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Issue: *Advances in Meditation Research***Mindfulness meditation and the immune system: a systematic review of randomized controlled trials**David S. Black¹ and George M. Slavich²¹Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California.²Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CaliforniaAddress for correspondence: David S. Black, Ph.D., M.P.H., Department of Preventive Medicine, Keck School of Medicine, University of Southern California, 2001 N. Soto Street, Suite 302D, Los Angeles, CA 90032. davidbla@usc.edu

Mindfulness meditation represents a mental training framework for cultivating the state of mindful awareness in daily life. Recently, there has been a surge of interest in how mindfulness meditation improves human health and well-being. Although studies have shown that mindfulness meditation can improve self-reported measures of disease symptomatology, the effect that mindfulness meditation has on biological mechanisms underlying human aging and disease is less clear. To address this issue, we conducted the first comprehensive review of randomized controlled trials examining the effects of mindfulness meditation on immune system parameters, with a specific focus on five outcomes: (1) circulating and stimulated inflammatory proteins, (2) cellular transcription factors and gene expression, (3) immune cell count, (4) immune cell aging, and (5) antibody response. This analysis revealed substantial heterogeneity across studies with respect to patient population, study design, and assay procedures. The findings suggest possible effects of mindfulness meditation on specific markers of inflammation, cell-mediated immunity, and biological aging, but these results are tentative and require further replication. On the basis of this analysis, we describe the limitations of existing work and suggest possible avenues for future research. Mindfulness meditation may be salutogenic for immune system dynamics, but additional work is needed to examine these effects.

Keywords: mindfulness; meditation; intervention; immune system; inflammation; biology; cytokines; aging; health; disease

Introduction

Mindfulness is an intrinsic and modifiable capacity of the human mind. As a state and process of consciousness, it is most commonly defined as “the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment” (p. 145).¹ Mindfulness meditation, in turn, represents a systematic framework and process for cultivating mindfulness in daily life by intentional and sustained practice.

Several standardized programs have been developed for cultivating mindfulness meditation, with the goal of realizing its potential benefits for human health and well-being. Credit is ordinarily assigned to the 1970s Mindfulness-Based Stress Reduction (MBSR) program as the first standardized

mindfulness-based intervention (MBI). These programs are based on secularized teachings from various historical mindfulness meditation traditions, especially Eastern humanistic contemplative traditions rooted in the cultivation of personal insight and wisdom.^{2,3} To reduce symbolic dissonance and surmount cultural barriers to access and participation, MBIs serve as a template for translating ancient teachings into a language and practice that is acceptable and easily understood by contemporary society.

The presence of MBIs in major healthcare settings is at an all-time high. Indeed, almost 80% of the 140 accredited medical schools or their associated universities in the United States presently incorporate MBIs into their treatment, education, and/or research programs.⁴ Reviews of randomized controlled trials (RCTs) have shown

that MBIs can exert some beneficial effects on stress-related ailments, psychiatric disorders, and disease symptomatology.^{5–9} However, mindfulness meditation is not regarded as a therapeutic panacea for all ailments, and the effects of MBIs on health appear similar in magnitude to those demonstrated by other conventional approaches for treating stress, pain, and illness, including the administration of psychoactive medications, psychotherapy, health education, and behavior modification.^{6,10–15} MBIs nevertheless enjoy increasing appeal, stemming from a mix of promising empirical evidence, a modern medicine paradigm that increasingly emphasizes the role of patients as active and accountable participants in health care (e.g., self-management of disease and engagement in preventive behaviors),^{16–18} and a growing emphasis on transtherapeutic interventions.¹⁹

So far, the research base documenting the effectiveness of MBIs relies heavily on participants' self-reports of their own health status, which can be prone to bias.^{2,8,10,20} A more recent, yet relatively small, literature also exists examining how MBIs affect objective biological markers of human health,²¹ but to date, no comprehensive literature reviews have been conducted to evaluate how mindfulness meditation influences biological processes that are most centrally involved in disease pathogenesis. Markers of immune system activity are particularly relevant in this context, given that immune system dynamics have been implicated in several major mental and physical health problems, including asthma, rheumatoid arthritis, metabolic disorders, neurodegenerative disorders, certain types of cancer, posttraumatic stress disorder, and depression.^{22,23} Therefore, in the present review, we examined the question of whether MBIs can influence peripheral biomarkers of immune system activity.

To conduct this review, we performed a comprehensive literature search that involved identifying all of the RCTs that tested the effects of mindfulness meditation on immune system biomarkers. We focused specifically on five immune system outcomes that are relevant for health, namely (1) circulating and stimulated inflammatory proteins, (2) cellular transcription factors and gene expression, (3) immune cell count, (4) immune cell aging, and (5) antibody response. Below, we describe the methods and results of this systematic

review. We then discuss the findings and highlight lingering issues and possible avenues for future research in order to help advance the goal of better understanding how mindfulness meditation may shape biological aging and disease.

Literature review methods and findings

We scanned all potentially relevant articles published between January 1966 and July 2015 to examine the literature on mindfulness meditation and immune system activity. The year 1966 was selected as a start date because this was when the first empirical paper on mindfulness meditation appeared. The terms *immune*, *inflammation*, *cytokine*, *proinflammatory*, *biomarker*, *blood*, *saliva*, *urine*, *telomere*, and *infection* were used to search the American Mindfulness Research Association's publication database (www.goAMRA.org), which archives over 4000 published journal articles, pulling from comprehensive monthly literature searches of PubMed, Ovid, PsycINFO, Web of Science, and Google Scholar. Citations were also received from researchers in the field, and table-of-content searches were conducted for topic-specific journals. In addition to the computer-assisted searches, bibliographies of previous publications on the topic were screened for relevant articles. When required, authors were contacted to clarify details regarding their study methods or blood sampling protocols. Articles were included if they (1) used an RCT design, (2) administered mindfulness meditation as the main intervention element, (3) objectively assessed a biomarker of immune-related activity, and (4) were published in English.

Description of the field of work

Included studies

A total of 20 RCT studies met the inclusion criteria mentioned above and were thus included (Table 1). Two studies resulted in multiple publications, but these data were only counted once (Table 1; Study column). The mean sample size of these 20 studies was $n = 80$ (range: 21–201), and a total of 1602 participants were included in the analysis.

Comparison conditions

Less than half of the studies ($n = 8$; 40%) administered a comparison condition that accounted for the nonspecific effects of the intervention protocol, including time, attention, and group

Table 1. Randomized controlled trials reporting the effects of mindfulness meditation on immune system parameters

Reference	Main purpose of study	Analysis sample (n)	Comparator/ control group	Participants	Intervention description	Specimen collection	Immune-related findings
Barrett <i>et al.</i> ²⁴	Test effect of mindful meditation or exercise on incidence, duration, and severity of acute respiratory infection illness	149	Moderate-intensity exercise ^a ; waiting list	Older community adults; 82% female; ages 59.3 ± 6.6 years	MBSR derived; 8 weekly 2.5-h group sessions	Nasal wash; blood (serum, PBMCs) with influenza vaccine	>IL-8; ~neutrophils; ~virus prevalence; ~IgA, ~IgG; ~IFN-γ; ~IL-10
Hayney <i>et al.</i> ⁴⁴							
Black <i>et al.</i> ^{12,75}	Test effect of mindful meditation or sleep hygiene on sleep quality in older adults	49	Sleep hygiene education ^a	Community adults; 67% female; ages 66.3 ± 7.4 years	MAPs; 6 weekly 2-h group sessions	Blood (PBMCs)	<NF-κB (both groups)
Bower <i>et al.</i> ³⁷	Test effect of mindful meditation on stress and depressive symptoms in women diagnosed with early stage breast cancer	71	Waiting list	Breast cancer patients; 100% female; ages 46.1 (± 28.4–60 range) years	MAPs; 6 weekly 2-h group sessions	Blood (PBMCs, plasma)	<NF-κB; >IFN-1; <IL-6 (dependent on practice dosage); ~CRP; ~sTNF-RII
Carlson <i>et al.</i> ⁶⁵	Test effect of mindful meditation or group therapy/stress management on telomere length in distressed breast cancer survivors	88	Supportive-expressive group therapy ^a ; 1-day stress management seminar	Breast cancer survivors; 100% female; ages 54.4 ± 9.0 years	MBSR derived; 8 weekly 1.5-h group sessions + retreat	Blood (WBCs)	>telomere length (trend for attenuated decrease when treatment groups combined vs. seminar)
Creswell <i>et al.</i> ⁵⁹	Test effect of mindful meditation on CD4 ⁺ T lymphocyte declines in distressed HIV ⁺ adults	48	1-day stress education seminar	HIV-1 ⁺ community adults; 9% female; ages 40.0 ± 9.0 years	MBSR; 8 weekly 2-h group sessions + retreat	Blood (plasma)	>CD4 ⁺ T lymphocyte count (buffered decline vs. controls)
Creswell <i>et al.</i> ³⁸	Test effect of mindful meditation on loneliness in older adults	40	Waiting list	Lonely older adults; 80% female; ages 64.4 ± 6.0 years	MBSR; 8 weekly 2-h group sessions + retreat	Blood (PBMCs, plasma)	<NF-κB; <CRP (trend); ~IL-6
Daubenmier <i>et al.</i> ⁶⁷	Test effect of mindful meditation on telomerase activity in overweight and obese women	37	Waiting list	Overweight/obese women; 100% female; ages not indicated	MBSR derived; 9 weekly 2.5-h group sessions + retreat	Blood (PBMCs)	>Telomerase activity (trend dependent on practice dosage)
Davidson <i>et al.</i> ⁷³	Test effect of mindful meditation on brain and immune function	41	Waiting list	Corporate employees; 71% female; ages 36.0 (± 23–56 range) years	MBSR; 8 weekly 2.5-h group sessions + retreat	Blood (serum) with influenza vaccine	>Influenza antibodies
Elsenbruch <i>et al.</i> ⁴³	Test effect of mindful meditation + multimodality program on neuroendocrine and immune measures in patients with ulcerative colitis	30	Waiting list	Ulcerative colitis patients; 50% female; ages 42.9 ± 8.6 years	MBSR + mind-body program; 10 weekly 6-h group sessions	Blood (EDTA whole stimulated)	<TNF-α (trend)
Fogarty <i>et al.</i> ⁴⁶	Test effect of mindful meditation on disease activity in rheumatoid arthritis patients	42	Waiting list	Rheumatoid arthritis patients; 88% female; ages 52.0 ± 12.0 years	MBSR; 8 weekly group sessions; hours not indicated	Blood (serum)	~CRP
Gonzalez-Garcia <i>et al.</i> ⁶⁰	Test effect of mindful meditation on quality of life, emotional status, and immune status among long-term HIV patients	35	Usual care	HIV ⁺ patients; 49% female; ages 49.4 ± 5.2 years	MBCT; 8 weekly 2.5-h group sessions	Blood (WBCs)	>CD4 ⁺ T lymphocyte count (up 3 months)

Continued

Table 1. *Continued*

Reference	Main purpose of study	Analysis sample (<i>n</i>)	Comparator/control group	Participants	Intervention description	Specimen collection	Immune-related findings
Jacobs <i>et al.</i> ⁵⁸	Test effect of meditation practice on immune cell telomerase activity	46	Waiting list	Meditation retreat participants; 53% female; ages 49.0 (\pm 23–69 range) years	Mindfulness, compassion, and equanimity meditations; 3-month group residential retreat	Blood (PBMCs)	>Telomerase activity
Jedel <i>et al.</i> ³⁹	Test effect of mindful meditation on flare ups and quality of life in ulcerative colitis patients	53	Mind-body medicine course ^a	Ulcerative colitis patients in remission; 56% female; ages 46.0 ± 12.8 years	MBSR; 8 weekly 2.5-h group sessions	Blood (serum); stool	<CRP (among non-flared); ~IL-6; ~IL-8; >IL-10 (among flared); ~calprotectin
Lengacher <i>et al.</i> ^{45,66}	Test effect of mindful meditation on immune recovery following breast cancer recovery	82; 124, respectively	Waiting list	Breast cancer patients; 100% female; ages 58.0 ± 9.0 years	MBSR-derived; 6 weekly 2-h sessions	Blood (WBCs)	>T cell activation; >IFN- γ /IL-4 ratio; >CD4 $^+$ /CD8 $^+$ ratio (trend); ~CD3 $^+$, CD4 $^+$, CD8 $^+$; ~NK cells; ~B lymphocytes; >telomerase activity; ~telomere length
Malarkey <i>et al.</i> ⁴⁰	Test effect of mindful meditation on inflammatory markers in workers with cardiovascular disease risk	170	Lifestyle education course ^a	University faculty/staff with cardiovascular disease risk; 88% female; ages $51.0 (\pm 0.8$ SE) years	MBSR derived; 8 weekly 1-h group sessions + retreat	Blood (serum)	<CRP (trend); ~IL-6
Moynihan <i>et al.</i> ⁷²	Test effect of mindful meditation on brain function and antibody response in older adults	201	Waiting list	Older adults; 62% female; ages 73.3 ± 6.7 years	MBSR; 8 weekly 2-h group sessions + retreat	Blood (serum) with KLH challenge	>IgG (immediate post); <IgG (24 weeks)
Oken <i>et al.</i> ⁴¹	Test feasibility of mindfulness meditation in a clinical trial design for a larger study among caregivers	21	Dementia education course ^a ; respite care	Community-dwelling caregivers; 76% female; ages 62.5 ± 11.6 years	MBCT-derived; 6 weekly 1.5-h group sessions	Blood (serum)	~TNF- α ; ~IL-6; ~CRP
Rosenkranz <i>et al.</i> ²⁵	Test effect of mindful meditation on physiological stress and neurogenic inflammation responses	49	Health enhancement program ^a	Community volunteers; 80% female; ages 45.9 ± 10.9 years	MBSR; 8 weekly 2.5-h group sessions + retreat	Skin (blister fluid)	<TNF- α (dependent on practice dosage); ~IL-8
SeyedAlinaghi <i>et al.</i> ⁶¹	Test effect of mindful meditation on CD4 $^+$ T lymphocyte count in HIV patients	171	Education and support resources	HIV $^+$ patients; 31% female; ages 35.1 ± 6.5 years	MBSR; 8 weekly 2.5-h group sessions	Blood (plasma)	>CD4 $^+$ T lymphocyte count (up to 6 months)
Zautra <i>et al.</i> ⁴²	Test effect of mindful meditation or cognitive behavioral therapy on pain in patients with rheumatoid arthritis	137	Cognitive behavioral therapy ^a ; arthritis education course ^a	Rheumatoid arthritis diagnosed; 68% female; ages 57.3 ± 15.3 years	MBSR/MBCT derived; 8 weekly 2-h group sessions	Blood (PBMCs stimulated)	~IL-6

^aCondition is comparable based on nonspecific treatment factors, such as time, attention, and group support.

MBSR, mindfulness-based stress reduction; MAPs, mindful awareness practices; MBCT, mindfulness-based cognitive therapy; PBMCs, peripheral blood mononuclear cells; WBCs, white blood cells; KLH, keyhole limpet hemocyanin; <, decrease; >, increase; ~, null change; IL, interleukin; CRP, C-reactive protein; Ig, immunoglobulin; NF- κ B, nuclear factor- κ B; IFN, interferon; TNF, tumor necrosis factor; sTNF-RII, soluble tumor necrosis factor receptor type II; Th, T helper; and NK, natural killer.

effects. Active comparator programs included exercise, sleep hygiene, group therapies, mind–body medicine, health education courses, and cognitive behavioral therapy. Half of the studies used a waiting list or usual care group for comparison to mindfulness meditation ($n = 10$; 50%), which did not account for nonspecific effects. Other nonequivalent comparator groups included less intensive single-day educational courses, access to resource services, and short-term respite care for caregivers ($n = 2$; 10%).

Sample selection

Females were oversampled, as 14 of the 20 studies examined (70%) had samples that were 60% or more female. This is partly due to disease-specific recruitment of breast cancer patients, but may also indicate possible participation bias favoring females due to sex differences in motivation to practice mindfulness meditation or participation in research studies focused on health and wellness. Supporting this last possibility, studies sampling the general community, university staff, and corporate employees also showed proportionately greater female participation. Ten studies (50%) selected samples on the basis of disease inclusion criteria (e.g., breast cancer, HIV positive, ulcerative colitis, and rheumatoid arthritis), and five studies (25%) recruited participants on the basis of a proposed risk factor (e.g., aging, poor sleep, loneliness, overweight/obesity, cardiovascular disease). Finally, five studies (25%) recruited healthy volunteers (e.g., corporate employees, older adults, meditators, or community residents).

Intervention dosage

All but three studies included in this review administered an MBSR or MBSR-derived program (i.e., MBSR with cognitive therapy or additional psychoeducational content), indicating high similarity in intervention type across studies. Of the remaining interventions, two studies reported on the use of a standardized Mindful Awareness Practices (MAPs) course, and one study broadly defined their program as mindfulness, compassion, and equanimity meditations led by a senior meditation teacher. Of note, MAPs and the generalized mindfulness program appeared to be conceptually the same as MBSR and differed only in program dosage and degree of documented standardization. All classes were administered in weekly group-based sessions

spanning 6–10 weeks. Eight of the studies (40%) held an additional single-day intensive meditation retreat per conventional MBSR administration. Participants in one study lived at the retreat location for 3 months and practiced daily meditation.

Collection of biological specimens

Eighteen studies (90%) collected peripheral blood via venipuncture for processing of the target blood specimen or cell type. The most commonly reported processing protocol was the extraction of peripheral blood mononuclear cells (PBMCs) using ficoll for immune bioassay. This method is used to isolate leukocytes (white blood cells consisting of T, B, and natural killer (NK) cells) from other more predominant immune cells (i.e., granulocytes, including neutrophils, eosinophils, and basophils). Nasal mucous was collected in one study using a nasal wash approach during participant acute respiratory infection episodes.²⁴ Another study induced skin blisters using a vacuum-pressurized blister template and subsequently collected blister fluid.²⁵

Excluded studies

Six studies tested the effect of a mindfulness meditation intervention on at least one immune parameter,^{26–33} but were excluded because they lacked an RCT design. In brief, these quasi-experimental studies used nonrandomized matched control and single-group cohort designs. The median sample size of these six studies was $n = 51$ (range: 34–66), with samples consisting of breast cancer and prostate cancer patients, experienced meditators, HIV-diagnosed individuals, and women with a trauma history. Blood was collected in five studies (83%), and saliva was collected in one study. All interventions were MBSR or MBSR-derived programs. Significant changes in immune measures were observed for levels, count, activity, or expression of interleukins (IL)-4, IL-6, and IL-10; interferon gamma (IFN- γ); NK cells; monocytes; eosinophils; receptor-interacting serine–threonine kinase (RIPK2); cyclooxygenase (COX2); regulated upon activation normal T cell expressed and presumably secreted to stromal-derived factor ratio (RANTES/SDF-1); and telomere length. Findings from these studies may suggest potential biomarker targets for future investigation, but the results are preliminary and should be interpreted with caution.

Summary of evidence from randomized controlled trials

Below, we report the results of our systematic review of the 20 RCT studies that met all of the inclusion criteria, organized by outcome. Table 1 provides descriptions and the results of the 20 studies included in this review.

Circulating and stimulated inflammatory proteins

Inflammatory proteins are produced by immune cells and serve as extracellular communicators during immune system activity. When circulating, these proteins propagate proinflammatory (e.g., liver-derived C-reactive protein; CRP) or anti-inflammatory (e.g., cell-derived IL-10 cytokine) effects. These proteins are essential for systemic preservation (i.e., protection against autoimmunity and septic shock) and immune cell differentiation; however, dysregulated and chronically elevated levels of proinflammatory proteins increase risk for disease, poor healing, and mortality.^{34–36} Of the 20 studies reviewed, nine measured inflammatory cytokines, including IL-6, IL-8, IL-10, tumor necrosis factor (TNF)- α and its receptor agonist sTNF-RII, and IFN-I, as well as CRP.

Five studies quantified circulating levels,^{37–42} and one additional study reported on stimulated levels,⁴² of IL-6 in blood. Of these studies, one study of female breast cancer patients engaging in a 6-week MAPs course (compared to a waiting-list control group) showed a relative reduction in post-intervention circulating levels of IL-6 that was dependent on the frequency of practice dosage.³⁷ Three studies measured IL-8,^{24,25,39} one of which showed a relative increase in IL-8 in nasal secretions in older community-dwelling adults after an 8-week MBSR course (compared to moderate-intensity exercise).²⁴ In addition, two studies measured IL-10 in blood,^{24,39} one of which showed a relative increase in IL-10 in ulcerative colitis patients after MBSR (compared to a matched mind–body medicine program), specifically among patients who experienced a symptomatic flare up.³⁹ Four studies measured TNF- α ,^{25,37,41,43} of which one study of healthy community volunteers showed reductions in TNF- α in blister fluid following MBSR, with these effects being dependent on practice time,²⁵ and a second study of ulcerative colitis patients showed a trend effect for reductions in lipopolysaccharide-

stimulated TNF- α production following MBSR intervention.⁴³ Furthermore, three studies measured IFN,^{37,44,45} one of which showed a relative increase in IFN-I in female breast cancer patients after a 6-week MAPs intervention.³⁷ A second study showed that females recovering from breast cancer who received MBSR had an increased IFN- γ /IL-4 ratio. Finally, six studies measured CRP,^{37–41,46} of which three showed a reduction in CRP, with one study showing reduced CRP levels after MBSR among non-flared patients with ulcerative colitis,³⁹ and two other studies showing a trend for reduced CRP levels after MBSR-type programs among non-diseased samples displaying an inflammatory risk factor.^{38,40}

Cellular transcription factors and gene expression

Transcription factors are intracellular molecules that, in immune cells, modulate the activity of immune response genes and their production of extracellular proteins.⁴⁷ For example, nuclear factor- κ B (NF- κ B) is a transcription factor that, when activated, translocates into the cell nucleus and binds to DNA at the promoter region, thus activating genes for expression.⁴⁸ NF- κ B functions as a precursor to increased concentrations of proinflammatory cytokines in peripheral blood and thus helps coordinate the inflammatory response.^{49,50} Some psychoneuroimmunologic models propose that NF- κ B activity is a key intracellular pathway linking the central nervous system psychological threat cascade with neuroendocrine signal-mediated peripheral immune system dysregulation.^{51,52} Consistent with these models, acute psychological stress has been shown to activate NF- κ B in PBMCs.^{53–55}

Of the studies reviewed, three measured NF- κ B in PBMCs^{37,38,56} and showed a reduction in NF- κ B after the MBI. Two studies—one in lonely older adults and the other in breast cancer patients—showed a relative reduction in the expression of NF- κ B after MBSR and MAPs (compared to waiting-list controls) using promoter-based bioinformatics measures of functional genomic activity.^{37,38} A third study showed that MAPs produced a reduction in activated NF- κ B p65 in older adults exhibiting sleep disturbances; however, NF- κ B was also significantly decreased in the highly active sleep hygiene comparison condition.⁵⁶

Immune cell count

When engaged by an immune challenge, immune cells are differentially activated, generated, and then deployed by the immune system to target regions to protect the body against infection and promote tissue recovery. As such, cell distribution or count is used as a diagnostic marker for various immune-compromising diseases. For example, a decline in CD4⁺ T lymphocyte count is a standard immune cell signal of disease progression in HIV patients.⁵⁷ Further, chronic stress and depression can inhibit immune cell activity and proliferation, and thus weaken defenses against tumorigenic surveillance and growth.⁵⁸

Immune cell counts pertain to cells constituting the innate (neutrophils) and adaptive (T, B, and NK cells) subsets, and these counts were quantified in five studies.^{24,45,59–61} In one of these studies, there was no relative change in neutrophils (mucous from nasal wash) after an MBSR-derived intervention in older adults experiencing an acute respiratory illness.²⁴ Of the other four studies that enumerated lymphocytes in blood, all identified either an increase or a buffered decline in T lymphocyte cell count (CD4⁺ T, CD4⁺/CD8⁺ ratio, T helper (Th)1/Th2) and/or activation (% activated T cells) after mindfulness meditation in samples of patients diagnosed with a disease (i.e., HIV or breast cancer) as compared to controls.^{45,59,61,62} Three of these studies were restricted to people diagnosed with HIV.^{59,61,62} B lymphocyte and NK cell counts did not show relative changes in a study of breast cancer patients after intervention.⁴⁵

Immune cell aging

Immune cell telomeres are protective DNA and protein complexes that function as caps to protect and stabilize the ends of eukaryotic chromosomes, which truncate during cell division.⁶³ Shortened telomeres are a marker of immune cell aging and vulnerability to apoptosis, and are associated with poorer clinical outcomes and premature death in various age-related diseases.⁶⁴ Telomere length is protected in part by the naturally occurring enzyme telomerase, which helps slow or reverse cell aging.⁶³ Longer telomeres and higher telomerase activity are thus considered to be salutogenic immune system profiles.

Four studies measured telomere length and/or telomerase activity.^{65–68} Of the two studies that

quantified telomere length,^{65,66} one examining breast cancer survivors showed a trend for the MBSR-derived intervention to attenuate the telomere shortening observed in the control group;⁶⁵ however, these effects were observed only when samples from the mindfulness meditation and supportive group therapy groups were combined to increase statistical power. Of the three studies that measured telomerase activity, all showed an increase in telomerase activity after mindfulness meditation, at least at the trend level, among a diverse set of samples (e.g., meditation retreat participants, overweight/obese women, and breast cancer patients).^{66–68} In one of these three studies, the increase was dependent on program attendance—specifically, only high treatment-regiment adherers showed a trend for mindfulness meditation-related increases in telomerase activity.⁶⁷

Antibody response

Antibodies are immunoglobulins (IgG, IgA, IgM, IgD, and IgE) or molecules secreted by immune cells (B lymphocytes) that identify and neutralize pathogens (via antigen flagging). Antibodies constitute humoral immunity and help immune cells inactivate toxic substances, attack viruses and bacteria, and assist in the function of other immune cells. Suboptimal antibody response is commonly found in immune-compromised individuals (e.g., HIV disease progression),⁶⁹ persons experiencing chronic stress,⁷⁰ and older adults (>60 years of age).⁷¹ Antibody titer tests demonstrate serologic immunity by quantifying the level of antibodies in blood, mucous, or other tissue samples.

Antibodies were measured in three studies,^{44,72,73} two of which examined antibody response to influenza vaccination;^{44,73} one revealed that MBSR led to a significantly greater rise in hemagglutination-inhibition influenza antibody titers from the 4- to 8-week blood draw period (compared with controls in a sample of corporate employees).⁷³ The second study did not show relative changes in serum influenza antibody or nasal IgA in older adults.⁴⁴ The antigen keyhole limpet hemocyanin was administered in a third study of older adults, which showed a relatively greater increase in IgG immediately after MBSR intervention; additionally, a smaller increase in IgG was observed at the 24-week assessment.⁷²

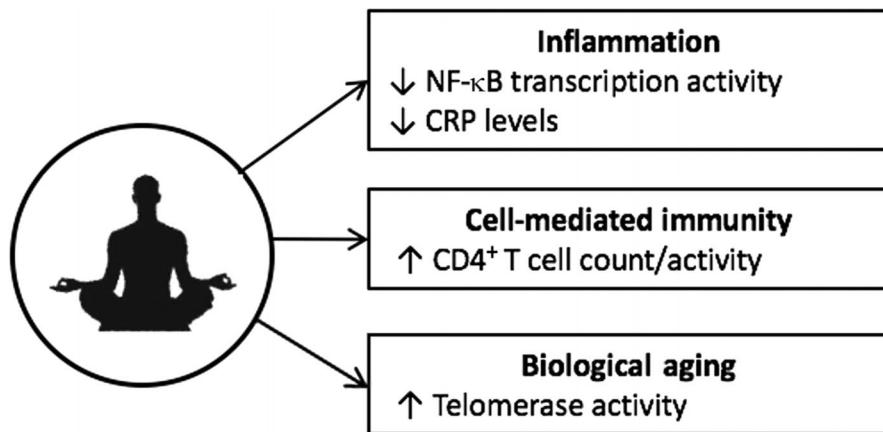


Figure 1. Mindfulness meditation and immune system biomarkers. This systematic review of 20 randomized controlled trials, comprising more than 1600 participants, revealed replicated, yet tentative, evidence that mindfulness meditation is associated with changes in select immune system processes involved in inflammation, immunity, and biological aging. NF- κ B, nuclear factor- κ B; CRP, C-reactive protein.

Summary of evidence and implications for future research

The present review is the first to interrogate the findings of the RCTs that have been conducted to date on mindfulness meditation and the immune system. This comprehensive examination included data from 1602 participants and revealed tentative evidence that mindfulness meditation is associated with changes in select biomarkers of immune system activity. When using the criteria of three or more RCTs showing that mindfulness meditation has at least a trend-level or dosage-dependent effect on immune parameters, we identified mindfulness meditation-related effects for the following four parameters: reductions in the activity of the cellular transcription factor NF- κ B, reductions in circulating levels of CRP, increases in CD4 $^{+}$ T cell count (in HIV-diagnosed individuals), and increases in telomerase activity (Fig. 1). In contrast, null findings or a lack of replicated effects were found for antibodies (IgA, IgG, influenza), interleukins (IL-1, IL-6, IL-8, IL-10), IFN- γ , TNF- α , and various measures of cell count. Considered together, these data point to promising areas of future investigation, but we caution against exaggerating the positive effects of mindfulness meditation on immune system dynamics until these effects are further replicated and additional studies are performed.

With respect to the abovementioned preliminary positive effects that replicated across studies,

if robust and maintained over time, these types of shifts in immune system activity could potentially have beneficial effects on health by influencing mechanisms that are known to affect biological aging and disease. For example, countering a dysregulated or hypersensitive immune system profile with mindfulness meditation could theoretically function to improve organism fitness by enhancing immune defenses that protect against viral and bacterial infection, as well as various age-related disease conditions, including cardiovascular disease, osteoporosis, arthritis, type 2 diabetes, frailty, and some cancers. To test this possibility, future studies will need to examine associations between mindfulness meditation, immune function, and disease symptomatology.

Insights garnered from this review provide the basis for further theory building and empirical investigation into if, and if so, how, mindfulness meditation influences biological processes involved in aging and disease. For example, these findings extend existing models of mindfulness meditation, which suggest that mindfulness meditation may downregulate the activity of major stress axes in the body, such as the sympathetic-adrenal-medullary and hypothalamic-pituitary-adrenal axes,²¹ which are known to influence some of the immune system mechanisms identified in this review. To fully realize the benefits of this work for improving health, however, additional RCTs are needed that examine the robustness and

generalizability of the present immune-related findings, as well as their relevance for predicting changes in clinical outcomes over time.

Looking forward, there are several points that should be considered when planning future studies on mindfulness meditation and immune system dynamics. First, only 40% of the RCTs reviewed used control programs that could account for non-specific treatment effects. This leaves substantial room for improving study designs by using comparator groups that are better than a waiting-list control condition. Indeed, a description of a standardized active control condition that can be used alongside MBIs was recently made available for trial researchers.⁷⁴ Second, the effects of mindfulness meditation on immune system biomarkers were dosage dependent in some instances. As a result, beyond obtaining adequate sample sizes, future studies and interventions will benefit from maximizing treatment adherence. This also highlights a need for researchers to collect data on individuals' class attendance and/or home practice schedules, and to report on both the overall effects and dosage-dependent effects when publishing trial results.

Third, in the studies reviewed, immune biomarkers were often included as ancillary measures and, consequently, hypothesis tests were frequently underpowered. To truly advance this area of study, future projects will need to power studies and calibrate tests for changes in immune parameters as primary outcomes, *a priori*, to avoid false negative results. It will also be important to provide clearer rationales for the immune biomarkers chosen for inclusion and better descriptions of how those biomarkers relate to the pathophysiologic process being studied. Fourth, almost all of the RCTs examined (19/20 studies) employed peripheral blood as the main human specimen with which to quantify immune function. This is a notable and consistent strength across studies, but it also highlights an opportunity for future studies to investigate other less invasive specimens (e.g., mucous, saliva, urine, hair) that could be validated against blood and potentially used as biomarkers of mindfulness meditation-related changes in immune system dynamics. Finally, the specimen collection and processing procedure employed by several studies was not well described, thus highlighting an opportunity to improve the reporting of study procedures to enhance researchers' ability to replicate study

protocols, especially with respect to the timing of specimen collection, steps taken for sample processing and storage, and procedures used for assay quantification.

In conclusion, across 20 RCTs and more than 1600 participants, we found tentative evidence that mindfulness meditation modulates some select immune parameters in a manner that suggests a more salutogenic immune profile. Specifically, mindfulness meditation appears to be associated with reductions in proinflammatory processes, increases in cell-mediated defense parameters, and increases in enzyme activity that guards against cell aging. Although these findings replicated and are based on well-designed RCTs, they are restricted to particular populations, subgroup analyses, and disease types. Consequently, additional research is needed to test the effects of mindfulness meditation on immune system biomarkers to provide a clearer understanding of the robustness and generalizability of findings, and to examine the relevance of these findings for clinical symptoms and overall health.

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Conflicts of interest

The authors declare no conflicts of interest.

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