS CoV-2,[19] and up to 10% might have more serious symptoms.[20]

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Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) shares some features of Long COVID including fatigue, cognitive difficulty, unrefreshing sleep, and post-exertional malaise.[21] These most commonly reported protracted symptoms overlap with PASC[17,22–24] with neurocognitive symptoms being among the most disabling for both illnesses.

The National Health Service Long COVID Clinics[25] are attempting to help patients with Long COVID.[26] The World Health Organization has recommended more treatment to help patients with post-viral illness manage this illness.[27] In addition, the National Institutes of Health created the RECOVER initiative to better understand the pathophysiology of this illness and ultimately find treatment options for individuals with PASC.[28]

To deal with PASC, we can learn from research conducted in other areas, such as the effects of psychosocial factors on various components of the immune system.[29–31] Reviews of this research have shown that positive well-being boosts the human body's immune response, improving its resistance to infection.[32] One promising form of treatment for those with PASC involves meditation.

Mindfulness meditation involves sitting still and focusing exclusively on one's breath, to hone one's attention and maximize unmediated direct experience. According to Kabat-Zinn, "Mindfulness is awareness that arises through paying attention, on purpose, in the present moment, non-judgementally".[33] Mindfulness meditation is the basis of stress reduction programs operationalized by Kabat-Zinn et al[33] and Richard Davidson.[34] The effects of meditation may rely on the brain shifting to an alpha state during meditation, helping slow brain rhythms. As meditation practice is stabilized, these parasympathetic responses may be habituated and translated to daily life.[35] Meditation might be an effective treatment for those with PASC. Below we first review what is known about how PASC and other post-viral illnesses such as ME/CFS affect the immune system.

Immune Functioning

There is some evidence that ME/CFS causes the immune system to overreact following infection[36] causing oxidative stress.[37] Immune dysregulation is thought to be related to COVID-19 pathophysiology after infection by SARS-CoV-2.[38] In PASC, immunological symptoms may develop after the acute infection when the viral load is decreasing.[39] A key driver of PASC might be continuing inflammation.[40,41]

Examination of the aberrant activation of innate immune signaling pathways has led to an examination of interleukin-6 (IL-6) as a prime candidate for mediating inflammation in Long COVID-19. IL-6 might be a potential biomarker,[42] and a meta-analysis has found IL-6 is related to the development of hypoxemia.[43] Those who at initial assessment evidence high IL-6 might be at increased risk of respiratory failure. IL-6 might be related to inflammation in patients with COVID-19 as it induces a pro-inflammatory response.[44]

Increases in other pro-inflammatory lymphocyte markers have also been proposed as a biomarker for post-viral fatigue, specifically related to ME/CFS in the case of interleukin-8 (IL-8).[45,46] This might be similar to what occurs in a number of inflammatory conditions (eg, lupus).[47] Recent research suggests that patients with PASC have elevated inflammatory proteins[48,49] perhaps indicating an unbalanced inflammatory/anti-inflammatory cytokine response in PASC.

One cause of systemic inflammation is infectious agents.[50] While there are multiple causes of systemic inflammation, many of which have been defined in establishing the Systemic Inflammatory Response Syndrome criteria, they are considered a subset of all "cytokine storm" syndromes. According to Fajgenbaum and June,[51] they have inflammatory etiologies and can result in systemic inflammation and multiple organ dysfunction. More recently, cytokine storm syndrome is now thought to include all inflammatory conditions with elevated cytokines,[35,52] including PASC.[53,54]

Helper thymus cells include T-helper (Th) 1 or Th2 effector cells.[55] When polarized toward Th2 dominance, there is a Th2/Th1 imbalance. This imbalance is related to inflammation and diseases,[56] including pyelonephritis, and systemic lupus erythematosus.[57,58]

A systemic Th2/Th1 imbalance might occur in patients with PASC, with variable duration and severity of disease related to systemic inflammation as indicated by differential cytokine expression. For example, Pavel et al[59] suggest a Th2/Th1 imbalance may be related to higher mortality in COVID-19 patients. A similar pattern of these cytokine profiles with very high levels of mixed Th1/Th2 affinity occur in some patients with COVID-19 infection.[60] These findings suggest a Th1 to a Th2 shift in cytokine response with superantigen-associated progression for the duration, perhaps as an adaptive process by the immune system in an attempt to down-regulate abnormal inflammatory Th1 immune responses.[38]

Individuals with COVID-19 display a pattern of immunologic association reflective of a more global pattern of activation, characterized by increased interrelationship among proteins with a differential grouping of proteins.[61,62] Taken together, this research suggests that a pro-inflammatory cytokine profile occurs with PASC,[63] as is the case in patients with other types of post-viral infections (eg, ME/CFS).[64] These mechanisms have been hypothesized as causing oxidative stress,[36] and the patient's immune system overreacts following infection,[45] which may be due to an underlying post-viral infection in general.[36,65]

Anti-Inflammatory Effects Associated with Meditation

Meditative practices have been related to anti-inflammatory cytokine activity in a variety of studies,[66–71] and has been reported in systematic reviews.[72,73] For example, after 6 weeks of daily meditation, each lasting only 20 minutes, Bower et al[66] found a downregulation of pro-inflammatory genes in cancer survivors.[65]

Meta-analyses of immunological and psychological efficacy of mindfulness meditation interventions indicate effectiveness with an 8-week intervention as measured by improvement in immune markers for people with AIDS.[74] Creswell et al[5] and Naoroibam[75] found that after an 8-week intervention, CD4+ T lymphocytes changes in AIDS evidenced significant improvements. In Creswell et al[5] study, the decline in CD4 levels was halted after a meditation course lasting 8 weeks.[5] These immunological findings were also validated and generalized in other short-term random control trials (6–12 weeks) for relatively inactive college students,[76] for breast cancer patients awaiting surgery or after treatment.[77] Other meditation studies have shown reductions in pro-inflammatory cytokine interleukin-12 (IL12) and anti-inflammatory cytokine IL-10 increases.[66–70] Among those who are obese, meditation studies found reductions in C-reactive protein and IL-6,[66–69] but other investigators were not able to replicate such findings.[67]

Concerning inflammatory cytokines, Sanada et al[78] in a meta-analysis found mindfulness-based interventions yielded significant positive effects on cytokine blood levels related to low-grade inflammation. Another meta-analysis found that meditation outcomes of reduced C-reactive protein and blood pressure.[73] They concluded that meditation practice leads to the moderation of important physiological markers in a range of populations. From these studies, it is clear that mindfulness meditation has been associated with a number of healthy inflammatory process changes.[2]

Seated meditation has been related to sympathetic nervous system reductions in activation.[48,69,73] The studies that have been reviewed have also found positive meditation on immune cell subsets related to the immune systems.[79,80]

It had also been found that meditation has led to increasing vagal tone,[81,82] as well as inflammatory-based diseases.[68,71,83,84] The benefits of meditation practice have also occurred with 90 minutes of yogic practice over a 2-week period, which found increased expression of important antimicrobial peptides,[85] which is of interest for work with COVID patients as they are expressed in respiratory epithelial cells.[8] A mind-body intervention down-regulated cytokine receptors and C-reactive protein.[86] Epel et al[87] (2016) found that combined meditation/yoga regulated levels of the proinflammatory tumor necrosis factor alpha. In a study by Jang et al,[69] in contrast to healthy controls, patients in a meditation arm demonstrated a significantly decreased expression of pro-inflammatory cytokines, with a shift towards anti-inflammatory cytokine secretion (Th2 response).

Bushell et al[88] summarized this extensive literature by indicating that meditation can be effective as an adjunctive intervention for a range of infectious diseases. In summary, common features of the inflammatory-driven pathogenesis of virulent infectious diseases can be modified by the anti-stress and anti-inflammatory properties of meditation practice (see Table 1).[89–91]

Epigenetics and DNA Methylation

Developmental epigenetics also has implications for what occurs with Long COVID and meditation,[92] as we will review below. DNA methylation is one molecular epigenetic phenomenon that corresponds to emergent structural states and modified gene activity.[93,94] Epigenetic factors such as movements in mindful activities are important means of environmental enrichment.[95]

As an example of this literature, differential methylation at genes occurred when comparing patients with and without sepsis.[96]

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Table 1 Summary of findings on biomarkers associated with meditation practices

Immunology	Study Design	Biomarker Specimen	Purpose	Intervention	Duration (Weeks)	Population	N	Control Intervention	Outcome Conclusions
Black, 2015	RCT	Blood (PBMCs)	Test effect of mindful meditation or sleep hygiene on sleep quality in older adults	MAPs mindful awareness practices	6	Community adults; 67% female; ages 66.3 ± 7.4 years	49	Sleep hygiene education	Improved insomnia symptoms, depression symptoms, fatigue interference, and fatigue severity ($P < 0.05$ for all). Differences were not observed for anxiety, stress, or NF-κB, although NF-κB concentrations significantly declined over time in both groups ($P < 0.05$).
Bower, 2015	RCT	Blood (PBMCs, plasma)	To evaluate a brief, mindfulness-based intervention to reduce stress, depression, and inflammatory activity.	MAPs mindful awareness practices	6	Breast cancer patients; 100% female; ages 46.1 (± 28.4–60 range) years	65	Waiting list: Usual care	Significant decline in pro-inflammatory gene expression from baseline to post-intervention (p = 0.009). <NF-B; > IFN-1; < IL-6 (dependent on practice dosage); CRP; sTNF-RII
Cahn, 2017	Open	Blood (PBMCs, plasma); Saliva	To test the positive effects of meditative practices on mental fitness, autonomic homeostasis and inflammatory status.	Yoga Meditation	12	Thirty-eight individuals (mean age: 34.8 years old)	38	None: Pre-post	Decrease in inflammatory processes resulting from the yoga and meditation practices, we found that the plasma level of the anti-inflammatory cytokine Interleukin-10 was increased and the pro-inflammatory cytokine Interleukin-12 was reduced after the retreat. Increases in the plasma levels of BDNF and increases in the magnitude of the cortisol awakening response (CAR) were also observed
Carlson, 2003	Open	Blood (PBMCs, plasma)	This study investigated the relationships between a mindfulness-based stress reduction meditation program for and quality of life, mood states, stress symptoms, lymphocyte counts, and cytokine production.	MBSR	8	Early stage breast and prostate cancer patients	59	None: Pre-post	Decreased stress symptoms: NK cell production of IL-10 decreased

Carlson, 2007	Open	Blood (PBMCs, plasma)	Investigated the ongoing effects of participation in a mindfulness-based stress reduction (MBSR) program on quality of life (QL), symptoms of stress, mood and endocrine, immune and autonomic parameters	MBSR	8 (one year follow-up)	Early stage breast and prostate cancer patients	59	None: Pre-post	Reduction in Th1 (pro-inflammatory) cytokines. T-cell population of TNF, IFN-γ, and IL-4 decreased
Carlson, 2015	RCT	Whole blood	Test effect of mindful meditation or group therapy/stress management on telomere length i	MBSR	8	Breast cancer survivors	88	Supportive-expressive group therapy; 1-day stress management seminar	> telomere length (trend for attenuated decrease when treatment groups combined vs seminar)
Creswell, 2009	RCT	Blood (plasma)	Test effect of mindful meditation on CD4+ T lymphocyte declines in distressed HIV+ adults	MBSR	8	HIV	48	Education	>CD4+ T lymphocyte count (buffered decline vs controls)
Creswell, 2012	RCT	Blood (PBMCs, plasma)	Test effect of mindful meditation on loneliness in older adults	MBSR	8	Healthy	40	Wait List	IL-6. Decrease in log-transformed CRP between pre- and post-intervention (p = 0.08). <NF-B; < CRP (trend)
Davidson, 2003	RCT	Blood (serum) with influenza vaccine	Test effect of mindful meditation on brain and immune function	Meditation	8	Healthy	41	Wait List	> Influenza antibodies
Eda, 2013	Open	Salivary HBD-2 concentration was measured using an enzyme-linked immunosorbent assay	To determine the effect of yoga stretching on mucosal immune functions, primarily human b-defensin 2 (HBD-2)	Yoga	<1 (2 90 min sessions)	Healthy	15	None: Pre-post	HBD-2 concentration after yoga stretching (165.4 ± 127.1 pg/mL) was significantly higher than that before yoga stretching (84.1 ± 63.4 pg/mL; p \ 0.01). HBD-2 expression rate after yoga stretching (232.8 ± 192.9 pg/min) was significantly higher than that before yoga stretching (110.7 ± 96.8 pg/min; p \ 0.01)
Elsenbruch, 2005	RCT	Blood (EDTA whole stimulated)	Test effect of mindful meditation + multimodality program on neuroendocrine and immune measures in patients with ulcerative colitis	Meditation	10	Ulcerative colitis patients; 50% female; ages 42.9 ± 8.6 years	30	Wait List	Basal levels of TNF-alpha (trend) Significantly greater improvement in the SF-36 scale Mental Health and the Psychological Health Sum score compared with changes observed in the usual-care waiting control group. Patients in the intervention group showed significantly greater improvement on the IBDQ scale Bowel Symptoms compared with the control group.

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Table 1 (Continued).

Gallegos, 2013	RCT	Blood (PBMCs, plasma)	Test effects of (yoga, sitting and informal meditation, body scan) on immune function, circulating insulin-like growth factor (IGF)-1 concentrations, and positive affect	MBSR	8	100 community-dwelling older adults ≥65 years of age and English-speaking	200	Wait List	IGF-1 levels and yoga, and sitting meditation ($p < 0.01$). Higher post-treatment IGF-1 levels and greater improvement in positive affect from study entry to postintervention (practice effects). Sitting meditation was positively associated with post-treatment IGF-1
Infante, 2014	CT	Blood monoclonal antibodies	To evaluate the immune system in these meditation practitioners, by determining leukocytes and lymphocytes subsets	TM (TM-Sidhi is an advanced meditation technique)	< 1 (40 mins); Ongoing, LTP	Healthy: TM Practitioners	35	Selected: Not previously used any relaxation technique	TM group had higher values than the control group in CD3+CD4−CD8+ lymphocytes ($P < 0.05$), B lymphocytes ($P < 0.01$) and natural killer cells ($P < 0.01$), whereas CD3+CD4+CD8− lymphocytes showed low levels in meditation practitioners ($P < 0.001$).
Jang, 2017		Blood (PBMCs, plasma)	To assess the effects of MBT on plasma cytokines and their interactions with catecholamines	Mind-body training (MBT)	Ongoing LTP	Healthy: practicing MBT (44 months (range, 3–144 months) recruited; 18 to 36 years (mean ±SD, 26±3)	142	Selected: Not previously using MBT	A significant increase in IL-10+IFN-gamma was found in females and a significant increase of IL-10 (anti-inflammatory cytokine); TNF-alpha and IL-6 (pro-inflammatory cytokines) are almost absent (≤1 ng/L) compared with controls. Positive correlations were found between IL-10 and the NE/E ratio and between IL-10 and the DA/E ratio.
Jedel, 2014	RCT	Blood (serum); stool	Test effect of mindful meditation on flare ups and quality of life in ulcerative colitis patients	MBSR	8	Ulcerative colitis patients in remission; 56% female; ages 46.0 ± 12.8 years	53	Mind–body medicine course	< CRP (among non-flared); IL-6; IL-8; > IL-10 (among flared); calprotectin
Lengacher, 2011	RCT	Plasma	Test effect of mindful meditation on immune recovery following breast cancer recovery	MBSR	6	Breast cancer patients; 100% female; ages 58.0 ± 9.0 years	82	Usual care	>T cell activation; > IFN-/IL-4 ratio; > CD4+ /CD8+ ratio (trend); CD3+, CD4+, CD8+; NK cells; B lymphocytes; > telomerase activity; telomere length. reduction in salivary IL-6 in all MBSR participants pre- to post-intervention ($p = 0.002$)

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Li, 2005	CT	Blood (WB neutrophils)	To determine the effect of QG on genomic profile and function of neutrophils	QG: Falun Gong (FLG)	Ongoing, LTP	Healthy: practitioners of QG for 1 year (range, 1–5 years)	12	Normal healthy controls did not perform Qigong, yoga, t'ai chi, or any other type of mind–body practice	Enhanced immunity, downregulation of cellular metabolism, and alteration of apoptotic genes in favor of a rapid resolution of inflammation
Malarkey, 2013	RCT	Blood serum (chemilluminescencand electrochemiluminescence); Saliva (Cortisol)	Test effect of mindful meditation on inflammatory markers in workers with cardiovascular disease risk	Meditation	8	CVD risk	84	Education	A larger MBI-ld effect on CRP (as compared to control) occurred among participants who had a baseline BMI<30 (−2.67 mg/mL) than for those with BMI>30 (−0.18mg/mL)
Manzaneque, 2009	CT	Blood Serum (Cytokines)	To assess the effects of qigong practice on serum cytokines, mood and subjective sleep quality	QG	4	Healthy	16	None	QG enhanced psychological well-being, including sleep duration. The practice of qigong for one month did not alter serum cytokines,
Naoroibam, 2016	CT	Blood serum (flow cytometry	To study the effect of integrated yoga (IY) intervention on anxiety, depression, and CD4 counts	Integrated Yoga	4	HIV	44	Normal care: anti-retroviral therapy (ART)	Between-group comparison revealed a significant reduction in depression scores ($F[1, 21] = 5.64$, $P < 0.05$) and significant increase in CD4 counts ($F[1, 21] = 5.35$, $P < 0.05$) in the yoga group
Rosenkranz, 2013	RCT	IL8	Test effect of mindful meditation on physiological stress and neurogenic inflammation responses	QG	8	Healthy	49	Education	< TNF- (dependent on practice dosage)
Vera, 2016	RCT	Blood serum	To assess the acute effects of Taoist qigong practice on immune cell counts	QG	4	Healthy	43	None: Normal Routine	Statistically significant differences were found be- tween the experimental and control groups, with the experi- mental group showing higher values in the number ($p = 0.006$) and the percentage ($p = 0.04$) of B lymphocytes, as well as lower values in the percentage of NK cells ($p = 0.05$), as com- pared to control.

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Table 1 (Continued).

Wang, 2011	RCT	Blood serum	To test the effects of tai chi chuan (TCC) practice on immune function	TC	12	Healthy: female college students (19.3 ± 1.8 years)	144	Education	Significantly higher plasma levels of IgG (P=0.000), IgM (P=0.05) and CD4+ (P=0.032) after practice compared with their respective pre-practice levels.
Witek-Janusek (2008)	CT	Peripheral blood mononuclear cells	To evaluate the effect and feasibility of a mindfulness based stress reduction (MBSR) program on immune function, quality of life (QOL), and coping	MBSR	8	Beast Cancer (recent diagnoisis)	38	N/A	Reduction in IFN- γ production with increased IL-4, IL-6, and IL-10 production between pre- and 1-month post-intervention. In contrast, breast cancer patients in the Non-MBSR group exhibited continued reductions in NKCA and IFN-gamma production with increased IL-4, IL-6, and IL-10 production
Genetics	**Study Design**	**Biomarker**	**Purpose**	**Intervention**	**Duration (weeks)**	**Population**	**N**	**Control Intervention**	**Outcome Conclusions**
Alda, 2016	CT	Genomic DNA: Telomere Length	To determine if the practice of meditation is associated with longer leukocyte telomere length.	Zen	Ongoing: Zen LTP	Healthy: Zen practitioners	40	Selected: not previously meditated	The meditators group had a longer MTL (p = 0.005) and a lower percentage of short telomeres in individual cells (p = 0.007) than those in the comparison group.
Chaix, 2017	CT	DNA methylome from blood cell: Telomees	To examine whether meditation practice influences the epigenetic clock, a strong and reproducible biomarker of biological aging, which is accelerated by cumulative lifetime stress and with age-related chronic diseases	Meditation	Ongoing: LTP	LTP (> 3 years)	38	Selected: not previously meditated	A significant negative correlation between Intrinsic Epigenetic Age Acceleration (IEAA) and the number of years of regular meditation practice
Chaix, 2020	CT	peripheral blood mononuclear cells DNA methylation	To evaluated the impact of a day of intensive meditation practice (t2-t1 = 8 hours) on the methylome of peripheral blood mononuclear cells in experienced meditators	Mindfulness Based	Ongoing: LTP	LTP	34	Selected: not previously meditated	61 differentially methylated sites (DMS) were enriched in genes associated with immune cell metabolism and ageing and in binding sites for several transcription factors involved in immune response and inflammation

Chandran, 2021	RCT	Pro-inflammatory gene expression	The examine the molecular mechanisms underlying the positive impact of meditation on human wellbeing	Yoga and Lifestyle	1 (8 days)	Normal	106	COVID 19 patients and Multiple Sclerosis (MS)	220 genes directly associated with immune response, including 68 genes related to interferon (IFN) signaling were upregulated, with no significant expression changes in the inflammatory genes
Dasanayaka, 2022	CT	Plasma Telomerase Levels	To investigate if continued practice of meditation benefited quality of life, state of mindfulness, and plasma telomerase level in healthy adults	Mindfulness Based	Ongoing Midfulness: LTP	Healthy LTP	60	Selected: not previously meditated	Plasma telomerase levels were observed in skilled meditators compared to non-meditators ($p = 0.002$). Trait mindfulness level and plasma telomerase level showed a significant relationship with the duration of meditation practice ($p = 0.046$ and $p = 0.011$, respectively). Regression analysis indicated that trait mindfulness level ($p < 0.001$) significantly predicts the plasma telomerase level.
Dutcher, 2022	RCT	Pro-inflammatory gene expression	To study the immunoregulatory impact of Mindfulness meditation training	Smartphone mindfulness meditation: Headspace mindfulness training program or	4	Stressed Adults 18 to 60 (M = 34.03 years, SD = 11.07)	100	Recharge control program	Mindfulness training reduced activity of the pro-inflammatory NF-κB transcription control pathway compared to the active control.
Epel, 2016	RCT	Blood plasma, gene expression and Telomerase activity	To examine improved cellular health due to meditation while controlling for vacation effects	Meditation retreat	< 1 (6 days)	Healthy	102 Average age was 47 (s.d. =8.1, range 31–60 years)	Vacation: relaxing on-site	Regular meditators showed post-intervention differences in a gene network characterized by lower regulation of protein synthesis and viral genome activity. Day-5 follow-up t-tests showed a significant increase in telomerase activity only in the regular meditation group (P=0.004
Harkess, 2016	RCT	DNA methylation and inflammation markers	To evaluate the potential psychological benefits of yoga to a non-clinical population, and address limitations in literature (cross-sectional designs, sample sizes ≤ 20, and limited exploration of community populations) and	Yoga	8	Chronic Stress	116	Wait List	Yoga is only beneficial when practiced regularly, or that 8-weeks is not long enough to cultivate ongoing benefits.

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Table 1 (Continued).

Genetics	Study Design	Biomarker Specimen	Purpose	Intervention	Duration (Weeks)	Population	N	Control Intervention	Outcome Conclusions
Le Nguyen, 2019	RCT	Telomere Length	To probe the distinct effects on telomere length (TL) of mindfulness meditation (MM) and loving-kindness meditation (LKM)	Loving-kindness and Mindfulness meditation	12	Healthy	142	Waiting list: Usual care	The LKM and MM group showed increase in TL that were directional but not significant
Mendioroz, 2020	CT	Telomere Length and DNA methylation (DNA methylation levels, measured by the Infinium HumanMethylation450 BeadChip (Illumina) array	To examine previously described, specific subtelomeric regions in long-term meditators compared to controls		Ongoing Midfulness: LTP	LTP (10 years consistently)	17	Healthy: non-meditators	Specific subtelomeric regions containing GPR31 and SERPINB9 genes were associated with telomere length in long-term meditators with a strong statistical trend when correcting for multiple testing. Notably, age showed no association with telomere length in the group of long-term meditators.
Qu, 2013	RCT	Gene Expression and Peripheral blood mononuclear cells (PBMCs), Lymphocytes	To investigate the mechanisms of how yoga may positively affect the mind-body system	Yoga (gentle yoga postures, breathing exercises, and meditation (Sudarshan Kriya and Related Practices – SK&P)	<1 (4 sessions)	Healthy: attending a one-week yoga retreat	14	Wait list: Nature walk and relaxing music	We show that the SK&P program has a rapid and significantly greater effect on gene expression in PBMCs compared with the control regimen. These data suggest that yoga and related practices result in rapid gene expression alterations which may be the basis for their longer term cell biological and higher level health effects.
Neurology	**Study Design**	**Biomarker**	**Purpose**	**Intervention**	**Duration (weeks)**	**Population**	**N**	**Control Intervention**	**Outcome Conclusions**
Buchwitz, 2021	RCT	Neuropsychological test performance	To evaluate feasibility and effects of a newly developed mindfulness intervention tailored to specific needs of patients with Parkinson's disease	Mindfulness Training	8	Parkinson's disease	30	Wait List	Greater performance in sustained attention and language tasks over time. Additional changes included greater mindfulness as well as less sleeping problems and anxiety.
Dissanayaka, 2016	Recruited	Neuropsychological test performance	To effectiveness of a manualized group mindfulness intervention tailored to improving both motor and neuropsychiatric deficits in Parkinson's disease	Mindfulness Training	8	Parkinson's disease	4000	None: Pre-post	Increase in PDCRS-Subcortical scores, and an improvement in postural instability, gait, and rigidity motor symptoms

Engel, 2000	Recruited	Electromyography (EMG)	To investigate the psychological and physical effects of training of body awareness and slow stretching on persons with chronic toxic encephalopathy (CTE)	Mind-Body	8	Chronic toxic encephalopathy	8	None: Pre-post	The body–mind training resulted in an improved ability for physical and mental relaxation as indicated from the lower EMG, the higher alpha% and the decrease in state anxiety. The mean alpha% increased 52% during the training period (P,0.01), and the EMG decreased 31% (P, 0.001).
Herzog, 1990	Recruited	positron emission tomography (PET); Regional glucose metabolism	To delineate cerebral metabolic responses to external or mental stimulation. In order to examine possible changes of brain metabolism due to Yoga meditation	Yoga	Ongoing Yoga: LTP	Yoga meditative relaxation (YMR)	8	Normal control state	The ratios of frontal vs occipital rCMRGlc were significantly elevated ($p < 0.05$) during YMR. These altered ratios were caused by a slight increase of frontal rCMRGlc and a more pronounced reduction in primary and secondary visual centers.
Kosunen, 2016	Open	EEG	To assess the effectiveness of RelaWorld: a neuroadaptive virtual reality meditation system that combines virtual reality with neurofeedback	Virtual Reality Meditation System	Unreported (6 sessions; 2 and 2.5 hours)	Healthy: College students 20 and 48 years (M=28.7)	43		RelaWorld system elicits deeper relaxation, feeling of presence and a deeper level of meditation when compared to a similar setup without head-mounted display or neurofeedback.
Levinson, 2014	RCT	fMRI functional connectivity	To present construct validation of a behavioral measure of mindfulness, breath counting	Mindfulness BCT	4	Normal	400	Normal	Skill in breath counting associated with more meta-awareness, less mind wandering, better mood, and greater non-attachment (ie, less attentional capture by distractors formerly paired with reward).
Lim, 2018	Open	fMRI functional connectivity	To study time-varying connectivity patterns associated with naturally varying and objectively measured trait mindfulness using dynamic functional connectivity (DFC) analysis of resting-state fMRI.	Mindfulness BCT	< 1 (1 session)	Normal, Score selected: High Mindfulnes	39	Normal, Score selected: High vs.Low Mindfulness	DFC analysis of resting state fMRI data revealed that the High Mindfulness group spent significantly more time in a brain state associated with task-readiness - a state characterized by high within-network connectivity and greater anti-correlations between task-positive networks and the default-mode network (DMN).

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Table 1 (Continued).

Neurology	Study Design	Biomarker Specimen	Purpose	Intervention	Duration (Weeks)	Population	N	Control Intervention	Outcome Conclusions
Wang, 2011	Recruited	fMRI, Cerebral Blood Flow	To advance the understanding of the neural pathways of meditation by addressing the cerebral blood flow (CBF) responses associated with meditation	Meditation: "focused-based" practice and "breath-based" practice	< 1 (1 session)	LTP	10	Normal	Strong correlations between depth of meditation and neural activity in the left inferior forebrain areas including the insula, inferior frontal cortex, and temporal pole. There were persistent changes in the left anterior insula and the precentral gyrus even after meditation was stopped.
Steffen, 2015	RCT	Cardiovascular variables	To investigate the effectiveness of brief mindfulness meditation in reducing cardiovascular reactivity and recovery during a laboratory stressor	Mindfulness Training	< 1 (1 session)	Normal: laboratory stressor	62	Wait List: meditation-naïve participants	Mindfulness participants showed lower systolic blood pressure following the mindfulness exercise and decreased systolic and diastolic blood pressure reactivity during a speeded math stressor.
Wong, 2018	Recruited	EEG and psychomotor vigilance task (PVT)	Test the effectiveness of Mindfulness to improve general wellbeing through developing enhanced control over metacognitive processes	Mindfulness Training	8	Nurses, (mean age = 30.3, SD = 8.52	32	None	Following the MBT program, we observed changes in alpha power across all scalp regions during meditation that were correlated with attendance.
Zeidan, 2010	RCT	Neuropsychological test performance	To examine the effects of brief mindfulness meditation training on cognition	Mindfulness Based	4 sessions	Healthy: no prior meditation experience; ave age 20 years	63	Healthy: College Students	Brief mindfulness training significantly improved visuo-spatial processing, working memory, and executive functioning

In one bioinformatics study of COVID-19, Balnis et al[97] activation associated was associated with a predominance of autoimmune disorders. For those patients that were COVID-19-positive, those with a hyper-methylated status had worse outcomes, and COVID-19 severity was related to seventy-seven differentially methylated positions. Another study of COVID-19 severity identified differentially methylated genes, such as those related to interferon response to viral infections.[98] These candidate biomarkers may be useful in the identification of those infected by SARS-CoV-2.

Epigenetic and DNA Methylation Effects of Meditation

As indicated earlier in this article, it is possible meditation may help patients by re-regulating pro-inflammatory to anti-inflammatory processes and by reducing sympathetic nervous system over-activation through the relaxation response.[68,99] However, research on DNA methylation may indicate more profound biological mechanisms, such as telomere stability, the hypothalamic-pituitary-adrenal axis[100] and inflammatory pathways.[101,102] Le Nguyen et al[103] found that mindfulness meditation was related to increased telomerase activity. In a meta-analysis, Schutte and Malouff[104] found the effect size across all telomere studies including both novice and long-term meditators to be 0.46. Research by Dasanayaka et al[105] with long-term meditators found telomerase changes, and comparable results with meditation on telomeres length, also with strong effect sizes (0.66-0.88) for relatively small sample sizes ($n < 20$).[106,107]

A few epigenetic studies have been conducted with meditators involving DNA methylation.[90] Black and Slavich's[72] meta-analysis reported that meditation led to increases in telomerase activity. Subsequent longitudinal observations revealed that meditation can bring about gene expression changes.[108] Profiling at CpG sites, research by Harkess et al[109] focused on tumor necrosis factor alpha (TNF-α), IL-6, and C-reactive protein. Chaix et al[110] also used peripheral blood mononuclear cells and methylation levels of 353 CpG sites were highly correlated with chronological age, which is a measure of epigenetic age (DNAm age).[111,112] For those involved in mindfulness and compassion meditation, Chaix et al[110] found decreased epigenetic aging rate. For genes associated with immune metabolism aging, Chaix et al[113] found meditation to influence the methylome. In a Smartphone mindfulness meditation training, researchers[81,82] found reduced pro-inflammatory gene expression. One thousand twenty-seven gene transcripts differed by greater than 50% between groups from baseline to post-intervention.[114] We conclude from this literature that meditation can improve the immune response for those with persistent inflammation (see Table 1).

Neurocognitive Functioning and Central Autonomic Network

The neurocognitive problems that intensify over time in some patients with PASC seem similar to those seen in patients with ME/CFS.[23,115] Regarding patients with PASC, Jason et al[23] found over approximately 6 months, the one group of symptoms that got worse were from the neurocognitive domain,[23] findings similar to that reported by the Body Politic COVID-19 support group.[17]

It has been suggested that some viral infections or parts of the contribute to the prolonged neurocognitive impairment, with some theorizing that the post-viral fatigue patient's immune system overreacts following infection-causing oxidative stress.[37] The literature cited above suggests that the immune state may affect the central nervous system of those with PASC and ME/CFS.[36,61,64,116] These causal reactivations may be similar to cerebral toxoplasmosis.[117,118] In post-viral infections, such as ME/CFS, there is evidence of aberrant low natural killer cell cytotoxicity, cortisol deficiency, and sympathetic nervous system hyperactivity.[37]

The central autonomic network is critically involved in homeostatic situational control and bi-directional signaling of visceral function,[119] and it operates at different levels throughout the central nervous system, including the lower/upper brainstem and forebrain levels, integrating visceral sensation with autonomic and neuroendocrine responses.[120] SARS-Cov-2 may cause long-term changes to central autonomic network structure (eg, brainstem-forebrain connections) and damage to ascending-descending visceral pathways involved in interoceptive awareness (perception of senses and autonomic functioning).[121] Furthermore, interoceptive signals could be disrupted by perfusion abnormalities, micro-vascular injury, and increased inflammation,[122] which can be seen with acute SARS- Cov-2 infection, leading to worsening function following initial infection.

Central Nervous System

The Central Nervous System is highly integrated,[123] sending dynamic signals that promote physiologic stability in response to internal and external demands.[124] Post-infectious, chronic inflammatory processes within the central nervous system can lead to disease states, which are known to disrupt the body's homeostatic regulatory mechanisms and create an imbalance that favors sympathetic nervous system dominance.[125] In addition, the neuroendocrine system regulates a cascade of chemical biological mediators between health and disease.[126] Biological and behavioral features of PASC might be linked to the central nervous system.[127,128] Neurologic manifestations (eg, encephalopathy) in hospitalized patients have been associated with a poorer prognosis, independent of respiratory disease severity.[129] There is growing evidence that adaptive mechanisms underlying symptom maintenance and magnification in post-viral illnesses crucially involve the cortico-limbic-brainstem circuits.[130–135] A neuroimaging study found that alterations in brain activity in the parietal lobe and cingulate gyrus were related to worsening post-viral symptoms.[136] Lu et al[122] found increased registered fractional anisotropy (directionality) and decreased mean and axial diffusivity in the corona radiata, external capsule, and superior frontal-occipital fasciculus in recovered SARS Cov-2 patients.

Structural, functional, cerebrovascular, and electrical CNS abnormalities have been identified in post-viral fatigue. Regarding structural brain abnormalities, using T1-weighted spin echo MR imaging, Barnden et al[130] detected decreased signal intensity in the brainstem and increased signal intensity in the sensorimotor white matter of subjects with post-viral fatigue compared to healthy controls. Stüber[137] postulated that these sensorimotor findings may reflect altered myelin levels, given that 90% of T1 contrast in white matter is due to myelin, but were cautious to apply the same interpretation for the brainstem results due to its more complex tissue composition. Further support for myelin alterations in white matter tracts of patients with post-viral fatigue was shown in a study by Thapaliya et al.[138] Tracts within these structures carry motor signals between primary motor areas of the cortex, brainstem, pons, and lower motor areas in the spinal cord. In a separate longitudinal study using T1w/T2w imaging, Shan et al[139] found progressive atrophy in the left inferior fronto-occipital fasciculus in a sample of patients with post-viral fatigue measured 6 years apart. The connection fibers of the IFOF are widespread, connecting the ipsilateral frontal lobe to the superior parietal lobe, inferior occipital lobe, and basal surface of the temporal lobe. These fibers assume a critical role in the transport of information between regions of large-scale networks (eg, fronto-parietal, default-mode, dorsal attention) for the integration of auditory and visual association cortices with the prefrontal cortex.

White matter volume reduction has also been found in the midbrain and pons of patients with post-viral fatigue using volumetric analysis.[139] Diffusion tensor imaging is another MRI technique that uses microstructure (eg, myelin integrity). Diffusion tensor imaging provides a quantitative analysis of the magnitude and directionality of molecules. A Diffusion tensor imaging-based prospective study with patients who recovered from COVID-19 found changes in fractional anisotropy, mean diffusivity, axial diffusivity, indicating a possible disruption in tissue and functional brain integrity.[122]

In addition to abnormal structural integrity mainly of white matter, MRI has also detected functional alterations in post-viral fatigue. Functional MRI (fMRI) has detected abnormal activity in patients with post-viral fatigue related to the ventral anterior cingulate during the erroneous performance of a motor imagery task,[134] increasing task load,[140] and fatigue-inducing cognitive tasks.[141,142] Compensatory mechanisms may also explain the association of higher gray matter volume in the supplementary motor area with worse neurological symptom scores in a longitudinal MRI study of patients with post-viral fatigue.[139]

A growing number of studies also use functional connectivity methods to investigate changes in brain networks in post-viral fatigue. Convergent findings of these studies have pointed to the salience network which handles functional properties of many brain systems.[143] For example, significantly decreased connectivity was found by Gay et al.[144] Using arterial spin labeling based functional connectivity, patients with post-viral fatigue had reduced functional connectivity within the salience network between the anterior cingulate cortex and right insula.[145] In an adolescent patient sample with post-viral fatigue who underwent resting-state fMRI, Wortinger et al[146] found that decreased connectivity to the right posterior insula of the salience network was related to post-viral fatigue severity. Investigating resting-state fMRI in female patients with post-viral fatigue, Kim et al[114] reported aberrant connectivity between the posterior and anterior cingulate cortex. These studies all reported abnormalities consistent with central autonomic regions (left posterior cingulate, anterior cingulate, right insula), suggesting a need for research that assesses the integrity of the central autonomic network[114] in patients with post-viral fatigue.

Although fMRI provides useful insight into brain function, it is a semi-quantitative measure dependent on many variables, one of which is cerebral blood flow. Early studies suggested that hypoperfusion may underlie abnormalities in patients with post-viral fatigue leading to deficiencies in energy metabolism.[147,148] Using MRI-based Arterial spin labeling, these findings were later extended.[149,150] Finally, using positron emission tomography, Tirelli et al[151] patients with post viral fatigue were differentiated from those with Major Depressive Disorder due to hypo-metabolism as did Helms et al[152] and Chougar et al.[153] There is also emerging evidence for disruption of central nervous system vascular health in acute COVID-19 infection. Koralnik and Tyler[154] an increased risk for stroke for COVID-19 patients, even in younger individuals and those with milder COVID-19 infections.

Neurological Effects of Meditation

Among the different effects of meditation, one involves increased blood flow to the frontal cortex, parietal and temporal lobes,[155] as well as increase glucose metabolism[156] and improve global functioning.[34] Meditation has also been demonstrated to cause neural reorganization and re-regulation in practitioners.[34] Mind-body techniques have been used by individuals as a remedy for symptoms related to the brain and cognitive dysfunctions.[157–159]

Meditation has been demonstrated to cause neural reorganization and re-regulation in both novices and long-term practitioners.[34,160] These studies on the neurochemical effects of meditation on neurotransmitters, coupled with the established research on salutogenic immune profiles of meditators,[72] indicate several wide-ranging neuroimmune benefits of a regular practice of meditation. Meditation may help patients by re-regulating pro-inflammatory to anti-inflammatory processes and/or by reducing sympathetic nervous system over-activation through the relaxation response.[68] As meditation practice is stabilized, these parasympathetic responses may be habituated and translated to daily life (see Table 1).[35]

Meditation Effect Sizes

A recent meta-analysis on meditation by Whitfield et al[161] examined 180 pooled, effect sizes from 46 studies of meditation with small to moderate effect sizes (0.27-0.36). Another recent study by Zhang[162] found large effect sizes for improved sleep, depression and anxiety, as well as large neurophysiological changes (0.59). In the largest meta-analysis of meditation to date, Goldberg et al[163] found overall effect size ranged from small (0.21, for well-being) to moderate (0.55, for psychiatric symptoms). Another meta-analysis concluded that mind-body interventions effects endured at 3 months post-intervention.[164] In Morgan et al[7] and Black's et al[72] meditation reviews, overall significant weighted effect sizes were moderate (0.34-0.58) on specific markers, suggesting a sound effect size relative to biomedical interventions. Similarly, a meta-analysis by Leucht et al[165] found somewhat higher effect sizes. Interestingly, meta-analyses from meditation interventions report the average standardized effect size (0.30), which is similar to effect sizes from mainstream medical interventions across a variety of health domains (0.30).

In Schutte et al's[104] meditation study, changes in telomere length also had a promising, moderate effect size (0.40). In a meditation review by Dasanayaka et al,[105] DNA methylation research found telomere length had a moderate effect size (0.40) for novice meditators (0.40). These findings outperformed the majority of reviewed biomedical interventions.[166] In summary, given comparable effects and the absence of adverse side effects in alternative non-pharmacological interventions in biomedical populations,[167] meditation appears to be a promising intervention for those with post-viral complications (see Table 2).

Intervention Duration Parameters

It has long been suggested that longevity and intensity of practice is an important aspect of the efficacy of practice.[168–171] There is some positive studies with briefer meditation interventions, such as 20-minute meditation that helped depression and anger in a college sample.[172] A study by Zeidan et al[173] found that only three sessions of meditation could also improve cardiovascular variables related to anxiety reactivity. However, these studies and others[174] involved healthy populations, and did not include individuals with underlying disease pathology.

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Table 2 Meta and Reviews

	Study Design	Biomarker	Purpose	Intervention	Search Terms	Outcome Conclusions
Black, 2016	Systematic Review RTCs	Circulating and stimulated inflammatory proteins, cellular transcription factors and gene expression, immune cell count, immune cell aging, and antibody response	A comprehensive review of randomized controlled trials examining the effects of mindfulness meditation on immune system parameters.	Mindfulness based	Immune, inflammation, cytokine, proinflammatory, biomarker, blood, saliva, urine, telomere, and infection.	Effects on specific markers of inflammation, cell-mediated immunity, and biological aging.
Bower, 2016	Qualitative Review	Circulating, cellular, and genomic markers of inflammation	To describe the effects of mind-body therapies (MBTs) on circulating, cellular, and genomic markers of inflammation.	MBTS: Mind-body therapies (Tai Chi, Qigong, yoga, and meditation).	Mind-body therapies, tai chi, qigong, meditation, mindfulness, or yoga; and inflammation, cytokines, or proinflammatory.	Decreased expression of inflammation-related genes and reduced signaling through the proinflammatory transcription factor NF-κB.
Bushell, 2020	Qualitative Review	Unspecified testing	Explore pioneering studies in stem cell and regenerative biology, associated with Meditation.	Cognitive behavioral practices	Unspecified	Downregulated substances are proinflammatory cytokines (IL-1β, IL-6, TNF-α) and transforming growth factor (TGF-β).
Buric, 2017	Systematic review	Gene expression involved in inflammatory reactions	To examine changes in gene expression that occur after MBIs and to explore how these molecular changes are related to health.	MBIs (ie, mindfulness, yoga, Tai Chi, Qigong, relaxation response, and breath regulation)	Meditation OR mindfulness OR relaxation response OR yoga OR tai chi OR Qigong) and (gene expression OR microarray OR transcriptome.	Downregulation of nuclear factor kappa B pathway; this is the opposite of the effects of chronic stress on gene expression and suggests that MBI practices may lead to a reduced risk of inflammation-related diseases.
Chen, 2012	Systematic review and meta-analysis	Unspecified	The efficacy of meditation for anxiety specifically.	Meditative techniques	RCTs: various, unspecified types of meditation and anxiety.	Twenty-five of 36 (70%) of studies reported statistically superior outcomes in the meditation group compared to control. No adverse effects were reported.
Cramer, 2012	Systematic review (US National Health Interview Survey (NHIS) data)	Self Report: QOL, Mental Health	To determine the popularity of meditation is increasing, little is known about the prevalence, patterns, and predictors of meditation use in the general population.	Meditation	NHIS Community Sample (4525 adults).	Meditation was mainly used for general wellness (76.2%), improving energy (60.0%), and aiding memory or concentration (50.0%). Anxiety (29.2%), stress (21.6%), and depression (17.8%) were the top health problems for which people used meditation; 63.6% reported that meditation had helped a great deal with these conditions.

Dunn, 2022	Meta	RCTs: biomarkers were selected for this meta-analysis: *CD4+, CRP, IL-6, NF-κB, TL, TA*	Mindfulness-based interventions (MBIs) may offer a salutogenic effect on somatic disorders is by enhancing immune function.	Mindfulness-based interventions (MBIs)	RCTs examining the effect of MBIs on three immune parameters: inflammation (C-reactive protein, interleukin-6, nuclear factor-κB), infection response (CD4+ cells), and biological ageing (telomere length, telomerase activity) at post-intervention and follow-up.	Pooled effect sizes indicated a reduction in C-reactive protein (SMCD = −0.14, 95% CI [−.26 – −0.01]) and interleukin-6 (SMCD = −0.35, 95% CI [−.67 – −0.03]), and an increase in CD4+ (SMCD = 0.09, 95% CI [−.05 – 0.22]), telomere length (SMCD = 0.12, 95% CI [0.00 – 0.24]) and telomerase activity (SMCD = 0.81, 95% CI [0.17–1.46]) at post-intervention. At follow-up, results showed a reduction in interleukin-6 (SMCD = −0.13, 95% CI [−.29 – 0.03]) and C-reactive protein (SMCD = −0.39, 95% CI [−.68 – −0.10]) and increase in CD4+ (SMCD = 0.22, 95% CI [−.08 – 0.52]). Meta-regression results showed that some heterogeneity in effect size could be accounted for by intervention dosage, study population, and study design. Our findings quantify MBIs' potential for improving immune function and thus impacting somatic disorders.
Goldberg, 2022	Meta	A wide range of populations, problems, interventions, comparisons, and outcomes (PICOS)	To evaluate the scientific basis for mindfulness-based interventions (MBIs).	Mindfulness-based interventions (MBIs).	RCTs: effect sizes based on four or more trials that did not combine passive and active controls.	MBIs were similar or superior to specific active controls and evidence-based treatments. MBIs showed superiority to passive controls across most PICOS (ds = 0.10–0.89).
Dalpati, 2022	Review	A variety of immune markers	Summarise the effect of COVID 19 lockdowns and positive impacts of yoga and meditation on various psychological, emotional, and immunological parameters.	Summarise the available evidence on the effect of yoga and meditation on various psychological, emotional, and immunological parameters.	Unspecified	Improved respiratory health, reduced inflammation, better innate and adaptive immune cell function, reduced inflammatory cytokines.

(*Continued*)

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Table 2 (Continued).

	Study Design	Biomarker	Purpose	Intervention	Search Terms	Outcome Conclusions
Goleman, 2017	Book: Qualitative Review	EEG and other neurological markers	To evaluate the claims about the efficacy of mindfulness and meditation.	Meditation	Unspecified	“Quickie, one-time interventions”—like a weekend meditation course—are unlikely to make a lasting difference”; The amygdala, a key node in the brain’s stress circuitry, shows dampened activity from a mere 30 or so hours of MBSR practice; Long-term practice was associated with greater functional connectivity between the prefrontal areas that manage emotion and the areas of the amygdala that react to stress, resulting in less reactivity; an improved ability to regulate attention accompanies some of the beneficial impact of meditation on stress reactivity.
Jiang, 2021	Meta	Self Report: Sleep Quality from Pre- to Post-intervention	To evaluate the effect of virtual mindfulness-based interventions (MBIs) on sleep quality.	Virtual mindfulness-based interventions (MBIs)	Online OR internet OR digital OR m-health OR e-health OR computer* OR web* OR app OR smartphone OR mobile application) AND (mindful* OR meditate* OR Vipassana OR “acceptance and commitment therapy”) AND (sleep [TIAB] OR insomnia [TIAB]	Virtual MBIs are more effective at improving sleep quality than usual care controls and waitlist controls. Studies provide preliminary evidence that virtual MBIs have a long-term effect on sleep quality.
Khanpour, 2021	Systematic Review	Self Report: Signs and symptoms of ME/CFS and QOL	To systematically review studies using MBIs for the treatment of ME/CFS symptoms.	Mind-Body (MBIs): mindfulness-based stress reduction and mindfulness-based cognitive therapy, relaxation, Qigong, and yoga.	ME/CFS: Various	Fatigue severity, mental functioning and anxiety/depression improved when compared to the control group.
Linardon, 2020	Systematic review and meta-analysis	Outcome measure of acceptance, mind- fulness, or self-compassion	To examine whether principles of acceptance, mindfulness, and self-compassion can be learned through smartphone apps.	Smartphone-Based Meditation App.	Smartphone* OR “mobile phone” OR “cell phone” OR “mobile app*” OR iphone OR android OR mhealth OR m-health OR “cellular phone” OR “mobile device*” OR mobile-based OR “mobile health” OR tablet-based AND random* OR trial* OR allocat* AND mindful* OR accept* OR ACT OR meditate* OR compass*.	Smartphone apps also resulted in significantly lower levels of psychological distress than comparisons (k=22; g=−0.32; 95% CI= −0.48, −0.16). Meta-regression revealed a negative relationship between the effect sizes for mindfulness/acceptance and the effect sizes for distress. Smartphone apps produced significantly greater increases in self-compassion than comparisons (k=9; g=0.31; 95% CI=0.07, 0.56)

Pascoe, 2017	Meta	Neurobiological effects	To investigate the effects of focused attention, open monitoring and automatic self-transcending subtypes, compared to an active control, on markers of stress.	Mindfulness-Based Interventions (MBIs).	Unspecified	When all meditation forms were analysed together, meditation reduced cortisol, C - reactive protein, blood pressure, heart rate, triglycerides and tumour necrosis factor-alpha. Overall, meditation practice leads to decreased physiological markers of stress in a range of populations.
Rathore, 2018	Systematic Review	Telomere Stability	To investigate telomere stability and its implication from the point of view of asana, pranayama, and meditation.	Pranayama Yoga and Meditation.	"telomere length" AND "yoga."	The results of this review highlight the positive effects of yoga intervention on telomere length. The study suggests that the impact is mediated through upregulation of enzymes that degrades ROS and thereby prevents the accumulation of ROS in cells. ROS is produced as a normal product of cellular metabolism.
Sanada, 2020	Meta	Measurements were collected from the outcomes of such indices as adrenocorticotropic hormone (ACTH), cortisol (area under the curve or AUC, awakening response or CAR, and diurnal slope), cytokines (IL-6, IL-8 and TNF-α), nuclear factor enhancer of the kappa light chains of activated B cells (NF-kB), high-sensitive CRP (hsCRP) and epidermal growth factor (EGF)	To examine the effects of MBIs on biomarkers in psychiatric illness used to summarise the effects of low-grade inflammation.	Mindfulness-Based Interventions (MBIs).	Extensive: psychiatric disorders"[All Fields] OR "psychiatric disturbances"[All Fields] OR "psychiatric"[All Fields]) AND ("mindfulness"[MeSH Terms] OR "mindfulness"[All Fields] OR mbct [tiab] OR mbsr[tiab] OR "Mindfulness-Based Cognitive Therapy"[tiab] OR "Mindfulness Based Stress… Etc.	MBIs showed significant improvements in the event-related potential amplitudes in attention-deficit hyperactivity disorder, the methylation of serotonin transporter genes in post-traumatic stress disorder, the salivary levels of interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α) in depression, and the blood levels of adrenocorticotropic hormone (ACTH), IL-6, and TNF-α in generalised anxiety disorder. MBIs showed significant effects on health status related to biomarkers of low-grade inflammation ($g = -0.21$).
Schlechta Portella, 2021	Evidence Map of Systematic Reviews	Physical and Metabolic Effects; Mental Health; Vitality, Well-Being, and Quality of Life	To addressed the effects of meditation on various clinical and health conditions.	Meditation types based on open state practices accounted for the highest number of results (390 results), followed by mixture of techniques (93 results), mantra-focused practices (15 results), state-focused practices (8 results), and focused mindfulness practices.	Extensive: MH:Meditation OR TI: Meditation OR TI:Meditação OR TI: Meditacion OR TI:Mindfulness OR Cogitat* OR Pranayam* OR kapalabhati OR TI:zen OR TI: transcendental OR "M-Sidhi" OR mahayana OR hiniyana OR theravada* OR vajrayana OR vipassana OR… Etc.	Physical and Metabolic outcomes presents a total of 87 results. The effect of meditation was positive in 41 results, potentially positive in 29 results, inconclusive in 15 results, and with no effects in two results. The most common outcomes were improvements regarding high blood pressure, general cancer symptoms, and chronic pain.

(*Continued*)

Table 2 (Continued).

	Study Design	Biomarker	Purpose	Intervention	Search Terms	Outcome Conclusions
Schutte, 2013	Meta	Telomerase activity	To determine the effect of mindfulness meditation on telomerase.	Mindfulness-based interventions (MBIs)	Various: Mindfulness meditation leads to increased telomerase activity in peripheral blood mononuclear cells.	Effect size of d=0.46 indicated that mindfulness meditation leads to increased telomerase activity in peripheral blood mononuclear cells.
Venditti, 2020	Systematic Review	DNA Methylation; molecular and epigenetic mechanisms influenced by different mindful practices	To uncover the molecular and epigenetic mechanisms influenced by different mindful practices.	Mindfulness meditation, Vipassana, Yoga, Tai Chi, and Quadrato Motor Training.	Unspecified	Meditation practices act on the same gene targets, such as FKBP5, SLC6A4, and BDNF, and promote endocrinal, neuronal, and behavioral functions. This suggests that the achievement of a state of inner silence through the practice of meditation can prevent or reverse the detrimental effects of a stressful environment.
Whitfield, 2021	Meta	Cognition	To review objective cognitive outcomes across multiple domains from randomized MBP studies.	Mindfulness-based interventions (MBIs)	Mindfulness-based programs (MBPs) on cognitive functioning and objective cognitive outcomes.	Pooling data across cognitive domains, the summary effect size for all studies favored MBPs over comparators and was small in magnitude (g = 0.15; [0.05, 0.24]). Across subgroup analyses of individual cognitive domains/subdomains, MBPs outperformed comparators for executive function (g = 0.15; [0.02, 0.27]) and working memory outcomes (g = 0.23; [0.11, 0.36]) only.
Zhang, 2021	Review	Unspecified	To provide an overall review on mindfulness-based interventions (MBIs).	Mindfulness-based interventions (MBIs)	Various: 'mindfulness', "meditation", and "review", "meta-analysis" or their variations.	MBIs are effective for improving many biopsychosocial conditions, including depression, anxiety, stress, insomnia, addiction, psychosis, pain, hypertension, weight control, cancer-related symptoms and prosocial behaviours.

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Dobkin and Zhao[9] have argued that short-term interventions of less than 8 weeks of practice may not be enough to support significant clinical changes or physiological effects in chronically ill populations. Similarly, a recent review of meditation for post-viral fatigue (eg, ME/CFS) did not find significant differences at follow-up for any interventions lasting less than 8 weeks.[175] Interventions shorter than 8 weeks did not find changes in underlying biomarkers, immune markers, or neurocognitive functioning. The research appears to support bringing about positive biological processes in 8–12 weeks of meditation (see Tables 1 and 2).

There is one recent study reporting positive biological outcomes after short-term intervention, and this involved 8 days of intensive practice during a full-time on-site retreat.[175] The retreat was also tightly controlled: participants meditated more than 10 hours a day, remained silent for 8 days, ate vegan meals prepared for them, did not work, and followed a regular sleep schedule. This suggests that short-term interventions may compensate for a small duration of practice, by intensifying the amount of time spent in meditation.

Situ versus eMobile Interventions

An important question is the use of meditation with virtual and mobile implementation.[176] It has been claimed by meditation teachers that watching videos or just reading about meditation may be less effective.[177] However, there is some evidence that guided, smartphone-based meditation apps alone can be used to facilitate mindfulness practice and promote feelings of well-being and social connectedness.[178] For example, one group meditation intervention included a smartphone-based meditation app - the Breath Counting Task from MindFi. This intervention was effective in facilitating mindfulness practice,[179–182] as well as reducing stress,[178] and increasing well-being.[183] However, there are limitations to the research available, as the above findings are restricted to positive responses on self-report questionnaires of perceived well-being in relatively healthy samples.

Meditation for PASC and ME/CFS

Meditation and several other mind-body practices are being used to treat COVID-19 symptoms.[184,185] Studies in this area are beginning to appear in the literature, but there is a larger body of work with other post-viral illnesses. For example, Porter, Jason, Boulton, Bothne, and Coleman[3] reviewed mind-body trials for patients with ME/CFS; the most effective intervention was meditation. In addition, a recent review of meditation for post-viral fatigue (eg, ME/CFS) concluded that the basic symptoms were shown to be improved in patients receiving mind-body interventions.[175]

Mahendru[4] found that those provided meditation after SARS-CoV-2 infection reported improvement in multiple sleep indicators. Bushell et al[8] review suggested that meditation interventions were of importance to moderating immune function, specifically for SARS-CoV-2 infection and Long COVID. If COVID-19 has a runaway hyperinflammatory response to a viral infection,[53] this pathway is moderated by both short-term acute meditation intervention and long-term practice. The review also asserted that meditation may be effective at reducing future sequelae to negative inflammatory factors, and acknowledges additional, rigorous research is needed on therapeutic efficacy.[8]

Patients with PASC who regularly practice meditation also evidence more dominant wave frequency due to a reorganization of specific cortical areas such as a hemispheric slowing and multifocal epileptiform discharges from the frontotemporal and temporoparietal head regions as well as decreased self-reported fatigue, sleeplessness, pain, and cognitive and motor dysfunction.[186,187]

In one study[168] mentioned earlier in this article, participants with COVID-19 were provided a retreat and they reported positive immune-modulatory effects after 80 hours of meditation practice. The researchers concluded that findings support discrete benefits to those with COVID-19.

Conclusions

Our review suggests that there are immunological problems in patients with post-viral infections that may also lead to abnormal epinephrine and norepinephrine levels.[188] In addition, patients with post-viral fatigue exhibit similar patterns as those with post-viral encephalopathy, including a generalized and focal slowing in the frontal cortex.[189] This review suggests immunological mechanisms that may underly the effects of meditation on the physiological functioning of multiple related systems for individuals with PASC and ME/CFS. Studies reviewed indicate the wide-ranging neurophysiological consequences of a regular practice of meditation. The studies also suggest a neurophysiological basis for the health benefits that are attributed to meditation (see Table 1).

What occurs with PASC has been characterized by some as a Th2/Th1 cytokine imbalance, which is associated with a higher risk of mortality.[59] Meditation may help patients with PASC by balancing pro-inflammatory to anti-inflammatory processes and by reducing sympathetic nervous system over-activation through the relaxation response.[67] Increased blood oxygen level-dependent responses to an attentional measure due to a reorganization of specific cortical areas such as dorsolateral prefrontal cortex activation, and deactivation of Default network and medial prefrontal cortex, as well as decreased self-reported fatigue, sleeplessness, pain, and cognitive and motor dysfunction.

Mind-body techniques have been used by individuals as a treatment many of the symptoms experienced by those with PASC[157–159] and have the potential to bring about structural and functional changes to the brain.[3,155] Investigators and practitioners are beginning to explore the use of meditation for those with PASC.[4,190] This was mentioned by a meta-analysis by Khanpour Ardestani et al,[175] where mind-body practices were effective at reducing symptom severity in post-viral fatigue (eg, ME/CFS), including fatigue, anxiety, and depression, and improved physical and mental functioning.

Another meta-analysis recommends the use of mobile health meditation for COVID, given its overall effectiveness and availability of sessions in situ.[191] A retrospective of mindfulness meditation using app-based interventions for those dealing with the COVID-19 pandemic found they reduced mental health worsening.[192] Another recent review by Schlechta Portella et al[99] found meditation research was the most comprehensive intervention, showing a substantial number of positive mental and physical health outcomes. They concluded mindfulness meditation can promote neural plasticity, has important physical and metabolic impacts, and improves the immune system.

Meditation research indicates that short-term interventions (<6–8 weeks) can moderate responses on self-reports of quality of life, elevate mood and decrease stress for both mobile app-based and real-time group practices in relatively healthy participants. However, there is also evidence that moving underlying biomarkers in a population with disease pathology only achieves effects during longer interventions (>8–12 weeks).[194–196] Taken together, these studies of meditation suggest that effective and sustainable outcomes may be achieved for symptomatology and underlying pathology of post-viral fatigue (PASC and ME/CFS) (see Tables 1 and 2).

There are several limitations to the conclusions of meditation studies involving patients with PASC. First, there are few investigations that have been implemented and evaluated. Second, data are not available on intervention effects for patients with PASC over extended time. Thirdly, the exact cause of the Long COVID symptoms is still unknown, and in a recent study after extensive diagnostic evaluations of patients with PASC, Seller et al[193] did not find persistent viral infection or abnormal immune activation.

There is a need for more high-quality studies assessing the frequency and duration required for the efficacy of meditation interventions for those with post-viral fatigue, using measures of the types of biological measures that were reviewed in this article. Meditation interventions that are at least 8 weeks in duration appear to have the most promise, but there is a need to investigate how such interventions might best be implemented, such as through new internet possibilities.

Disclosure

The authors report no conflicts of interest in this work.

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