Brain, Behavior, and Immunity 104 (2022) 6–15

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Mindfulness-based stress reduction increases stimulated IL-6 production among lonely older adults: A randomized controlled trial

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ARTICLE INFO

Keywords:
Mindfulness
Meditation
Stimulated cytokine response
Loneliness
Older adulthood
Immune function

ABSTRACT

Loneliness is a potent psychosocial stressor that predicts poor health and mortality among older adults, possibly in part by accelerating age-related declines in immunocompetence. Mindfulness interventions have shown promise for reducing loneliness and improving markers of physical health. In a sample of lonely older adults, this two-arm parallel trial tested whether mindfulness training enhances stimulated interleukin-6 (IL-6) production, a measure of innate immune responsivity. Lonely older adults (65–85 years; N = 190) were randomized to an 8-week Mindfulness-Based Stress Reduction (MBSR) or control Health Enhancement Program (HEP) intervention. Lipopolysaccharide (LPS)-stimulated production of IL-6 was measured *in vitro* by blinded outcome assessors at pre-intervention, post-intervention, and 3-month follow-up. Mixed-effects linear models tested time (pre, post, follow-up) by condition (MBSR vs. HEP) effects. As predicted, a significant time × condition effect on stimulated IL-6 production was observed across pre, post, and follow-up timepoints. Significant MBSR vs. HEP differences emerged from pre- to post-intervention (p =.009, d = 0.38) and from pre-intervention to 3-month follow-up (p =.017, d = 0.35), with larger increases in IL-6 production following MBSR compared to HEP. No study-related adverse events were reported. Results show that mindfulness training may be effective for boosting innate immunocompetence among lonely older adults. Given that immunocompetence tends to decline with age, mindfulness training may help to counteract the effects of aging and psychosocial stress on infection risk and recovery from injury.

1. Introduction

Loneliness is a potent psychosocial stressor and robust predictor of poor health and mortality among older adults (Holt-Lunstad et al., 2015). Loneliness is thought to accelerate age-related declines in immunocompetence (Hawkley and Cacioppo, 2004), which may contribute to morbidity and mortality risk. Mindfulness interventions have shown promise for reducing loneliness (Creswell et al., 2012; Lindsay et al., 2019) and improving a variety of physical health outcomes (Creswell et al., 2019). By training an attitude of equanimity with present-moment experience, including the distress associated with feeling alone, mindfulness interventions are thought to diminish loneliness and social threat (Lindsay et al., 2019); in turn, mindfulness interventions show potential to interrupt hypothalamic–pituitary-adrenal (HPA) axis and sympathetic-adrenal-medullary (SAM) stress response cascades (Lindsay et al., 2018) in ways that may improve immunocompetence (Creswell and Lindsay, 2014). To date, few studies have focused on whether mindfulness interventions can alter innate immunocompetence (Elsenbruch et al., 2005; Witek-Janusek et al., 2008; Zautra et al., 2008), and none to our knowledge have examined this question in the context of healthy aging. In a large sample of lonely older adults, the current study tests the impact of 8-week Mindfulness-Based Stress Reduction (MBSR) vs. control Health Enhancement Program (HEP) interventions on stimulated interleukin-6 (IL-6) production, an *in vitro* measure of innate immune responsivity to bacterial challenge.

In response to infection or injury, a rapid and robust innate immune

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https://doi.org/10.1016/j.bbi.2022.05.001
Received 6 December 2021; Received in revised form 15 April 2022; Accepted 6 May 2022
Available online 10 May 2022

response contributes to the elimination of harmful pathogens, repair of damaged tissue, and restoration of health (Dhabhar, 2009, 2014). This response is initiated when receptors on monocyte/macrophage cells recognize pathogen- and damage-associated molecular patterns and activate intracellular signaling pathways that upregulate local production of proinflammatory cytokines, such as IL-1β, TNF-α, and IL-6. For example, toll-like receptor 4 recognizes lipopolysaccharide (LPS), a component of many gram-negative bacteria, and activates NF-κB signaling to upregulate cytokine production, which coordinate the local innate inflammatory response (Liu et al., 2017). A robust initial inflammatory response defends against infection (Janeway and Medzhitov, 2002) and facilitates later stages of wound healing (Werner and Grose, 2003; Eming et al., 2007); when IL-6 production is prevented in mice, for example, wound healing is three times slower (Gallucci et al., 2000).

It is widely accepted that aging is associated with declines in immune system function, including decreased inflammatory competence (Panda et al., 2009; Shaw et al., 2010; Solana et al., 2012). Cells isolated from older adults and stimulated with LPS show attenuated production of IL-6, IL-1β, and TNF-α when compared to cells from younger adults (Bruunsgaard et al., 1999; Delpedro et al., 1998; Nyugen et al., 2010; Gon et al., 1996), possibly due to lower levels of toll-like receptors on immune cells (Panda et al., 2009; Renshaw et al., 2002). In turn, age-related decreases in stimulated cytokine production contribute to increased infection risk (Effros, 2001), delayed recovery from injury (Gosain and DiPietro, 2004), and heightened mortality risk (van den Biggelaar et al., 2004).

Critically, chronic psychosocial stress may accelerate aging-related immune function decline (Hawkley and Cacioppo, 2004; Khanfer et al., 2011). Midlife and older adults exposed to chronic psychosocial stress, such as bereavement and dementia caregiving, show lower stimulated cytokine production in association with slower wound healing compared to lower stress adults (Glaser et al., 1999; Kiecolt-Glaser et al., 1995; Gouin and Kiecolt-Glaser, 2011; Walburn et al., 2009); glucocorticoids released over periods of chronic psychosocial stress may attenuate inflammatory responsivity in ways that impair wound healing (Glaser et al., 1999; Kiecolt-Glaser et al., 1995; Hübner et al., 1996). Loneliness is one such psychosocial stressor that may dysregulate the body's ability to mount a robust immune response. Loneliness has been associated with lower LPS-stimulated IL-1β and TNF-α production—cytokines that induce IL-6 production as part of a coordinated inflammatory response (Del Giudice and Gangestad, 2018)—as well as slower wound healing (Hawkley and Cacioppo, 2003; Marucha et al., 1998). Similarly, depressive symptoms—which often accompany loneliness (Erzen and Çikrikci, 2018)—have been related to lower LPS-stimulated cytokine production (Cyranowski et al., 2007; Krause et al., 2012; Majd et al., 2018; Sjögren et al., 2006). Overall, existing literature showing associations of age and psychosocial stress with lower stimulated cytokine production and slower wound healing suggest that aging and chronic psychosocial stress may act synergistically to downregulate innate immunocompetence. Loneliness may exacerbate age-related declines in immunocompetence with implications for infection and healing.

This report examines the effect of mindfulness training on inflammatory competence among lonely older adults. LPS-stimulated production of IL-6 was measured *in vitro* in a sample of lonely older adults (N = 190) before, after, and 3 months following 8-week MBSR or control HEP interventions. Our primary hypothesis tested whether MBSR would increase the stimulated IL-6 response from pre- to post-intervention and 3-month follow-up compared to HEP, reflecting improved inflammatory competence. Second, to indirectly evaluate the assumption that higher IL-6 production reflects immunocompetence in this older adult sample, we also tested the prediction that pre-intervention IL-6 production would be lower (i.e., compromised) among participants reporting higher loneliness at baseline. Exploratory sensitivity analyses were conducted to test whether participants higher in loneliness at baseline would show larger changes in IL-6 production and whether changes in loneliness associate with changes in IL-6 production.

2. Materials and methods

2.1. Participants

190 lonely older adults aged 65–85 years were enrolled and randomized in this two-arm parallel trial (see Table 1 for baseline characteristics and Fig. 1 for CONSORT flow chart). The study design and outcomes were pre-registered with Clinical Trials identifier NCT02888600. The parent trial was funded through NIH project R01AT008685, with primary outcomes including loneliness and circulating biomarkers to be reported separately (Dutcher et al., in preparation). This report describes stimulated IL-6 production collected as part of an NIH postdoctoral National Research Service Award (F32AT009508; PI: Lindsay). Primary findings from this supplemental project show that MBSR buffers post-intervention increases in glucocorticoid receptor resistance observed following HEP (Lindsay et al., 2021).

Eligible participants were healthy, lonely, meditation-naïve adults aged 65 years or older. Participants were recruited from the greater Pittsburgh area through the Center for Social and Urban Research, the Clinical and Translational Science Institute, and the Pepper Registry at the University of Pittsburgh, Osher Lifelong Learning Institutes at University of Pittsburgh and Carnegie Mellon University, outreach events at local organizations and senior housing, and newspaper, radio, bus, email, and mailed advertisements. The study was advertised for older adults interested in ways to reduce stress and increase social connection. Potential participants were screened for the following eligibility criteria, with the first reason for ineligibility listed in Fig. 1: English speaking; between the ages of 65 and 93; no diagnosis or treatment of a current health problem or chronic disease known to affect inflammatory biology; no prescribed medication usage affecting cardiovascular or immune system function, except blood pressure medications in the final two intervention cohorts (n = 54; a criterion changed to increase enrollment); moderate to high levels of perceived loneliness (>=4 on the Short Form UCLA-R (Hughes et al., 2004)); no current substance abuse problem; no diagnosis or treatment of severe mental illness; <90 min/week spent in regular mind–body practice; no significant cognitive impairment; and no problems with attending study assessments. Written informed consent was obtained from all participants, and study procedures were approved by the Carnegie Mellon University and University of Pittsburgh IRBs. Study data were collected between October 2016 and February 2020. Trial recruitment concluded when recruitment goals had been reached. Intervention instructors were blind to outcome measures and outcome assessors were blind to condition.

The planned sample size for the trial was determined by estimating a small-medium effect ($d = 0.3$) of MBSR compared to HEP and a pre-post correlation of $r = 0.80$; N = 188 participants were needed to achieve > 80% power. These estimates are based on a broad range of effect sizes in prior work related to the primary aims of the parent trial (Creswell et al., 2012; MacCoon et al., 2012; Rosenkranz et al., 2013).

2.2. Procedure

The study was run in eight intervention cohorts. Participants were pre-screened for eligibility by phone. At a pre-intervention study appointment, eligible participants completed questionnaire assessments, including a measure of chronic loneliness (see *Measures*). At a separate afternoon blood draw appointment an average of 47 days later (SD = 39 days, median = 39 days, range = 0 – 253 days), participants provided 30 mL blood, including 8 mL in sodium heparin for the assessment of stimulated IL-6 and 4 mL in ethylenediaminetetraacetic acid (EDTA) for an absolute cell count (see *Measures*). They then completed three days of ambulatory assessments before being randomly

Table 1
Baseline characteristics of randomized participants.

Characteristic	Full Sample (N = 190)	MBSR (N = 93)	HEP (N = 97)	Condition Difference
Age in years	69.77 (0.31)	69.96 (0.45)	69.59 (0.43)	$F(1,189) = 0.35$, $p = .55$
Sex				$\chi^2(1) = 0.53$, $p = .47$
Female	149 (78.42%)	75 (80.65%)	74 (76.29%)	
Male	41 (21.58%)	18 (19.35%)	23 (23.71%)	
Race				$\chi^2(3) = 0.27$, $p = .97$
American Indian/ Alaska Native	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Asian	2 (1.05%)	1 (1.08%)	1 (1.03%)	
Black/African American	22 (11.58%)	11 (11.83%)	11 (11.34%)	
White/Caucasian	161 (84.74%)	78 (83.87%)	83 (85.57%)	
Bi- or Multi-Racial	5 (2.63%)	3 (3.23%)	2 (2.06%)	
Ethnicity				$\chi^2(1) = 2.58$, $p = .11$
Hispanic or Latino	6 (3.16%)	1 (1.08%)	5 (5.15%)	
Not Hispanic or Latino	184 (96.84%)	92 (98.92%)	92 (94.85%)	
Education Level				$\chi^2(8) = 8.96$, $p = .35$
No High School Diploma	3 (1.58%)	1 (1.08%)	2 (2.06%)	
GED	2 (1.05%)	0 (0.00%)	2 (2.06%)	
High School Diploma	9 (4.74%)	2 (2.15%)	7 (7.22%)	
Technical Training	6 (3.16%)	2 (2.15%)	4 (4.12%)	
Some College, no degree	23 (12.11%)	11 (11.83%)	12 (12.37%)	
Associate Degree	6 (3.16%)	4 (4.30%)	2 (2.06%)	
Bachelor's Degree	57 (30.0%)	34 (36.56%)	23 (23.71%)	
Master's Degree	71 (37.37%)	33 (35.48%)	38 (39.18%)	
MD, PhD, JD, PharmD	13 (6.84%)	6 (6.45%)	7 (7.22%)	
Marital Status				$\chi^2(4) = 0.83$, $p = .93$
Married/Living with partner	82 (43.16%)	39 (41.94%)	43 (44.33%)	
Widowed	27 (14.21%)	14 (15.05%)	13 (13.40%)	
Separated	5 (2.63%)	2 (2.15%)	3 (3.09%)	
Divorced	43 (22.63%)	23 (24.73%)	20 (20.62%)	
Single	33 (17.37%)	15 (16.13%)	18 (18.56%)	
BMI[a]	27.94 (0.44)	27.41 (0.62)	28.44 (0.61)	$F(1,189) = 1.40$, $p = .24$
UCLA Loneliness[b]	42.39 (0.70)	43.09 (1.00)	41.72 (0.98)	$F(1,187) = 0.95$, $p = .33$
Current mind–body practice[c]	21 (11.60%)	11 (12.79%)	10 (10.53%)	$\chi^2(1) = 0.23$, $p = .64$
Pre-intervention monocyte count (per mL)[d]	491144 (11910)	480295 (17111)	500718 (16570)	$\chi^2(1) = 0.74$, $p = .39$
Pre-intervention IL-6 production (pg/ 1000 cells)[e]	81.23 (2.54)	77.97 (3.66)	84.17 (3.52)	$\chi^2(1) = 1.49$, $p = .22$

Note: Data reported as means and (SEs) or (%). [a]For N = 34, height used in BMI calculations estimated from averages for females and males. [b]UCLA Loneliness data available for N = 188 at baseline (MBSR N = 92; HEP N = 96). [c]Information about pre-intervention mind–body practice (regular practice < 90 min per week) available for N = 181 at baseline (MBSR N = 86; HEP N = 95). [d]N = 187 (MBSR N = 92; HEP N = 95). [e]N = 183 (MBSR N = 90; HEP N = 93).

assigned to condition at the first intervention session. Participants were allocated 1:1 to MBSR or HEP interventions using a computerized random number generator, with procedures implemented separately for each of eight intervention cohorts. Randomization was blocked by age (≤75 vs. > 75 years) and baseline depressive symptoms (Beck Depression Inventory-II (Beck et al., 1996) score ≤ 13 [minimal depression] vs. > 13 [mild, moderate, or severe depression]) to ensure balance across groups. Allocation sequence was concealed, such that only author AGCW had access to the sequence and otherwise was not involved with conducting the study. At post-intervention, participants completed an afternoon blood draw, questionnaire assessment, and ambulatory assessment as at pre-intervention. Afternoon blood and questionnaire assessments were again collected at three-month follow-up. Participants were debriefed and compensated up to $475, including bonus payments for high adherence (with stepped bonuses for completing 85–100% of ambulatory assessments and 75–100% of intervention sessions plus retreat).

2.3. Materials

2.3.1. Intervention programs

Participants were randomly assigned to Mindfulness-Based Stress Reduction (MBSR) or a structurally matched Health Enhancement Program (HEP) (MacCoon et al., 2012). Both 8-week interventions are standardized curriculum-based group programs. In this study, the structure was adapted so that interventions consisted of 8 weekly 2-hour group sessions (rather than 2.5-hour sessions), a day-long retreat during the sixth week, and approximately 45 min of home practice assignments six days per week. Content covered in each class is detailed in Supplementary Table 1 and summarized below. During the 3-month follow-up period, participants were encouraged to continue mindfulness (MBSR) or health (HEP) practices; they received a list of community resources for continued support, weekly practice reminder emails, and continued access to meditation audios (MBSR only).

The MBSR program followed the MBSR Curriculum Guidelines (Center for Mindfulness in Medicine, Health Care, and Society, University of Massachusetts Medical School). MBSR includes guided mindfulness meditations intended to foster awareness of present-moment experiences and an open, accepting, and nonjudgmental perspective. Guidance and group discussions also encourage nonjudgmental awareness in everyday life, including when experiencing stress or other challenging emotions. Group discussions involve exploration of habitual reactions to stress and the cultivation of skills such as pausing before responding. The daylong retreat after Week 6 involved silent guided meditation practice and reflection. Foundationally, the course centers on self-care and group support, including support around meeting the challenge of integrating meditation practice into daily life. Home practice recordings guide participants through body awareness, mindful movement, and seated meditation.

The HEP program, which was originally developed to enhance health and to match the structure of MBSR without training mindfulness, followed guidelines outlined in MacCoon et al. (2012). HEP utilizes behavioral health principles to counteract the effects of stress. Participants engage in group discussions and activities to promote experiential learning of strength, aerobic, flexibility, and balance exercises, nutritional concepts such as inflammatory and anti-inflammatory properties of food, and stress management through creative expression, particularly music. The daylong retreat after Week 6 involved conversation, group meal preparation, functional movement exercises, and creative expression. Home practice assignments guide participants through age-appropriate physical fitness, nutrition and meal preparation, and music engagement exercises.

MBSR classes were taught by one of two certified MBSR instructors. The senior teacher, who taught cohorts 1 and 4–8, had been teaching MBSR for 14 years and had a personal meditation practice of 25 years, and the teacher for cohorts 2–3 had been teaching MBSR for 8 years and

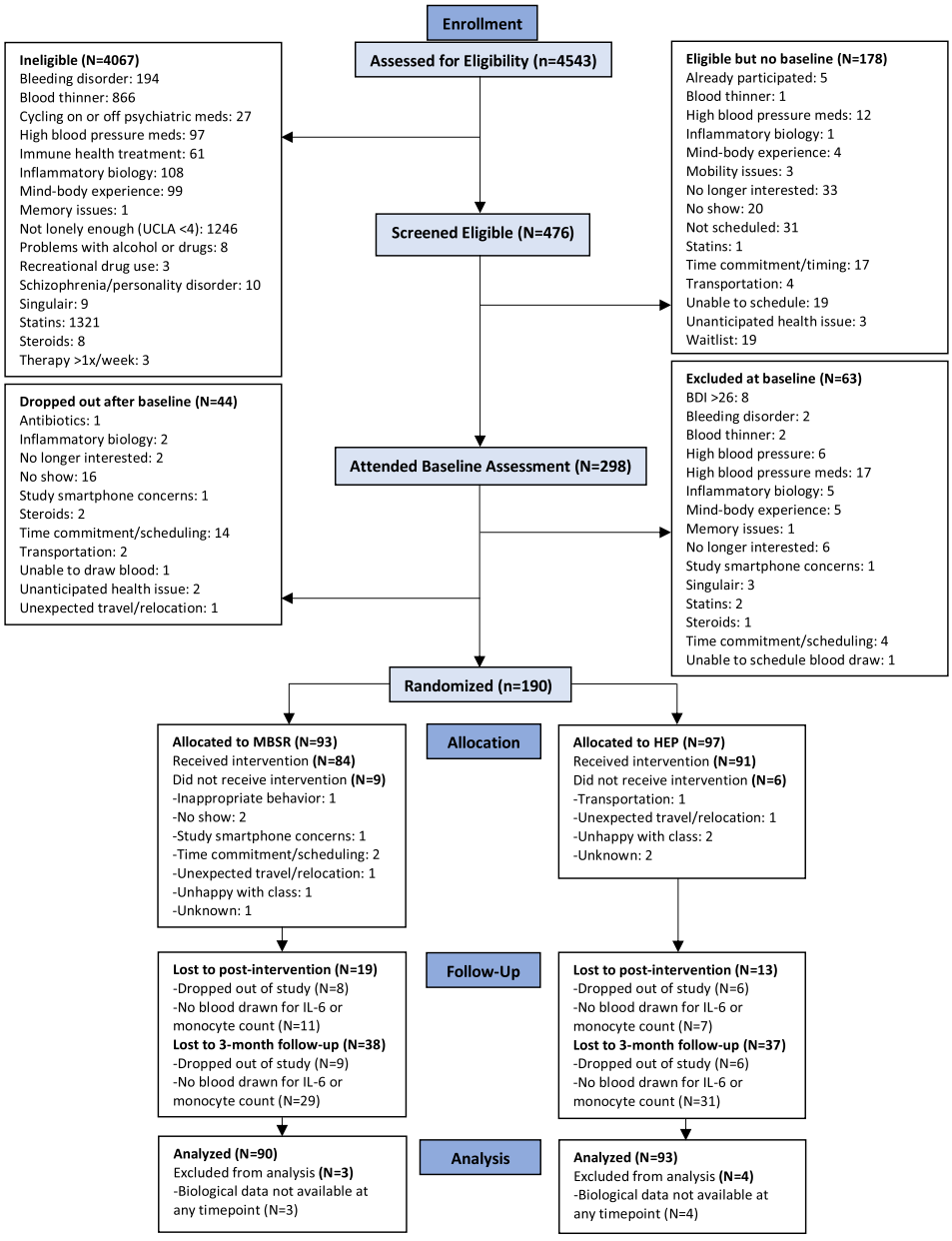

Fig. 1. CONSORT Flow Chart.

had a personal meditation practice of 13 years. The senior teacher also provided peer support and monitoring every two weeks for cohorts 2–3. Both teachers completed all MBSR teacher trainings required by the U Mass Center for Mindfulness in Medicine, Health Care, and Society. HEP classes were taught by one of two Registered and Licensed Dietitian Nutritionists. The teacher for cohorts 1–5 was a senior research nutritionist and medical writer, and the teacher for cohorts 6–8 was a nutrition educator and exercise coach. MBSR and HEP instructors followed a written template of activities and discussion topics for each session. All intervention sessions were monitored in real time by trained research staff who attended for the purpose of monitoring intervention fidelity and addressing questions about the research procedures.

2.3.2. Measures

Stimulated IL-6 production was assessed at baseline and post-intervention (all cohorts) and at 3-month follow-up (cohorts 4–8 only due to budget constraints) in the Behavioral Immunology Lab at University of Pittsburgh (PI: ALM). Blood draws occurred between 1 pm and 8 pm (with 85% of draws between 3 pm and 7 pm) and draw times were standardized within participants across the three assessments (mean difference in blood draw time = 8 min, SD = 52 min). Biological data were available for at least one of the three assessments from 183 participants for analysis (see Fig. 1). This assay measures cellular production of the pro-inflammatory cytokine IL-6 in response to stimulation with lipopolysaccharide (LPS) endotoxin. As part of an assay assessing the sensitivity of immune cells to glucocorticoids (Lindsay et al., 2021), stimulated IL-6 production was measured by incubating 1.25 mL of whole blood (diluted 7.35:1 with saline) with 150uL LPS at 30 ng/mL in phosphate buffer within 3 h of each blood draw. Samples were incubated for 18 h at 37 °C with 5% CO_2. Supernatants were then removed for storage at −80 °C. IL-6 was measured in batches via ELISA (using BD Biosciences kits, catalog # 555220, lot # 8151888EU), with all available timepoints for each participant assayed on the same plate. Inter- and intra-assay coefficients of variability were 12.7% and 4.4%, respectively.

Since monocytes are the primary immune cells that produce IL-6

when stimulated with endotoxin and monocyte numbers differed by blood sample, IL-6 production was adjusted for monocyte count. Stimulated levels of IL-6 (pg/mL) were divided by monocyte number per mL, determined from a Complete Blood Count analyzed in a clinical laboratory, then multiplied by 1000 to derive a metric of IL-6 production per 1000 monocytes (pg/1000 cells). Two outlying IL-6-per-1000-monocytes values were removed prior to analysis (both > 6SD above the mean). The same pattern of results was observed for raw stimulated IL-6 (pg/mL) when monocyte count was included as a covariate in the statistical model.

Intervention and Home Practice Adherence: Class attendance was recorded via sign-in sheet, with adherence calculated as total number of sessions out of nine. Self-reported home practice was assessed via daily Qualtrics links; daily practice duration was averaged across the eight-week intervention. Formal and informal home practice during follow-up was encouraged with weekly reminder emails and assessed during monthly phone calls. Participants reported the frequency and duration of formal practice (3 types introduced in MBSR and 6 types in HEP) and informal practice (15 examples in MBSR and 6 in HEP) each week in the past month; self-reported weekly practice durations were averaged across the follow-up period to create indexes of formal and informal practice. In MBSR, formal practice included mindfulness meditation exercises (e.g., body scan, seated meditation, mindful yoga) and informal practice involved incorporating mindful awareness into daily life activities (e.g., conversations, walking, housework, eating, preparing food, and mindful responding to stressful circumstances). In HEP, formal practice was defined as dedicating structured time to health practices (e.g., endurance, strength, stretching, or balance exercises; music; meal tracking) and informal practice was described as incorporating health practices into daily life (e.g., stretching before reaching for something; taking the stairs).

Loneliness was assessed at pre-intervention, post-intervention, and 3-month follow-up using the UCLA Loneliness Scale (Russell, 1996) (N = 188). This 20-item scale measures the extent to which participants felt lonely "in general" over the past month on a 4-point Likert scale ranging from 1 (never) to 4 (always) (sample item: "I lack companionship"). Relevant items were reverse-coded and all items were summed to create a total loneliness score (reliability: Cronbach's α = 0.93), with higher scores reflecting higher loneliness. This scale has shown good test–retest reliability across a one-year period ($r = 0.73$) (Russell, 1996) and is thus used as a measure of chronic loneliness at study entry. Dutcher et al. (in preparation) report primary R01 trial findings, including intervention-related changes in loneliness.

2.3.3. Analyses

Analyses were conducted using Stata 17 software (StataCorp, College Station, Texas). Preliminary analyses tested for condition differences in demographics and other baseline characteristics using chi-square (for categorical variables) and ANOVA tests (for continuous variables). Intervention adherence and home practice were evaluated as covariates using ANOVA to test for significant condition differences. Preliminary regression analyses also tested the assumption that larger IL-6 responses associate with lower psychosocial stress (i.e., lower loneliness), adjusting for age and sex.

Primary analyses were conducted blind to condition assignment and inferences were made before unblinding occurred. Mixed-effect linear models (MLMs) tested for time (pre-intervention, post-intervention, or 3-month follow-up) × condition (MBSR vs. HEP) differences on stimulated IL-6 production using the Stata Mixed procedure. Planned comparisons testing for MBSR vs. HEP differences from pre- to post-intervention and pre-intervention to 3-month follow-up were calculated within these MLMs. Hypothesis tests were 2-sided and a priori significance was set at α = 0.05; the primary hypothesis tested in this report is the second of two hypotheses proposed for project F32AT009508. Following intent-to-treat (ITT) principles, all available data were included in analyses, including pre-intervention data for 15 participants who dropped out; however, biological data were not available at any time point for 7 participants. MLMs model all available data and provide unbiased estimates to account for data missing at random (MAR). MLMs capture both within- and between-individual variability. Time was modeled as a random effect with an independent covariance structure, with pre-intervention values used as the first repeated measure to test for time × condition interactions. Condition and home practice duration were modeled as fixed effects using maximum likelihood estimation.

Exploratory sensitivity analyses used (1) MLMs to test for time (pre-intervention, post-intervention, or 3-month follow-up) × condition (MBSR vs. HEP) × baseline loneliness (<= median vs. > median) differences on stimulated IL-6 production, and (2) correlation analyses to explore associations between change in loneliness and change in IL-6 production, with change represented by slopes across three time points.

Within-group Cohen's *d* effect sizes were calculated by dividing the pre-post (or pre-follow-up) mean difference by the pooled standard deviation. Between-group effect sizes were calculated by dividing the difference between pre-post (or pre-follow-up) mean change in each condition by the pooled standard deviation of change.

3. Results

3.1. Preliminary analyses: Baseline characteristics and adherence

Participants had a mean age of 69.77 years (SD = 4.27; range: 65–85 years) and were predominantly female (78%), white (85%), non-Hispanic (97%), and college-educated (74%). Table 1 describes demographic and baseline characteristics by condition; there were no group differences in age, sex, race, ethnicity, education, marital status, or pre-intervention BMI, UCLA loneliness scores, or mind–body practice (all < 90 min/week).

Participants in both groups were highly adherent to the intervention, completing on average 8 of the 9 intervention sessions (8 weekly sessions plus retreat day), with 63% of participants attending all 9 sessions. There were no group differences in intervention adherence, but HEP participants were more likely to attend the day-long retreat (87% vs. 74%; $p = .031$). Participants completed an average of 35.70 (SE = 1.26) minutes per day of home practice, with HEP participants practicing significantly more than MBSR participants (39.90 [95% CI: 36.42–43.38] vs. 31.31 [95% CI: 27.76–34.87] minutes per day; $p = .001$). Home practice is included as a covariate in primary analyses, but results were consistent without controlling for home practice. HEP participants also tended to practice more during the three-month follow-up period, reporting significantly more formal practice than MBSR participants (59.31 [95% CI: 52.43–66.20] vs. 17.15 [95% CI: 9.98–24.32] minutes each week; $p < .001$), but total home practice (formal and informal practice combined) was equivalent. Fifteen participants dropped out of the study, with 9 from MBSR and 6 from HEP. There were no group differences in dropout rate (MBSR: 9.68% vs. HEP: 6.19%; $p = .37$, *Cramér's V* = 0.06) and dropouts did not differ from completers by age ($F(1,188) = 0.01$, $p = .92$, $d = 0.03$), sex ($\chi^2(1) = 1.33$, $p = .25$, $V = 0.08$), race ($\chi^2(3) = 2.93$, $p = .40$, $V = 0.12$), or ethnicity ($\chi^2(1) = 0.66$, $p = .42$, $V = 0.06$). There were also no differences between dropouts and completers by condition on any baseline characteristics (Supplementary Table 2). Table 2 provides descriptive statistics for adherence outcomes. No study-related adverse events were reported.

There were no baseline group differences in monocyte counts ($M_{difference} = 20423.68$, $SE = 23818.93$, 95% CI: [-26260.56, 67107.91], $\chi^2(1) = 0.74$, $p = .39$) or differences in monocyte count change over time (time × condition effect: $\chi^2(2) = 3.01$, $p = .22$) (Table 1). Monocyte count was significantly correlated with stimulated IL-6 production ($r = 0.44$, $p < .0005$), such that greater IL-6 production associated with higher numbers of monocytes. There were no baseline group differences in stimulated IL-6 production per monocyte ($M_{difference} = 6.19$, $SE = 5.08$, 95% CI: [-3.76, 16.15], $\chi^2(1) = 1.49$, $p = .22$) (Table 1).

Table 2
Adherence and pre-intervention outcomes of randomized participants.

Characteristic	Full Sample (N = 190)	MBSR (N = 93)	HEP (N = 97)	Condition Difference
Intervention Drop-outs	15 (7.89%)	9 (9.68%)	6 (6.19%)	$\chi^2(1) = 0.80$, $p = .37$
Intervention Adherence (sessions out of 9)	8.04 (0.15)	7.94 (0.21)	8.13 (0.21)	$F(1,188) = 0.45$, $p = .50$
Weekly Class Attendance (sessions out of 8)	7.23 (0.13)	7.19 (0.19)	7.27 (0.18)	$F(1,188) = 0.08$, $p = .77$
Sessions attended:				$\chi^2(3) = 3.82$, $p = .28$
Attended < 5 sessions	15 (7.89%)	9 (9.68%)	6 (6.19%)	
Attended 5–7 sessions	12 (6.32%)	4 (4.30%)	8 (8.25%)	
Attended 8 sessions	43 (22.63%)	25 (26.88%)	18 (18.56%)	
Attended 9 sessions	120 (63.16%)	55 (59.14%)	65 (67.01%)	
Retreat Attendance	153 (80.53%)	69 (74.19%)	84 (86.60%)	$\chi^2(1) = 4.66$, $p = .031$
Home Practice Adherence (minutes per day)	35.70 (1.26)	31.31 (1.80)	39.90 (1.76)	$F(1,188) = 11.59$, $p = .001$
Home Practice during Three-Month Follow-Up (minutes per week)				
Formal Practice[a]	39.08 (2.52)	17.15 (3.63)	59.31 (3.49)	$F(1,173) = 70.06$, $p < .001$
Formal + Informal Practice[b]	129.90 (9.88)	112.27 (14.13)	146.72 (13.80)	$F(1,168) = 3.04$, $p = .083$

Note: Data reported as means and (SEs) or (%). [a]N = 175. [b]N = 170.

3.2. Preliminary Analyses: Association of chronic loneliness and immunocompetence at baseline

Better baseline psychosocial functioning was expected to associate with larger stimulated IL-6 responses in this older adult sample. As predicted, lower baseline loneliness ($\beta = -0.18$, 95% CI: [−0.11, −0.25], $p = .021$; N = 167) associated with higher IL-6 production per monocyte.

3.3. Primary analyses

MBSR was predicted to increase stimulated IL-6 production compared to HEP from pre- to post-intervention and 3-month follow-up. MLMs tested for time (pre, post, follow-up) × condition (MBSR, HEP) interactions on stimulated IL-6 production per monocyte, controlling for home practice duration.

As predicted, a significant time × condition effect on stimulated IL-6 production was observed across pre, post, and follow-up timepoints ($\chi^2(2) = 8.48$, $p = .014$) (Fig. 2). Significant MBSR vs. HEP differences emerged from pre- to post-intervention (time × condition: $M_{difference} = -16.23$, $SE = 6.24$, 95% CI: [−28.46, −4.00], $\chi^2(1) = 6.76$, $p = .009$, $d = 0.38$) and from pre-intervention to 3-month follow-up (time × condition: $M_{difference} = -17.48$, $SE = 7.32$, 95% CI: [−31.82, −3.14], $\chi^2(1) = 5.71$, $p = .017$, $d = 0.35$) (Table 3). MBSR participants showed significant increases in IL-6 production from pre- to post-intervention ($M_{change} = 14.66$, $SE = 4.59$, 95% CI: [5.67, 23.65], $\chi^2(1) = 10.21$, $p = .001$, $d = 0.37$) and from pre-intervention to 3-month follow-up ($M_{change} = 27.69$, $SE = 5.32$, 95% CI: [17.27, 38.11], $\chi^2(1) = 27.13$, $p < .0005$, $d = 0.62$). HEP participants showed no changes in IL-6 production from pre- to post-intervention ($M_{change} = -1.57$, $SE = 4.24$, 95% CI: [-9.89, 6.74], $\chi^2(1) = 0.14$, $p = .71$, $d = 0.04$), but showed significant increases from pre-intervention to 3-month follow-up ($M_{change} = 10.21$, $SE = 5.04$, 95% CI: [0.34, 20.08], $\chi^2(1) = 4.11$, $p = .043$, $d = 0.23$).

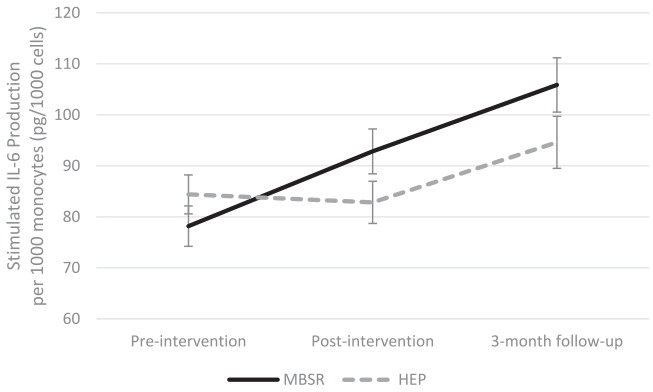

Fig. 2. Stimulated IL-6 production over time in MBSR and HEP. Means and standard errors are plotted.

Table 3
Stimulated IL-6 production at pre-intervention, post-intervention, and 3-month follow-up in MBSR and HEP.

Characteristic	MBSR (N = 89)	HEP (N = 93)	Pre-Post Cohen's *d*	Time × Condition Difference
Pre-intervention IL-6 production (pg/1000 cells)	78.18 (3.96)	84.41 (3.82)	–	–
Post-intervention IL-6 production (pg/1000 cells)	92.84 (4.39)	82.84 (4.13)	0.38	$\chi^2(1) = 6.76$, $p = .009$
3-month follow-up IL-6 production (pg/1000 cells)[a]	105.87 (5.32)	94.62 (5.10)	0.35	$\chi^2(1) = 5.71$, $p = .017$

Note: Analyses include home practice as a covariate. Data reported as means and (SEs). Cohen's *d* estimates between-group differences in change from pre-intervention to post-intervention and 3-month follow-up. [a]Data estimated for N = 68.

3.4. Sensitivity analyses

Exploratory sensitivity analyses showed no moderation of intervention effects on stimulated IL-6 production by baseline loneliness; there was no time × condition × baseline loneliness effect on stimulated IL-6 production ($\chi^2(2) = 0.13$, $p = .94$) and primary time × condition effects remained with baseline loneliness score in the model (time × condition: $\chi^2(2) = 7.18$, $p = .028$). However, there was a two-way time × baseline loneliness interaction within this model; across both conditions, effects were significantly larger among participants with higher baseline levels of loneliness (time × baseline loneliness: $\chi^2(2) = 6.86$, $p = .033$), especially MBSR participants (Table 4).

Second, exploratory analyses showed no association between change in loneliness and change in IL-6 production across conditions ($r = -0.07$, $p = .30$) or within MBSR participants only ($r = -0.09$, $p = .42$), indicating that intervention-related improvements in loneliness did not explain increases in inflammatory responsivity.

4. Discussion

Psychosocial stressors like loneliness are thought to accelerate age-related declines in innate immunocompetence (Hawkley and Cacioppo, 2004). This study shows that mindfulness training may

Table 4
Stimulated IL-6 production from pre-intervention to post-intervention and 3-month follow-up in MBSR and HEP by baseline UCLA Loneliness score.

Group	Pre-Intervention	Post-Intervention	Pre-Post within-group effect	*d*	3-month Follow-up[a]	Pre-Follow-up within-group effect	*d*
High Baseline Loneliness							
MBSR (N = 54)	72.43 (5.30)	90.24 (5.65)	$\chi^2(1) = 8.96$, $p = .003$	0.44	108.43 (6.84)	$\chi^2(1) = 27.53$, $p < .0005$	0.80
HEP (N = 41)	79.75 (5.80)	83.88 (6.44)	$\chi^2(1) = 0.41$, $p = .52$	0.11	100.28 (7.62)	$\chi^2(1) = 7.65$, $p = .006$	0.47
Low Baseline Loneliness							
MBSR (N = 39)	85.11 (5.85)	96.43 (6.85)	$\chi^2(1) = 2.63$, $p = .11$	0.28	101.57 (8.27)	$\chi^2(1) = 4.09$, $p = .043$	0.37
HEP (N = 56)	88.03 (5.01)	82.07 (5.33)	$\chi^2(1) = 1.17$, $p = .28$	−0.15	89.94 (6.75)	$\chi^2(1) = 0.08$, $p = .78$	0.04

Note: Analyses include home practice as a covariate. Data reported as means and (SEs) in units of pg/1000 cells. Cohen's *d* estimates within-group differences in change from pre-intervention to post-intervention and 3-month follow-up. [a]Data estimated for N = 68.

counteract this pattern and improve innate inflammatory competence among lonely older adults. Specifically, 8-week MBSR significantly increased LPS-stimulated IL-6 production at post-intervention and 3-month follow-up compared to a structurally matched Health Enhancement Program (HEP). HEP participants also showed an increase in stimulated production of IL-6 at 3-month follow-up (12% increase), but MBSR effects were larger at both post-intervention (19% increase) and follow-up (35% increase). This work suggests that mindfulness interventions—which train skills in observing present-moment thoughts, sensations, and emotions through a lens of openness and equanimity—can increase inflammatory responsivity.

Indeed, this trial provides evidence that mindfulness skills specifically are capable of driving changes in inflammatory competence; mindfulness training showed stronger effects than a comparison intervention matched on non-mindfulness-specific treatment factors (e.g., placebo expectancies, social contact, a live instructor, effort toward a practice goal). Whereas mindfulness skills, especially acceptance of momentary experiences, are thought to impact psychosocial processes that interrupt stress response cascades (Creswell and Lindsay, 2014; Lindsay and Creswell, 2017), HEP may impact immune function through distinct health behavior pathways. Indeed, leading models linking stress with disease processes suggest that psychosocial threat (e.g., loneliness) influences both negative emotions that activate physiological stress pathways as well as negative health behaviors; both pathways (and their interaction) have potential to influence disease-related physiological changes (Cohen et al., 2016). HEP provides training and practice in exercise and nutrition, two positive health behaviors associated with innate immunocompetence, faster wound healing, and reduced risk of infection among older adults (Emery et al., 2005; Scrimshaw and San-Giovanni, 1997; Wild et al., 2010). As such, it is not surprising that an intervention focused on promoting these health behaviors also increased inflammatory competence.

However, the training-specific mechanisms underlying the observed effects are unclear. Although people who reported higher levels of loneliness at baseline showed greater increases in inflammatory responsivity across both conditions, changes in loneliness did not explain changes in inflammatory response following either intervention. It is not uncommon in behavioral intervention research for psychosocial and biological outcomes to diverge (Campbell and Ehlert, 2012); improvements in psychosocial outcomes are commonly found following both mindfulness and active comparison interventions (influenced by many factors, including expectancies) (Goyal et al., 2014), whereas improvements in biological stress processes are often more specific to mindfulness intervention (Lindsay et al., 2018). Further research is needed to determine precise psychosocial mechanisms linking mindfulness training with changes in stress-related biological processes. Mindfulness training cultivates a lens shift for relating to daily life experiences with equanimity, a commonly reported phenomenon that has been elusive to assess via self-report (Grossman, 2019). This shift may explain why MBSR participants showed larger increases in inflammatory competence despite greater home practice among HEP participants; whereas health behaviors must be practiced regularly to maintain benefit, the informal integration of mindfulness skills into daily life might reinforce mindful responding toward psychosocial stress in ways that interrupt stress response cascades.

This study adds to a sparse literature testing the effects of mindfulness and other mind–body interventions on stimulated cytokine production. To our knowledge, this study is the first to show that mindfulness training increases stimulated IL-6 production, and it is the only study to examine this question in the context of healthy aging (Elsenbruch et al., 2005; Witek-Janusek et al., 2008; Zautra et al., 2008). In doing so, this study contributes to a longstanding question in psychoneuroimmunology about whether stress management interventions enhance or suppress stimulated cytokine production (Carlson et al., 2003). To date, mindfulness and mind–body interventions have shown no effects or *reductions* in stimulated cytokine production in midlife adults with inflammatory disease or breast cancer (Elsenbruch et al., 2005; Witek-Janusek et al., 2008; Zautra et al., 2008; Irwin et al., 2014; Kiecolt-Glaser et al., 2014). Together with this previous work, the current study suggests that intervention effects on stimulated cytokine response depend heavily on disease status and lifespan factors. In the context of existing chronic inflammatory disease, a reduction in the magnitude of stimulated cytokine response may be beneficial, decreasing the contribution of inflammatory processes to the exacerbation of disease processes and symptoms (Ward and Lentsch, 1999). However, among healthy older adults as in this study, an increase in stimulated production may protect against infection, enhance recovery from injury, and boost vaccine responsiveness (Dhabhar, 2009), outcomes that become increasingly important with age.

In addition to sample characteristics (e.g., age; disease status), psychosocial factors are thought to moderate whether enhanced vs. suppressed cytokine responsivity is adaptive (Dhabhar, 2009, 2014). In particular, stress chronicity moderates the effects of psychosocial stress on immune function. Acute stress tends to enhance inflammatory potential while chronic stress suppresses inflammatory potential; acute stressors boost endogenous and LPS-stimulated cytokine production to protect the body from infection (Marsland et al., 2017), but chronic psychosocial stress is associated with a diminished initial response to bacterial challenge and a slower recovery (Dhabhar, 2014). Consistent with this pattern, loneliness has been associated with higher LPS-stimulated and unstimulated cytokine production following acute stress exposure (Jaremka et al., 2013; Hackett et al., 2012), and, as replicated in the present findings, lower LPS-stimulated cytokine production under resting conditions (Hawkley and Cacioppo, 2003; Marucha et al., 1998). It is possible that mindfulness training boosts both the enhancement and suppression of inflammatory responsivity depending on stress chronicity; previous work has shown that mindfulness training can reduce acute stress-induced inflammatory activity (Rosenkranz et al., 2013), and we show here that mindfulness training can increase stimulated inflammatory activity among chronically lonely older adults. It is worth noting that methodological factors reflect these contextual factors (e.g., incubation length models initial vs. recovery stages of the inflammatory response; environmental conditions of blood draw can model acute stress vs. resting conditions [i.e., the presence or absence of an acute stress induction]) and can thus moderate cytokine response (Panda et al., 2009).

LPS-stimulated IL-6 production, an *in vitro* index of inflammatory potential, is one of many independent markers of immune system

function that declines with age and psychosocial stress. Indeed, frequent or chronic activation of physiological stress response systems can cause complex adaptations that contribute to chronic disease over time (McEwen, 1998). For example, chronic glucocorticoid exposure has been shown to suppress the magnitude of inflammatory responsivity (Hübner et al., 1996), consistent with the results observed here. Glucocorticoids bind to receptors on immune cells and downregulate inflammatory gene expression, and as such, elevated levels of cortisol in circulation may inhibit the inflammatory response. However, chronic exposure to glucocorticoids also leads to glucocorticoid receptor resistance; receptors on immune cells adapt by developing resistance to cortisol and its anti-inflammatory effects (Cohen et al., 2012). This adaptation may result in insufficient recovery following activation of the inflammatory response, possibly contributing to inflammatory disease processes and heightened systemic inflammation. We previously showed in this sample of lonely older adults that MBSR buffered post-intervention increases in glucocorticoid resistance observed following HEP, with no changes in glucocorticoid resistance following MBSR (Lindsay et al., 2021). Taken together, this study suggests that mindfulness training can enhance the initiation of the inflammatory response while preserving the sensitivity of immune cells to cortisol, potentially allowing for an efficient return to baseline levels of inflammation.

Importantly, the magnitude of inflammatory response is distinct from circulating cytokine levels. In the absence of acute stress or infection, elevated circulating cytokine levels, including IL-6, are markers of systemic inflammation that associate with aging (Ershler, 1993), age-related chronic disease (Papanicolaou et al., 1998), and mortality (Harris et al., 1999). Indeed, 'inflammaging', thought to result from chronic overstimulation of the innate immune response, in part by immune cell adaptations to chronic cortisol exposure (i.e., glucocorticoid resistance), is marked by chronic low-grade systemic inflammation and contributes to age-related chronic disease (Franceschi et al., 2018). There is some evidence that mindfulness interventions decrease circulating cytokine levels among high-risk samples, including lonely older adults (Creswell, 2012), although not all evidence is consistent (Black and Slavich, 2016; Bower and Irwin, 2016; Morgan et al., 2014). However, changes in circulating inflammatory markers are independent of changes in stimulated cytokine production (Irwin et al., 2015), a functional measure of inflammatory competence when presented with an immune challenge.

It is important to note that the measure of stimulated IL-6 production used here is an index of inflammatory potential, but does not duplicate the complex dynamics of the inflammatory response *in vivo*. Cells were isolated from a complex internal milieu of influences and incubated with supra-physiologic doses of LPS to model the inflammatory response. For example, although mindfulness training has been shown to modulate SAM and HPA-axis stress response cascades (Lindsay et al., 2018; Pascoe et al., 2017) and catecholamines and glucocorticoids are known to influence the inflammatory response *in vivo*, it remains to be determined whether mindfulness-related changes in circulating hormone levels are sufficient to influence the *in vitro* stimulated inflammatory response assessed here. Overall, it is unclear how closely the observed results mimic *in vivo* responses. Although previous studies show an association between *in vitro* inflammatory responsiveness and wound healing and mortality (van den Biggelaar et al., 2004; Kiecolt-Glaser et al., 1995), further research is needed to test whether the observed results translate to objective health outcomes.

Indeed, although increased stimulated cytokine production has potential to benefit health among older adults, this study did not assess long-term health outcomes. This is the first study to examine the effect of MBSR in a sample subject to the synergistic impact of age and psychosocial stress on immune function. Given evidence that innate immunocompetence tends to decline with age and psychosocial stress can exacerbate this effect (Hawkley and Cacioppo, 2004), we conclude that mindfulness and health enhancement interventions both boost immune responsivity among lonely older adults. However, further research is needed to test the maintenance of these effects beyond 3-month follow-up as well as their clinical significance.

Further research is also needed to determine whether the current findings generalize to older adults with chronic health problems. Although we aimed to recruit an at-risk sample, the participants enrolled in this study were relatively healthy (e.g., free of chronic disease and medications) and advantaged (e.g., high educational attainment). It is unclear whether mindfulness training may enhance immunocompetence among older adults at greater health risk. A more robust inflammatory response to challenge may have adverse effects in certain older adult populations (e.g., those with auto-immune or inflammatory disease); hyperactivation of the inflammatory response that fails to resolve (i.e., cytokine storm following exposure to infection) risks organ dysfunction (Fajgenbaum and June 2020). This study did not measure the efficiency of inflammatory resolution, a critical process for long-term recovery and important question for future research.

We note several methodological limitations. First, IL-6 is one of many cytokines involved in the innate inflammatory response; an assessment of proinflammatory cytokines IL-1β and TNF-α, which induce IL-6 production (Del Giudice and Gangestad, 2018), would more fully capture inflammatory dynamics and strengthen conclusions. However, LPS-stimulated production of IL-1β, TNF-α, and IL-6 are highly correlated (Knight et al., 2020). Second, baseline assessments of loneliness occurred approximately 1–2 months prior to baseline assessments of stimulated IL-6 production. Although the UCLA Loneliness scale shows good test–retest reliability across one year, this gap in assessment limits precision in estimating the relationship between loneliness and inflammatory responsivity at baseline. Third, this trial compared effects of two active interventions; without an inactive control group, we cannot rule out the possibility that participating in the trial alone, which involved regular communication with the study team, could have influenced results. However, in a similar MBSR trial, lonely older adults in a waitlist control group showed no changes on biological outcomes (Creswell, 2012). Finally, this study was fully powered to detect pre- to post-intervention changes, but stimulated cytokine data was collected from a smaller subsample of participants at follow-up; thus, changes from pre-intervention to follow-up should be interpreted with caution.

Despite these limitations, mindfulness (and health enhancement) interventions appear to have a beneficial effect on innate immune competence among lonely older adults, effects that persist and strengthen over time. The direction of the observed responses raises the possibility that these vulnerable older adults may be better protected against acute infection and injury. During the three months following intervention, 15 to 20 min of daily formal and informal practice was enough to maintain these benefits, although practice estimates were self-reported monthly and may be limited by memory bias. Interestingly, mindfulness participants reported approximately one session of formal practice per week, suggesting that the integration of mindfulness skills into daily living (rather than continued daily formal meditation practice) promoted lasting benefits.

4.1. Conclusion

Mindfulness training may be effective for boosting innate immune responsivity among lonely older adults. Given that innate immune competence tends to decline with age, these findings have potential implications for susceptibility to infection and wound healing.

Acknowledgments

This research was supported by grants from the National Center for Complementary & Integrative Health (NCCIH) of the National Institutes of Health (NIH) (F32AT009508 to EKL for glucocorticoid resistance subproject; R01AT008685 to JDC for parent trial). Recruitment was supported by the NIH Clinical and Translational Science Award (CTSA) program (grant UL1TR001857). These funding sources had no

involvement in study design; data collection, analysis, or interpretation; writing of this report; or the decision to submit this article for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The parent trial (R01AT008685) was conducted in David Creswell's Health and Human Performance Lab and the inflammatory biology (F32AT009508) was conducted in Anna Marsland's Behavioral Immunology Lab. We thank Carol Greco, Bonnie Gillis, Laura Kinzel, and Deanna Burkett for teaching MBSR and HEP classes, Hayley Rahl, Jeffrey DeBoer, Megan Lipsett, Sarah Lipitz, and Adrian Williams for help with study management, and the many research assistants who collected and processed specimens and data.

Appendix A. Supplementary materials

Supplementary materials for this article can be found online at https://doi.org/10.1016/j.bbi.2022.05.001.

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