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Differential Reduction of IP-10 and C-Reactive Protein via Aerobic Exercise or Mindfulness-Based Stress-Reduction Training in a Large Randomized Controlled Trial

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Abstract

Exercise and meditation improve health and well-being, potentially through decreasing systemic inflammation. In this study, healthy adults ($N=413$) were randomized to 8 weeks of training in aerobic exercise, matched mindfulness-based stress reduction, or wait-list control. Three inflammation-related biomarkers (C-reactive protein, interleukin-6, and interferon-gamma-inducible protein-10) were assessed preintervention, directly postintervention, and 17 weeks later. Within-group analyses found that exercise participants had decreased serum interferon-gamma-inducible protein-10 postintervention and 17 weeks later, whereas C-reactive protein was lower in mindfulness-based stress-reduction participants 17 weeks postintervention only. Self-reported physical activity or amount of meditation practice did not predict biomarker changes. This study suggests that (a) training in aerobic exercise can lower interferon-gamma-inducible protein-10, a chemokine associated with interferon activity and illness, and (b) training in mindfulness meditation may have a delayed effect on C-reactive protein, an important inflammatory biomarker. The findings highlight the likelihood of multiple, distinct pathways underlying the health-promoting effects of these lifestyle interventions.

Keywords

inflammation; intervention; meditation; physical activity

Numerous studies have demonstrated the importance of inflammatory processes in the progression from health to illness. Elevated inflammatory indicators are associated with both physiological and psychological disturbance, including chronic stress (Libby, 2002, 2007; Miller, Maletic, & Raison, 2009; Rosenkranz, 2007; Wellen & Hotamisligil, 2005). Commonly employed measures include C-reactive protein (CRP) and interleukin-6 (IL-6),

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which respond acutely to infection or trauma but can also reflect subclinical pro-inflammatory activity. In addition, in clinical settings, interferon gamma-induced protein 10 (IP-10 or CXCL10), has recently been employed as an early diagnostic chemokine marker of infection, although its normal variation in healthy individuals is largely unexplored. Elevations in serum levels of inflammatory biomarkers are found in patients with chronic inflammatory conditions, supporting their use as surrogate markers to assess the inflammatory state of the body (Gabay & Kushner, 1999; Lyons & Basu, 2012). In addition, tissue pathophysiology results from the chronic release of pro-inflammatory cytokines (e.g., IL-6) involved in the acute-phase response and associated proteins (e.g., CRP and IP-10), and the systemic levels of inflammatory proteins appear related to both physical and mental health (Ridker, Hennekens, Buring, & Rifai, 2000; Sternberg, 1997).

It is clear that the practice of meditation has substantive health benefits (Eberth & Sedlmeier, 2012; Goyal et al., 2014; Keng, Smoski, & Robins, 2011). Along with the cognitive and emotional state of mindfulness, or being focused in the present, meditation has additional benefits for overall psychological well-being. Not only are mindfulness and meditation associated with improved attentional skills and emotional regulation, recent neuroimaging studies have demonstrated specific effects of mindfulness and meditation on key brain areas thought to be involved in these processes, including the anterior cingulate cortex, frontal, and prefrontal regions (Marchand, 2014; Tang, Hölzel, & Posner, 2015). While activity in some brain regions may be involved in the benefits of meditation, the mechanisms through which training in meditation and mindfulness acts to improve health remain unclear. A recent review (Black & Slavich, 2016) on the immune effects of mind-fulness meditation found reports of decreases in CRP in three out of six studies that measured CRP following training in mindfulness-based stress reduction (MBSR), but inconsistent or null findings on other circulating immune biomarkers. However, considerable research links systemic inflammation to significant effects on brain functioning (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Perry, 2004) and reductions in systemic inflammation may be one way that MBSR exerts its positive effects. Although speculative, MBSR may also lead to decreased stress and decreased stress hormones (e.g., cortisol), which could result in improved cytokine regulation (Webster, Tonelli, & Sternberg, 2002). Based on the extant literature, our a priori hypothesis was that training in MBSR would lead to a decrease in biomarkers associated with inflammatory activity. Most importantly, the variation in findings across smaller studies indicated that a larger trial could be of value, especially with a contemporaneous control arm to provide a more robust evaluation of the potential anti-inflammatory effects of meditation training.

More consistent results have been found on the health-promoting benefits of regular exercise, including that regular moderate exercise can reduce inflammatory physiology (Nieman, 2012; Nieman & Pedersen, 1999). Various mechanistic pathways have been proposed to link inflammation with exercise behavior. For example, exercise can acutely stimulate the release of stress hormones during each session and for a period afterward, which may dampen and regulate general inflammatory activity in the long term (Nieman, 2003). In addition, toll-like receptors, which are involved in cytokine production, are expressed at lower rates after exercise training, potentially leading to decreased circulating cytokine levels in circulation (Gleeson, McFarlin, & Flynn, 2006). While the specific

pathways linking exercise to inflammatory activity are unclear, population-based studies and randomized controlled trials (RCTs) have consistently demonstrated significant associations between physical activity or fitness and lower levels of CRP and IL-6 (Lavie, Church, Milani, & Earnest, 2011; Nieman, 2012). In addition, increased fitness or exercise frequency is associated with fewer acute respiratory tract infections (Nieman, Henson, Austin, & Sha, 2011), supporting the conclusion that regular exercise is associated with enhanced immune defense and competence. However, few studies have directly compared the relative inflammatory marker benefits of an intervention to promote exercise with the outcomes of a different, matched lifestyle intervention, such as MBSR. A direct, within-study comparison would provide an important step in identifying optimal lifestyle interventions for improving inflammatory and health-related biomarkers.

The inflammatory chemokine, IP-10, is expressed in response to stimulation by both interferon gamma and interferon alpha (Dufour et al., 2002; Liu et al., 2011; Neville, Mathiak, & Bagasra, 1997). Patients with a number of inflammation-related diseases present with increased IP-10: obesity, insulin resistance, and autoimmune diseases, as well as being present at elevated levels in Alzheimer's disease models (Antonelli et al., 2014; Liu et al., 2011; Parachikova, Nichol, & Cotman, 2008). It also appears that IP-10 may be useful as a biomarker of symptom severity in a number of infectious diseases (Hayney et al., 2017; Liu et al., 2011; Ruhwald et al., 2008; Ruhwald, Bjerregaard-Andersen, Rabna, Eugen-Olsen, & Ravn, 2009). Thus, it was reasonable to hypothesize that anti-inflammatory lifestyle interventions, such as MBSR or exercise training, could induce some of their health benefits through limiting the production or activity of this chemokine.

Therefore, the purpose of the present analysis was to assess the influence of 8 weeks of two popular lifestyle interventions (aerobic exercise training and MBSR) or a wait-list control condition on serum levels of three inflammatory biomarkers (CRP, IL-6, and IP-10). Through this analysis, we aimed to identify the relative benefits of these lifestyle interventions on immune parameters as one potential pathway to better overall health. We hypothesized that both aerobic exercise training and MBSR would decrease the levels of inflammatory biomarkers in circulation (CRP, IL-6, and IP-10). Furthermore, in their review of the mindfulness RCT literature, Black and Savich (2016) found that the magnitude of change in biomarkers in response to mindfulness programs was related to the amount of practice, suggesting a potential dose-response relationship between practice and anti-inflammatory benefits. Accordingly, we also hypothesized that if significant changes occurred following an intervention, time spent (i.e., minutes of meditation practice or exercise) would be significantly related to magnitude of the reduction in biomarker levels supporting the benefits of participating and adhering to the intervention.

Methods

This report summarizes a secondary analysis from a RCT assessing the utility of exercise or meditation training for reducing the incidence, duration, and severity of acute respiratory infection (MEPARI-2). A description of the trial can be found at [clinicalTrials.gov](https://clinicaltrials.gov) (NLM identifier: NCT01654289) and elsewhere (Barrett et al., 2018; Goldstein, Topitzes, Brown, & Barrett, 2018; Hayney et al., 2017; Maxwell, Barrett, Chase, Brown, & Ewers, 2015;

Meyer et al., 2018). All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the local institutional review board for Human Subjects Research. Our study considered CRP, IL-6, and IP-10 together as a coherent inflammatory panel for evaluating the health-promoting benefits of exercise and meditative practice to reduce general inflammatory activity in healthy middle-aged and older adults.

Adults aged between 30 and 69 years were recruited from the community. Study participants were generally healthy but reported being inactive and having at least one cold annually to improve the likelihood for seeing effects on cold severity and duration in the primary analysis (see Barrett et al., 2018). Participants were recruited through local advertisements, and following phone screening, participants were invited to enroll in an initial 2-week run-in phase (during which no interventions were received). Run-in tasks included in-person baseline questionnaires, at least one phone contact, completion of self-report questionnaires at home, and return for the subsequent visit 2 weeks later. Upon successful completion of the run-in period, participants gave informed consent for the main trial and were randomized (1:1:1) to one of three parallel arms: exercise, meditation, or observational control. Each participant received the next sequentially numbered sealed envelope containing randomization codes generated by the study statistician using permuted variable-sized block randomization (SAS software; SAS Institute Inc., Cary, NC). Those randomized to the exercise and meditation arms participated in 8 weeks of training in their assigned intervention. The in-class training including one weekly group class (2.5 hr) and instructions to practice the intervention starting at 20 min each day and working up to 45 min of daily practice across the intervention. Practice was encouraged both during and after the 8-week interventions. Participants were followed from August to May of the following year with the exercise or meditation training occurring in September and October. Participants in the wait-list control group were provided the opportunity to enroll in MBSR or aerobic exercise classes after the study period. Study personnel who interacted with participants and processed biological specimens were blind to group assignment.

Biomarker and demographic assessments were obtained at study entry prior to randomization (baseline); blood samples were collected, and body mass index (BMI) determined again following the 8-week interventions in December (follow-up 1, FU1) and at week 25, approximately 17 weeks postintervention in March (follow-up 2, FU2). Participants exited the main trial in May. Self-reported physical activity level over a typical week was recorded using the Global Physical Activity Questionnaire (GPAQ), a valid and reliable self-report questionnaire (Bull, Maslin, & Armstrong, 2009), which was filled out at study entry (baseline), at November (FU1), and at March (FU2). Participants were queried about their health status when reminder calls were made for their follow-up appointments. Participants who indicated that they were sick prior to any of their visits were rescheduled to 7 days after their last symptom abated, ensuring that no participants were ill at the time of their follow-up visits. The GPAQ total score provides a value in MET-minutes (metabolic equivalents $\times$ minutes), which represents the sum of self-reported physical activity accumulated across three domains: work, transport, and leisure time. Values at FU1 include November data for the GPAQ and December data for biomarkers, whereas values used at FU2 represent measures obtained in March for both the GPAQ and biomarkers.

Interventions

The MBSR intervention consisted of 2.5-hr sessions once per week for 8 weeks with an additional “half-day retreat.” This summed to roughly 25 hr of contact time. Class involved systematic training in the development of a sustained, nonaroused state of attention and clear awareness. The goal was to cultivate attitudes of self-appreciation, compassion, and empathy, with each class period generally involving a review of assigned practice, new content, and hands-on practice/experience with new techniques or skills. Participants were instructed to practice either formal or informal meditation at home each day. Mindfulness practice was further defined as “*Formal practice* is when you schedule specific time to just do that particular activity. For example, scheduling 15 minutes to sit and focus on your breath is formal meditation practice. Taking a moment to notice your breath during your work day is *informal practice*. Scheduling time to take a walk for the purpose of practicing meditation is formal practice. Walking mindfully from your kitchen to the living room is *informal practice*.”

The exercise intervention also consisted of 2.5-hr sessions once per week for 8 weeks with an additional “half-day retreat.” Again, totaling 25 hr of contact time. Class time included 1.5 hr focused on cognitive behavioral concerns related to exercise initiation and participation and 1 hr of exercise including a warm-up, aerobic exercise, and a cooldown. Participants were instructed to exercise at either moderate or vigorous intensity on their own each day. Exercise intensity was defined as “A *moderate* level of physical activity noticeably increases your heart rate and breathing rate. You may sweat, but you are still able to carry on a conversation. With *vigorous* activity, you are breathing rapidly and are only able to speak in short phrases. Your heart rate is substantially increased, and you are likely to be sweating.” Intensity monitoring was also performed through using Borg’s 6–20 rating of perceived exertion scale (Borg, 1998) following standardized instructions provided in-class.

Interventions were completed in a group setting with approximately eight participants in each group. The half-day retreats included individual and group practice, presentations, and group discussions.

Biomarker Assessments

Blood samples were collected in a plasma separator tube containing lithium heparin and a second vacutainer with no anticoagulant by nurse phlebotomists using standard venipuncture techniques. The plasma separator tube was sent to UW Hospital and Clinics Laboratory, where high-sensitivity CRP was measured using a turbidimetric assay (Beckman Coulter, Brea, CA). Serum samples were aliquoted from the second tube and stored at –80 °C until processing. Serum IL-6 and IP-10 concentrations were measured using enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN). A standard curve was generated using the calibrators included in the kit, and the concentrations of IL-6 and IP-10 in the serum samples were calculated with respect to this reference curve. Samples were run in duplicate and the values were averaged.

Weekly Practice Logs

Participants in each intervention were instructed to record the minutes they spent practicing each day and to enter these data using online software each week throughout the intervention and follow-up period using the above definitions for informal/formal meditation and moderate/vigorous exercise. Participants in the exercise group reported their moderate and vigorous exercise in minutes each day. To assess practice engagement, weekly activity from these logs was averaged separately across the weeks prior to FU1 and FU2 to generate mean weekly practice minutes to compare with biomarker changes.

Data Analysis

Based on the nonnormality of the biomarker and practice measures, nonparametric tests were employed for all analyses. As is common in biomarker analyses, skewness at each time point was quite high across biomarkers and skewed to the right (skewness range: 2.65–13.81), while kurtosis values were also high across biomarkers and time points (kurtosis range: 12.90–236.22). Thus, most of the statistical comparisons were conducted with nonparametric tests. Low-grade systemic inflammation has been associated with BMI (Fantuzzi, 2005), so to confirm the expected relationships between BMI and inflammatory markers, Spearman correlations (ρ) were computed to assess associations at baseline. To assess the relative influence of the interventions on each biomarker, the Kruskal–Wallis test was employed to compare groups (nonparametric test for independent samples), and Friedman's test was used to assess changes over time (nonparametric test equivalent to repeated-measures analysis of variance). Follow-up pairwise comparisons using Wilcoxon signed-rank tests or Mann-Whitney U tests assessed significant differences between two time points or between two groups, respectively. Effect sizes were calculated by dividing the Z score by the square root of the number of observations over the time points, and values were interpreted based on Cohen's ranges: 0.1 for a small effect, 0.3 for a medium effect, and 0.5 for a large effect (Cohen, 1988).

To evaluate effects of intervention practice on biomarkers, Spearman correlations were calculated to assess relationships between minutes practicing the interventions and changes in biomarkers at FU1 and FU2. For these analyses, practice minutes were self-reported minutes per week of formal or informal meditation (meditation group) or moderate or vigorous exercise (exercise group). Mean minutes practicing in weeks prior to FU1 were correlated to biomarkers changes at FU1, whereas mean minutes practicing across intervention and the follow-up period were correlated with biomarker changes at FU2. Total scores from the GPAQ were compared across time points (Friedman's test) and across groups (Kruskal-Wallis) to assess the effects of the interventions on overall physical activity. Total scores from the GPAQ were also correlated to changes in significant biomarkers in the exercise group using Spearman correlations as a further assessment of the potential relationship between biomarker changes and self-reported exercise.

Results

The full trial included 413 participants who completed the run-in assessment, provided informed consent, and were randomized. Of these, 385 (mean age: 49.7 ± 11.6 years; mean

BMI: 29.3 ± 7.2 kg) provided complete baseline data, had at least one follow-up sample for each of the biomarkers, and completed the FU2 assessment (Figure 1). The overall RCT was run in four annual waves from August 2012 to May 2016, with randomization to each of the three conditions in each cohort. Participants were predominantly overweight, female, White, and employed full-time (Table 1). In the entire cohort, mean BMI at FU1 was 29.4 ± 7.7 and at FU2 was 29.3 ± 7.4 demonstrating stability of BMI across the follow-up period and the interventions. Relationships at baseline between BMI and biomarkers were $\rho = .37$ ($p < .001$) for IL-6, $\rho = .44$ ($p < .001$) for CRP, and $\rho = .19$ ($p < .001$) for IP-10. In the entire cohort, mean BMI at FU1 was 29.4 ± 7.7 and at FU2 was 29.3 ± 7.4 demonstrating stability of BMI across the follow-up period and the interventions.

Biomarkers Across Groups and Time

Between-group analyses indicated that there were no statistically significant differences between the people assigned to the three study conditions in the overall levels of the biomarkers at any time point (Kruskal-Wallis tests; all $ps > .05$). However, significant within-group changes did occur across time (Table 2).

C-Reactive Protein.—Small but statistically significant changes in CRP were found over time. In the entire cohort, CRP peaked at FU1 and then declined below baseline values at FU2, with both FU1 and FU2 being significantly different from baseline (Friedman's two-way analysis of variance by ranks test; $p < .05$). These temporal trends during the extended follow-up were observed primarily in the meditation condition. At FU1 in the meditation group, CRP was higher compared with baseline (not significant), and CRP was significantly lower at FU2 than either baseline or FU1 ($p < .05$).

Interleukin-6.—Serum IL-6 levels were not significantly affected by either the intervention condition or time point across the study (all $ps > .05$). The concentrations remained relatively stable and did not change following the initiation of meditation practice or exercise, although IL-6 was moderately correlated both with CRP levels ($\rho = .54-.59$; $p < .001$ for all three time points) and with BMI across all participants ($\rho = .52-.56$; $p < .001$ for all three time points).

Interferon Gamma-Induced Protein 10.—Overall, serum IP-10 concentrations decreased for the entire study cohort over time ($p = .007$). However, this observed effect was accounted for primarily by the individuals assigned to the exercise group. Serum IP-10 decreased significantly in the exercising participants across time ($p = .005$) from baseline to FU1 ($p < .001$), remaining significantly lower than baseline at FU2 ($p = .017$; Figure 2). Significant changes in IP-10 concentrations were not observed in the controls over time ($p = .32$) nor for those assigned to meditation ($p = .59$).

Self-Reported Physical Activity Across the Study

Global Physical Activity Questionnaire.—At baseline, prior to assignment to interventions, there appeared to be a small but statistically significant difference between the groups in the total amount of physical activity self-reported on the GPAQ ($p = .05$). There was a significant pairwise difference between participants that would be assigned to be

observational controls versus exercise training, with controls self-reporting more exercise at baseline ($p = .014$), prior to randomization. Pairwise comparisons indicated that participants who would be assigned to meditation training did not differ from either the controls or those assigned to exercise training ($p > .22$). Confirming the expected effect of the intervention, MET-minutes changed from baseline to FU1 and from baseline to FU2 ($p < .001$) in those assigned to the exercise group and were significantly different than controls or meditators at FU1 and FU2 ($p < .001$ for all comparisons; Table 3). Across study time points, GPAQ values did not change significantly in either the MBSR or control group.

Practice Logs.—Median weekly practice values (Table 4) indicated that participants in the exercise group generally engaged in approximately 4.5 hr/week in moderate or vigorous physical activity up to FU1 and more than 5 hr/week up to FU2. Participants assigned to MBSR training self-reported approximately 5 hr of total practice per week during the training period and a sustained practice of nearly 4 hr/week up to FU2.

Association Between Self-Reported Practice and Significant Changes in Serum Biomarkers

Neither the time spent in self-reported physical activity practice (weekly logs) nor the duration of moderate and vigorous exercise at FU1 or FU2 (GPAQ) was significantly related to the magnitude of change in serum IP-10 over time for those in the exercise group (all p s $> .05$). Similarly, time spent in self-reported meditation practice was not significantly related to the magnitude of the decrease in plasma CRP for those in the MBSR group (all p s $> .05$). Table 5 summarizes the nonsignificant correlations between practice and serum IP-10 in exercise or plasma CRP in meditation participants, respectively. Thus, variation in adherence to the training recommendations in terms of minutes of meditative practice or exercise did not appear to account for the group effects on IP-10 and CRP levels.

Discussion

These results indicate that 8 weeks of aerobic exercise training was associated with a decrease in serum IP-10 in healthy adults. The observed significant reduction in CRP levels 17 weeks after MBSR training is the first in a large-scale randomized-controlled trial, corroborating and extending previous data from much smaller studies (Malarkey, Jarjoura, & Klatt, 2013). It was somewhat surprising that the cytokine, IL-6, did not show similar changes, as it is thought to be responsive to psychological state, behavior, and lifestyle as well as adiposity and other physiological states. The stability of the participants' BMI across time, even in those who exercised more often, could indicate that IL-6 levels may be influenced more by adiposity and potentially by weight loss than by either exercise behavior or meditation training in healthy adults. Serum levels of IP-10 did not change over time in those assigned to meditation training or serving as observational controls, suggesting that the decrease in IP-10 may reflect a specific physiological adaptation aside from weight or BMI changes that is associated with regular exercise (e.g., increased muscle mass).

The CRP and IL-6 results corroborate and extend those of another randomized controlled study in generally healthy individuals. Malarkey et al. (2013) reported a nonsignificant decrease in CRP ($p = .08$) following a modified 8-week mindfulness-based intervention in

university faculty and staff ($n = 84$) with initially elevated CRP (>3.0 mg/ml) along with no changes in serum IL-6. The present results extend those findings to individuals more representative of the general population. The reduction in CRP only in the MBSR group, and only after 17 weeks postintervention, suggests that the influence of meditation's influence on the body is different from exercise, and may be delayed. Although this finding concurs with a previous report, it should be acknowledged that our study enrolled only participants in good health, with generally normal CRP levels below the level thought to increase risk for clinical disease (Ridker, 2003). Although the CRP changes observed were relatively small (from 1.6 to 1.7 to 1.3 mg/L), this relative magnitude of change could be important, given the known association between CRP, immune responses to infection, and cardiovascular disease (Pearson et al., 2003). The significant decrement in CRP was not evident until the second follow-up time point (FU2), which may indicate that meditative practice must be sustained before eliciting this beneficial effect on hepatic function and CRP production.

A tentative connection between IP-10 and exercise is beginning to emerge. Both resistance and aerobic exercise training appear to attenuate high-fat diet-related increases in IP-10 in mice (Mardare et al., 2015). Similarly, resistance exercise prevented the increase in circulating IP-10 seen following 60 days of bed rest (Hoff et al., 2015). On the other hand, intramuscular IP-10 increases following muscle-damaging exercise. Significant increases in IP-10 occur after a single (Hyldahl, Olson, Welling, Groscost, & Parcell, 2014) and a second (Deyhle et al., 2015) eccentric exercise bout, suggesting a role in the acute inflammatory response (and, potentially, in the damage-to-repair response) to exercise. Therefore, the present investigation adds evidence from a large-scale RCT in the general population to this developing body of literature by demonstrating that chronic aerobic exercise training may reduce circulating IP-10 levels in healthy adults.

The decrease in circulating IP-10 with exercise in the present investigation is also interesting in the context of previous research evaluating IP-10 in obesity and its relationship to exercise training. Mendelson et al. (2015) found that IP-10 concentration decreased following 12 weeks of exercise training in obese adolescents, and the authors presented this as evidence of an improved inflammatory profile. Circulating IP-10 levels are higher in obese individuals, although they have not previously appeared to be largely influenced by physical activity in adults (Kitahara et al., 2014). Kitahara et al. (2014) assayed 78 different immune markers in a large cohort of healthy older individuals (55–74 years old) and, although greater self-reported physical activity was associated with lower serum IP-10 levels, the association did not reach statistical significance. To our knowledge, however, the decrease in circulating IP-10 following exercise training seen in the present study in healthy, generally overweight adults has not been reported previously.

The exercise group reported significantly increasing their physical activity, both during and for months after the intervention. The effectiveness of the training evident in scores on the GPAQ was mirrored by reports of substantially increased physical activity from the weekly logs across the intervention and through FU2. Nevertheless, the physical activity data from both the GPAQ and the exercise logs were not directly related to the magnitude of the decline in IP-10 at either FU1 or FU2 (Table 5; Figure 2). Further research is now needed to determine if there is a threshold effect associated with increased activity, and that one should

not expect a linear relationship, or if IP-10 levels really reflect a multitude of factors associated with physical activity. Similarly, we did not find that minutes engaged in meditative practice were directly linked to the magnitude of the decrease in CRP at FU2 (Table 5). It is important to note that both meditation and exercise, aside from potential effects on inflammatory biomarkers, consistently lead to significant mental and physical health benefits (Grossman, Niemann, Schmidt, & Walach, 2004; US Department of Health and Human Services, 2018), and practicing either intervention for hours each week for months after the intervention is likely to have provided other substantial benefits. Future research may need to evaluate other components of the response to these interventions, such as the specific physical activities, changes in objective measures of exercise (i.e., accelerometry or fitness testing), or other changes in lifestyle, which may account for the anti-inflammatory effects. It should also be acknowledged that our physiological indices were derived solely from peripheral blood, and a delineation of mediators may require a more detailed and mechanistic probing of cellular processes.

Strengths and Limitations

The data were derived from a large RCT conducted in healthy adults to investigate whether meditation or exercise would reduce the incidence of respiratory infection (Barrett et al., 2018). Thus, it should be acknowledged that neither CRP nor IP-10 was originally the primary endpoint, and this analysis is a secondary one focused on inflammatory pathways. Because the inclusion and exclusion criteria for this RCT also led to the participants being quite healthy, the magnitude of changes in these biomarkers might not have been as large as what would occur in a patient population selected for having an inflammatory condition. In addition, while the effectiveness of the exercise training was impressive in that participants reported increased activity across the 25 weeks, even this change in physical activity was not sufficient to reduce the participants' BMI. One would expect larger changes in inflammatory biomarkers following interventions that impact adiposity.

This study found that both the exercise and meditation training led to self-reports of 4–5 hr each week spent practicing, an effect that may have been partially inflated by the tendency of people to positively bias self-reported health behaviors (Brenner & DeLamater, 2014; Taber et al., 2009). Nevertheless, the daily logs and weekly self-report methods used in this study did capture day-to-day meditative and exercise practice across the 25-week period, providing excellent time resolution for a trial of this size. Although self-reported physical activity in the MBSR group showed little change in physical activity to FU1 or FU2 (Table 3), we did not have any measure of meditative practice in the exercise group, which could have been initiated as a result of participation in this study. Finally, care should be taken when interpreting the relative benefits of exercise versus meditative practice as the significant effects reflected differential changes in values over time, rather than a large main effect between the two interventions at either time point during the follow-up period. However, one important strength of the RCT design was that the duration of the training for both exercise and MBSR was closely matched, and both were comprised of eight weekly training sessions. Moreover, participants were randomly assigned to each condition and did not self-select exercise or meditative practice, which could also influence the magnitude of the benefits.

Future Directions

Although the present findings should be interpreted cautiously as they derive from secondary analyses, further research is now needed to determine if the decrease in IP-10 plays a mediating role for some of the anti-inflammatory and health benefits of moderate exercise. At a minimum, these results highlight the potential utility of IP-10 as a biomarker sensitive to exercise, given that it has been more commonly used as a clinical indicator of viral and bacterial infection (Liu et al., 2011). At the same time, these results suggest potentially independent physiological effects of MBSR and exercise, indicating that future research that combines these two lifestyle practices could lead to additive immunological effects. Indeed, mindfulness training may influence exercise behavior (Meyer et al., 2018; Ulmer, Stetson, & Salmon, 2010) and dual mind-body approaches to improving health may be more effective than targeting either the “mind” or “body” separately.

Conclusions

The findings indicate that IP-10 was uniquely influenced by exercise training and not by meditation training. Thus, IP-10 may provide an important reflection of the anti-inflammatory effects of sustained, moderate exercise training in healthy adults. The changes in IP-10 appeared to be the result of a general increase in physical activity and were not specifically related to the amount of exercise per week. By contrast, the decrease in CRP levels occurred only in those who were meditating and was delayed until 17 weeks after training. Together, these findings suggest there may be different anti-inflammatory processes associated with the health-promoting benefits of these widely used behavioral health practices.

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Figure 1 —. CONSORT (Consolidated Standards of Reporting Trials) diagram for MEPARI-2 (meditation or exercise for preventing acute respiratory infection) main trial with exclusions specific to the present analysis.

Figure 2 —.
Serum IP-10 concentration (in picograms per milliliter) in the exercise group across the intervention. IP-10 = interferon-gamma-inducible protein-10.

Table 1

Demographic Information

	Entire cohort	Control	Meditation	Exercise
<i>n</i>	385	132	127	126
Age (years), mean (SD)	49.7 (11.6)	50.9 (12.1)	49.3 (11.2)	49.0 (11.4)
Body mass index, mean (SD)	29.3 (7.2)	29.0 (6.6)	29.6 (7.8)	29.3 (7.0)
Male sex, <i>n</i> (%)	92 (24)	33 (25)	32 (25)	27 (21)
Race, <i>n</i> (%)				
Black/African American	19 (5)	5 (4)	3 (2)	11 (9)
White	331 (86)	118 (89)	113 (89)	100 (79)
Asian	13 (3)	3 (3)	4 (3)	6 (5)
More than one race	11 (3)	3 (3)	1 (1)	7 (6)
Other/missing	11 (3)	3 (3)	6 (5)	2 (2)
Education, <i>n</i> (%)				
Some high school	3 (1)	1 (1)	1 (1)	1 (1)
High school graduation/GED	11 (3)	3 (2)	2 (2)	6 (5)
Some college/tech school	71 (18)	29 (22)	24 (19)	18 (14)
College graduation (bachelor's)	133 (35)	51 (38)	40 (31)	42 (33)
College postgraduation (master's/doctoral)	166 (43)	48 (36)	60 (47)	58 (46)
Missing	1 (<1)	0 (0)	0 (0)	1 (1)

Serum Biomarkers Over Time

Table 2

Biomarker	Baseline	Follow-up 1	ES change from baseline	Follow-up 2	ES change from baseline	^a <i>p</i>
C-reactive protein (mg/L)						
Entire cohort (<i>N</i> = 380)	1.4 (0.7–4.4)^c	1.6 (0.7–4.2)^d	0.0026	1.3 (0.6–3.4)^{c,d}	0.18	.005
Control (<i>n</i> = 130)	1.5 (0.7–4.7)	1.6 (0.7–4.2)	0.026	1.4 (0.6–3.8)	0.14	.22
Meditation (<i>n</i> = 126)	1.6 (0.7–4.5)^c	1.7 (0.8–4.8)^d	0.034	1.3 (0.7–3.4)^{c,d}	0.25	.001
Exercise (<i>n</i> = 124)	1.4 (0.6–4.0)	1.7 (0.7–3.3)	0.0060	1.3 (0.6–3.2)	0.16	.073
Interleukin-6 (pg/ml)						
Entire cohort (<i>N</i> = 383)	1.7 (1.0–2.9)	1.6 (1.0–2.9)	0.052	1.7 (1.0–2.7)	0.058	.36
Control (<i>n</i> = 131)	1.7 (1.0–2.9)	1.5 (1.0–2.5)	0.11	1.8 (1.1–3.0)	0.16	.33
Meditation (<i>n</i> = 126)	1.6 (1.0–2.8)	1.6 (0.9–3.2)	0.023	1.7 (0.9–2.6)	0.029	.68
Exercise (<i>n</i> = 126)	1.8 (1.1–2.9)	1.7 (1.0–3.0)	0.064	1.6 (0.9–2.5)	0.017	.31
Interferon gamma-inducible protein-10 (pg/ml)						
Entire cohort (<i>N</i> = 382)	149 (123–195)^b	143 (117–185)^{b,d}	0.19	147 (115–191)^d	0.11	.007
Control (<i>n</i> = 131)	152 (127–198)	148 (120–206)	0.15	147 (122–190)	0.14	.32
Meditation (<i>n</i> = 126)	141 (117–184)	140 (116–183)	0.10	148 (115–192)	0.049	.59
Exercise (<i>n</i> = 125)	156 (126–199)^{b,c}	139 (116–172)^b	0.35	146 (111–191)^c	0.12	.005

Note. Data are reported as median (interquartile range). No statistically significant differences among study groups were noted at any time point (Kruskal-Wallis *H* test, *p* > .05). Bold indicates significant main effect of time via Friedman's test.

^a Friedman's test.

^b Baseline to Follow-up 1 comparison (Wilcoxon signed-rank test), *p* < .05.

^c Baseline to Follow-up 2 comparison (Wilcoxon signed-rank test), *p* < .05.

^d Follow-up 1 to Follow-up 2 comparison (Wilcoxon signed-rank test), *p* < .05.

Table 3

GPAQ Median Scores Over Time and Among Groups

	p^a			p^a			p^a		
	Baseline	Vs. exercise	Vs. MBSR	FU1	Vs. exercise	Vs. MBSR	FU2	Vs. exercise	Vs. MBSR
Control	880 (310–2,410)	.014	.22	700 (160–1,585)	<.001	.97	600 (4–1,740)	<.001	.71
Meditation	780 (225–1,995)	.23		720 (140–1,806)	<.001		720 (180–1,560)	<.001	
Exercise	560 (150–1,380)			1,560 (800–2,795)			1,210 (600–2,215)		
Groupwise p^b	.05			<.001			<.001		

Note. Medians (interquartile ranges) and comparisons among the groups for the GPAQ total score across baseline, FU1, and FU2 in total MET-minutes. The exercise group increased their GPAQ scores from baseline to FU1 and FU2 where they were significantly different from the control and meditation groups. MBSR = mindfulness-based stress reduction; GPAQ = Global Physical Activity Questionnaire; FU1 = Follow-up 1; FU2 = Follow-up 2; MET-minutes = metabolic equivalents $\times$ minutes.

^aMann-Whitney *U* test.

^bFriedman's test.

Table 4

Average Weekly Practice Aggregated Over Time

Exercise group	<i>n</i>	Moderate exercise minutes	Vigorous exercise minutes	Total exercise minutes (MVPA)
Weeks before FU1	126	191 (140–258)	55 (19–108)	268 (200–330)
Weeks before FU2	121	159 (25–149)	69 (0–210)	313 (149–321)
Meditation group		Informal meditation minutes	Formal meditation minutes	Total meditation minutes
Weeks before FU1	127	66 (37–91)	244 (150–298)	306 (227–377)
Weeks before FU2	123	53 (26–95)	156 (66–238)	223 (134–305)

Note. Data are reported as median (interquartile range). MVPA = moderate or vigorous physical activity; FU1 = Follow-up 1; FU2 = Follow-up 2.

Table 5

Change in Biomarkers and Self-Reported Practice Correlations

	Exercise/IP-10		Meditation/CRP	
	Spearman ρ	P	Spearman ρ	P
Follow-up 1 ($n = 123$ for exercise and $n = 127$ for meditation)				
GPAQ total score (MET-minutes)	-.017	.85		
Moderate/informal minutes	-.052	.57	-.038	.67
Vigorous/formal minutes	-.011	.90	-.022	.65
Total minutes	-.028	.76	-.017	.85
Follow-up 2 ($n = 119$ for exercise and $n = 123$ for meditation)				
GPAQ total score (MET-minutes)	-.012	.90		
Moderate/informal minutes	-.026	.78	-.032	.73
Vigorous/formal minutes	-.059	.52	-.041	.65
Total minutes	-.051	.58	-.043	.64

Note. Correlations were performed between changes in self-reported physical activity minutes (GPAQ and logs) with changes in IP-10 in the exercise group or self-reported meditation (logs) and changes in CRP in the meditation group. IP-10 = interferon gamma-inducible protein-10; CRP = C-reactive protein; GPAQ = Global Physical Activity Questionnaire; MET-minutes = metabolic equivalents $\times$ minutes.