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Social Relationships and Inflammatory Markers in the MIDUS Cohort: The Role of Age and Gender Differences

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Abstract

Objective: To better understand age and gender differences in associations of social relationships with chronic inflammation. **Method:** Using a sample of middle-aged and older adults (*N* = 963) from the Midlife Development in the United States (MIDUS) biomarker project, we examined interactions of age and gender with structural and functional social network measures in predicting interleukin-6 (IL-6) and C-reactive protein (CRP). **Results:** Significant interactions involving age and gender showed that social support was associated with lower IL-6 in older women, whereas perceived positive relationships and social integration were related to lower IL-6 in both men and women of advanced age. Functional measures were associated with higher CRP in both men and women after adjustment for health conditions and behaviors, with some further variation by age. **Discussion:** Greater social support may be related to lower IL-6 in older women. Further research is needed to understand observed associations of social support with higher CRP.

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A growing literature has linked measures of social relationships to biomarkers of physiological function, including blood pressure (Yang, Boen, & Mullan Harris, 2015), leukocyte telomere length (Carroll, Diez Roux, Fitzpatrick, & Seeman, 2013), allostatic load (Brooks et al., 2014; Seeman, Gruenewald, Cohen, Williams, & Matthews, 2014), and chronic inflammation (Kiecolt-Glaser, Gouin, & Hantsoo, 2010), indicating potential biological mechanisms underlying protective effects of social connectedness on morbidity, disability, and mortality (Holt-Lunstad, Smith, & Layton, 2010; James, Boyle, Buchman, & Bennett, 2011; Lett et al., 2005; Uchino, 2006). Chronic inflammation, involving a prolonged and systemic immune response, has been implicated in the pathophysiology of chronic diseases of aging as well as geriatric frailty, sarcopenia, and functional disability (Ershler & Keller, 2000; Maggio, Guralnik, Longo, & Ferrucci, 2006). Inflammatory biomarkers including interleukin-6 (IL-6) and C-reactive protein (CRP) predict cardiovascular disease (Danesh et al., 2008; Rodondi et al., 2010), diabetes (Pradhan, Manson, Rifai, Buring, & Ridker, 2001), physical/functional decline (Adriaensen et al., 2014; Ferrucci et al., 2002; Visser et al., 2002), and mortality (Harris et al., 1999; Heffner, Waring, Roberts, Eaton, & Gramling, 2011; Singh & Newman, 2011). Social relationships might influence levels of inflammation directly by affecting the regulation of the stress system (Rohleder, 2014), as both positive (e.g., social support) and negative (e.g., interpersonal conflict) dimensions have been shown to modulate neuroendocrine and inflammatory reactivity to stressors (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007; Kiecolt-Glaser et al., 2005). Social relationships might also affect inflammation by influencing health behaviors and related factors, including smoking, physical activity, diet and body mass/obesity, although both positive and negative influences are possible (Bennett, Gillie, Lindgren, Fagundes, & Kiecolt-Glaser, 2013; Christakis & Fowler, 2007; Conklin et al., 2014; Umberson, Crosnoe, & Reczek, 2010).

Although some studies have indeed linked social support, broadly defined, to markers of chronic inflammation in adults, the relevant literature is characterized by considerable inconsistency. In a series of early studies, measures of social integration (a structural dimension representing social ties and participation in four specific domains; Cohen, 2004) were associated with lower levels of inflammatory markers and particularly CRP in older men but not women (Ford, Loucks, & Berkman, 2006; Loucks, Berkman, Gruenewald, & Seeman, 2006; Loucks, Sullivan, et al., 2006). A subsequent study with

middle-aged and older adults (Glei, Goldman, Ryff, Lin, & Weinstein, 2012) found no associations with IL-6 or CRP in either gender. Findings with regard to functional measures of social relationships are even more equivocal, as low network emotional support has been associated with higher CRP in men (Mezuk, Diez Roux, & Seeman, 2010), associated with *lower* CRP in both genders (Glei et al., 2012), and unrelated to CRP in other investigations (Kamiya, Whelan, Timonen, & Kenny, 2010; Nowakowski & Sumerau, 2015; Yang et al., 2016). Support from one's spouse specifically was related to lower IL-6 and CRP in women but not men (Donoho, Crimmins, & Seeman, 2013), while perceptions of positive relationships with others in general were associated with lower IL-6 in older women (Friedman, Hayney, Love, Singer, & Ryff, 2007), as well as married older adults of both genders (Eisenlohr-Moul & Segerstrom, 2013).

In sum, the literature suggests considerable heterogeneity in associations of social relationships with inflammatory markers across gender, age, structural versus functional measures, and specific inflammatory markers. Taken together, prior studies suggest that structural dimensions are more strongly related to inflammation (particularly CRP) in older men, and more tentatively, that functional dimensions might be more closely associated with IL-6 in older women. Further research is needed to formally evaluate these possibilities, as noted in a recent review that called for closer examination of gender differences in the inflammatory and other immunological concomitants of social relationships in adulthood (Jaremka, Derry, & Kiecolt-Glaser, 2014). Therefore, we investigated both age and gender differences in associations of structural and functional measures of social relationships with IL-6 and CRP in a population-based sample of middle-aged and older adults. We also examined the impact of adjustment for health conditions and behaviors on these associations.

Method

Participants and Procedures

Study data were drawn from the Midlife Development in the United States (MIDUS) study, a national longitudinal survey spanning early through older adulthood. Initiated in 1995, MIDUS 1 surveyed approximately 7,000 noninstitutionalized, English-speaking adults ages 25 to 74. A second wave of data (MIDUS 2) was collected between 2004 and 2006 (N = 4,963), with an average follow-up interval of 9 years and a mortality-adjusted response rate of 75%. A subsample of MIDUS 2 participants (N = 1,054) subsequently participated in a Biomarker study, which involved an overnight visit at one of

three clinical research centers between 2004 and 2009 and included a fasting blood sample. On average, this data collection occurred two years after assessment of social relationships in MIDUS 2. Biomarker study procedures and response rates are detailed elsewhere (Love, Seeman, Weinstein, & Ryff, 2010). The biomarker sample was comparable with the broader MIDUS 2 sample on most sociodemographic and health characteristics, although participants were more likely to have a college degree and less likely to smoke (Love et al., 2010).

Participants missing data on any study variable (8.6%) were excluded, resulting in a final analytic sample of 963 participants. Those with missing data were comparable to those with complete data on age, gender, race, education, income, CRP, and all measures of social relationships (described below), although they had higher levels of IL-6, $t(54.6) = -2.07$, $p = .043$, and chronic disease, $t(104.9) = -3.66$, $p < .001$, and were more likely to have at least one limitation in activities of daily living (ADLs), $\chi^2 = 8.54$, $p = .003$.

Measures

Inflammatory markers. Inflammatory outcomes included circulating concentrations of IL-6, a cytokine closely involved in the regulation of systemic inflammatory processes, and CRP, a protein synthesized in response to stimulation by IL-6 and other pro-inflammatory cytokines (Singh & Newman, 2011). IL-6 was measured from serum using an enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN), and CRP from plasma with a particle enhanced immunonephelometric assay (BNII nephelometer from Dade Behring, Deerfield, IL). The laboratory intra- and inter-assay coefficients of variance were in acceptable ranges for IL-6 (3.25% and 12.31%) and CRP (4.4% and 5.7%). A base-10 logarithm transformation was applied to IL-6 and CRP variables to reduce skew in the distributions. Participants with CRP values exceeding 10.0 mg/L, which is typically indicative of acute inflammation resulting from active infection or injury, rather than chronic inflammation, were excluded from analyses (Pearson et al., 2003). IL-6 and CRP were correlated at .31 (.42 after log-transformation) in the analytic sample.

Measures of social relationships

Social integration. As in other recent studies (Glei et al., 2012; Yang et al., 2016), we constructed a structural measure of social integration based on the Berkman–Syme Social Network Index (Berkman & Syme, 1979), a well-validated and widely used measure in research examining inflammation and other health outcomes. One point was assigned for being married or living

with a partner/companion, having at least weekly contact with nonresident family members and friends, attending religious services at least monthly, and participating in meetings of social groups or organizations at least monthly.

Positive relations with others. The Positive Relations With Others scale (Ryff & Keyes, 1995) measures the perceived quality of one's social relationships. It consisted of seven items in MIDUS 2 (e.g., "I know that I can trust my friends, and they know they can trust me") rated on a 7-point Likert-type scale from *strongly agree* to *strongly disagree*. Internal consistency was moderately high ($\alpha = .76$).

Social support. The MIDUS Social Support scale (University of Wisconsin, Institute on Aging, 2010) measures perceived support from family, friends, and spouse/partner. Support from each was measured with four items (e.g., "How much do your family members/friends/partner really care about you?") for family and friends and six items for spouse/partner, rated on a 4-point scale (from *a lot*, to *not at all*). Internal consistency was high for family ($\alpha = .82$), friends ($\alpha = .87$), and spouse/partner ($\alpha = .91$). A substantial portion of the sample (~30%) did not report a spouse/partner at MIDUS 2. Therefore, the total network support score was generated by averaging scores on each potential source of support, with valid scores on two out of three sources required. As such, being married did not automatically result in a higher score for support.

Social strain. Respondents rated perceived strain in relationships, with four items (e.g., "How often do family members/friends/partner criticize you?") for family and friends and six items for spouse/partner, rated on a 4-point scale (from *a lot*, to *not at all*). Internal consistency was moderately high for family ($\alpha = .76$) and friends ($\alpha = .77$) and high for spouse/partner ($\alpha = .87$) at MIDUS 2. The required number of scale items and domain scores were the same as described above.

Covariates. Sociodemographic covariates included age, racial/ethnic minority status (non-Hispanic White as compared with all other participants), and education. For education, dummy coding was used to compare participants with at least some college, college degrees, and graduate or professional degrees with participants with a high school degree or less. We also adjusted for medications, chronic diseases, functional limitations, and common health behaviors that might affect inflammation. Following recommendations (O'Connor et al., 2009), we included dummy variables for antihypertensive and cholesterol medications. We operationalized chronic disease burden as

the self-reported number of up to 14 doctor-diagnosed medical conditions (e.g., heart disease, stroke, high blood pressure, diabetes, cancer; Friedman & Ryff, 2012) that were associated with either IL-6 or CRP in bivariate analyses. Functional limitations were measured using a dummy variable for whether or not participants reported having any difficulty in basic ADLs including bathing or dressing, walking one block, and climbing one flight of stairs.

Smoking status was measured as a three-category variable, with dummy variables comparing former and current smokers to lifetime nonsmokers. Hours per week of physical exercise was assessed using survey items asking separately about light (e.g., "light housekeeping"), moderate (e.g., "brisk walking"), and vigorous activities (e.g., "high intensity aerobics"). Following other studies (Brooks et al., 2014), we used a weighted average of light (1 × number of hours), moderate (2 × number of hours), and vigorous exercise (3 × number of hours). Body mass index (BMI; expressed in kg/m^2) was calculated from height and weight measured at the clinic visit. We also included a composite measure of dietary quality constructed by Boehm, Williams, Rimm, Ryff, and Kubzansky (2013). Participants were asked about their average weekly consumption of several types of foods. One point was assigned for each of seven healthy diet indicators (three or more servings per day of fruits and vegetables and whole grains, one or more serving per week of fish and lean meats, two or fewer servings per week of beef or high fat meat, no sugary beverages, and fast food less than once per week). All health covariates were measured at the biomarker study clinic visit, other than functional limitations which were measured at MIDUS 2.

Statistical Analysis

We employed linear regression, beginning with a baseline model including only a given measure of social relationships and demographic covariates of age, gender, race, and education. We also included an interaction of gender and age given prior findings of sex differences in age trajectories of inflammation (Yang & Kozloski, 2011). We first tested main effects of each social measure. Next, we tested three-way interactions involving both gender and age, and if these were nonsignificant, proceeded to test two-way interactions with age and gender separately. We also tested interactions with age-squared, as potential differences in social functioning and health across midlife as well as the "young-old" and "old-old" segments of older adulthood (Baltes & Smith, 2003; Yasuda et al., 1997) suggest the possibility of nonlinear age effects across adulthood. We repeated this process in a second model that further adjusted for medications, chronic disease, and ADL limitations, followed by a

third model adding health behaviors and BMI. As these covariates were measured concurrently with the inflammatory markers and hence do not meet the temporal sequencing requirement for mediation, we aimed simply to determine whether they statistically explained any observed associations and simple slopes (Turiano, Mroczek, Moynihan, & Chapman, 2013).

In the case of a significant three-way interaction, we performed analyses stratified by gender, testing two-way interactions of social relationship measures with age separately in women and men. Where indicated by significant interactions, we probed simple slopes, examining regions of statistical significance and where relevant focusing on associations between the given social measure and inflammatory marker at the mean of the moderator age (approximately age 60) and at one standard deviation above (age 70) and below (age 45) the mean (Aiken & West, 1991). To place all social variables on the same metric, we standardized each to a *Z* score. We estimated regression models with cluster-robust standard errors due to the inclusion of siblings and twins in the MIDUS 2 biomarker project (129 in the analytic sample); these standard errors differed little from standard estimates. Finally, we performed supplementary analyses using scores on social measures averaged across MIDUS 1 and MIDUS 2, which may better reflect characteristic levels of social functioning over time. For each social measure (other than the positive relations scale, which was not included in this analysis due to fewer items and lower reliability at MIDUS 1), scores at MIDUS 1 and MIDUS 2 were correlated between .55 and .6. Analyses were performed using Stata (Version 14, StataCorp, College Station, Texas).

Results

Descriptive statistics for the analytic sample are shown in Table 1. The combined sample ranged in age from 35 to 86 years, with a mean age of approximately 58 years. The sample was predominantly White and more than half of the sample had a college degree. As shown in Table 1, women scored higher on the Social Support and Positive Relations With Others scales and had better diet quality scores and slightly lower BMI, although they reported lower levels of exercise and had higher levels of CRP.

Social Relationships and IL-6

Results from regression models predicting IL-6 are shown in Table 2. Social integration exhibited a marginal association with IL-6 in Model 1, which was attenuated in Models 2 and 3. There were no other main effect associations. We found an interaction of social strain with age predicting IL-6, which

Table 1. Descriptive Statistics for Analytic Sample (N = 963) by Gender.

	Women (n = 525)		Men (n = 438)	
Variables	%/*M* (*SD*)	Range	%/*M* (*SD*)	Range
Demographics				
Age	57.7 (11.4)	35-86	58.2 (11.8)	36-85
Non-Hispanic White	93.3%	—	93.4%	—
Education				
High school/equivalency	27.4%	—	19.9%	—
Some college	29.0%	—	28.3%	—
Graduate 4-year college	24.2%	—	32.4%	—
Graduate/professional Degree	19.1%	—	19.4%	—
Social relationships				
Social integration	2.65 (1.12)	0-4	2.64 (1.02)	0-4
Positive relations scale	6.01 (0.96)[a]	2.0-7.0	5.70 (0.96)[a]	2.7-7.0
Network support	3.52 (0.45)[b]	1.8-4.0	3.44 (0.46)[b]	1.7-4.0
Network strain	2.00 (0.44)	1.0-3.6	1.97 (0.41)	1.0-3.6
Medical covariates				
Blood pressure medication	35.1	—	33.6	—
Cholesterol medication	23.1	—	35.8	—
1+ ADL limitations	19.4	—	14.6	—
Chronic disease	2.22 (1.77)	0-7	2.04 (1.65)	0-7
Behavioral covariates				
Lifetime nonsmoker	59.4	—	52.1	—
Former smoker	30.1	—	35.8	—
Current smoker	10.5	—	12.1	—
Hours exercise/week	3.81 (4.76)[c]	0-24.7	5.27 (7.34)[c]	0-25.0
BMI	28.4 (6.21)[d]	15.0-60.4	29.5 (5.17)[d]	19.6-57.4
Diet quality score	4.48 (1.32)[e]	1-7	3.85 (1.41)[e]	0-7
Inflammatory markers				
IL-6 (pg/mL)	2.67 (2.68)	0.16-21.8	2.52 (2.24)	0.27-23.0
CRP (µg/mL)	2.40 (2.30)[f]	0.14-9.98	1.80 (1.89)[f]	0.14-9.91

Note. Pairs of superscript lowercase letters indicate means different at $p < .05$ per t tests. ADL = activities of daily living; BMI = body mass index; IL-6 = interleukin-6; CRP = C-reactive protein.

persisted upon further covariate adjustment. Simple slopes showed that social strain was related to higher IL-6 only at the lower end of the age distribution, being statistically significant below age 45 (b = .031, p = .056 at age 45). These associations were attenuated to nonsignificance in Models 2 and 3.

Table 2. Coefficients From Linear Regression Models Predicting Log IL-6.

	Model 1		Model 2		Model 3	
Variable	*b* (*SE*)	*p*	*b* (*SE*)	*p*	*b* (*SE*)	*p*
Network strain	.011 (.01)	.360	−.001 (.01)	.911	−.005 (.01)	.649
Strain × Age × Gender	−.001 (.00)	.612	−.001 (.00)	.360	−.002 (.01)	.299
Strain × Gender	−.005 (.02)	.830	−.020 (.02)	.375	−.025 (.02)	.251
Strain × Age	−.002 (.00)	**.041**	−.002 (.00)	**.041**	−.002 (.02)	**.038**
Network support	−.012 (.01)	.276	−.006 (.01)	.561	.001 (.01)	.940
Support × Age × Gender	−.004 (.00)	**.020**	−.004 (.00)	**.015**	−.004 (.00)	**.009**
Support × Age (Women)	−.002 (.01)	**.033**	−.003 (.00)	**.015**	−.003 (.00)	**.019**
Support × Age (Men)	.002 (.00)	.170	.001 (.00)	.236	.002 (.00)	.148
Positive relations w others	−.006 (.01)	.604	.001 (.01)	.916	.003 (.01)	.742
Positive. × Age × Gender	−.002 (.00)	.378	−.001 (.00)	.471	−.002 (.00)	.306
Positive. × Gender	−.032 (.02)	.137	−.031 (.02)	.141	−.036 (.02)	*.064*
Positive. × Age	−.001 (.01)	.169	−.001 (.00)	.163	−.001 (.00)	.125
Positive. × Age^2	−.0002 (.00)	**.007**	−.0002 (.00)	**.011**	−.0002 (.00)	**.004**
Social integration	−.021 (.01)	.050	−.014 (.01)	.188	−.010 (.01)	.344
Integration × Age × Gender	−.002 (.01)	.237	−.002 (.00)	.323	−.002 (.00)	.192
Integration × Gender	−.018 (.02)	.400	−.012 (.02)	.566	−.010 (.02)	.608
Integration × Age	−.000 (.00)	.883	−.000 (.00)	.819	−.001 (.00)	.410
Integration × Age^2	−.0002 (.00)	**.009**	−.0002 (.00)	**.021**	−.0001 (.00)	.052

Note. All social variables were entered in separate models. Model 1 adjusted for age, gender, Age × Gender, race, education, and income. Model 2 added medications, chronic disease, and ADL limitations. Model 3 added BMI, smoking, exercise, and diet quality. IL-6 = interleukin-6; Positive. = Positive relations with others scale.

As shown in Table 2, we found a three-way interaction of social support with age and gender. In stratified analyses, support interacted with age in women but not in men (with no main effect in men), and this interaction remained significant in Models 2 and 3. Examination of simple slopes in women showed that higher support was more strongly associated with lower IL-6 with increasing age. These associations were statistically significant at age 60 and above ($b = -.031$, $p = .030$ at age 60; $b = -.054$, $p = .003$ at age 70), and rather than being attenuated increased in size slightly upon further covariate adjustment. Figure 1 shows simple slopes for the support-IL-6 association at different ages in women (Model 3). In the full sample, the only other covariates to be significantly associated with IL-6 were smoking (higher), BMI (higher), and exercise (lower). Only BMI was associated with IL-6 in the female subsample.

We also found significant interactions of both the Positive Relations With Others scale and social integration with age-squared, which generally

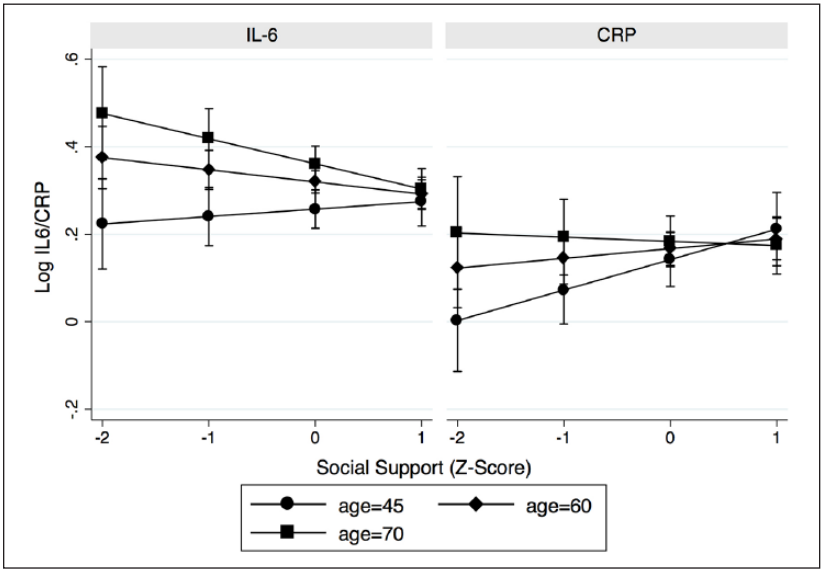

Figure 1. Simple slopes and 95% confidence intervals for log IL-6 and log CRP regressed on social support in women at different ages (Model 3).
Note. IL-6 = interleukin-6; CRP = C-reactive protein.

persisted upon further covariate adjustment. Analysis of simple slopes showed larger inverse associations with IL-6 toward the upper end of the age distribution, which were significant at age 70 for positive relations ($b = -.032$, $p = .044$) and at age 75 for social integration ($b = -.044$, $p = .009$).

Social Relationships and CRP

Results from regression models predicting CRP are shown in Table 3. There were no main effect associations of social measures with CRP in Model 1. A nonsignificant association of social support with higher CRP increased in size with further covariate adjustment, consistent with suppression effects (MacKinnon, Krull, & Lockwood, 2000) and became significant in Model 3. However, this association was further qualified by a three-way interaction of support with age and gender. In stratified analyses, a two-way interaction of support and age was only statistically significant in women in Model 3. Analysis of simple slopes showed that social support was related to higher CRP at younger ages, with statistically significant associations below age 55 ($b = .070$, $p = .009$ at age 45) and nonsignificant associations in the opposite

Table 3. Coefficients From Linear Regression Models Predicting Log CRP.

	Model 1		Model 2		Model 3	
Variable	*B* (*SE*)	*p*	*B* (*SE*)	*p*	*B* (*SE*)	*P*
Network strain	.004 (.02)	.808	−.015 (.02)	.384	−.021 (.02)	.169
Strain × Age× Gender	.002 (.00)	.434	.001 (.00)	.769	.000 (.00)	.883
Strain × Gender	.048 (.03)	.127	.023 (.03)	.465	.011 (.03)	.695
Strain × Age	−.001 (.00)	.262	−.001 (.00)	.323	−.001 (.00)	.262
Network support	.012 (.02)	.447	.021 (.02)	.183	.037 (.01)	**.011**
Support × Age × Gender	−.005 (.00)	**.046**	−.006 (.00)	**.035**	−.006 (.00)	**.007**
Support × Age (Women)	−.002 (.00)	.263	−.003 (.01)	.101	−.003 (.00)	**.027**
Support × Age (Men)	.003 (.00)	.131	.003 (.00)	.186	.003 (.00)	*.082*
Positive relations	.027 (.02)	.118	.037 (.02)	**.028**	.039 (.01)	**.008**
Positive. × Age × Gender	−.002 (.00)	.474	−.001 (.00)	.630	−.001 (.00)	.469
Positive. × Gender	−.014 (.03)	.676	−.011 (.03)	.744	−.02 (.03)	.430
Positive. × Age	−.001 (.00)	.400	−.001 (.00)	.330	−.001 (.00)	.295
Social integration	−.016 (.02)	.330	−.007 (.02)	.677	−.002 (.01)	.913
Integration × Age × Gender	.001 (.00)	.764	.002 (.00)	.455	.001 (.00)	.618
Integration × Gender	.019 (.03)	.550	.027 (.03)	.377	.027 (.03)	.337
Integration × Age	.001 (.00)	.328	.001 (.00)	.465	.000 (.00)	.937

Note. All social variables were entered in separate models. Model 1 adjusted for age, gender, Age × Gender, race, education, and income. Model 2 added medications, chronic disease, and ADL limitations. Model 3 added BMI, smoking, exercise, and diet quality. CRP = C-reactive protein; ADL = activities of daily living; BMI = body mass index.

(inverse) direction at older ages (Figure 1). In men, an interaction in the opposite direction did not reach statistical significance ($p = .082$).

An initially nonsignificant main effect association of the positive relations scale with higher CRP increased in size with further covariate adjustment and reached significance in Model 2. There were no two-way or three-way interactions involving this measure. There were also no main effects or interactions involving social strain or social integration in CRP models. In the combined sample, covariates significantly associated with CRP in Model 3 included cholesterol medication (lower), chronic disease (higher), current

smoking (higher), exercise (lower), BMI (higher), and better dietary quality (lower). In stratified analyses, exercise and diet were not significant in women, whereas cholesterol medication and chronic disease were not significant in men.

Supplementary Analyses

Results of supplementary analyses using social support and integration scores averaged across MIDUS 1 and 2 were highly similar, with the same main effects and interactions exhibiting statistical significance as in primary analyses. The only noteworthy difference was that in men, there was a significant main effect of social support on higher CRP in Model 3 ($b = .050$, $p = .009$), with no age interaction.

Discussion

We found several gender and age differences in associations of various social network measures with inflammatory markers in middle-aged and older adults. In general, protective associations of positive functional and structural measures with IL-6 were stronger in women and older persons. In both men and women, however, there were associations of functional measures with higher CRP after adjustment for health conditions and behaviors, with some further variation by age.

In the present study, social support was associated with lower IL-6 in older but not younger women or men of any age. Prior laboratory and observational studies have shown that marital quality is more closely linked to immune function, including inflammatory markers, in women (Donoho et al., 2013; Jaremka et al., 2014). Our findings suggest that in older adults, a similar gender difference extends to total support across one's social network. In addition, both social integration and general perceptions of positive relationships with others were associated with lower IL-6 in men and women ages 75 and older. These findings echo prior reports of more robust associations between social measures and self-rated health, as well as other biomarkers of disease risk, in older as compared with middle-aged adults (Umberson, Williams, Powers, Liu, & Needham, 2006; Yang et al., 2016). In addition, multiple studies have observed stronger effects of social network characteristics on mortality at older ages (70 plus) in female as well as mixed-gender samples of older adults (Litwin & Shiovitz-Ezra, 2006; Yasuda et al., 1997). It may be that social support acquires more salience or emphasis in the psychosocial milieu of old age, resulting in greater health impact (Umberson et al., 2006; Yasuda et al., 1997). Yang and colleagues (2016) suggested that weaker

protective associations in midlife may be due in part to the potential strain associated with balancing multiple social roles and intergenerational responsibilities at this stage of the life course. To the extent that this is the case, strain or conflict in relationships might also be more impactful earlier in adulthood, consistent with an observed age interaction in which associations of social strain with higher IL-6 were larger at younger ages (although significant only at the lower end of the age range).

In the present study, associations of social support with IL-6 in older women were not diminished upon adjustment for health conditions and behaviors. This finding is consistent with the potential involvement of physiological mechanisms including the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is implicated in the inflammatory response (Rohleder, 2014). It may be that social relationships modulate stress-related stimulation of inflammatory cytokines to a greater extent in women, given evidence for their greater engagement in "tend and befriend" responses to stress (providing nurturance and seeking affiliation; Taylor et al., 2000). Moreover, protective effects on inflammation might be greater at older ages given age-related impairment in regulation of IL-6 (Singh & Newman, 2011) as well as more potent effects of stress (which may be countered by supportive social ties) on immune function in older adults (Kiecolt-Glaser & Glaser, 2001). With regard to clinical significance, several studies have observed graded associations of IL-6 with cardiovascular disease and physical/functional decline in middle-aged and older adults (Adriaensen et al., 2014; Danesh et al., 2008; Schram et al., 2007; Visser et al., 2002), suggesting that even modestly lower levels of IL-6 may be associated with lower related risk.

We found a different pattern of results for CRP than for IL-6, which is not atypical as these inflammatory markers were only moderately correlated, as in other studies, and often show differential associations with social and behavioral factors (Mezuk et al., 2010). Here, social support was associated with *higher* CRP in middle-aged but not older women. In supplementary analyses, social support scores averaged across MIDUS 1 and MIDUS 2 were also associated with higher CRP in men independent of age. In both sets of analyses, the Positive Relations With Others scale was associated with higher CRP in both men and women. Importantly, the foregoing associations became more pronounced and were only significant after adjustment for health conditions, BMI, and health behaviors. This finding suggests that any effects of these social measures on higher CRP do not operate through poorer health status or behaviors. Rather, positive and supportive social relationships may have countervailing, if smaller, indirect associations with lower CRP through better health status and behaviors, partly offsetting associations

with higher CRP transmitted through other mechanisms. One plausible explanation is that although social relationships are generally protective of health, they may also be physiologically demanding (Brooks et al., 2014; Yang et al., 2016) and potentially redirect energetic resources away from immune regulation (Segerstrom, 2008). The suggestion that potential strain associated with maintaining social relationships may be most pronounced in midlife (Yang et al., 2016) appears consistent with the observed age differences in associations of social support with higher CRP in women, although the same was not found in men.

Notably, a prior study reported that low emotional support was related to higher CRP, although not IL-6 in men (Mezuk et al., 2010), a contrasting finding that might be due in part to the more ethnically diverse sample. A recent study (Uchino et al., 2016), albeit one with a considerably younger sample, found associations of social support with lower CRP in African Americans but not in other racial/ethnic groups. With regard to structural measures of relationships, prior studies have consistently, although not exclusively (Heffner et al., 2011), reported associations of marital status and social integration with lower CRP in men but not in women (Ford et al., 2006; Loucks, Berkman et al., 2006; Mezuk et al., 2010). In the present study, however, social integration was not associated with CRP in either gender. One possible reason may be range restriction owing to higher levels of social integration in the MIDUS sample, as compared with other large cohorts (Yang et al., 2016). As noted, the MIDUS sample is also characterized by a relatively high level of educational attainment. Thus, the moderating role of socioeconomic status (SES) as well as race/ethnicity should be further investigated in future work.

Findings should be interpreted in the context of study strengths and limitations. With regard to the timing of study measurements, it is possible that a slightly different pattern of results would emerge if social relationships and inflammatory markers were measured concurrently rather than 2 years apart. Nevertheless, both inflammatory markers and social support show considerable stability over several years in older adults (Das, 2016; Martire, Schulz, Mittelmark, & Newsom, 1999). Consistency of social functioning in the short term is further supported by the moderate correlations, observed here, between social support and integration scores measured nearly 10 years apart. Nevertheless, additional biomarker measurement at baseline would have permitted us to disentangle longitudinal increases or decreases from high values of these inflammatory markers that persist over time. Despite the time lag, some degree of reverse causality remains possible in that IL-6 may serve as a proxy for physical health status, which may influence social relationships. In a similar vein, the temporal relationship of explanatory

covariates (e.g., exercise, BMI) to social relationships and inflammatory markers is empirically ambiguous. Finally, it is possible that observed age differences reflect cohort effects rather than aging processes. As noted, due to certain characteristics of the MIDUS biomarker sample, particular caution should be exercised in generalizing to different demographic segments. The major strength of the present study lies in its more fine-grained approach to this topic, examining age and gender differences in associations of several aspects of social relationships (structural and functional, positive and negative) with two of the most strongly prognostic markers of chronic inflammation, as well as the impact of adjusting for various health-related factors.

In summary, our findings point to intersecting age and gender differences in linkages of social relationships with inflammatory markers. Future studies examining associations of social relationships and markers of physiological function should consider potential moderation by age and gender, screening for three-way as well as two-way interactions with these demographic characteristics. Further work is needed to elucidate the reasons for the age and gender differences observed here and to understand implications for interventions seeking to leverage social relationships.

Authors' Note

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