Mindfulness-Based Stress Reduction Buffers Glucocorticoid Resistance Among Older Adults: A Randomized Controlled Trial

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ABSTRACT

Objective: Mindfulness interventions have been effective for improving a range of health outcomes; however, pathways underlying these effects remain unclear. Inflammatory processes may play a role, possibly through increased resistance of immune cells to the anti-inflammatory effects of glucocorticoids (i.e., glucocorticoid resistance, or GCR). Here, we conducted an initial examination of whether mindfulness training mitigates GCR among lonely older adults.

Methods: Lonely older adults (65–85 years; $n = 190$) were randomly assigned to an 8-week Mindfulness-Based Stress Reduction (MBSR) or a matched Health Enhancement Program (HEP). Whole blood drawn before and after the intervention and at 3-month follow-up was incubated with endotoxin and varying concentrations of dexamethasone, and interleukin-6 production was assessed using enzyme-linked immunosorbent assay. GCR was assessed as the concentration of dexamethasone required to decrease the stimulated interleukin-6 response by 50% (half maximal inhibitory concentration), with higher concentrations indicating greater GCR. Mixed-effects linear models tested time (pre, post, follow-up) by condition (MBSR versus HEP) effects.

Results: There was no overall time by condition effect on GCR across all time points. However, a significant time by condition effect was observed from preintervention to postintervention ($d = 0.29$), such that MBSR buffered increases in GCR observed in the HEP group. Although MBSR showed small, nonsignificant reductions in GCR from preintervention to 3-month follow-up, group differences were not maintained at the 3-month follow-up ($d = 0.10$).

Conclusions: Results suggest that MBSR may protect against declines in the sensitivity of immune cells to the anti-inflammatory effects of glucocorticoids among at-risk lonely older adults and show value in studying this biological mechanism in future trials.
Trial Registration: Clinical Trials identifier NCT02888600.

Key words: mindfulness, glucocorticoid, loneliness, older adulthood, immune function.

Mindfulness meditation is a popular integrative health practice, with nearly 10% of Americans practicing meditation to improve health (1). Randomized controlled trials have shown that mindfulness training is effective in improving a broad range of stress-related health outcomes (2), particularly in at-risk samples like lonely older adults (3). Still, little is known about the biological processes underlying these effects. One possibility is that mindfulness training impacts glucocorticoid (GC) receptor sensitivity, a primary mechanism controlling the magnitude of inflammatory response, which is thought to play a role in the association of chronic psychosocial stress and inflammatory disease risk (4,5). In a large sample of lonely older adults, the present study tests whether mindfulness training influences cellular sensitivity to GCs.

Evidence suggests that GC resistance (GCR) develops in response to chronic activation of the hypothalamic-pituitary-adrenal (HPA) stress response system and plays a key physiological role in the negative health effects of social stress (6). HPA activation leads to the peripheral release of the GC cortisol, which binds to GC receptors in immune cells and downregulates inflammatory gene expression. Contrary to expectations, however, chronic social stress is associated with increased rather than decreased cellular production of inflammatory mediators. Converging evidence suggests this may be the result of increased resistance of cells to the anti-inflammatory effects of cortisol, an adaptation that accompanies chronic social stress and may result from prolonged exposure to high cortisol levels. In short, this GCR disrupts physiological mechanisms that downregulate inflammation and may thus increase

GC = glucocorticoid, **GCR** = glucocorticoid resistance, **HEP** = Health Enhancement Program, **HPA** = hypothalamic-pituitary-adrenal, **IC50** = half maximal inhibitory concentration, **IL-6** = interleukin-6, **MBSR** = Mindfulness-Based Stress Reduction, **MLM** = mixed-effects linear model

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chronic inflammatory disease risk (7). Indicators of GCR have been observed both in animal models of social stress (8) and in human populations with high social stress burdens, notably among lonely older adults (7,9).

GCR is a leading candidate mechanism linking loneliness with inflammatory disease (4). Loneliness is a potent social stressor that may alter the body's ability to regulate inflammation (10). Because social connection is a basic human survival mechanism (11,12), chronic social isolation, including subjective feelings of loneliness, represents a threat to survival (4). When enduring, it is proposed that this chronic social stress dysregulates HPA axis function, leading to the development of GCR and ultimately increasing the risk of chronic inflammatory conditions (13). In support of this possibility, epidemiological studies have shown that loneliness puts people at risk for multiple inflammatory diseases and mortality (e.g., cardiovascular disease) (14–17), and this risk is comparable in magnitude to traditional behavioral risk factors (e.g., substance use and lack of physical activity) (18). Incidence of subjective social isolation is steadily increasing, situating loneliness as an important public health concern (18).

Mindfulness interventions, which guide participants to monitor their present-moment experiences with an attitude of acceptance, have shown promise for reducing loneliness (3,19–22). These interventions may be uniquely efficacious for reducing loneliness by training equanimity toward feelings of social stress (20). One intriguing hypothesis is that mindfulness training diminishes social threat in ways that reduce the peripheral release of cortisol (23,24) and, over time, restore cellular sensitivity to GCs. Promisingly, initial trials show that mind-body interventions increase GC receptor gene expression within breast cancer populations (25,26). These studies provide an important indication that GC transcriptional signaling processes are malleable and respond to psychological intervention. Still, it is not clear whether mind-body interventions also increase the functional ability of immune cells to downregulate inflammation (27). Controlling the magnitude of inflammatory responses is critical for health, with excessive or prolonged responses increasing the risk of the pathogenesis of chronic inflammatory disease.

To test the impact of mindfulness training on GC sensitivity, functional GCR was assessed before, after, and 3 months after a Mindfulness-Based Stress Reduction (MBSR) or control Health Enhancement Program (HEP) intervention in a sample of lonely older adults (n = 190). Functional GCR was assessed via a direct ex vivo assay testing the responsiveness of immune cells activated by endotoxin exposure to dexamethasone, a synthetic GC. MBSR was expected to decrease GCR (and restore GC receptor sensitivity) compared with HEP from preintervention to postintervention and 3-month follow-up. Supplemental sensitivity analyses explored moderators of this effect, testing whether those at highest risk for inflammatory disease (lower educational attainment, racial minority) (28) show the greatest improvement in GCR after MBSR.

METHODS

Participants

One hundred ninety lonely older adults aged 65 to 85 years were enrolled in the trial (see Table 1 for baseline characteristics). Of the 190 randomized participants, GCR and control variable data were available for at least one of the three assessments from 182 participants (see Figure 1 for CONSORT flowchart). The study design and outcomes described here were preregistered with Clinical Trials identifier NCT02888600. This report describes GCR outcomes, with hypotheses proposed in National Institutes of Health project F32AT009508 awarded to E.K.L.

Eligible participants were healthy meditation-naive adults 65 years or older with moderate to high levels of perceived loneliness. 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, e-mail, and mailed advertisements. Participants were then screened for the following eligibility criteria: English speaking; between the ages of 65 and 93 years at the time of randomization; moderate to high levels of perceived loneliness, as assessed by a score of 4 or greater on the Short Form UCLA-R (29); no diagnosis or treatment of severe mental illness (including personality or schizophrenic disorders, baseline Beck Depression Inventory score of 29 or greater (30), or therapy twice a week or more); no diagnosis or treatment of a current health problem or chronic disease known to affect inflammatory biology (e.g., HIV, rheumatoid arthritis, cancer, diabetes type 1, and lupus); no prescribed medication usage affecting cardiovascular or immune system function, except blood pressure medications in cohorts 7 to 8; no current substance abuse problem; no more than 90 min/wk spent in regular mind-body practice (e.g., guided meditation or relaxation, yoga, tai chi, massage, or journaling); no significant cognitive impairment, as assessed by a Telephone Interview for Cognitive Status score >30 (31); and no problems with attending study assessments or treatment visits regarding transportation, ambulation, or geographic accessibility. Written informed consent was obtained from all participants, and study procedures were approved by the Carnegie Mellon University and University of Pittsburgh institutional review boards. Study data were collected between October 2016 and February 2020. Trial recruitment concluded when recruitment goals had been reached.

The planned sample size for the trial (n = 188) was determined by estimating a small-medium effect (d = 0.3) of MBSR compared with HEP at postintervention and a pre-post correlation of r = 0.80. These estimates are based on a broad range of effect sizes in prior work related to the primary aims of the parent trial (3,32,33). This sample size was expected to be adequately powered (>0.90 for α = .05) to detect changes in GC sensitivity.

Procedure

Participants were prescreened for eligibility by telephone. At a preintervention study appointment, eligible participants completed a questionnaire and task battery and were oriented to the study. Participants attended a separate preintervention blood draw appointment; they provided 30 ml blood, including 8 ml in sodium heparin for the assessment of GCR and 4 ml in EDTA for the assessment of absolute cell counts (see Measures). They then completed 3 days of preintervention ambulatory assessments before being randomly assigned to condition at the first intervention session. Participants were allocated to MBSR or HEP using a computerized random number generator, with procedures implemented separately for each of eight cohorts (n = 9, 20, 29, 29, 20, 30, 20, and 33 in each cohort). Randomization was blocked by age (≤75 versus >75 years) and baseline depressive symptoms (Beck Depression Inventory score ≤13 versus >13). Allocation sequence was concealed, such that only author A.G.C.W. had access to the sequence and otherwise was not involved with participants or the running of the study. After the 8-week intervention, participants completed a 1-week postintervention blood draw appointment, a separate questionnaire assessment visit, and ambulatory assessment as at preintervention. Postintervention assessments were scheduled within 1 week of the final intervention class, and for the majority of participants (89%), the postintervention blood draw occurred on the same day as other assessments. Blood and questionnaire assessments were again collected at

TABLE 1. Baseline Characteristics of Randomized Participants

Characteristic	Full Sample (n = 190)	MBSR (n = 93)	HEP (n = 97)	Condition Difference
Age, y	69.77 (0.31)	69.96 (0.45)	69.59 (0.43)	$F(1,188) = 0.35$, $p = .55$
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%)	
Biracial or multiracial	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], kg/m^2	27.94 (0.44)	27.41 (0.62)	28.44 (0.61)	$F(1,188) = 1.40$, $p = .24$

Data reported as means and (SEs) or (%).

MBSR = Mindfulness-Based Stress Reduction; HEP = Health Enhancement Program; GED = General Equivalency Diploma; BMI = body mass index.

[a] For n = 34, height used in BMI calculations estimated from averages for females and males.

3-month follow-up. Participants were debriefed after the completion of all assessments. Participants were compensated up to a total of $475, including bonus payments for high adherence. Other outcomes from the larger trial will be reported in separate articles.

Materials

Intervention Programs

Participants were randomly assigned to programs based on MBSR or a structurally matched HEP (32). Both 8-week interventions are standardized curriculum-based group programs. In this study, interventions consisted of 8 weekly 2-hour group sessions, a daylong retreat during the sixth week, and 45-minute home practice assignments 6 days per week.

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. 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, seated meditation, and daily life awareness exercises.

HEP uses 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. Home practice assignments guide participants through age-appropriate physical fitness, nutrition, and music engagement exercises.

The study was run in eight cohorts ranging in size from 9 to 33 participants, with class sizes ranging from 3 to 17 participants. MBSR classes were taught by two instructors: Deanna Burkett, who had 13 years of personal meditation practice and 8 years of experience teaching MBSR, instructed cohorts 2 to 3; Carol Greco, who had 25 years of personal meditation practice and 14 years of experience teaching MBSR, instructed

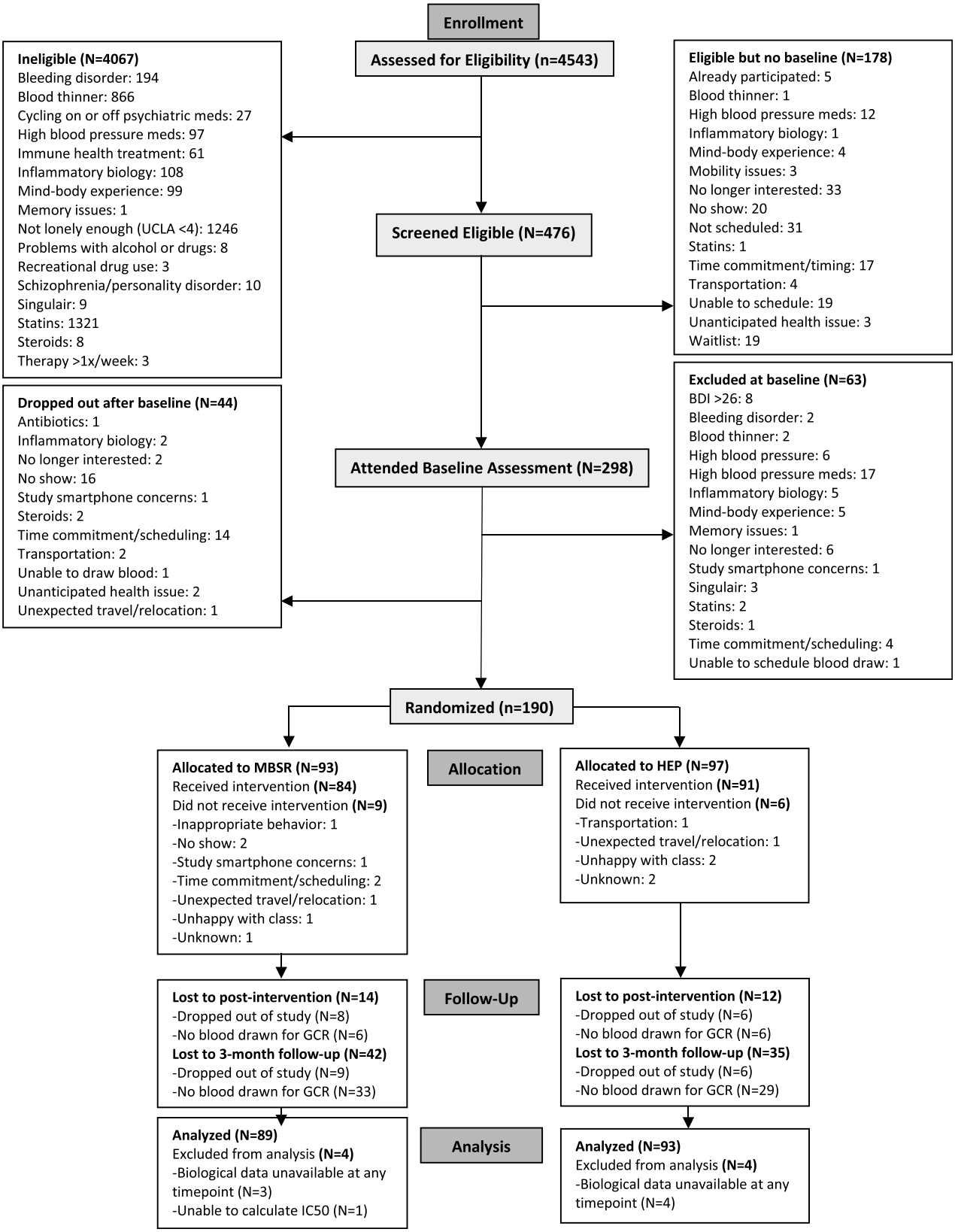

FIGURE 1. CONSORT flowchart.

cohorts 1 and 4 to 8. Both are certified MBSR teachers. HEP classes were also taught by two instructors: Bonnie Gillis, senior research nutritionist and medical writer, instructed cohorts 1 to 5; Laura Kinzel, nutrition educator and exercise coach, instructed cohorts 6 to 8. Both are registered and licensed dietitian nutritionists. Instructors were blind to outcome measures.

Measures

Functional GCR was assayed at baseline and postintervention (all cohorts; $n = 185$) and at 3-month follow-up (cohorts 4–8; $n = 115$) in the Behavioral Immunology Lab at the University of Pittsburgh (principal investigator: A. L.M.). This assay measures the ability of a synthetic GC (dexamethasone) to downregulate cellular production of the proinflammatory cytokine interleukin-6 (IL-6) in response to stimulation with endotoxin (lipopolysaccharide); higher IL-6 production indicates GC receptor insensitivity (i.e., GCR) to dexamethasone. Within 3 hours of each blood draw, 6 wells containing 1.2 ml of whole blood (diluted 10:1 with saline) were incubated with 150 μl dexamethasone of increasing concentrations (0 nM + NaCl, 10^{-9}, 10^{-8}, 5×10^{-8}, 10^{-7}, and 10^{-6} nM) and 150 μl lipopolysaccharide at 30 ng/ml in phosphate buffer. Samples were incubated overnight (18 hours) at 37°C with 5% CO_2. Supernatants were then removed for storage at −80°C. IL-6 was measured in batches via enzyme-linked immunosorbent assay (using BD Biosciences kits, catalog no. 555220, lot no. 8151888EU), with all available time points for each participant assayed on the same plate. Interassay and intra-assay coefficients of variability were 12.7% and 4.4%, respectively. GCR was quantified by calculating the concentration of dexamethasone that reduced the stimulated IL-6 response by 50% (the half maximal inhibitory concentration, or IC50). A higher IC50 indicates greater GCR; thus, decreases in IC50 reflect improvement in GC sensitivity over time.

Absolute cell counts were assayed from whole blood samples in a commercial laboratory, with absolute number of monocyte cells of particular interest. Monocyte count was included as a covariate in GCR analyses because a) monocytes are the primary immune cells that produce IL-6 when stimulated with endotoxin and b) absolute number of monocytes varies in each blood sample.

To assess *intervention and home practice adherence*, attendance at each of the eight classes and the daylong retreat was recorded via sign-in sheet, with adherence calculated as the total number of sessions out of nine. Home practice audio files and weekly assignments were distributed in class and measured each day using Qualtrics links that asked participants to self-report the duration of their practice. These daily durations were averaged across the 8-week intervention. Home practice during the 3-month follow-up period was assessed during monthly telephone calls. Participants reported the duration of formal practice and informal practice per week in the previous month; weekly durations were averaged across the 3-month follow-up period.

Analyses

Analyses were conducted using Stata 16 software (StataCorp, College Station, Texas). Preliminary analyses tested for condition differences in demographics and other baseline characteristics using χ^2 (for categorical variables) and analysis of variance tests (for continuous variables). Intervention adherence, home practice, and body mass index were evaluated as covariates using analysis of variance to test for significant condition differences.

To test primary predictions, mixed-effects linear models (MLMs) tested for time (preintervention, postintervention, or 3-month follow-up) by condition (MBSR versus HEP) differences on GCR using the Stata Mixed procedure. Planned comparisons testing for MBSR versus HEP differences from preintervention to postintervention and preintervention to 3-month follow-up were calculated within these MLMs. MLMs model all available data and provide unbiased estimates to account for data missing at random; thus, MLMs are robust to missing data. MLMs capture both within- and between-individual variabilities. Time was modeled as a random effect and condition as a fixed effect using maximum likelihood estimation. Time was modeled with an exchangeable covariance structure, with preintervention values used as the first repeated measure to test for time by condition interactions. Covariates were modeled as fixed effects.

Within-group Cohen *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.

RESULTS

Preliminary Analyses

Participants had a mean (standard deviation) age of 69.77 (4.27) years (range, 65–85 years) and were predominantly female (78%), White (85%), non-Hispanic (97%), and college-educated (74%). Table 1 describes demographic characteristics by condition. There were no group differences in age ($F(1,188) = 0.35$, $p = .55$), sex ($\chi^2(1) = 0.53$, $p = .47$), race ($\chi^2(3) = 0.27$, $p = .97$), ethnicity ($\chi^2(1) = 2.58$, $p = .11$), education ($\chi^2(8) = 8.96$, $p = .35$), marital status ($\chi^2(4) = 0.83$, $p = .93$), or preintervention body mass index ($F(1,188) = 1.40$, $p = .24$).

Participants in both groups were highly adherent to the intervention, completing on average eight of the nine intervention sessions, with 63% of participants attending all nine sessions. There were no group differences in intervention adherence ($F(1,188) = 0.45$, $p = .50$), but HEP participants were more likely to attend the daylong retreat ($\chi^2(1) = 4.66$, $p = .031$). Participants completed an average of 35.70 (SE = 1.26) minutes per day of home practice. HEP participants averaged significantly more home practice than MBSR participants ($F(1,188) = 11.59$, $p = .001$). Home practice is included as a covariate in primary analyses, but it did not impact results. HEP participants also tended to practice more during the 3-month follow-up period, reporting significantly more formal practice compared with MBSR participants ($F(1,173) = 70.06$, $p < .001$) but not total home practice (formal and informal practice combined; $F(1,168) = 3.04$, $p = .083$). Fifteen participants dropped out of the study, with nine from MBSR and six from HEP. There were no group differences in dropout rate ($\chi^2(1) = 0.80$, $p = .37$), and dropouts did not differ from completers by age, sex, race, or ethnicity (all p values > .25). Table 2 provides descriptive statistics for these characteristics.

There were no baseline group differences in monocyte counts ($\chi^2(1) = 0.74$, $p = .39$) or differences in monocyte count change over time (time by condition effect: $\chi^2(2) = 3.00$, $p = .22$). Monocyte count was significantly correlated with GCR IC50 ($r = -0.10$, $p = .029$), such that higher GCR was associated with lower numbers of monocytes. Monocyte count was included as a covariate in primary analyses. There were no baseline group differences on GCR as assessed by IC50 ($\chi^2(1) = 2.39$, $p = .12$).

Primary Analyses

MBSR was predicted to have protective effects on GCR compared with HEP from preintervention to postintervention and 3-month follow-up, with decreases in GCR after MBSR relative to HEP. MLMs tested for time (pre, post, follow-up) by condition (MBSR, HEP) interactions on GCR IC50 controlling for monocyte counts and home practice duration. A higher IC50 reflects greater GCR; lower IC50s reflect GC sensitivity.

TABLE 2. Adherence and Preintervention Outcomes of Randomized Participants

Characteristic	Full Sample (n = 190)	MBSR (n = 93)	HEP (n = 97)	Condition Difference
Intervention dropouts	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)	$F(1,188) = 0.08$, $p = .77$
Retreat attendance	153 (80.53%)	69 (74.19%)	84 (86.60%)	$\chi^2(1) = 4.66$, $p = .031$
Home practice adherence, min/d	35.70 (1.26)	31.31 (1.80)	39.90 (1.76)	$F(1,188) = 11.59$, $p = .001$
Home practice during 3-mo follow-up, min/wk				
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)	$F(1,168) = 3.04$, $p = .083$
Preintervention monocyte count[c]	0.49 (0.01)	0.48 (0.02)	0.50 (0.02)	$\chi^2(1) = 0.74$, $p = .39$
Preintervention GCR (IC50)[d]	51.85 (1.59)	54.48 (2.30)	49.55 (2.21)	$\chi^2(1) = 2.39$, $p = .12$

Data reported as means and (SEs) or (%).

MBSR = Mindfulness-Based Stress Reduction; HEP = Health Enhancement Program; GCR = glucocorticoid resistance.

[a] n = 175.

[b] n = 170.

[c] n = 187.

[d] n = 182, controlling for monocyte count.

MLM analyses did not show a significant time by condition effect on GCR across pre, post, and follow-up time points ($\chi^2(2) = 4.01$, $p = .135$). However, planned contrasts testing for differences from preintervention to postintervention showed a significant time by condition effect on IC50 ($\chi^2(1) = 3.95$, $p = .047$, $d = 0.29$). This interaction was driven by significant increases in IC50 in HEP ($M_{change} = 8.02$, SE = 3.21; $\chi^2(1) = 6.26$, $p = .012$, $d = 0.37$), reflecting a relative worsening in GCR. In contrast, MBSR had a GCR buffering effect, such that there were no significant changes from preintervention to postintervention in the MBSR group ($M_{change} = -1.26$, SE = 3.40; $\chi^2(1) = 0.14$, $p = .71$, $d = 0.06$). This group difference was not maintained at 3-month follow-up; there were no time by condition effects from preintervention to follow-up ($\chi^2(1) = 0.43$, $p = .51$, $d = 0.10$). Despite a further small reduction in IC50 in the MBSR group, neither condition showed significant change in IC50 from preintervention to 3-month follow-up (MBSR: $M_{change} = -3.59$, SE = 3.90; $\chi^2(1) = 0.85$, $p = .36$, $d = 0.14$; HEP: $M_{change} = -0.10$, SE = 3.63; $\chi^2(1) = 0.00$, $p = .98$, $d = 0.00$; Table 3).

DISCUSSION

Mindfulness interventions show benefits for improving a broad range of health outcomes, yet the biological pathways underlying these effects remain unclear. This study tested the possibility that mindfulness interventions increase the sensitivity of immune cells to the anti-inflammatory effects of GCs, a biological mechanism that may link reductions in loneliness with improvements in inflammatory disease outcomes. In a large sample of lonely older adults, there was no evidence that mindfulness training significantly alters GC sensitivity. Instead, results suggest the possibility that mindfulness training buffers against the development of GCR in the short-term. Specifically, whereas GCR did not change after 8-week MBSR, preintervention to postintervention increases in GCR were observed after a well-matched 8-week HEP. Although MBSR participants showed small (but nonsignificant) reductions in GCR at 3-month follow-up, MBSR versus HEP group differences were not maintained. This study provides an initial examination of whether mindfulness interventions can influence GC receptor sensitivity, thus targeting a primary physiological pathway linking loneliness with inflammatory disease risk.

Contrary to expectations, MBSR did not significantly reduce GCR at postintervention or follow-up; instead, it seemed to buffer against increased GCR observed in the HEP group at postintervention. Although not what we predicted a priori, this pattern is consistent with other studies showing that mindfulness interventions buffer immune (34) and working memory (35) declines in at-risk stressed samples. Another possibility is that post-HEP increases in GCR relate to aspects of the study design; for many participants

TABLE 3. GCR IC50 At Preintervention, Postintervention, and 3-Month Follow-Up in MBSR and HEP

Characteristic	MBSR (n = 89)	HEP (n = 93)	Pre-Post, Cohen's d	Time by Condition Difference
Preintervention GCR (IC50)	54.67 (2.30)	49.45 (2.21)	—	—
Postintervention GCR (IC50)	53.41 (2.51)	57.48 (2.32)	0.29	$\chi^2(1) = 3.95$, $p = .047$
3-mo follow-up GCR (IC50)[a]	51.08 (3.15)	49.35 (2.88)	0.10	$\chi^2(1) = 0.43$, $p = .51$

Analyses include monocyte count and home practice covariates. Data reported as means and (SEs). Cohen's d estimates between-group differences in change from preintervention to postintervention and 3-month follow-up.

MBSR = Mindfulness-Based Stress Reduction; HEP = Health Enhancement Program; GCR = glucocorticoid resistance; IC50 = half maximal inhibitory concentration.

[a] Data estimated for n = 69.

across conditions, the postintervention blood sample was drawn on a day that included other assessments in a different location, which may have introduced additional demand and acute stress. In addition to the body of evidence that chronic stress associates with GCR (13,36–39), acute stress has been shown to induce rapid increases in GCR, particularly among older adults (40). Consistent with a mindfulness-stress-buffering hypothesis (41), mindfulness training may have helped to buffer stress at postintervention compared with HEP, leading to acute differences in receptor sensitivity that may also have implications for inflammatory disease risk (42).

It is worth noting that the HEP comparison condition involved nutrition and exercise content, which both have the potential to influence biological pathways. Specifically, there is evidence that dietary factors and physical activity associate with lower inflammatory disease risk (43,44), as well as evidence that interventions focused on improving these health behaviors can impact markers of inflammatory disease risk (45). Moreover, high rates of home practice in the HEP group indicate adherence to health behaviors (e.g., regular exercise) throughout the follow-up period, which may help to explain why group differences were not observed at follow-up; these health behaviors may have buffered long-term increases in GCR. Indeed, given longitudinal evidence that chronic stress increases GCR over time (39), it is plausible that with no intervention, GCR would have continued to increase in this lonely older adult sample. Thus, HEP is a stringent comparison condition to test the hypothesis that mindfulness training specifically targets psychosocial stress pathways with implications for improving immune cell function. Research including inactive control groups is needed to evaluate whether mindfulness training buffers longer-term increases in GCR.

The possibility that declines in GC receptor sensitivity may be buffered through psychological intervention has important implications for public health. Converging evidence shows that GCR develops in response to chronic social stress, including chronic loneliness (7,9) and caregiving stress (13,36–39), as well as to ongoing synthetic GC treatment (e.g., steroids) (46,47). Whether GC sensitivity can be maintained in these contexts is an open question. Although initial evidence suggests that GC receptor gene expression can increase after a psychological intervention (25,26,48), to our knowledge, only one previous study tested the malleability of functional GCR. In that study, regardless of participation in a cognitive behavioral stress management intervention, functional GCR increased in mothers in the year after their child's cancer diagnosis (39). In contrast, mindfulness interventions reduce reactivity to uncomfortable emotions (49), which may uniquely attenuate social stress in ways that influence HPA axis activity (23) and thereby preserve GC receptor function.

The potential for mindfulness interventions to buffer against increases in GCR may have implications for the development of chronic inflammatory diseases as well as the efficacy of synthetic GCs used to treat many inflammatory diseases (e.g., asthma). Indeed, individual differences in cellular sensitivity to GC medications impacts clinical response. For example, compared with European Americans, African Americans have higher GCR (50), higher incidence of asthma (51), increased resistance to GC treatments (52), and disproportionate asthma morbidity (53). Of course, the relative benefits of MBSR compared with HEP observed here were not maintained long-term and may not have clinical impact. However, it is possible that mindfulness effects on GCR may be more pronounced in high-risk and clinical samples.

Indeed, one working hypothesis is that mindfulness interventions only impact inflammatory processes among people at highest risk (2). For example, there is equivocal evidence that mindfulness interventions reduce markers of systemic inflammation in healthy samples, with some evidence for reductions in C-reactive protein and IL-6 in higher-risk subgroups: lonely older, stressed, and overweight adults and those with elevated baseline levels of systemic inflammation (3,54–56). Mindfulness interventions may be even more likely to influence GCR among high-risk individuals; as a reflection of local inflammatory response dynamics, GCR is more proximal to the pathophysiology of inflammatory disease than biomarkers of systemic inflammation (which reflect proteins released from multiple sources in addition to immune cells) (57). Although the present study attempted to recruit a sample at risk for inflammatory disease, it is possible that the stringent inclusion criteria yielded an unusually healthy and low-risk sample despite high levels of loneliness. Indeed, 60% of potential participants were excluded based on physical health criteria (e.g., cholesterol medications). The remaining sample primarily reported their own health as excellent (19%), very good (51%), or good (26%), ratings that relate to infectious disease susceptibility and mortality in a graded fashion (58,59) and, in this sample, to GCR ($r = 0.16$, $p = .03$). Moreover, the final sample was highly educated, a robust predictor of health (60); 74% had attained a college degree and 44% an advanced degree, rates 2 to 3 times higher than US averages (31% and 13%, respectively) (61). Thus, it is possible that many of the lonely older adults sampled have some protection from the negative health effects of loneliness. For example, people who reach very old age (75+ years) without health complications are considered "biologically elite" by some (62); the sample recruited here may fit this description.

Supplemental analyses explored the possibility that MBSR was effective for reducing GCR among those at greatest inflammatory disease risk in the study. Consistent with epidemiological research showing a relationship between educational attainment and health (60), participants with a college degree had a 15% lower GCR than did those without. Among MBSR participants without a college degree, there was a significant reduction in GCR from pre- to post-MBSR, a change that was maintained at follow-up (Figure S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A727). Similarly, there were significant baseline differences in GCR by race, with White participants showing 17% lower GCR than non-White participants. This pattern is consistent with evidence that African Americans have higher GCR (50) and are less sensitive to GC treatment (52). Again, there was some suggestion that MBSR was effective for lowering GCR among racial minority participants, albeit in a very small subsample (Figure 2S, Supplemental Digital Content, http://links.lww.com/PSYMED/A727). Although underpowered, these exploratory analyses are consistent with the idea that mindfulness interventions have health protective effects in higher-risk subgroups. To confirm this hypothesis, it will be important for future mindfulness intervention studies to carefully balance the recruitment of high-risk participants with exclusion criteria to minimize the interference of health conditions and medications on biological outcomes of interest (63).

We note one additional important limitation: 3-month follow-up GCR data were not collected from participants in the first three

cohorts (n = 58) for funding reasons, so estimates of change in GCR from preintervention to follow-up should be interpreted with caution. Data from nearly the full sample support the finding that MBSR buffered declines in GC sensitivity observed among HEP participants from preintervention to postintervention.

CONCLUSIONS

Overall, MBSR did not alter immune cell sensitivity to GCs. Instead, mindfulness interventions may protect against declines in immune cell function among people at high psychosocial risk. These findings point to a potential biological mechanism through which mindfulness interventions may impact health and inspire further research among people at risk for poor health across the lifespan.

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