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Authors
Moieni, Mona
Irwin, Michael R
Haltom, Kate E Byrne
et al.

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Exploring the Role of Gratitude and Support-Giving on Inflammatory Outcomes

Mona Moieni, Michael R. Irwin, Kate E. Byrne Haltom, Ivana Jevtic, Meghan L. Meyer, Elizabeth C. Breen, Steven W. Cole, and Naomi I. Eisenberger
University of California, Los Angeles

Although there has been much interest in understanding the effect of gratitude on health-related outcomes, this remains an understudied area of research, particularly regarding mechanisms and measurement of biological outcomes. The present study explored whether a gratitude intervention could reduce inflammatory outcomes and whether this occurred through increased support-giving. Healthy women ($n = 76$) were randomly assigned to a 6-week gratitude intervention (i.e., writing on topics intended to induce gratitude) or a control condition (i.e., neutral writing). Support-giving and markers of inflammation were measured pre- and postintervention. Those in the gratitude intervention (vs. control) reported higher postintervention levels of support-giving. Moreover, those with lower levels of psychological distress gave more support as a function of the gratitude intervention. Regarding inflammatory outcomes, although there was no effect of the gratitude intervention on postintervention inflammatory markers, increases in support-giving across the entire sample were related to decreases in inflammatory markers. These results, along with a scarcity of work in this area, suggest that further work is needed to more fully understand the relationships between gratitude and biological markers relevant to health. Finally, these novel findings linking support-giving and decreases in inflammation also indicate that the mammalian caregiving system, associated with enhanced support-giving and reduced physiological stress responding, is a mechanism worth further examination to elucidate the links between social support and health.

Keywords: gratitude, support-giving, social support, inflammation, caregiving

Supplemental materials: http://dx.doi.org/10.1037/emo0000472.supp

Across many cultures and many centuries, there has been long-standing interest in understanding gratitude—an emotional state resulting from the perception that one has received something of value from others—and its potential benefits for well-being and health. Indeed, previous research has backed the notion that gratitude is related to and may lead to better psychological well-being (Emmons & McCullough, 2003; Wood, Froh, & Geraghty, 2010). Although limited, there is also some evidence that greater gratitude is associated with physical health outcomes, such as better self-reported health (Hill, Allemand, & Roberts, 2013) and sleep (Mills et al., 2015). Still, despite the interest in and previous studies looking at gratitude and health, there is a dearth of work assessing

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Mona Moieni, Department of Psychology, University of California, Los Angeles; Michael R. Irwin, Semel Institute for Neuroscience and Human Behavior, Cousins Center for Psychoneuroimmunology, University of California, Los Angeles; Kate E. Byrne Haltom, Ivana Jevtic, and Meghan L. Meyer, Department of Psychology, University of California, Los Angeles; Elizabeth C. Breen, Semel Institute for Neuroscience and Human Behavior, Cousins Center for Psychoneuroimmunology, University of California, Los Angeles; Steven W. Cole, Semel Institute for Neuroscience and Human Behavior, Cousins Center for Psychoneuroimmunology; Department of Medicine, Division of Hematology–Oncology, and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles; Naomi I. Eisenberger, Department of Psychology, University of California, Los Angeles.

Meghan L. Meyer is now at the Department of Psychological and Brain Sciences, Dartmouth College.

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Correspondence concerning this article should be addressed to Naomi I. Eisenberger, Department of Psychology, University of California, Box 951563, 4444 Franz Hall, Los Angeles, CA 90095-1563. E-mail: neisenbe@ucla.edu

the effect of gratitude on biological measures that are associated with health outcomes. In fact, only one prior study has examined the experimental effect of gratitude on inflammation (Redwine et al., 2016), and, due to baseline differences in inflammation, results from this study must be interpreted with caution. Moreover, no work has explored the mechanisms that might underlie the relationship between gratitude and improved health. Here, we examine whether a gratitude intervention leads to changes in biological measures (i.e., inflammation) and whether support-giving may be associated with these health benefits.

Although much has been suggested about the health benefits of gratitude, psychological theories explaining the mechanisms behind these health benefits are lacking. One possible pathway through which gratitude may exert its health benefits may be through the activation of the mammalian caregiving system, which is involved in providing support and care to offspring and which also reduces physiological stress responses in the caregiver (Inagaki & Eisenberger, 2012).

Thus, one of the key proposed functions of gratitude is to promote reciprocal altruism by increasing prosocial acts of giving, which may be critical for building and maintaining social relationships (McCullough, Kimeldorf, & Cohen, 2008). Indeed, prior work has shown that gratitude can increase prosocial behavior (Bartlett & DeSteno, 2006; Layous, Nelson, Kurtz, & Lyubomirsky, 2017; Tsang, 2006), such as giving more support to others (Emmons & McCullough, 2003). Interestingly, the caregiving system relies on neural regions that reinforce prosocial behavior and may be relevant to the prosocial benefits associated with gratitude. For example, providing support to a loved one in need increases activity in neural regions associated with a mammalian caregiving system, such as the ventral striatum and septal area (Inagaki & Eisenberger, 2012). Thus, it is possible that gratitude coopted the caregiving system to promote support-giving and reinforce social bonds.

Furthermore, activation of the mammalian caregiving system could be a pathway for the health benefits of gratitude, because the caregiving system is related to neurobiological processes that reduce physiological responding to threat in both humans (Inagaki & Eisenberger, 2012) and nonhuman animals (Covian, Antunes-Rodrigues, & O'Flaherty, 1964; Malmo, 1964). Indeed, to the extent that the mammalian caregiving system reduces physiological threat responding, giving support to others should have beneficial effects on health. In support of this idea, it has been found that giving social support to others is associated with better health outcomes (Konrath & Brown, 2013). For example, adults who give more support to others have better self-perceived health (Abolfathi Momtaz, Ibrahim, & Hamid, 2014), reduced cardiovascular arousal (Piferi & Lawler, 2006), and a lower risk of mortality (Brown, Nesse, Vinokur, & Smith, 2003). Moreover, experimentally manipulating support-giving leads to reductions in sympathetic nervous system responses to stress (Inagaki & Eisenberger, 2016). These reductions in sympathetic nervous system induced by support-giving (possibly via activations in caregiving-related neural regions) may ultimately alter inflammatory processes, given that sympathetic nervous system activity enhances inflammatory activity (Eisenberger & Cole, 2012; Irwin & Cole, 2011).

Given that gratitude increases prosocial behavior, such as giving support, and that giving support is related to better health, it is possible that gratitude may lead to improvements in health via increases in support-giving to others. This effect on support-giving may then extend to prosocial behavior more broadly. However, to our knowledge, this idea has not previously been explored.

Thus, the current study seeks to fill in some of the gaps in this literature. In the present study, we examined the effect of a gratitude intervention on support-giving to others and inflammation. We hypothesized that the gratitude intervention would lead to reduced inflammatory activity through increases in prosocial support-giving behavior. Because inflammation plays a role in a wide host of both physical and mental health disorders (Choy & Panayi, 2001; Depino, 2013; Grivennikov, Greten, & Karin, 2010; Libby, 2006; Miller, Maletic, & Raison, 2009), this may ultimately have important implications for health.

Because of calls to understand which individuals will benefit the most from a specific positive psychological intervention (Lyubomirsky & Layous, 2013), we were also interested in examining moderating effects of the gratitude intervention. Prior work has suggested that individuals with moderate depression may not derive as much benefit from gratitude interventions (Sin, Della Porta, & Lyubomirsky, 2011). As such, we tested psychological distress (i.e., depression, loneliness, perceived stress) as a moderator of the effects of the gratitude intervention in this sample of healthy women. We predicted that those with higher levels of psychological distress would not derive as much benefit from the intervention, showing less improvement in feelings of gratitude, giving of support to others, and inflammatory outcomes.

Method

Participants

The study sample size was based on the imaging component of the study (not discussed here; please see the online supplemental materials for power calculations). The sample consisted of 76 middle-aged women (mean age = 42.6 ± 4.8 years) who were randomized into either a gratitude condition or control condition for 6 weeks. Of these 76 participants who were randomized, eight participants (four in each condition) did not complete the study, leaving a final sample of 68 participants. Five of these eight participants were removed by the investigators for not meeting study eligibility or for failing to complete study procedures, and three participants dropped out before completing the study. All participants provided written consent before participating. All procedures were approved by the UCLA Human Subjects Protection Committee.

Participants were recruited from the University of California, Los Angeles (UCLA), and the greater Los Angeles community using flyers posted around the UCLA campus, advertisements in campus and local newspapers, and online postings (e.g., Craigslist). Interested participants were screened for eligibility using a structured telephone interview. Inclusionary criteria included (a) being a healthy woman between 35 and 50 years of age, (b) fluency in English, and (c) access to a computer and the Internet to complete the weekly study sessions. Prospective participants with the following conditions were excluded: claustrophobia; left-handedness; metal in their body (relevant for a neuroimaging component not reported here); chronic physical or mental health problems that may impact the study's physiological or psychological outcomes (e.g., autoimmune disorders, major depression); regular

use of certain prescription medications (e.g., anti-inflammatory medications, psychotropic medications, steroids, opioids); body mass index (BMI) greater than 30; current smoker or excessive caffeine user; or recent nightshift work or time zone shifts (>3 hr).

Procedure

Overview. All participants completed a preintervention session, 6 weeks of gratitude or control writing sessions, and a postintervention session. Participants began the study with a preintervention session at the UCLA Clinical and Translational Research Center (CTRC). Here, a nurse who was blind to condition drew blood for assessment of inflammatory measures. Participants then completed self-report questionnaires, and the study coordinator (Kate E. Byrne Haltom) gave them instructions for their weekly study assignments. Over the next 6 weeks, participants completed gratitude or control writing assignments (detailed in the next section). After the 6-week intervention, participants returned to the CTRC for a postintervention session involving another blood draw, self-report questionnaires, and a neuroimaging component (not described here). At the end of the study, participants were thanked, debriefed, and paid for their participation.

Intervention. Participants were randomized into either a 6-week gratitude or control condition. The intervention was structured as a weekly, variable writing task based on several recommendations regarding the characteristics of positive psychological interventions that may improve efficacy (Layous, Nelson, & Lyubomirsky, 2013). Participants wrote once a week (Sunday evening) and reviewed their writing later on in the week (on Wednesday evening, as a booster) because of evidence that performing a task too often can make it burdensome and therefore diminish its benefits (Lyubomirsky & Layous, 2013; Lyubomirsky, Sheldon, & Schkade, 2005). Furthermore, prior research has suggested that increasing variety in positive psychological interventions can increase efficacy (Sheldon, Boehm, & Lyubomirsky, 2012). Thus, participants were given slightly different prompts each week of the intervention. All six gratitude and control prompts in their entirety are included in the online supplemental materials.

Once a week for 6 weeks, participants in both conditions were e-mailed a link to log in to an online system (i.e., SurveyMonkey) to complete a weekly writing assignment. The general instructions for both conditions were identical. They were instructed to complete the session when they were able to sit quietly, alone, and without outside distractions. Participants were told they would be asked to write about various topics—a new topic each week—across the 6 weeks. They were asked to spend at least 5−10 min writing but were welcome to spend further time writing if they desired. Participants were told not to worry about grammar, spelling, or sentence structure and that the exercise was "really just intended to get you to think about the topic listed on the next page." Participants were assured their writings would be confidential and were instructed to "really try to get into the writing experience."

Participants in the gratitude condition then received a prompt intended to induce feelings of gratitude. Given that we expected support-giving to be the mechanism through which gratitude may impact health, all prompts in the gratitude condition were purposefully designed to be social in nature. That is, all six prompts in the gratitude condition focused participants on their feelings of gratitude toward other people, rather than asking them to be grateful toward any topic of their choosing, which could potentially lead to feelings of gratitude toward nonsocial entities (e.g., food, occupation, income, shelter, good weather).

For example, one gratitude prompt (abbreviated here) read:

> Think of someone in your life who you feel like you have never fully or properly thanked for something meaningful or important that they did for you. . . . In the space provided below, please write a note to this person that describes why you feel like you never properly thanked them and letting them know why you feel thankful for something important that they did for you. Though this letter will not actually be sent to this person and is simply an exercise for you, please use this as an opportunity to really explore those feelings surrounding how you feel about what they have done for you and write honestly and openly from your heart.

Participants in the control group received a prompt intended to be a descriptive, neutral writing prompt, such as describing things like rooms or what they had for lunch. They were repeatedly instructed to focus on descriptive details rather than social features such as people they were with or what they were thinking. For example, one prompt (abbreviated here) read:

> Think about the longest distance that you walked today. In the space provided below, please describe the longest distance that you walked today and what you saw along the way. . . . Please try to focus on the details of the types of things that you saw along your walk, rather than on who you were with or what you were thinking about during this time. Use this writing session as an opportunity to paint a detailed picture of what you experienced visually along your walk, including as much specific information as you can recall.

Each week, 3 days after their weekly writing session, all participants were e-mailed their writing from their previous writing session. Participants were asked to read over their writing, which was intended to reinforce feelings of gratitude for those in the gratitude condition. They were then asked questions about how they felt in response to the writing (detailed in the next section).

Measures

Self-report measures.

Trait gratitude. Trait gratitude was measured both pre- and postintervention using the Gratitude Questionnaire–6 (GQ-6), a standardized six-item trait measure of gratitude (McCullough, Emmons, & Tsang, 2002). Participants were asked how much they agreed with statements such as "I have so much in life to be thankful for" and "I am grateful to a wide variety of people" on a 7-point scale ranging from 1 (*strongly disagree*) to 7 (*strongly agree*). The six items were averaged at each time point for a measure of trait gratitude. The reliability of the scale (assessed at preintervention) was high ($\alpha = .88$).

Giving of social support. Giving of social support to others was measured using the 2-Way Social Support Scale (Shakespeare-Finch & Obst, 2011) pre- and postintervention. This instrument provides subscales for giving of emotional support to others (example item: "I give others a sense of comfort in times of need") and giving of instrumental support to others (example item: "I help others when they are too busy to get everything done"), rated on a 6-point Likert scale ranging from 0 (*not at all*) to 5 (*always*). We combined these two

subscales into one overall measure of giving of social support by averaging items across the two subscales at each time point. Due to technical issues, one item from the giving emotional support subscale ("People close to me tell me their fears and worries") was missing. However, the reliability of this combined giving social support scale (assessed at preintervention) was high ($\alpha = .84$).

Composite score for psychological distress. Prior work has suggested that individuals with moderate depression may not derive as much benefit from gratitude interventions (Sin et al., 2011). Because our sample was composed of healthy women, and current depression was an exclusionary criteria to participate, we tested psychological distress (i.e., a composite of depression, loneliness, and perceived stress) instead of relying solely on depression scores as a moderator of the primary outcomes of interest.

To create a composite for psychological distress, we standardized and summed three widely used, reliable measures for assessing depression, loneliness, and perceived stress. Depression was assessed with the Beck Depression Inventory (Beck, Steer, & Carbin, 1988). Loneliness, or subjective feelings of social isolation, was measured with the UCLA Loneliness Scale (Russell, 1996). Perceived stress was measured with the Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983). These measures were all assessed at baseline.

Conceptually, these constructs all reflect forms of psychological distress (Engeland et al., 2016). Rather than looking at the effect of these highly interrelated concepts separately, we created a composite score that reflected psychological distress by standardizing and summing the three measures mentioned. Indeed, these three scales were significantly correlated with each other ($rs = .5-.6$, $ps < .0001$), and the results of a principal components analysis revealed that the composite of these three scales reflects a single factor or component. Based on the commonly used Kaiser criteria (Field, 2009; Kaiser, 1960), only one component emerged; only one component had an eigenvalue over 1 (eigenvalue = 2.109), and this single component explained 70% of the variance in the indicator variables. Furthermore, all variables had a loading of .8 or better, indicating strongly loading items (Osborne & Costello, 2009).

Weekly state measures of gratitude and other feelings after rereading writing. Each week, after participants were asked to reread their weekly writing (3 days after they completed the writing, not on the same day as they completed the writing), they were presented with the item stem "In response to rereading your writing, to what extent did you feel . . ." followed by adjectives including "grateful," "thankful," "appreciative," "connected," "loving," "happy," "pleasant," and "reflective." These were rated on a 7-point scale ranging from 1 (*not at all*) to 7 (*extremely*). The three items related to gratitude (grateful, thankful, appreciative) were averaged to reflect a single state gratitude measure ($\alpha = .95$, assessed at Week 1).

Inflammatory measures. Inflammation was measured using two distinct, complementary assessments: (a) in vitro assessment of intracellular production of inflammatory cytokines following stimulation by lipopolysaccharide (LPS), which assesses the sensitivity of the immune system to a potent inflammatory stimulus, and (b) in vivo assessment of circulating levels of inflammatory cytokines, which provides a measurement of systemic levels of inflammation.

Monocyte intracellular production of cytokines. Production of proinflammatory cytokines by monocytes following ligation of the Toll-like receptor 4 with LPS was assessed as previously described (Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006) using flow cytometry (Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006) with minor modifications. Briefly, heparin-treated whole blood was mixed with a final concentration of 100 pg/mL LPS (Sigma, St. Louis, MO) and 10 μg/mL brefeldin A (Sigma), or brefeldin A alone, and incubated for 4 hr at 37°C. Red blood cells were lysed, and remaining cells were fixed with fluorescence-activated cell-sorting (FACS) Lysis Buffer (BD Biosciences, San Diego, CA), then frozen at −80 °C. Fixed cells were thawed, washed, stained with fluorescence-conjugated antibodies for cell-surface CD14, then permeabilized in FACS Permeabilizing 2 Buffer (BD Biosciences, San Diego, CA) and stained for intracellular cytokines. Five thousand CD14+ events were acquired, and the net percentage of LPS-stimulated cytokine-secreting monocytes was determined, with quadrant coordinates set based on unstimulated (brefeldin A only) cells. The dependent variables of interest here were the percentage of monocytes producing interleukin–6 (IL-6), percentage of monocytes producing tumor necrosis factor–α (TNF-α), and percentage of monocytes coproducing IL-6 and TNF-α.

Plasma levels of cytokines. Venous whole blood was collected using ethylenediaminetetraacetic acid (EDTA) and held on wet ice until centrifuged at 4°C, and plasma aliquots were prepared and frozen at −80°C until performance of immunoassays. Plasma concentrations of IL-6 and TNF-α were determined by high-sensitivity ELISA (R&D Systems, Minneapolis, MN) according to the manufacturer's protocol. All samples were assayed in duplicate, and pre- and postintervention samples from each woman were assayed on the same plate.

Statistical Analyses

All analyses were done using a standard statistical program (SPSS 21.0). When testing between-groups effects, analyses of covariance (ANCOVA) were conducted, testing the effect of condition (gratitude vs. control) at postintervention, controlling for baseline (preintervention) values. ANCOVA (vs. using repeated measures to detect changes from baseline) is the recommended, more powerful analytic strategy for randomized studies (Van Breukelen, 2006).

For moderation analyses, the PROCESS macro for SPSS (Hayes, 2012) was used; it estimates coefficients using ordinary least squares regression, automatically calculates interaction terms for moderation analyses, and generates conditional effects by default, allowing for easy analysis of significant interactions in moderation models. The PROCESS macros for SPSS was also used when conducting mediation analyses (i.e., to investigate whether the gratitude intervention reduced inflammatory outcomes via increases in support-giving).

Due to known effects of BMI on markers of inflammation, we controlled for BMI (regardless of significance) in all analyses involving inflammatory measures. Because circulating cytokine values were not normally distributed at any time point, values were natural log-transformed for analyses. Additionally, participants whose scores were over 3 *SD*s on the variables of interest were removed from the respective analyses to improve the robustness of the results to replication, improve accuracy, and reduce errors (Osborne & Overbay, 2004).

Results

Characteristics of the Sample

As mentioned earlier, eight participants who were randomized did not complete the study and did not have postintervention data, leaving a total of 68 participants whose data were analyzed (100% female; mean age = 42.8 ± 4.7 years). Of these 68 participants, 32 were randomized into the control condition and 36 were randomized into the gratitude condition. The groups were not significantly different ($ps > .1$) on average age, BMI, or any of the primary variables at baseline (i.e., gratitude, support-giving, inflammatory measures, psychological distress). However, the groups were significantly different on racial distribution of White versus non-White participants (Fisher's exact $p < .05$), with White participants making up 56.3% of the control group and 83.3% of the gratitude group. As such, race was included as a covariate (regardless of significance) in all analyses comparing the two groups. Demographics of the sample and full information on main effects results are available in the online supplemental materials.

Weekly Intervention

Overall, there was a high completion rate for the weekly writings across the 6-week intervention, with 100% of participants completing all six weekly writing assignments. Participants in the gratitude group averaged 1,487 words over the 6-week period, and control group participants averaged 1,789 words; the average number of words was marginally different between the two groups, $F(1, 64) = 2.89$, $p = .09$.

Did the Gratitude Intervention Increase Weekly State Feelings of Gratitude and Other Positive Feelings?

We first assessed whether the intervention led to a greater self-reported state gratitude by testing differences between the two groups in how grateful they felt after rereading their weekly writings, averaged across all 6 weeks. Indeed, the gratitude group felt significantly more grateful (gratitude group adjusted $M = 6.256$; control group adjusted $M = 4.693$), $F(1, 65) = 38.09$, $p < .001$, $\eta_p^2 = .37$, as well as significantly more connected, loving, happy, pleasant, and reflective ($ps < .01$, $\eta_p^2s = .11-.43$) than did the control group, averaged across all 6 weeks and controlling for race. Thus, it appeared that the gratitude group, on average, had greater weekly feelings of state gratitude, as well as other positive feelings.

Did the Gratitude Intervention Increase Postintervention Trait Feelings of Gratitude?

Interestingly, although the intervention generated higher weekly state feelings of gratitude, it did not appear that the gratitude intervention altered postintervention trait feelings of gratitude. There were no between-groups differences (gratitude vs. control) in trait gratitude (gratitude group adjusted $M = 6.271$; control group adjusted $M = 6.273$; $p > .9$) postintervention, controlling for preintervention values and race. Furthermore, this effect was not moderated by feelings of preintervention psychological distress (Condition × Psychological Distress interaction $p > .6$).

Did the Gratitude Intervention Increase Postintervention Support-Giving?

We next assessed whether the gratitude intervention led to increases in support-giving. As expected, the gratitude intervention (vs. control) led to increases in giving of social support to others postintervention, $F(1, 63) = 6.199$, $p < .05$, $\eta_p^2 = .09$ (see Figure 1A), controlling for preintervention levels.

As hypothesized, there was also a significant Condition (gratitude vs. control) × Psychological Distress interaction effect on giving of social support. Lower levels of baseline psychological distress were associated with greater support-giving at postintervention (controlling for preintervention levels) in response to the gratitude intervention (vs. control group; see Figure 1B; Condition × Psychological Distress interaction: $b = -.0731$, $SE = .0303$, 95% confidence interval [CI] [−.1336, −.0126]), $t(60) = -2.42$ $p < .05$. Analysis of conditional effects revealed that within the gratitude group, lower psychological distress was related to more support-giving ($b = -.0929$, $SE = .0225$, 95% CI [−.1380, −.0479]), $t(60) = -4.12$ $p < .001$, but this effect was not present in the control group ($b = -.0199$, $SE = .0218$, 95% CI [−.0634, .0237]), $t(60) = -.911$ $p > .3$.

Did the Gratitude Intervention Reduce Postintervention Inflammatory Outcomes?

Contrary to our hypotheses, there were no between-groups differences (gratitude vs. control) in any of the inflammatory measures (i.e., percentage of monocytes producing TNF-α or IL-6 or coproducing TNF-α and IL-6, circulating levels of TNF-α and IL-6) postintervention ($ps > .1$), controlling for preintervention values, race, and BMI, and none of the effects were moderated by feelings of psychological distress ($ps > .1$).

Did the Gratitude Intervention Reduce Postintervention Inflammatory Outcomes via Support-Giving?

Although we did not find a total effect of the intervention on inflammation, we also tested the indirect effect of the intervention on inflammatory outcomes via support-giving, because some have suggested that the power to detect an indirect effect is often greater than the power to detect the total effect (Kenny & Judd, 2014). We used the PROCESS macro for SPSS (Hayes, 2012) to estimate 95% confidence intervals using bootstrapping (10,000 samples) to test the indirect effect of the intervention on inflammatory outcomes at postintervention (i.e., percentage of monocytes producing TNF-α or IL-6 or coproducing TNF-α and IL-6, circulating levels of TNF-α and IL-6) via support-giving postintervention. All analyses controlled for preintervention levels of inflammation and support-giving, as well as race.

Interestingly, there was some evidence for a significant indirect effect of the intervention on stimulated inflammatory outcomes via support-giving. The intervention had a significant effect on the percentage of monocytes producing IL-6 (effect = −1.7720, 95% CI [−5.3942, −.0403]), TNF-α (effect = −1.6718, 95% CI [−4.7183, −.1398]) and coproducing IL-6 and TNF-α (effect = −1.2029, 95% CI [−3.1893, −.1553]) via support-giving. Thus, although we did not observe a total effect of the intervention on inflammatory outcomes, it appears that it may have reduced inflam-

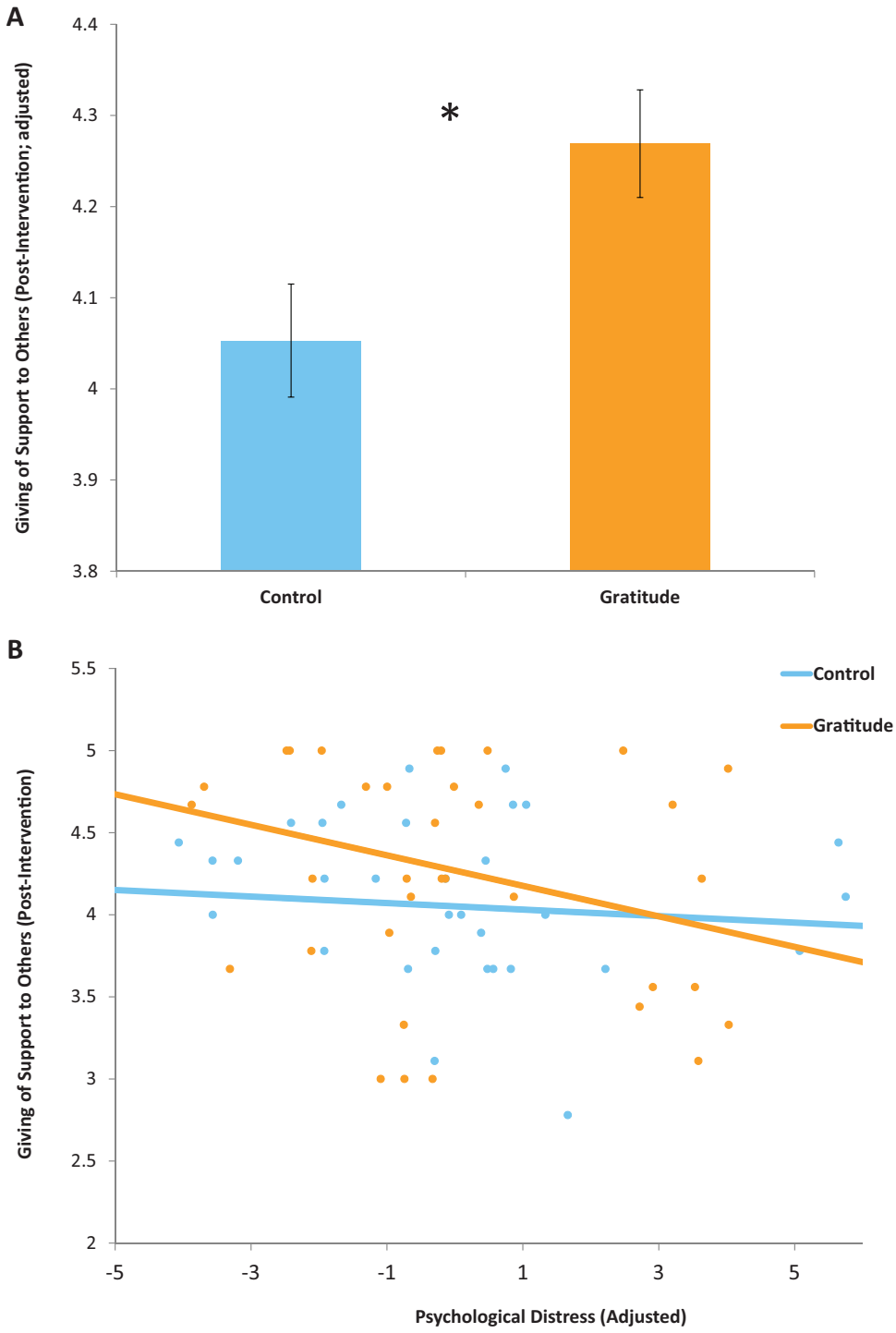

Figure 1. Panel 1A: Effect of gratitude (vs. control) intervention on giving of support to others. Plotted values and statistical analyses examined differences between conditions on postintervention values of support-giving, controlling for preintervention values of support-giving and race. Error bars reflect standard errors. Panel 1(B): Relationship between psychological distress and support-giving postintervention. Psychological distress scores, displayed regression lines, and all statistical analyses adjusted for preintervention support-giving values and race. * $p < .05$. See the online article for the color version of this figure.

matory outcomes via increases in support-giving. However, given the absence of evidence for our hypothesized total effect, we encourage caution when interpreting these results before corroboration by future studies. There was no indirect effect of the intervention on circulating IL-6 (effect = −.0190, 95% CI [−.0887, .0241]) or TNF-α (effect = −.0132, 95% CI [−.0977, .0360]) levels via support-giving, as indicated by zero's being included in the confidence intervals.

Relationships Between Support-Giving and Inflammation Across the Whole Sample

Although there was no total effect of the gratitude intervention on markers of inflammation, we also examined the relationships between support-giving and inflammation across the whole sample. To do this, we collapsed across the two experimental conditions and examined correlations between support-giving and the inflammatory measures (i.e., percentage of monocytes producing TNF-α or IL-6 or coproducing TNF-α and IL-6, circulating levels of TNF-α and IL-6). All analyses examined correlations between postintervention values (e.g., postintervention support-giving and postintervention levels of TNF-α), controlling for baseline values (e.g., preintervention support-giving and preintervention levels of TNF-α), condition, and BMI.

For the full sample, those who showed greater increases in support-giving over the course of the intervention also showed greater reductions in stimulated cytokine production over the same time period (see Figure 2A: percentage of monocytes coproducing TNF-α and IL-6: $r = -.32$, $p < .05$; see Figure 2B: percentage of monocytes producing TNF-α: $r = -.34$, $p < .01$; see Figure 2C: percentage of monocytes producing IL-6: $r = -.29$, $p < .05$). However, greater increases in support-giving were not associated with circulating cytokines ($ps > .3$) postintervention, controlling for preintervention values, condition, and BMI.

Interestingly, although there were relationships between increases in measures of support-giving and decreases in various inflammatory measures, changes in trait feelings of gratitude (postintervention, controlling for preintervention values) were not associated with changes in any of the inflammatory measures (postintervention, controlling for preintervention values, condition, and BMI; $ps > .2$) across the whole sample.

Discussion

Although prior work has shown that gratitude may be beneficial for health, this research is generally lacking measurement of biological outcomes and psychological mechanisms explaining the health-promoting nature of gratitude. Here, we hypothesized that gratitude may confer its benefits on health through increases in support-giving. Thus, we investigated the relationships between

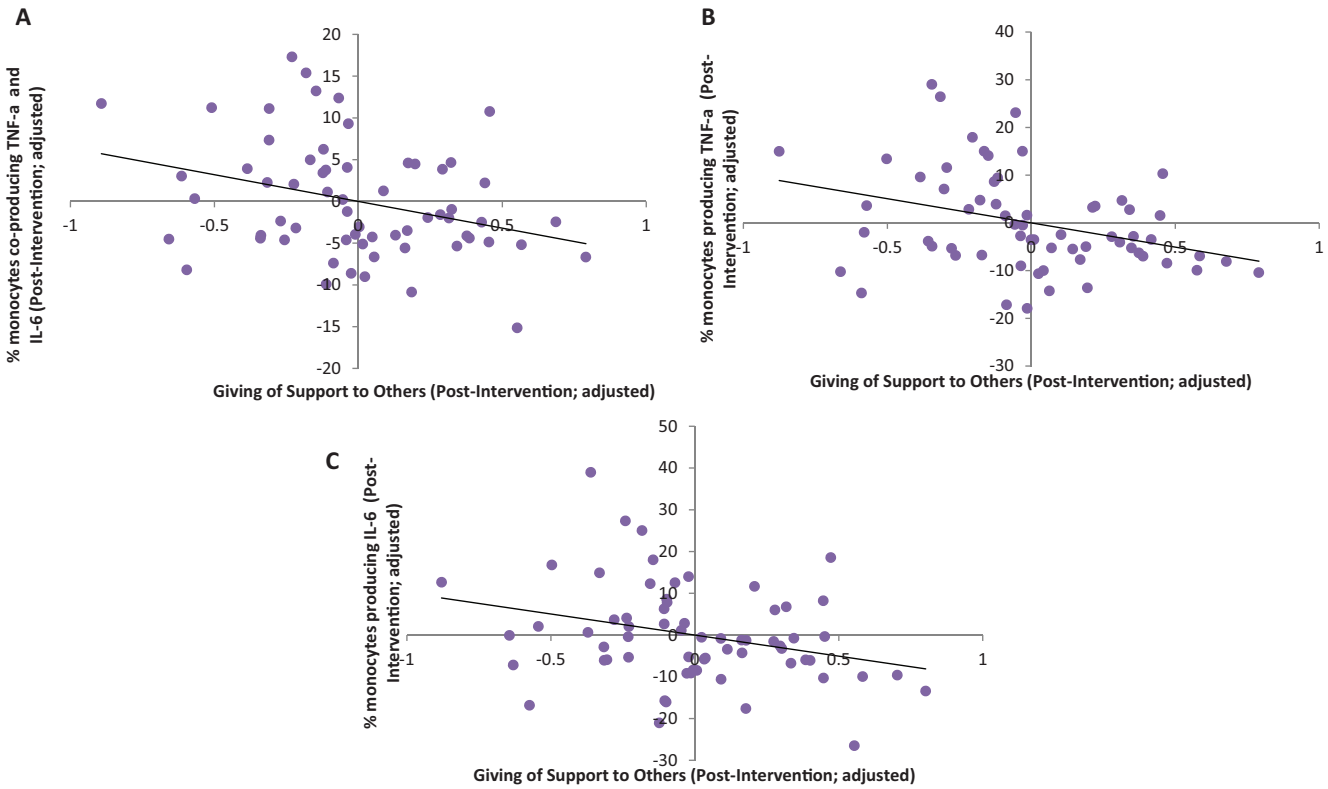

Figure 2. Correlations between giving support to others and stimulated cytokine production. Displayed values show relationships between support-giving (postintervention) and percentage of monocytes: coproducing tumor necrosis factor (TNF-α) and interleukin(IL)-6 (IL-6; Panel 2A), producing TNF-α (Panel 2B), and producing IL-6 (Panel 2C). All displayed values and statistical analyses controlled for body mass index, condition, and preintervention values of support-giving and stimulated cytokine production. See the online article for the color version of this figure.

gratitude, giving support to others, and inflammation to address these gaps in the literature.

As hypothesized and in line with results of prior work (Emmons & McCullough, 2003), the gratitude intervention led to increases in support-giving to others. Those in the gratitude (vs. control) group reported giving more support to those around them, suggesting that gratitude may motivate prosocial behavior. Thus, this finding generally provides backing for the idea that gratitude may be a driver of prosocial behavior and thus important for building and maintaining social relationships (Algoe, 2012; Bartlett, Condon, Cruz, Baumann, & Desteno, 2012; Emmons & Mishra, 2012; McCullough et al., 2008). More specifically, given that our results found increases in support-giving as a result of a gratitude intervention, our study provides support for the *find, remind, and bind* theory, which suggests that gratitude may have evolved to promote "upward spirals of mutually responsive behaviors" between individuals to foster social connections (Algoe, 2012, p. 466). Given this prosocial component of gratitude, it is possible that gratitude activates and relies on the mammalian caregiving system, a neurobiological system involved in promoting support-giving to offspring, one type of prosocial behavior, and reducing physiological stress responses (Inagaki & Eisenberger, 2012). This activation of the caregiving system may be one mechanism through which gratitude promotes prosocial giving behavior and builds social resources.

Furthermore, this support-giving effect was moderated by psychological distress, such that the effect of the gratitude intervention on support-giving was weaker for those who were experiencing more psychological distress. This finding implies that gratitude interventions may not benefit all individuals. Those who are psychologically distressed may not be in a position to benefit from an intervention that calls for them to feel grateful to those around them. These findings complement prior work finding that gratitude interventions may not be beneficial for moderately depressed individuals (Sin et al., 2011), as well as theoretical suggestions that gratitude may be particularly important for establishing and maintaining social relationships during "unstressful times" (Wood et al., 2010, p. 902). More broadly, these findings support the notion that positive psychological interventions should examine moderators to find populations who may benefit the most from particular exercises (Lyubomirsky & Layous, 2013), because a "one size fits all" approach may not be appropriate.

It is also worth noting that although the gratitude intervention led to increased feelings of state gratitude during the intervention, it did not increase more global, trait gratitude postintervention. There are several reasons this may have occurred. First, it is possible that the intervention truly increased state feelings of gratitude only while participants were immersed in their gratitude exercises but did not alter more global feelings of gratitude. Alternatively, it is possible that the GQ-6 measure used to assess gratitude pre- and postintervention is truly a "trait," fixed assessment of gratitude and is thus difficult to change and/or sensitively measure more global feelings of gratitude. Indeed, prior studies using the same measure of gratitude also did not find increases in self-reported feelings of gratitude as a result of gratitude interventions (O'Connell, O'Shea, & Gallagher, 2017; Toepfer, Cichy, & Peters, 2012). Additionally, trait gratitude shows a weaker relationship with prosociality than does state gratitude (Ma, Tunney, & Ferguson, 2017), indicating that regardless of measurement issues, it is possible that state feelings of gratitude may be more important for the prosociality effects observed in the present study.

Contrary to our hypotheses, the gratitude intervention did not lead to decreases in markers of inflammation. Although we did not find a total effect of the intervention on inflammation, we did find evidence for an indirect effect, such that the gratitude intervention led to decreases in inflammation via increases in support-giving. These mixed results strongly suggest the need for future research, because gratitude could be an important component of developing psychosocial interventions to decrease inflammation via social support. Indeed, although there has been much interest in the relationship between gratitude and health, this is an area of limited research. First, few studies have examined the relationship between gratitude and physical health. Furthermore, the majority of the work that has been done has focused primarily on correlations with self-reported health outcomes (Froh, Yurkewicz, & Kashdan, 2009; Hill et al., 2013; Mills et al., 2015; O'Connell, O'Shea, & Gallagher, 2016). Additionally, results have been mixed in this area, with some work pointing to no associations between gratitude and health outcomes, such as health behaviors (Huffman et al., 2016), which further supports the need to incorporate biological measures in the field.

Moreover, to our knowledge, only two prior studies have examined the experimental effects of gratitude on biological outcomes (Jackowska, Brown, Ronaldson, & Steptoe, 2016; Redwine et al., 2016), and the results from these prior studies are not straightforward. Jackowska et al. (2016) examined the effects of a gratitude intervention on blood pressure, heart rate, and cortisol and found that the gratitude intervention led to decreases in diastolic blood pressure but no changes in systolic blood pressure, heart rate, or cortisol. Thus, these results in combination with our present findings hint that it is possible that gratitude interventions simply do not lead to changes in these kinds of biological measures. Conversely, Redwine et al. (2016) did find reductions in inflammatory markers as a result of a gratitude intervention in patients with heart failure. However, the authors were careful to note that patients' IL-6 levels were different between groups at baseline and that the effects should therefore be interpreted with caution. Furthermore, this study did not have an active control group and used treatment-as-usual as the control, which also differentiates it from the present study. Finally, Redwine et al. used a sample of heart failure patients with presumably higher levels of inflammation at baseline that could be reduced compared to the present sample of healthy women. Together, these studies paint a complicated picture of the effects of gratitude on improving biological outcomes. Given our own study's mixed findings regarding the effect of gratitude on inflammation, we strongly recommend that future experimental work on the effect of gratitude on biological measures—including inflammation and other biological outcomes—be done before coming to conclusions about the effect of gratitude on health. One potential biological pathway related to inflammation that has also been proposed as playing a role in the effects of gratitude is the mu-opioid pathway (Henning, Fox, Kaplan, Damasio, & Damasio, 2017), which also warrants future research. Additionally, recent neuroimaging studies have also begun to shed light on neural processes that may be relevant to gratitude and the caregiving system (Karns, Moore, & Mayr, 2017; Yang, Wei, Wang, Yi, & Qiu, 2018).

More broadly, the existing literature on gratitude interventions on health and well-being is complicated and potentially problematic. A recent meta-analysis concluded that there is only "weak evidence for efficacy of gratitude interventions" on well-being (Davis et al., 2016, p. 25) and, along with a prior qualitative review (Wood et al., 2010), noted that the quality of the comparison groups of many of these studies may be inflating existing results. Indeed, some gratitude intervention studies included control conditions that may increase negative affect (e.g., listing hassles or recording worries; reviewed in Davis et al., 2016; Wood et al., 2010). As such, we included a descriptive, neutral control condition rather than a hassles condition in the present study, as more recent gratitude interventions have done. Future work examining the effects of gratitude interventions on health and well-being, including biological outcomes, should include neutral or, as an even more stringent control condition, other positive intervention conditions.

Finally, we further examined the potential of support-giving as a mechanism for the purported relationships between gratitude and health in the existing literature by testing the relationships between support-giving and inflammation across the entire sample, regardless of condition. As hypothesized, increases in support-giving were related to decreases in inflammatory markers, as discussed later. However, changes in gratitude were not related to changes in inflammation. To our knowledge, only one prior study has examined correlations between trait gratitude and inflammation, and in this study, gratitude was predictive of lower levels of inflammatory markers (Mills et al., 2015). The study differed from the present one in that it was conducted in heart failure patients and thus had a sample with higher inflammatory markers than did the healthy participants in this study. Given the limited number of studies in this area, further research is needed to determine whether gratitude is cross-sectionally related to inflammation.

Although these findings do not provide evidence for links between gratitude and health, it does shed light on the relationships between support-giving and health. To our knowledge, no prior work has examined the relationship between giving support to others and inflammation. However, these findings complement previous work showing that giving support is related to better health and that these health benefits may rely on activation of the mammalian caregiving system (Inagaki & Eisenberger, 2016; Konrath & Brown, 2013). Indeed, stimulating caregiving neural areas (septal area) in nonhuman animals leads to decreases in physiological threat responding, including markers of sympathetic nervous system activity (Covian et al., 1964; Malmo, 1964). Paralleling these results from the animal literature, some previous experimental research in humans has found that caregiving behaviors, such as giving support to others, leads to a pattern of neural activity that is suggestive of reduced responding to threatening situations (Inagaki & Eisenberger, 2012). There is also evidence that giving support to others leads to decreases in stress-related sympathetic nervous system activity (Inagaki & Eisenberger, 2016), which complements the present findings that giving support to others is related to decreases in inflammatory markers, because the sympathetic nervous system plays a role in enhancing inflammatory responses (Eisenberger & Cole, 2012; Irwin & Cole, 2011). Although these novel findings indicate that giving support to others is related to improved inflammatory outcomes, caution should be taken when interpreting these results because of their correlational nature. For example, although it is possible that increased support-giving led to reduced inflammatory outcomes, the other direction of effects (reductions in inflammation led to increases in support-giving) is equally possible and potentially driven by a third, unmeasured variable. Because giving of support was not experimentally manipulated in the present study, future experimental work is needed to corroborate these data.

Although this study provides insight into an understudied area of research, it is not without limitations. First, the study was conducted in a healthy sample of women. Thus, the findings may not generalize to men or clinical samples. This is especially true because gender differences in gratitude have been found in the literature (Froh et al., 2009; Kashdan, Mishra, Breen, & Froh, 2009). Second, given our a priori hypotheses about the caregiving system as a mechanism for the benefits of gratitude, the gratitude intervention was intentionally designed to be a very specific, socially oriented type of gratitude intervention, and as such, the results may not generalize toward a broader or different type of gratitude intervention (e.g., counting blessings, being thankful for nonsocial entities). Further, the power calculations for the sample size were based on an imaging component (not reported here; please see the online supplemental materials for power calculations), and it is possible that effects were not detected because the study was underpowered. One additional concern that may come to mind when thinking of gratitude interventions generally, including the present one, is susceptibility to social desirability and demand, as well as a potential priming effect through asking the control group about gratitude. Although this is a valid concern, this does not appear to have been a large issue in the present study, because we did not see any group differences in the GQ-6, which one would expect to see if demand characteristics played a large role. However, it is still possible that demand characteristics were present but there was also a ceiling effect regarding GQ-6 scores, because both groups started high on this measure (mean GQ-6 score, collapsed across groups, at baseline = 6.28, and 7 is the maximum score).

Conclusions

Understanding the relationships between gratitude, support-giving, and biological outcomes is an understudied area of research. Here, we investigated whether a gratitude intervention would lead to increases in support-giving and decreases in inflammation, as well as whether giving support would be related to reductions in inflammation. The gratitude intervention did lead to increases in support-giving. It is important to note that psychological distress was a moderator of the effects of the intervention on support-giving, such that those who were more psychologically distressed—and thus may not have had as many psychological resources to benefit from such an intervention—gave less support as a function of the gratitude intervention, emphasizing the importance of studying "fit" of interventions for particular populations. No decreases in inflammatory markers were observed as a function of the intervention. However, an indirect effect was detected such that the intervention impacted inflammatory outcomes via support-giving. Together, this suggests future research is needed on the effects of gratitude on biological outcomes.

Interestingly, increases in support-giving across the entire sample (regardless of condition) was related to decreases in inflam-

matory markers, which to our knowledge is the first demonstrated relationship between giving support and inflammation. However, changes in gratitude were not related to changes in inflammation. These results, in tandem with limitations in previous research, suggest that the relationship between gratitude and health, particularly regarding biological outcomes, is complicated and is in need of further study in varied populations to be more fully understood. Finally, given the relationship between support-giving and inflammation found in this study and in previous work on the links between giving support and health, elucidating these relationships and the role of the caregiving system may be key to a more comprehensive understanding of the links between social support and health and holds promise for future research.

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