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# Perceived social support-giving moderates the association between social relationships and interleukin-6 levels in blood

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ABSTRACT

Although positive social relationships are assumed to relate to lower levels of chronic systemic inflammation, the empirical evidence on this association is mixed. This study examines whether perceived social support-giving (i.e., the belief that one can be available to give social support to others, henceforward referred to as perceived support-giving) moderates associations between social relationships and inflammation using data from the longitudinal follow-up of the National Survey of Midlife Development in the U.S. (MIDUS II). Middle-aged adults ($N$ = 1054) completed self-report questionnaires on social integration, perceived support-availability from others, positive relations with others, perceived support-giving, socio-demographic information, and health-related information and provided blood samples for measurement of interleukin-6 (IL-6) as a marker of systemic inflammation. The results showed that perceived support-giving moderated the associations between IL-6 and indicators of positive social relationships, including social integration, perceived support-availability, and positive relations with others. Indicators of positive social relationships were associated with lower IL-6 among individuals higher, but not lower, in perceived support-giving. The moderating effects of perceived support-giving held after adjusting for socio-demographic and health-related covariates. Therefore, positive social relationships are associated with lower IL-6 only for individuals who believe they can give more support in those relationships. In addition, preliminary evidence indicated that the moderating effects of perceived support-giving might be further qualified by gender, being significant only in women.

## 1. Introduction

Social relationships are one of the most important predictors of physical health (Holt-Lunstad et al., 2010; House et al., 1988). Lack of social relationships is associated with a 50% increase in the odds of death, which is comparable to the effects of many well-established risk factors for mortality, such as smoking or obesity (Holt-Lunstad et al., 2010). Given the robust link between social relationships and physical health, researchers are keen to understand the mechanisms underlying this link so that theory-based interventions can be developed to improve people's physical health.

Inflammation is one important biological mechanism proposed to explain the link between social relationships and physical health (Kiecolt-Glaser et al., 2010; Uchino et al., 2018). Inflammation is an immune response not only to injury or infection but also to psychosocial stressors, such as social isolation or negative interpersonal interactions (Eisenberger et al., 2017; Glaser and Kiecolt-Glaser, 2005). Chronic psychosocial stressors can sensitize the inflammatory response and thus heighten chronic systemic inflammation, a well-known contributor to many health problems such as cardiovascular disease and cancer (see Kiecolt-Glaser et al., 2010 for a review). Positive social relationships can reduce psychosocial stress, which might reduce chronic systemic inflammation, and thus, improve physical health (Kiecolt-Glaser et al., 2010; Uchino et al., 2018).

Most research examining social relationships and inflammation has used social integration and/or perceived support-availability from others as indicators of positive social relationships (Uchino et al., 2018). Social integration refers to the amount of important social connections people have, and reflects a structural aspect of social relationships indicating the extent of access to social support and other positive effects of social relationships, such as positive affect and self-worth (Cohen, 2004). Perceived support-availability refers to the belief that

*Abbreviations:* IL-6, Interleukin-6; CRP, C-Reactive Protein.

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relationship partners are available and provide support when needed, and reflects a functional aspect of social relationships (Uchino et al., 2018). Both social integration and perceived support-availability are independently associated with physical health outcomes (Holt-Lunstad et al., 2010), and are assumed to relate to inflammation (Uchino et al., 2018).

Despite the theoretical connection between social relationships and inflammation, the empirical evidence on their association is mixed. Although early research showed an association between positive social relationships and lower inflammation (Kiecolt-Glaser et al., 2010; Uchino et al., 2018), recent large-scale studies have found inconsistent evidence (Jaremka et al., 2020; Nilsson et al., 2020; Smith et al., 2020). In addition, meta-analyses showed that the magnitude of the associations between social relationships and inflammation varies significantly across different studies (Smith et al., 2020; Uchino et al., 2018), suggesting that the associations might be moderated by some unexplored factors.

In the current research, we test whether the associations between social relationships and inflammation are moderated by perceived support-giving (i.e., the belief that one can be available to give social support to others). A growing literature has demonstrated that giving support to others is associated with reduced mortality risk and better physical health (see Inagaki, 2018 for a review). More importantly, recent studies have shown that the imbalance between receiving and giving support is associated with increased mortality risk (Chen et al., 2021) and higher inflammation (Austin et al., 2021). Thus, the effects of positive social relationships on inflammation may depend on perceived support-giving.

Because giving support is essential to good relationships (Crocker et al., 2017), it is somewhat surprising that most research examining social relationships and inflammation has overlooked the effect of giving support. A more nuanced understanding of their associations should incorporate giving support. Thus, the current study examines whether perceived support-giving moderates associations between social relationships and inflammation. In addition, because women's identities are more strongly linked to social relationships than men's (Cross and Madson, 1997), the current study also explores whether the moderating effects of perceived support-giving are stronger for women than men.

## 2. Method

### 2.1. Participants and procedure

The current study used the data from the longitudinal follow-up of the National Survey of Midlife Development in the U.S. (MIDUS II). Participants ($N = 4963$) were healthy middle-aged adults who reside in the U.S. They were originally recruited into MIDUS in 1995–1996 and were recruited again in 2004–2006 for follow-up. Participants completed questionnaires assessing behavioral, social, and psychosocial factors related to physical and mental health. Two years later on average, a subsample of participants ($N = 1054$) completed comprehensive biomarker assessments and additional questionnaires in a Biomarker project. Because the current study focused on inflammation, analyses used data from this subsample of participants who completed both the MIDUS II survey and Biomarker project (ages ranging from 34 to 84 years, $M = 55.26$, $SD = 11.78$; 54.7% female, 45.3% male). A sensitivity power analysis indicated that this sample size provided 80% power to detect an effect as small as $\Delta R^2 = 0.007$ at $p = .05$.

### 2.2. Measures

Markers of systemic inflammation were measured in the Biomarker project. Self-report measures were assessed in the MIDUS II survey unless otherwise noted.

#### 2.2.1. Inflammatory marker

The current study used interleukin-6 (IL-6) as the marker of systemic inflammation.[1] IL-6 is a cytokine that is a signaling molecule central for the inflammatory process (Hunter and Jones, 2015). Higher levels of IL-6 are associated with an increased risk for many diseases, such as cardiovascular disease, cancer, and diabetes (Hunter and Jones, 2015). IL-6 levels were determined using an enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN; see Glei et al., 2012 for a detailed description of the assay method and sensitivity). The IL-6 variable was log-transformed to adjust for skew in the distribution. Participants ($N = 16$) were excluded from analyses if they were taking corticosteroids (oral or inhaled) or other immunosuppressants (i.e., calcineurin inhibitors) as well as immunostimulants (i.e., Interferon-β) due to their robust effects on the dependent measure.

#### 2.2.2. Self-report measures

Following prior research (Uchino et al., 2018), variables of interest included measures of social integration and perceived support-availability (i.e., indicators of positive social relationships[2]), perceived support-giving, and socio-demographic and health-related covariates. When appropriate, items were reverse-coded to create composite scores, with higher scores reflecting higher levels of the constructs. For a detailed description of all measures, see Supplemental Online Materials ("SOM" henceforth).

**Social Integration**. A score based on Berkman's Social Network Index (see Glei et al., 2012) was calculated based on whether participants were: 1) married or cohabitating with a partner, 2) contacting their nonresident family members and friends at least once a week, 3) attending religious or spiritual services at least once a month, and 4) attending social groups or activities at least once a month. One point was assigned for each criterion met. Scores ranged from 0 (met no criterion) to 4 (met all four criteria).

**Perceived Support-Availability**. Following prior research (e.g., Elliot et al., 2018), a 14-item measure was used to assess how much participants believe they can rely on their relationship partners (i.e., family, friends, and spouse) for social support. Participants completed the items on a 4-point scale (1 = *a lot*, 4 = *not at all*), with 4 items each for family and friends and 6 items for spouse ($\alpha = 0.87$). Example items included: "How much can you rely on your family (friends/spouse) for help if you have a serious problem?".

**Perceived Support-Giving.** A parallel 14-item measure assessed how much participants believe they can be available to give support to their family, friends, and spouse ($\alpha = 0.76$). Among the 14 items, 12 items were assessed in the Biomarker project, and 2 family items were assessed in the MIDUS II survey. Example items included: "How much can your family (friends/spouse) rely on you for help if they have a serious problem?".

**Covariates.** Following prior research (e.g., Elliot et al., 2018), three sets of covariates were included in the analyses: socio-demographic variables (i.e., age, gender, income, and education), health behavior variables (i.e., body mass index, cigarette smoking status, engagement in regular exercise), medications that modulate inflammation (i.e., anti-depressants, anti-hypertensives, non-steroidal anti-inflammatory drugs

[1] C-Reactive Protein (CRP) was also assessed in the MIDUS Biomarker project. Because IL-6 and CRP are the two most studied markers of systemic inflammation, we also tested the hypotheses using CRP as an outcome. The results for CRP did not converge with those for IL-6 (see SOM for the full results for CRP and the discussion of discrepancies for CRP and IL-6).

[2] The MIDUS II survey included another indicator of positive social relationships: Positive Relations with Others, which assessed participants' subjective perceptions of relationship quality with others. Overall, the results for this measure were consistent with those for social integration (see SOM).

(NSAIDs), statins, Omega-3 fatty acids), and sixteen (of 24) physician-diagnosed medical conditions that correlated with IL-6 (e.g., heart disease).[3]

## 3. Results

Table S1 (see SOM) shows the means, standard deviations, and zero-order correlations for all key variables. Social integration, perceived support-availability, and perceived support-giving were all uncorrelated with IL-6.

A series of linear regression analyses using the MIXED command in SPSS (ver. 27) examined whether perceived support-giving moderates the associations of IL-6 with social integration or perceived support-availability. To aid interpretation, significant interactions were plotted and simple slopes were computed for higher and lower (i.e., 1 *SD* above and below the sample mean) levels of perceived support-giving. To adjust for relevant covariates that may account for the moderating effects of perceived support-giving, we controlled for socio-demographic covariates in Model 1, added health behavior covariates in Model 2, and added medical covariates in Model 3. We standardized all variables prior to conducting analyses. Because siblings and twins were included in the sample, all analyses included a random intercept effect for family to account for the interdependence among family members. Partial correlations (*pr*) are reported as estimates of effect sizes.

For social integration, we regressed IL-6 on perceived support-giving, social integration, and their interaction. As hypothesized, the interaction was significant (β = −0.08, 95% CI = [−0.14, −0.02], *pr* = −0.08, *p* = .015). Simple slopes analysis showed that social integration was associated with lower IL-6 for those higher in perceived support-giving (β = −0.12, 95% CI = [−0.21, −0.03], *pr* = −0.08, *p* = .008), but not for those lower in perceived support-giving (β = 0.04, 95% CI [−0.05, 0.13], *pr* = 0.03, *p* = .412; see Fig. 1, Panel A). The interaction remained significant after controlling for covariates in Model 1 (β = −0.10, 95% CI = [−0.16, −0.03], *pr* = −0.10, *p* = .002), Model 2 (β = −0.10, 95% CI = [−0.16, −0.05], *pr* = −0.11, *p* = .001), and Model 3 (β = −0.09, 95% CI = [−0.15, −0.03], *pr* = −0.10, *p* = .005; see Table S3).[4]

For perceived support-availability, we used the same analysis strategy. As predicted, perceived support-giving moderated the association between perceived support-availability and IL-6 (β = −0.05, 95% CI = [−0.10, −0.01], *pr* = −0.07, *p* = .027). Simple slopes analysis showed that perceived support-availability was associated with lower IL-6 for those higher in perceived support-giving (β = −0.11, 95% CI = [−0.21, −0.01], *pr* = −0.07, *p* = .025), but not for those lower in perceived support-giving (β = −0.004, 95% CI [−0.09, 0.08], *pr* = −0.003, *p* = .933; see Fig. 1, Panel B). The interaction remained significant after controlling for covariates in Model 1 (β = −0.05, 95% CI = [−0.10, −0.01], *pr* = −0.07, *p* = .027), Model 2 (β = −0.05, 95% CI = [−0.10, −0.01], *pr* = −0.07, *p* = .023), and Model 3 (β = −0.06, 95% CI = [−0.10, −0.01], *pr* = −0.08, *p* = .019; see Table S4).[5]

We also conducted three sets of sensitivity analyses to assess the robustness of the primary results. First, we re-ran all main analyses after excluding participants whose IL-6 levels may reflect acute inflammation due to infection. Because no cutoff point has been established for IL-6, we excluded outliers >3 SD above the sample mean (*N* = 20). Second, we re-ran all main analyses with the inclusion of individuals who were initially excluded for taking corticosteroids, immunosuppressants, or immunostimulants. Third, we adjusted for covariates for interaction effects by adding the interaction terms of the covariates with social integration or with perceived support-availability. In all these analyses, results were similar in terms of point estimates, confidence intervals, and p values, except that after excluding IL-6 outliers, the moderating effects of perceived support-giving on the association between perceived support-availability and IL-6 after adjusting for covariates in Models 1 and 2 became marginally significant (see SOM for the full results).

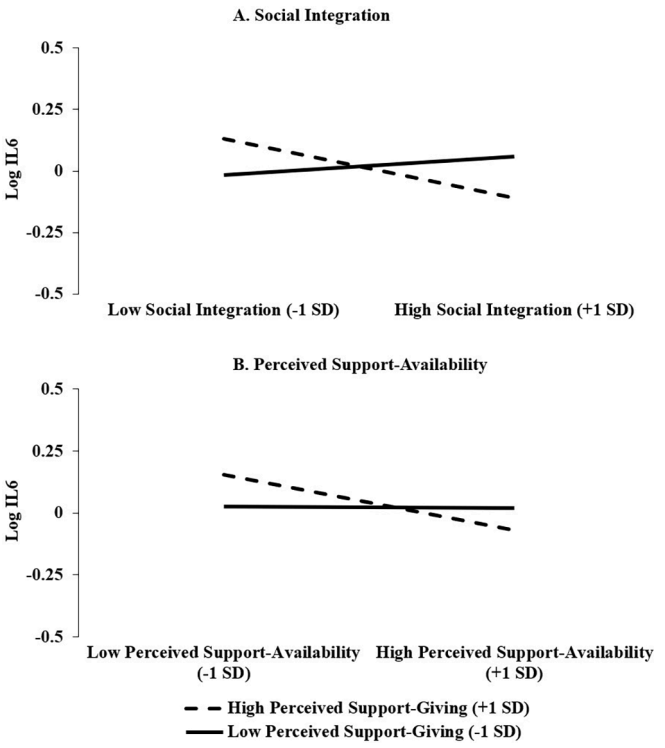


**Fig. 1.** Social integration (A) and perceived support-availability (B) predicting log-transformed IL-6 at higher and lower levels of perceived support-giving.

Exploratory analyses examined whether moderating effects of perceived support-giving on the associations between social relationships and IL-6 were further moderated by gender. The results showed that the moderating effect of gender was marginally significant for social integration (β = −0.13, 95% CI = [−0.26, 0.002], *pr* = −0.06, *p* = .054), but was nonsignificant for perceived support-availability (β = −0.06, 95% CI = [−0.15, 0.04], *pr* = −0.04, *p* = .258). For social integration, perceived support-giving moderated its association with IL-6 only for women (β = −0.13, 95% CI = [−0.22, −0.05], *pr* = −0.09, *p* = .003), but not for men (β = −0.01, 95% CI = [−0.10, 0.09], *pr* = −0.004, *p* = .906). However, the moderating effect of gender for social integration became nonsignificant after adjusting for covariates in Model 1, but became significant in Model 2 and remained marginally significant in Model 3 (see SOM for the full results, including results regarding positive relations with others, which were consistent with those for social integration).

## 4. Discussion

The current study examined whether perceived support-giving moderates the associations between social relationships and systemic inflammation. The primary results supported our hypothesis. Perceived support-giving in important social relationships (i.e., relationships with family, friends, and spouse) moderated the associations between IL-6 and indicators of positive social relationships, including social integration and perceived support-availability (see SOM for the converging

[3] Table S2 shows the descriptive statistics for all covariates and the zero-order correlations between the covariates and all key variables.

[4] Because perceived support-availability and perceived support-giving were correlated, we also tested whether perceived support-availability moderates the association between social integration and IL-6. It did not (see SOM).

[5] For all indicators of positive social relationships, the moderating effects of perceived support-giving held after controlling for the time lag between completion of the MIDUS II survey and Biomarker project (*ps* ≤ 0.028).

results regarding positive relations with others). Specifically, higher social integration, perceived support-availability, and positive relations with others were associated with lower IL-6 only for individuals higher, but not lower, in perceived support-giving. The moderating effects of perceived support-giving held after adjusting for socio-demographic and health-related covariates. These findings suggest one potential reason why previous research has shown inconsistent evidence on the link between social relationships and inflammation. Positive relationships may be associated with lower inflammation only for those who believe they can give more support in those relationships.

Why might perceived support-giving moderate the link between social relationships and systemic inflammation? Perhaps when people believe they can give more support in their positive relationships with others, these mutually supportive relationships are especially rewarding and stress relieving, which reduces inflammation (Inagaki, 2018). Although the current study cannot identify specific mechanisms underlying the effect of giving support, it underscores the importance of incorporating the concept of giving support into future research on the association between social relationships and inflammation.

Interestingly, exploratory analyses indicated that the moderating role of perceived support-giving on the association between social relationships and IL-6 might be further qualified by gender, being significant only in women. However, the evidence on the gender difference is preliminary because the results were inconsistent across different indicators of positive social relationships and were not robust when adjusting for covariates. Future research should examine this possible gender difference with better powered and longitudinal studies.

In addition, future work could identify the central and autonomic nervous system pathways by which positive social relationships lead to lower IL-6 for those who give more support (see SOM for a discussion of the effects of these models on CRP).

## 5. Conclusions

The current study showed that perceived support-giving moderates the associations between social relationships and IL-6. Positive social relationships are associated with lower IL-6 only for individuals who believe they can give more support in those relationships. These findings provide a more nuanced understanding of the link between social relationships and systemic inflammation.

## Open Practices Statement

The data from the MIDUS II survey and Biomarker project are publicly available and can be accessed through the Inter-university Consortium for Political and Social Research websites (https://doi.org/10.3886/ICPSR04652.v7 and https://doi.org/10.3886/ICPSR29282.v9). The analysis scripts for the current study are available via openICPSR link: https://www.openicpsr.org/openicpsr/project/134442/version/V6/view.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplemental Online Materials

Supplemental Online Materials [SOM] to this article can be found online at https://doi.org/10.1016/j.bbi.2021.11.002.

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