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# Social support, social strain and inflammation: Evidence from a national longitudinal study of U.S. adults

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ABSTRACT

Social relationships have long been held to have powerful effects on health and survival, but it remains unclear whether such associations differ by function and domain of relationships over time and what biophysiological mechanisms underlie these links. This study addressed these gaps by examining the longitudinal associations of persistent relationship quality across a ten year span with a major indicator of immune function. Specifically, we examined how perceived social support and social strain from relationships with family, friends, and spouse at a prior point in time are associated with subsequent risks of inflammation, as assessed by overall inflammation burden comprised of five markers (C-reactive protein, interleukin-6, fibrinogen, E-selectin, and intracellular adhesion molecule-1) in a national longitudinal study of 647 adults from the Midlife Development in the United States (1995–2009). Results from multivariate regression analysis show that (1) support from family, friends, and spouse modestly protected against risks of inflammation; (2) family, friend, and total social strain substantially increased risks of inflammation; and (3) the negative associations of social strain were stronger than the positive associations of social support with inflammation. The findings highlight the importance of enriched conceptualizations, measures, and longitudinal analyses of both social and biological stress processes to elucidate the complex pathways linking social relationships to health and illness.



A large and growing body of social, demographic, and epidemiologic research has firmly established the important role of social relationships and connections in shaping social and physical functioning and well-being of individuals. Social ties and support have been linked to improved mental and physical health (George et al., 1989; Cornwell and Waite, 2009), a greater capacity to cope with stress (Aneshensel and Stone, 1982; Thoits, 2011), and increased longevity (Berkman and Syme, 1979; House et al., 1988). As the empirical evidence for these links continues to accrue, recent studies have increasingly attended to various social, psychological, and behavioral processes linking social relations to health (Smith and Christakis, 2008; Thoits, 2011; Umberson et al., 2010). However, important gaps exist in measurements of social relationships, specifications of biophysiological mechanisms, and study designs. To address these gaps, the current study examined how both perceived social support and social strain from relationships with family, friends, and spouses are associated with five markers of inflammation in a national longitudinal study of adults in the United States. By assessing both the positive and the negative qualities of social relationships and associating different domains of such relationships with a more comprehensive measure of inflammation over time, the current study provides unique insight into the multifaceted and dynamic links between one's social and physical worlds and contributes to the understanding of the process by which social conditions "get under the skin" to influence health.

## 1. Social relationships and health: integration, support, and strain

Studies over the past several decades have provided overwhelming evidence for the importance of social involvement and interpersonal relationships on individual well-being. However, differences in the conceptualization and measurement of social relations across studies prohibit a direct comparison of the strengths or directions of the associations between specific aspects of social relationships with health, making generalization of these

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associations difficult. What is clear is that social relations are multidimensional and their links to health are multifaceted.

Some studies investigated social relations by using the number of an individual's significant social ties, the frequency of contact with social connections, and participation in social organizations and groups, thus emphasizing the role of quantitative or structural aspects of one's social network in predicting health outcomes (e.g., Berkman and Syme, 1979; Ertel et al., 2008). While the links between the number of social network ties and health are strong, a count of such relationship ties is not synonymous with the quality of social relationships, as individuals can still perceive isolation despite having many social ties, while conversely, having one or several close social connections may lead to greater perceived support (Kiecolt-Glaser et al., 2010). Aligned with this qualitative conceptualization of social relationships, a number of studies have measured social relationships through individual appraisal of the quality of support received from significant members of one's social network, including perceptions of closeness, caring, and understanding from others (Lett et al., 2007; George et al., 1989; Lyyra and Heikkinen, 2006). Furthermore, there is evidence that a lack of perceived support and companionship is predictive of poorer health (Cacioppo and Hawkley, 2003; Cornwell and Waite, 2009). Collectively, these suggest that perceived presence of supportive relationships has the capacity to protect individuals from the adverse health outcomes associated with chronic stress, while the perceived absence of such relationships increases disease risks.

Beyond studies of social support and health, less attention has been given to the detrimental effects of relational strain on mental and physical well-being. Investigations of social strain and health have acknowledged that social connections are not explicitly positive in nature, but instead function in a balance of both benefits and costs (Walen and Lachman, 2000). Studies investigating the relative contribution of social support and strain on individual well-being suggested that negative social relations represent a distinct construct from positive aspects of social networks (Finch et al., 1989; Rook, 1984), emphasizing the need to assess measures of both support and strain. Furthermore, there is evidence that negative social exchanges have a more substantial impact on mental health than positive aspects of social relationships. Social strain, characterized by greater interpersonal conflict, frequent criticisms, and excessive demands from significant members of one's social network, has the potential to act as a direct source of psychosocial distress (Finch et al., 1989; Newsom et al., 2003, 2005). Research has also identified negative effects of strained relationships on physical health outcomes, particularly linking spousal conflict to increased risk of coronary heart disease and mortality (Eaker et al., 2007; Umberson et al., 2006).

## 2. Inflammation: the biophysiological link between social relationships and health

The physiological processes underlying the association between social relationships and health have been increasingly investigated in recent empirical research. One area of growing interest is the role of inflammation in linking social factors to physical health outcomes. Inflammation has been identified as a reliable predictor of many morbidity conditions, including cardiovascular disease, diabetes, dementia, and arthritis (Ershler and Keller, 2000). While acute inflammatory response to a particular pathogen or injury is a crucial part of immunity, systemic and low-grade inflammation with no clear pathogenic target damages healthy tissues over time, therefore increasing risk for age-related chronic illnesses (McEwen, 1998; Alley et al., 2008; Hwang et al., 1997).

Research across behavioral neuroscience, immunology, and epidemiology has found chronic psychosocial stress to be a strong predictor of inflammation in the absence of infection or injury. Studies have found that the physiological processes involved in the stress response (i.e., the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system) can act to modulate inflammatory processes, thus providing evidence of a crucial biosocial linkage between experiences of psychosocial stress and the illness consequences of inflammation (Black and Garbutt, 2002). Several studies have documented that chronic stress diminishes the ability of the immune system to respond to anti-inflammatory signals (Cohen et al., 2012; Miller et al., 2002), and others have linked particular psychosocial stressors to immune dysregulation (Friedman and Herd, 2010; Kiecolt-Glaser et al., 2005).

## 3. Gaps in previous research

While the link between chronic stress and inflammation has been increasingly documented, the particular aspects of social relationships that contribute to immune function have not been fully specified due to several limitations in measurement and study design. First, measures of social relations that are used in biosocial research are often limited to indicators of social network size (Ford et al., 2006; Loucks et al., 2006; Yang et al., 2013). While a few studies have identified the beneficial effects of social support on immune function (Uchino, 2006), these have specifically focused on the role of social support in affecting the immune function and inflammatory processes of female cancer patients (Lutgendorf et al., 2005; Costanzo et al., 2005). An investigation of whether inflammatory processes are similarly influenced by social support in a national sample is needed to determine whether this association also exists in the absence of devastating medical events and the associated extreme physiological and health-related stress.

Second, studies assessing the role of social relationships in affecting inflammatory processes have not investigated whether it may differ by the function and source of the social relationship. While there is evidence for the physiological influence of social support, few studies have investigated the relation between poor relationship quality and adverse physiological outcomes. Evidence for the link between social strain and inflammation is limited but indicates a positive correlation. In particular, interpersonal stress from romantic partners, family and friends was associated with higher CRP and IL-6 levels six months later (Kiecolt-Glaser et al., 2005), and incidence of marital conflict increased long-term production of IL-6 and tumor necrosis factor alpha (TNFα) (Miller et al., 2009). Given the evidence of the differential effects of positive and negative functions of social relationships on health, we further investigated the relative contribution of social support and strain on physiological indicators of health. Assessment of both social support and strain expands upon prior research that links social support to better health outcomes, while also determining whether evidence implicating social strain as a more significant predictor of psychosocial distress extends to physiological outcomes. In addition to different functions that social relationship may serve, sources or domains of supportive or strained relationships from one's networks can also contribute to variations in health. For example, Mendes de Leon et al. (1999) found that the linkage between social relationships and disability in older adults varied by the type of relationship, such that the number of friend and relative contacts was significantly linked to disability and recovery, while ties with children and confidants were not associated with disability. Expanding these findings to an assessment of underlying physiological processes, our study distinguishes between three sources of social relations, including family, friends, and spouse, to assess both positive and negative functions of social relationships in relation to inflammation.

Third, the precise link between social relationships and inflammation also remains unclear due to the limited measures of inflammation. Inflammation has increasingly been recognized as a major physiological consequence of exposures to persistent psychosocial stressors such as socioeconomic strain (Friedman and Herd, 2010), marital distress (Kiecolt-Glaser et al., 2005), social isolation (Heffner et al., 2011), and perceived loneliness (Steptoe et al., 2004). However, most studies that assessed the links between social relationships and inflammation used only one or two inflammatory markers, such as C-reactive protein (CRP) or interleukin-6 (IL-6). A recent study of three markers of inflammation in relation to social isolation suggests that they differ in relative importance, with fibrinogen being more important than CRP or serum albumin as a correlate to social isolation (Yang et al., 2013). In addition, the study found that the cumulative inflammation burden that combines all high-risk markers at a point in time is much more strongly related to isolation than any individual marker alone. Therefore, a simultaneous assessment of multiple markers indicative of cumulative burden may more comprehensively capture the inflammatory effects of social factors.

Furthermore, most studies of the link between social relations and inflammation used cross-sectional study designs that are insufficient to capture chronic stress as the crucial biosocial linkage. It has long been postulated that lack of social ties and support signals stressful social circumstances that constitutes chronic stress (Pearlin et al., 1981), and chronic exposures to stress and reduced coping resources can induce a cascade of changes across multiple regulatory systems through activation of the physiological stress response that modulate immune function and inflammatory processes (Seeman et al., 2001). In cross-sectional studies, it is unclear whether assessments of relational support or strain are indicative of present relationship quality that may be transient or more long-term social relationship patterns that shape chronic stress exposure and response. To the extent that the latter may bear more important consequences for inflammation status, it is desirable for research to use longitudinal data to more properly measure chronic stress. Cross-sectional associations also make causal inference difficult due to the problem of reverse causation. While longitudinal data on both social exposures and biomarkers would be needed to fully address causality, repeated biomarker measures are currently rarely available. Nevertheless, longitudinal designs that provide the proper temporal order of the measurements of exposure and outcome, that is, chronic stressors measured at a prior point in time and biomarkers assessed later, may be utilized to improve upon cross-sectional studies of the associations.

Finally, previous studies are also limited in sample sizes and representativeness. Studies that have assessed the link between social support and immune function have primarily investigated this relationship in individuals affected by chronic illness (Theorell et al., 1995; Costanzo et al., 2005). Further study is necessary to determine whether these biosocial links continue to be salient in a larger heterogeneous sample.

In light of prior research, we hypothesize that perceptions of social support and strain over time are associated with inflammation at a later point in time. While high social support is expected to reduce subsequent inflammation, high social strain is expected to worsen inflammation. Based on evidence that implicates social strain as a more significant predictor of psychosocial distress and poor health than social support, we expect to see stronger associations of social strain with inflammation. Furthermore, we expect to observe that the social relationships and inflammation link will differ based on three domains of social relationships (i.e., family, friend and spouse). In addition to more detailed and multifaceted measures of perceived social relationship quality, this study distinguishes itself from earlier studies by measuring social relations longitudinally to capture persistent or chronic stress and by measuring overall inflammation burden that encompasses multiple inflammatory markers, several of which have not yet been included in research on social relations and health.

## 4. Data and methods

### 4.1. Data source

The data come from the National Survey of the Midlife Development in the United States (MIDUS), a longitudinal and nationally-representative study of behavioral, psychological, and social factors that contribute to age-related differences in overall health and well-being. A total of 7108 participants aged 25–74 were recruited for the original study in 1995–96 (wave I) by random digit dialing. Of the participants in the original sample, nearly 90 percent were white and only 5 percent were black. Phone interviews and self-administered questionnaires were completed by MIDUS participants. The wave II data was collected 9–10 years later (2004–2006), with a mortality-adjusted retention rate of 75%.

Biological data come from the MIDUS II biomarkers study (2004–2009), which consisted of a more detailed assessment of key biological parameters indicative of physical health. Eligible participants lived in the continental U.S. and completed the MIDUS II core phone interview and self-administered questionnaire. Of the 1255 participants in the Biomarkers study, 1054 participated in both survey waves. Our study excluded 345 unmarried individuals (32.7%) and 62 (6%) individuals due to missing income, relationship indicators, missing or invalid biological measures. The final sample consists of 647 married individuals who were present in all three stages of data collection and had no missing data for variables included in the analysis. Compared to the excluded sample, our final sample reported significantly higher social support and lower social strain, higher income, more frequent physical activity, and lower norepinephrine, suggesting that the final sample had overall better social relationships, socioeconomic standing, and physiological functioning compared to the excluded participants. Therefore, we expect our estimated associations between social relationships and inflammation to be more conservative than what would be observed in the initial sample.

### 4.2. Inflammation

Inflammation was measured by five markers including *C-reactive protein (CRP)*, *fibrinogen, interleukin-6 (IL-6), E-selectin*, and *intracellular adhesion molecule 1 (ICAM-1)* at wave II. Previous research suggests that a count of high risk biological parameters across bodily systems, termed the "allostatic load," is a generalized indicator of cumulative burden of physiological dysregulation and a powerful index of population frailty predicting major health outcomes (Seeman et al., 2001). Along this line, we constructed a summary count *index of inflammation burden* as the sum of the positive indicators based on the five dichotomous measures of inflammatory markers. For CRP, individuals were categorized as high-risk if they had CRP levels $>3.0$ mg/dL, which is defined in clinical practice as the cut point for immune dysregulation. Participants with CRP levels exceeding 10.0 mg/dL were excluded from analysis because CRP beyond this point is indicative of acute inflammation induced by infection or injury. Because clinical cut points have not been determined for the other four indicators of inflammation, the high-risk category for each of these inflammatory markers was defined as the top quartile. Although these cut points are

empirically defined and sample based, previous research using similar biomarkers suggests that they are meaningful representations of immunological abnormalities or less-than-optimal conditions that may signal pre-disease pathways (Crimmins et al., 2003; Yang and Kozloski, 2011). To confirm that these five indicators comprise a single indicator of inflammation, we used an oblique model in a principle components analysis. Factor analysis indicated that all five inflammatory markers load onto a single factor (36.9% of the variance, Eigen value 1.84), with loading coefficients for CRP = 0.77, fibrinogen = 0.69, IL-6 = 0.64, E-selectin = 0.38, and ICAM-1 = 0.46. Table 1 shows that inflammation burden varies from zero (34.9% of the sample) to being at high risk for all five inflammatory markers (1.4%).

### 4.3. Social support/strain measures

Table 1 presents descriptive statistics of all covariates in the analysis. *Perceived social support* and *social strain* from *family*, *friends*, and *spouse* were measured and constructed in MIDUS I and II. Support and strain from family and friends were each assessed using four survey items in both waves, while six survey items were used to measure spouse support and strain. Details of the survey items and variable construction can be found in the Appendix. For the social support variables, the respondent was asked how much family members, or friends, or spouse "care about you", "understand the way you feel", "how much you can rely on them", and "how much you can open up to them", with the response categories ranging from not at all (1), a little (2), some (3), to a lot (4). Spouse support scales included two additional items that ask respondents how much spouse "appreciates you" and how much "you can be yourself" around him or her. Values of social support at MIDUS I and II were then averaged to capture long-term perceptions of support from each relationship domain. *Total social support* for each wave was calculated by taking the mean of the three support scales, and total support for both waves was calculated by taking the average of the total support measured at two waves. For the social strain variables, the respondent was asked how often do family members, friends, or spouse "make too many demands on you", "criticize you", "let you down when you are counting on them", and "do they get on your nerves", with the same response categories as above. The spouse strain scale includes additional items that ask respondents how often a spouse "argues with you" and "makes you feel tense." Consistent with the measurement of social support, social strain variables were averaged across the two survey waves. *Total social strain* scales were also constructed similarly to total social support scales.

**Table 1**
Sample characteristics and descriptive statistics ($N = 647$): MIDUS 1995–2009.

| Variables | Mean/% (SD) | Min | Max |
|---|---|---|---|
| Inflammatory markers (2004–2009) | | | |
| C-reactive protein (mg/dL) (High risk: ≥3.00) | 2.13 (2.2) | 0.14 | 9.98 |
| Fibrinogen (mg/dL) (High risk: ≥385) | 386 (79) | 94 | 759 |
| Interleukin-6 (pg/mL) (High risk: ≥3.04) | 2.57 (2.5) | 0.16 | 23.00 |
| E-selectin (ng/mL) (High risk: ≥49.12) | 41.15 (21.0) | 0.09 | 161.85 |
| ICAM-1 (ng/mL) (High risk: ≥ 327.90) | 285.25 (97.10) | 74.45 | 896.47 |
| Inflammation burden index | 1.23 (1.2) | 0 | 5 |
| 0 | 34.9% | | |
| 1 | 30.0% | | |
| 2 | 18.9% | | |
| 3 | 10.5% | | |
| 4 | 4.3% | | |
| 5 | 1.4% | | |
| Social support (1995–2006) | | | |
| Family support | 3.53 (0.49) | 1.50 | 4 |
| Friend support | 3.30 (0.56) | 1.13 | 4 |
| Spouse support | 3.63 (0.45) | 1.58 | 4 |
| Total support | 3.47 (0.42) | 2 | 4 |
| Social strain (1995–2006) | | | |
| Family strain | 2.02 (0.49) | 1 | 3.75 |
| Friend strain | 1.83 (0.39) | 1 | 3.13 |
| Spouse strain | 2.17 (0.53) | 1 | 3.92 |
| Total strain | 2.01 (0.36) | 1.08 | 3.53 |
| Neuroendocrine markers (2004–9) | | | |
| Epinephrine (ug/dL)[a] | 0.14 (0.1) | 0.01 | 1.00 |
| Norepinephrine (ug/dL)[a] | 1.99 (1.5) | 0.23 | 14.30 |
| Sociodemographic status (2004–6) | | | |
| Female | 0.50 (0.5) | 0 | 1 |
| Age | 55.42 (11.3) | 34 | 83 |
| Household income (thousands) | 87.46 (63.7) | 0 | 300 |
| Educational attainment | | | |
| High school or less | 27.7% | | |
| Some college | 27.8% | | |
| College or more | 44.5% | | |
| Health behaviors (2004–9) | | | |
| Body Mass Index (BMI) | 29.02 (5.6) | 14.99 | 57.40 |
| Current smoker | 0.10 (0.3) | 0 | 1 |
| Exercise at least 3× a week | 0.81 (0.4) | 0 | 1 |
| Medications(2004–9) | | | |
| Blood pressure | 0.37 (0.4) | 0 | 1 |
| Cholesterol | 0.32 (0.5) | 0 | 1 |
| Corticosteroids | 0.12 (0.3) | 0 | 1 |
| Antidepressants | 0.13 (0.3) | 0 | 1 |

[a] Epinephrine and norepinephrine are adjusted for creatinine output.

### 4.4. Covariates

We adjusted for factors that have been associated with inflammation, including demographic characteristics, socioeconomic status, health-related behaviors, and medications (Yang et al., 2013). Table 1 presents the coding and descriptive statistics for the following covariates assessed at wave I: sex, age, household income, educational attainment, body mass index (BMI), current cigarette smoking, physical activity, and staff-verified medication uses for hypertension, cholesterol, corticosteroids, and antidepressants. We also adjusted for epinephrine and norepinephrine as markers of sympathetic nervous system (SNS) activity based on the 12-h urine collection, as SNS activity as a part of the physiological stress response has been shown to modulate inflammatory processes (Black and Garbutt, 2002; Hänsel et al., 2010). Measures of epinephrine and norepinephrine were divided by the level of urine creatinine output to adjust for diuresis. We did not adjust for race in our analysis because the MIDUS sample is homogeneous in race composition.

### 4.5. Analytic strategy

We estimated multivariate regression models to examine the associations between social support and strain assessed in wave I and wave II and subsequent risk of inflammation assessed in the Biomarker study in wave II. The analyses proceeded in three steps. First, we estimated models that included each individual domain of social support and the total support scale, respectively. Second, we estimated models that included the three domains of social strain and the total strain scale, respectively. Third, we estimated models that included measures of both social support and strain within each domain of relationships and for the total summary scales to assess their associations independent of each other and the relative importance of support and strain in affecting inflammation. In each of the three steps, we first estimated ordinary least squares regression models for continuous markers of inflammation, using log transformations for CRP, IL-6, and E-selectin to adjust for

skewness in the sampling distributions. We then estimated logistic regression models for each dichotomous marker of inflammatory risk included in the overall index. The use of continuous measures in OLS models assumes linearity in the associations of interest or dose–response relationships. The dichotomous outcome models, on the other hand, allow for non-linearity in the associations and can better capture threshold effects. We chose the best models based on both significance tests for regression coefficients and model fit statistics using the Bayes Information Criterion (BIC). We finally estimated ordinal logistic models for the summary inflammation burden index. For each of the three steps of the analyses, we also estimated models that simultaneously included all three domain-specific measures of social relationships to assess any individual domain's association with inflammation net of the others. The choice of final models was similarly based on significance tests and BICs. In all analyses, we adjusted for sex and age and compared results to models that adjusted for all additional covariates. To account for sampling of family members, we clustered the sample by family membership and reported robust standard errors. All statistical analyses were performed using Stata 12.0.

## 5. Results

Results of the first analysis using the logistic models displayed in Table 2 show modest protective effects of social support. Results of the OLS models of continuous inflammatory markers in this and subsequent analyses show fewer statistically significant associations (see Appendices 2 and 3) and vastly poorer model fit than the logistic models. These results thus favor nonlinear or threshold effects over linear or dose–response relationships between social exposures and inflammatory outcomes, which are consistent with prior studies of similar biomarkers in relation to social isolation using other nationally representative data (Ford et al., 2006; Yang et al., 2013).

In the age- and sex-adjusted models, domain-specific support and total support were associated with decreased risks of inflammation as indicated by not only individual markers but also the overall inflammation burden. Family support was associated with significantly lower odds of elevated IL-6 (Odds Ratio (OR) = 0.68; 95% Confidence Interval (CI), 0.48–0.97); spouse support was associated with significantly lower odds of elevated E-selectin (OR = 0.67, 95% CI, 0.46–0.97); and friend support was also negatively associated with elevated ICAM-1 (OR = 0.66, 95% CI, 0.48–0.92). The results for CRP and fibrinogen, on the other hand, did not show any significant coefficient estimates of social support. While the decreases in overall inflammation burden were not statistically significant for family or friend support, the inflammation burden was 27% lower for those with higher spouse support (OR = 0.73; 95% CI, 0.53–0.99). The results are similar when all three domain-specific support variables were entered simultaneously in the models (Appendix 4.1). Taking all domains into account, total support was associated with significantly lower risk of elevated ICAM-1 (OR = 0.70, 95% CI, 0.55–1.07) and inflammation burden (OR = 0.76; 95% CI, 0.54–1.06). Comparison of BICs shows superior fit of the models including total support as compared to the models with all three domain-specific support variables, suggesting that the total amount of support from any given source may be a more parsimonious way to summarize one's social relationship quality than alternatives. Adjusting for all other covariates attenuated these associations, suggesting that the immune function benefits of

**Table 2**
Prospective associations of social support with elevated inflammation ($N = 647$).

| | Family support | | Friend support | | Spouse support | | Total support | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | BIC | OR (95% CI) | BIC | OR (95% CI) | BIC | OR (95% CI) | BIC |
| C-reactive protein | | | | | | | | |
| Age & sex adjusted | 0.85 (0.60–1.21) | 734.01 | 0.90 (0.65–1.24) | 734.35 | 0.74 (0.50–1.07) | 732.35 | 0.80 (0.53–1.23) | 733.79 |
| Fully adjusted[a] | 1.02 (0.66–1.56) | 718.52 | 1.13 (0.79–1.60) | 718.12 | 0.94 (0.60–1.47) | 718.45 | 1.16 (0.71–1.89) | 718.19 |
| Fibrinogen | | | | | | | | |
| Age & sex adjusted | 1.04 (0.70–1.53) | 730.51 | 0.85 (0.60–1.21) | 730.49 | 0.76 (0.50–1.16) | 728.45 | 0.75 (0.47–1.19) | 728.81 |
| Fully adjusted[a] | 1.15 (0.74–1.77) | 778.83 | 0.93 (0.65–1.34) | 778.79 | 0.83 (0.53–1.28) | 778.01 | 0.85 (0.52–1.37) | 778.60 |
| IL-6 | | | | | | | | |
| Age & sex adjusted | 0.68** (0.48–0.97) | 730.22 | 0.84 (0.60–1.18) | 733.16 | 0.75 (0.51–1.11) | 732.28 | 0.74 (0.474–1.14) | 732.37 |
| Fully adjusted[a] | 0.76 (0.51–1.13) | 762.06 | 1.01 (0.71–1.43) | 763.86 | 0.9 (0.58–1.38) | 763.61 | 0.96 (0.59–1.57) | 763.83 |
| E-selectin | | | | | | | | |
| Age & sex adjusted | 1.14 (0.77–1.70) | 741.56 | 1.11 (0.81–1.53) | 741.62 | 0.67** (0.46–0.97) | 737.79 | 0.93 (0.61–1.43) | 741.96 |
| Fully adjusted[a] | 1.25 (0.81–1.95) | 786.90 | 1.29 (0.92–1.80) | 785.95 | 0.76 (0.52–1.12) | 786.34 | 1.14 (0.72–1.82) | 787.78 |
| ICAM-1 | | | | | | | | |
| Age & sex adjusted | 0.9 (0.62–1.32) | 736.31 | 0.66** (0.48–0.92) | 730.45 | 0.95 (0.63–1.43) | 736.53 | 0.70* (0.45–1.07) | 733.93 |
| Fully adjusted[a] | 1.03 (0.68–1.57) | 766.83 | 0.77 (0.55–1.07) | 764.61 | 1.14 (0.74–1.76) | 766.51 | 0.88 (0.56–1.37) | 766.55 |
| Inflammation Burden Index | | | | | | | | |
| Age- and sex-adjusted | 0.90 (0.68–1.20) | 1946.93 | 0.87 (0.67–1.12) | 1946.22 | 0.73** (0.53–0.99) | 1943.45 | 0.76* (0.54–1.06) | 1944.79 |
| Fully-adjusted[a] | 1.16 (0.85–1.57) | 1882.39 | 1.15 (0.88–1.50) | 1882.17 | 0.89 (0.64–1.23) | 1882.80 | 1.09 (0.77–1.56) | 1883.03 |

***$p < 0.01$, **$p < 0.05$, *$p < 0.1$; two-tailed test.
[a] Controls for age, sex, SNS activity (creatinine-adjusted epinephrine and norepinephrine levels), household income, education, BMI, current smoking status, and medications.

**Table 3**
Prospective associations of social strain with elevated inflammation ($N = 647$).

| | Family strain | | Friend strain | | Spouse strain | | Total strain | |
|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | BIC | OR (95% CI) | BIC | OR (95% CI) | BIC | OR (95% CI) | BIC |
| C-reactive protein | | | | | | | | |
| Age & sex adjusted | 1.39* (0.95–2.03) | 732.00 | 1.25 (0.78–1.99) | 733.89 | 1.18 (0.84–1.67) | 733.84 | 1.50 (0.90–2.50) | 732.34 |
| Fully adjusted[a] | 1.07 (0.71–1.61) | 718.43 | 1.07 (0.65–1.76) | 718.46 | 1.04 (0.71–1.51) | 718.49 | 1.10 (0.65–1.88) | 718.42 |
| Fibrinogen | | | | | | | | |
| Age & sex adjusted | 1.58** (1.05–2.37) | 724.58 | 1.45 (0.84–2.51) | 728.32 | 1.25 (0.85–1.83) | 727.55 | 1.80* (0.99–3.24) | 724.22 |
| Fully adjusted[a] | 1.43* (0.94–2.18) | 775.42 | 1.35 (0.78–2.32) | 777.45 | 1.27 (0.86–1.89) | 775.99 | 1.66* (0.91–3.02) | 774.41 |
| IL-6 | | | | | | | | |
| Age & sex adjusted | 1.62** (1.08–2.43) | 728.43 | 0.91 (0.56–1.48) | 734.09 | 1.01 (0.71–1.44) | 734.24 | 1.29 (0.75–2.19) | 733.35 |
| Fully adjusted[a] | 1.38 (0.91–2.09) | 761.57 | 0.84 (0.51–1.39) | 763.37 | 0.97 (0.67–1.39) | 763.83 | 1.09 (0.63–1.89) | 763.76 |
| E-selectin | | | | | | | | |
| Age & sex adjusted | 1.67** (1.13–2.48) | 734.95 | 1.97*** (1.23–3.14) | 733.90 | 1.39* (0.99–1.94) | 738.41 | 2.29*** (1.37–3.84) | 731.89 |
| Fully adjusted[a] | 1.60** (1.04–2.44) | 782.99 | 1.88** (1.15–3.08) | 781.48 | 1.38* (0.99–1.94) | 784.85 | 2.17*** (1.26–3.72) | 780.03 |
| ICAM-1 | | | | | | | | |
| Age & sex adjusted | 1.23 (0.80–1.89) | 735.52 | 1.21 (0.73–2.02) | 735.94 | 0.90 (0.62–1.30) | 736.22 | 1.13 (0.65–1.96) | 736.38 |
| Fully adjusted[a] | 1.07 (0.69–1.68) | 766.74 | 1.12 (0.67–1.87) | 766.66 | 0.86 (0.59–1.26) | 766.24 | 0.98 (0.56–1.72) | 766.85 |
| Inflammation Burden Index | | | | | | | | |
| Age- and sex-adjusted | 1.77*** (1.30–2.40) | 1934.20 | 1.50** (1.04–2.16) | 1942.68 | 1.2 (0.93–1.57) | 1945.52 | 1.87*** (1.25–2.79) | 1938.04 |
| Fully-adjusted[a] | 1.44** (1.05–1.99) | 1878.22 | 1.32 (0.91–1.93) | 1881.18 | 1.14 (0.86–1.49) | 1882.45 | 1.52* (0.99–2.30) | 1879.43 |

***$p < 0.01$, **$p < 0.05$, *$p < 0.1$; two-tailed test.
[a] Controls for age, sex, SNS activity (creatinine-adjusted epinephrine and norepinephrine levels), household income, education, BMI, current smoking status, and medications.

social support are partly attributed to higher SES, better health behaviors, or other factors present in good social relations with family, friends, or spouse.

Results from the second analysis in Table 3 show robust detrimental effects of social strain on multiple inflammatory markers and overall inflammation burden. Adjusting for age and sex, a higher degree of family strain was associated with vastly elevated odds of high-risk fibrinogen (OR = 1.58, 95% CI, 1.1–2.4), IL-6 (OR = 1.62, 95% CI, 1.1–2.4), and E-selectin (OR = 1.67, 95% CI, 1.1–2.5). The effect coefficient of family strain was the largest on overall inflammation burden (OR = 1.77, 95% CI, 1.3–2.4). Friend strain was associated with a 97% (95% CI, 1.2–3.1) higher risk of elevated E-selectin and 50% (95% CI, 1.0–2.2) higher inflammation burden. Spousal strain appeared to significantly predict inflammation only in terms of elevated E-selectin (OR = 1.39, 95% CI, 1.0–1.9). Total social strain had the strongest positive associations with inflammation as indicated by fibrinogen (OR = 1.80, 95% CI, 1.0–3.2), E-selectin (OR = 2.29, 95% CI, 1.37–3.84), and inflammation burden (OR = 1.87, 95% CI 1.3–2.8) compared to strain from each individual relationship source, suggesting that the overall perceptions of relationship strain from diverse sources were highly predictive of inflammation risks. Adjusting for all the other covariates reduced the effect coefficients, but the strong and significant risks of inflammation burden remained for those experiencing higher levels of family strain (OR = 1.44, 95% CI, 1.1–2.0) or total strain (OR = 1.52, 95% CI, 1.0–2.3), suggesting that strains associated with family relations or overall relations may contribute to inflammation independent from other known risk factors. Models including all three domain-specific variables yielded qualitatively similar results but fewer significant associations probably due to multicollinearity (Appendix 4.2). Similar to the previous analysis, these models show poorer fit compared to the models including the total strain variable.

Results shown in Table 4 indicate that when including both social support and social strain indicators in the models, the latter continue to be more robust predictors of inflammation index. In the models that adjusted for age and sex only, family strain, friend strain, and total social strain all were associated with significantly higher inflammation burden, with respective ORs of 1.84 (95% CI, 1.3–2.6), 1.47 (95% CI, 1.0–2.1), and 1.80 (95% CI, 1.2–2.8), net of social support from the corresponding domains. Of the three domains of social strain, only spouse strain did not have a significant

**Table 4**
Prospective associations of social support and social strain with elevated inflammation burden: Odds Ratios (OR) with 95% Confidence Intervals (CI).

| | Family relations | Friend relations | Spouse relations | Total |
|---|---|---|---|---|
| Age- and sex-adjusted | | | | |
| Support | 1.11 (0.84–1.46) | 0.90 (0.70–1.15) | 0.73 (0.46–1.15) | 0.93 (0.66–1.31) |
| Strain | 1.84*** (1.30–2.60) | 1.47* (0.99–2.16) | 1.00 (0.68–1.48) | 1.80** (1.13–2.85) |
| Fully-adjusted[a] | | | | |
| Support | 1.34 (0.99–1.79) | 1.19 (0.91–1.55) | 0.98 (0.59–1.63) | 1.3 (0.90–1.88) |
| Strain | 1.60** (1.12–2.28) | 1.37 (0.92–2.04) | 1.12 (0.74–1.70) | 1.71** (1.07–2.73) |

***$p < 0.01$, **$p < 0.05$, *$p < 0.1$; two-tailed test.
[a] Controls for age, sex, SNS activity (creatinine-adjusted epinephrine and norepinephrine levels), household income, education, BMI, current smoking status, and medications.

association with inflammation. Meanwhile, social support was not significantly related to inflammation burden when including measures of social strain. In the fully-adjusted models, family strain and total social strain remained to be significant predictors of higher inflammation burdens, with ORs of 1.60 (95% CI, 1.1–2.2; $p < .01$) and 1.71 (95% CI, 1.1–2.7; $p < .05$), respectively. The results for each individual marker show that the effects of social strain, net of social support, are only significant for E-selectin on family, friend, and total strain. These results collectively suggest that persistent social strain from several relationship sources is a risk factor for inflammation burden, and while these associations are partially due to differences in SES, health behaviors, and other physiological controls, family strain and total strain remain to be significantly and independently associated with inflammation burden after adjusting for these factors.

## 6. Discussion

Our analyses of multiple dimensions of perceived social relationships and inflammation support the hypothesis that long-term social support and strain, particularly social strain, are significantly related to inflammation levels in a national sample of adults. By assessing social support and strain simultaneously and longitudinally, we found that the prospective association with inflammation is only modest for social support, whereas that for social strain is more robust and remains significant after adjusting for all additional covariates. This finding is consistent with prior evidence that finds social strain to be a direct contributor to psychosocial distress that overrides the protective effect of support (Finch et al., 1989; Newsom et al., 2003, 2005), and further suggests that the psychosocial distress resulting from strained relationships has the potential to influence underlying physiological processes tied to later health.

In assessing the specific contribution of social support and strain within each relationship domain (i.e., family, friend, and spouse), we found variations in the association of support or strain with inflammation. Support from family, friend, and spouse modestly protected against inflammation as measured by different markers. Only spouse support and total support seemed to relate to the overall inflammation burden. And these associations were attenuated after adjusting for additional covariates such as health behaviors and socioeconomic factors that are closely related to social support and hence may confound the relationship of interest. The lack of strong protective effects of social support against inflammation is not expected based on prior research in several areas. Social support was linked to increased longevity and decreased risk of cardiovascular disease and cancer (Lyyra and Heikkinen, 2006; Orth-Gomér et al., 1993; Penwell and Larkin, 2010), as well as improved immune function among cancer or HIV patients (Lutgendorf et al., 2005; Costanzo et al., 2005; Theorell et al., 1995). Differences in both measurements of social support and sample compositions may have contributed to this difference. Instead of small clinical samples or older adult samples with a focus on particular diseases, our study provides evidence from a more heterogeneous national sample of community-dwelling Americans with more nuanced measures of function and sources of social interaction in everyday life. Perhaps social support plays a more salient role in immune regulation for individuals facing extreme physiological stressors than the general population.

Social strain showed consistently stronger associations with inflammation across relationship domains compared to social support. Whereas the positive associations for friend strain were explained away in the fully adjusted model, those for family strain remained substantial and significant. This suggests the need for further investigations of what role strain from family relations may play in the inflammatory processes. While several studies have identified a significant link between family relationships and individual well-being (Parkerson et al., 1989; Walen and Lachman, 2000), the reason why family strain is particularly influential to inflammatory health remains unclear. Compared to relationships with friends and even spouses, relationships with family members, including parents, children, extended family, are likely to endure across significant periods of the life course and are not based on individual choice in the way that friends and spouses are, which may make family strain particularly detrimental to health. When family relationships are particularly stressful, knowing that one must continue to maintain such relationships through time (rather than terminate a friendship relationship) may increase the strain experienced in such relationships. Future studies should assess whether specific characteristics of family relations, such as the expectations placed upon individuals by family members, sources of strain, or the duration of family relationships, make family relations a particularly powerful predictor of underlying physiological processes.

Surprisingly, spousal strain was not found to have a significant direct relationship with inflammation, although evidence from other studies implicates spousal conflict as a predictor of inflammation, health, and overall well-being (Eaker et al., 2007; Kiecolt-Glaser et al., 2005; Walen and Lachman, 2000). There are several potential reasons for this discrepancy. First, while prior studies have used acute inflammatory response immediately after physiological challenge, such as wound healing, as an indicator of immune function (Kiecolt-Glaser et al., 2005), our assessment focused on multiple physiological indicators of systemic inflammation in the absence of induced physiological stress or infections. This suggests that chronic and acute inflammation may be differentially influenced by social relationships. Furthermore, we used subjective perceptions of relationship quality rather than assessments of recent interactions within the relationship. It is possible that overall perceptions of relational strain, which capture broader longitudinal appraisals of relationship dynamics, measure a concept that is distinct from recollections of specific relationship events. Finally, the significance of spousal relations for inflammatory function might be dependent on the availability and reliance on other relationship sources. It is possible that spousal relations are most influential for those lacking support from other relationship domains. While our study did not find significant correlates of spousal relations net of family and friend relationship quality, future analysis of the importance of family, friend, and spouse relationships relative to one another using different and larger samples will help to test this possibility.

The inclusion of multiple inflammatory markers in the assessment of overall inflammation burden yielded important insights for future research. First, although prior research on social relations, chronic stress, and inflammation have most frequently examined CRP and IL-6 (Yang et al., 2013), our analysis of several additional individual inflammatory markers revealed that social relations had the weakest association with CRP and the strongest linkage to E-selectin. Future studies should benefit from more diverse measures of inflammation by using additional inflammatory indicators that are not as frequently used in biosocial studies, such as E-selectin, fibrinogen, and ICAM. Because our study sample consisted mostly of whites, more studies are needed to inform future research of their salience in the general population. Second, differences in the associations of social relations across markers of inflammation emphasize the need to better elucidate the specific physiological processes tying social relations to physical health outcomes. The inflammatory markers used in

our analyses are responsible for interrelated yet distinct immune functions that may have differential relevance to social factors. It is possible that certain inflammatory processes are more proximally related to physiological stress response (i.e., HPA axis or SNS activation), thus having a more robust response to psychosocial stressors. To the extent that heightened SNS activity could mediate the association between social stressors and inflammation, the analyses adjusting for these markers produced estimates that may be conservative. The removal of these controls did not change the results, however. The exact reasons for differences in the social relationship–biomarker associations remain unclear and call for further investigations.

In sum, our study of social relations and inflammation improved previous research in several ways. First, the assessments of perceived quality of relationships allowed for a deeper insight into the benefits and costs of social engagements that cannot be assessed through mere quantitative relationship measures. Second, our measure of inflammation burden included five indicators of inflammation, some of which were not previously examined. It thus helps to reveal the links between social relations and inflammatory status more comprehensively assessed. Simultaneous inclusion of multiple inflammatory markers also makes biological sense in that it improves the accuracy of overall inflammation levels, given that a single marker does not necessarily indicate immune function per se but could also indicate functioning in other bodily systems. For example, independently from binding leukocytes regulating inflammation, fibrinogen is coagulation factor that can stimulate thrombosis or blood clotting in response to endothelial damage in a wide variety of tissue, stroke or heart attack (Davalos and Akassoglou, 2012). Therefore, a composite measure of multiple markers forming a single underlying factor will be more specific in indicating inflammation status than any one alone (Yang et al., 2013). Finally, given the paucity of empirical evidence of chronic stress and its biophysiological consequences in population based studies, it is an important contribution for this study to document how persistent relationship quality across a ten year span was prospectively associated with outcomes of a major indicator of immune function in a national longitudinal sample of adults in the U.S.

Our study has several limitations that should be addressed in future research. First, while we observed a clear link between perceptions of relationship quality and subsequent inflammation burden, the interrelation between social, psychological, and physiological factors is difficult to disentangle, even with a longitudinal study design, because of the limited number of waves for which these variables were available. Second, because biological markers were only observed at one time point, we could not assess the simultaneous or lagged change of social relations and physiological state across time. We are also limited in the ability to observe the extent to which these biomarkers are good indicators of long-term inflammatory status. Although markers such as CRP and fibrinogen indicate systemic and chronic inflammation in theory, other markers included here were seldom studied in previous empirical research. Future availability of longitudinal data incorporating repeated measures of both social and biological measures will allow for more thorough assessments of the nature of specific biomarkers as well as biosocial linkages.

While our use of longitudinal data improves upon cross-sectional designs by specifying the temporal ordering of measurements, we acknowledge the possibility that the link between social relations and inflammation is confounded by additional factors. One confounder of particular concern is inflammation related illness and conditions at baseline, since prior status may influence how an individual perceives and relies on social relationships, while also having an influence on inflammation status at the follow-up. The adjustment for medication use decreased the degree of potential confounding due to some major conditions, but there may be other relevant indicators of health and functioning to control for that were not assessed in the present analysis. Furthermore, we limited our sample to married individuals to include measures of spouse support in our analysis. This decreased the sample size and hence statistical power for regression model estimates. The smaller sample sizes within marital status group also made it difficult to reliably estimate whether social support and strain have the same the physiological effects for unmarried individuals.

It is also possible that the effect of relationship quality on inflammation burden varies by individual attributes and statuses. Research has suggested that females are more likely to utilize and benefit from social support than males (Kendler et al., 2005; Taylor, 2000) and that the physiological effects of social relationships may differ by sex (Yang et al., 2013). Research has also supported the notion that the function of social relationships differs across the life course, as the amount of social support given and received by individuals has been found to have different effects on well-being by age (Keyes, 2002). To address these potential moderating effects, we conducted additional analyses on sex- and age-stratified subsamples and tested for interaction effects of social relationship variables with sex and age, respectively. We found no significant differences in the link between social relationships and inflammation by sex or age group (data not shown). Further analysis also found no moderating effect of the frequency of contact with friends and family, suggesting that the perceived quality of relationships may be a more substantial predictor of inflammatory processes than the frequency of social interaction. Whether the associations between social support or strain and inflammation may vary by other social environmental factors such as socioeconomic status is a question for additional investigations. In addition, because of a lack of racial diversity due to sample design, our findings mainly relate to whites and need to be corroborated in future studies of other race/ethnicity groups.

Based on our findings, future studies assessing the physiological effects of social relationship should consider qualitative aspects of these relationships. Furthermore, the social relation and inflammation link appears to differ by the function of the relationship, emphasizing the importance of conceptualizing social support and social strain as fundamentally distinct predictors of inflammation burden. Social relations also have differential associations with inflammation depending on whether family, friends, or marital partners are the source of support or strain. Finally, this study illuminates the importance of assessing the physiological correlates of social relations using a longitudinal design, thus capturing the cumulative effect of long-term relationship quality. Future investigations using longitudinal measures of both social and biological processes will help to elucidate the complex pathways linking social relationships and underlying physiological contributors to health and illness.

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## Appendix 1. Content and coding of variables in social support and strain

| Scale | Questionnaire items |
|---|---|
| Family/friend support | 1. How much do {members of your family/your friends} really care about you?<br>2. How much do they understand the way you feel about things?<br>3. How much can you rely on them if you have a serious problem?<br>4. How much can you open up to them if you need to talk about your worries? |
| Family/friend strain | 1. How often do {members of your family/your friends} make too many demands on you?<br>2. How often do they criticize you?<br>3. How often do they let you down when you are counting on them?<br>4. How often do they get on your nerves? |
| Spouse support | 1. How much does your spouse or partner really care about you?<br>2. How much does he or she understand the way you feel about things?<br>3. How much does he or she appreciate you?<br>4. How much do you rely on him or her for help if you have a serious problem?<br>5. How much can you open up to him or her if you need to talk about your worries?<br>6. How much can you relax and be yourself around him or her? |
| Spouse strain | 1. How often does your spouse or partner make too many demands on you?<br>2. How often does he or she argue with you?<br>3. How often does he or she make you feel tense?<br>4. How often does he or she criticize you?<br>5. How often does he or she let you down when you are counting on him or her?<br>6. How often does he or she get on your nerves? |

Coding for each item: 1 = a lot; 2 = some; 3 = a little; 4 = not at all.
Coding for each scale: Mean of all items across waves 1 and 2. Recoded so higher scores reflect higher support or strain.

## Appendix 2. Prospective associations of social support with inflammation ($N = 647$)

| | Family support | | Friend support | | Spouse support | | Total support | |
|---|---|---|---|---|---|---|---|---|
| | Coef. (SE) | BIC | Coef. (SE) | BIC | Coef. (SE) | BIC | Coef. (SE) | BIC |
| C-reactive protein (log) | | | | | | | | |
| Age & sex adjusted | 0.03 | 1930.22 | −0.04 | 1930.05 | −0.17* | 1927.03 | −0.10 | 1929.27 |
| | (0.08) | | (0.08) | | (0.09) | | (0.10) | |
| Fully adjusted[a] | 0.12 | 1807.54 | 0.08 | 1808.71 | −0.02 | 1810.09 | 0.08 | 1809.22 |
| | (0.08) | | (0.06) | | (0.08) | | (0.09) | |
| Fibrinogen | | | | | | | | |
| Age & sex adjusted | −3.87 | 7497.60 | −6.67 | 7496.54 | −7.12 | 7496.89 | −11.05 | 7496.35 |
| | (6.91) | | (5.24) | | (6.63) | | (7.32) | |
| Fully adjusted[a] | 1.42 | 7521.13 | −0.88 | 7521.16 | −0.66 | 7521.18 | −1.83 | 7521.19 |
| | (7.06) | | (5.23) | | (6.34) | | (7.35) | |
| IL-6 (log) | | | | | | | | |
| Age & sex adjusted | −0.06 | 1396.03 | −0.07 | 1395.44 | −0.12* | 1393.53 | −0.12* | 1394.01 |
| | (0.06) | | (0.05) | | (0.06) | | (0.07) | |
| Fully adjusted[a] | 0.00 | 1367.14 | 0.00 | 1367.15 | −0.03 | 1366.87 | 0.00 | 1367.15 |
| | (0.06) | | (0.05) | | (0.06) | | (0.07) | |
| E-selectin (log) | | | | | | | | |
| Age & sex adjusted | −0.01 | 1045.22 | 0.01 | 1045.18 | −0.05 | 1044.10 | −0.02 | 1045.20 |
| | (0.04) | | (0.03) | | (0.05) | | (0.06) | |
| Fully adjusted[a] | 0.01 | 1080.32 | 0.05 | 1078.56 | −0.01 | 1080.33 | 0.03 | 1080.00 |
| | (0.04) | | (0.03) | | (0.05) | | (0.05) | |
| ICAM-1 | | | | | | | | |
| Age & sex adjusted | −11.39 | 7758.28 | −17.99** | 7753.49 | −16.20** | 7756.71 | −19.33** | 7753.04 |
| | (8.89) | | (7.47) | | (8.02) | | (8.73) | |
| Fully adjusted[a] | −7.39 | 7787.69 | −12.68* | 7784.98 | −10.38 | 7787.01 | −10.20 | 7785.06 |
| | (8.84) | | (7.38) | | (8.07) | | (8.64) | |

***$p < 0.01$, **$p < 0.05$, *$p < 0.1$; two-tailed test.
[a] Controls for age, sex, SNS activity (creatinine-adjusted epinephrine and norepinephrine levels), household income, education, BMI, current smoking status, and medications.

## Appendix 3. Prospective associations of social strain with inflammation ($N = 647$)

| | Family strain | | Friend strain | | Spouse strain | | Total strain | |
|---|---|---|---|---|---|---|---|---|
| | Coef. (SE) | BIC | Coef. (SE) | BIC | Coef. (SE) | BIC | Coef. (SE) | BIC |
| C-reactive protein (log) | | | | | | | | |
| Age & sex adjusted | 0.06 | 1929.90 | 0.07 | 1929.87 | 0.08 | 1929.19 | 0.12 | 1929.20 |
| | (0.09) | | (0.10) | | (0.08) | | (0.11) | |
| Fully adjusted[a] | −0.09 | 1808.82 | 0.00 | 1810.14 | 0.01 | 1810.13 | −0.05 | 1809.93 |
| | (0.08) | | (0.09) | | (0.07) | | (0.10) | |
| Fibrinogen | | | | | | | | |
| Age & sex adjusted | 9.94 | 7495.67 | 2.17 | 7497.89 | 4.56 | 7497.34 | 10.06 | 7496.62 |
| | (6.46) | | (7.81) | | (6.63) | | (9.19) | |
| Fully adjusted[a] | 3.49 | 7520.89 | −1.32 | 7521.16 | 3.19 | 7520.86 | 3.88 | 7520.97 |
| | (6.32) | | (7.32) | | (6.46) | | (8.90) | |
| IL-6 (log) | | | | | | | | |
| Age & sex adjusted | 0.09 | 1395.11 | −0.02 | 1397.20 | 0.07 | 1395.48 | 0.09 | 1395.83 |
| | (0.06) | | (0.07) | | (0.06) | | (0.08) | |
| Fully adjusted[a] | 0.00 | 1367.15 | −0.06 | 1366.24 | 0.03 | 1366.88 | 0.00 | 1367.15 |
| | (0.05) | | (0.07) | | (0.05) | | (0.08) | |
| E-selectin (log) | | | | | | | | |
| Age & sex adjusted | 0.11** | 1039.13 | 0.16*** | 1036.33 | 0.04 | 1044.44 | 0.16** | 1038.21 |
| | (0.04) | | (0.06) | | (0.04) | | (0.06) | |
| Fully adjusted[a] | 0.08* | 1077.03 | 0.14** | 1072.84 | 0.03 | 1079.67 | 0.13** | 1075.35 |
| | (0.04) | | (0.06) | | (0.04) | | (0.06) | |
| ICAM-1 | | | | | | | | |
| Age & sex adjusted | 9.08 | 7759.13 | 9.18 | 7759.50 | 5.65 | 7759.77 | 13.21 | 7758.86 |
| | (8.51) | | (9.96) | | (7.04) | | (10.44) | |
| Fully adjusted[a] | 3.73 | 7788.39 | 4.22 | 7788.41 | 4.75 | 7788.14 | 7.47 | 7788.10 |
| | (8.52) | | (9.72) | | (6.86) | | (10.27) | |

***$p < 0.01$, **$p < 0.05$, *$p < 0.1$; two-tailed test.
[a] Controls for age, sex, SNS activity (creatinine-adjusted epinephrine and norepinephrine levels), household income, education, BMI, current smoking status, and medications.

## Appendix 4.1. Prospective associations of three domains of social support and elevated inflammation ($N = 647$)

| | C-reactive protein | Fibrinogen | IL-6 | E-selectin | ICAM-1 | Inflammation index |
|---|---|---|---|---|---|---|
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Age- and sex-adjusted | | | | | | |
| Family support | 0.94 | 1.04 | 0.72 | 1.28 | 1.17 | 1.11 |
| | (0.61–1.44) | (0.68–1.59) | (0.47–1.10) | (0.80–2.06) | (0.72–1.90) | (0.77–1.60) |
| Friend support | 0.97 | 0.97 | 0.99 | 1.12 | 0.62** | 0.86 |
| | (0.68–1.39) | (0.66–1.42) | (0.67–1.46) | (0.78–1.60) | (0.42–0.91) | (0.64–1.15) |
| Spouse support | 0.76 | 0.74 | 0.84 | 0.59*** | 1.03 | 0.72** |
| | (0.50–1.14) | (0.49–1.11) | (0.55–1.30) | (0.40–0.88) | (0.65–1.63) | (0.52–0.99) |
| BIC | 745.12 | 741.36 | 742.54 | 748.17 | 742.85 | 1955.81 |
| Fully-adjusted[a] | | | | | | |
| Family support | 0.97 | 1.10 | 0.71 | 1.25 | 1.21 | 1.23 |
| | (0.59–1.60) | (0.69–1.77) | (0.44–1.13) | (0.75–2.09) | (0.71–2.08) | (0.83–1.81) |
| Friend support | 1.16 | 1.06 | 1.16 | 1.28 | 0.70* | 1.05 |
| | (0.78–1.73) | (0.72–1.57) | (0.78–1.74) | (0.88–1.86) | (0.47–1.03) | (0.78–1.43) |
| Spouse support | 0.92 | 0.78 | 0.97 | 0.66** | 1.18 | 0.80 |
| | (0.57–1.47) | (0.51–1.20) | (0.61–1.54) | (0.44–1.00) | (0.73–1.88) | (0.57–1.14) |
| BIC | 730.86 | 790.53 | 774.44 | 795.13 | 776.17 | 1893.63 |

***$p < 0.01$, **$p < 0.05$, *$p < 0.1$; two-tailed test.
[a] Controls for age, sex, SNS activity (creatinine-adjusted epinephrine and norepinephrine levels), household income, education, BMI, current smoking status, and medications.

## Appendix 4.2. Prospective associations of three domains of social strain and elevated inflammation ($N = 647$)

| | C-reactive protein | Fibrinogen | IL-6 | E-selectin | ICAM-1 | Inflammation index |
|---|---|---|---|---|---|---|
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Age- and sex-adjusted | | | | | | |
| Family strain | 1.34 | 1.49* | 2.12*** | 1.31 | 1.27 | 1.65** |
| | (0.85–2.12) | (0.94–2.35) | (1.34–3.36) | (0.79–2.16) | (0.76–2.12) | (1.09–2.49) |
| Friend strain | 1.02 | 1.06 | 0.59* | 1.57 | 1.13 | 1.14 |

(continued on next page)

(*continued*)

| | C-reactive protein | Fibrinogen | IL-6 | E-selectin | ICAM-1 | Inflammation index |
|---|---|---|---|---|---|---|
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| | (0.59–1.76) | (0.61–1.85) | (0.34–1.03) | (0.89–2.78) | (0.63–2.02) | (0.70–1.86) |
| Spouse strain | 1.08 | 1.19 | 0.89 | 1.18 | 0.81 | 1.03 |
| | (0.74–1.57) | (0.83–1.73) | (0.61–1.31) | (0.81–1.70) | (0.54–1.23) | (0.78–1.36) |
| BIC | 744.78 | 736.53 | 737.27 | 744.12 | 747.20 | 1947.03 |
| Fully-adjusted[a] | | | | | | |
| Family strain | 1.05 | 1.34 | 1.80** | 1.24 | 1.09 | 1.35 |
| | (0.65–1.71) | (0.84–2.14) | (1.12–2.90) | (0.72–2.11) | (0.64–1.86) | (0.90–2.03) |
| Friend strain | 1.03 | 1.04 | 0.60* | 1.55 | 1.15 | 1.18 |
| | (0.56–1.88) | (0.59–1.82) | (0.33–1.09) | (0.86–2.82) | (0.63–2.09) | (0.72–1.91) |
| Spouse strain | 1.02 | 1.25 | 0.90 | 1.19 | 0.82 | 1.04 |
| | (0.67–1.54) | (0.86–1.81) | (0.61–1.33) | (0.82–1.73) | (0.53–1.25) | (0.77–1.41) |
| BIC | 731.35 | 787.02 | 771.12 | 792.45 | 778.57 | 1891.04 |

***$p < 0.01$, **$p < 0.05$, *$p < 0.1$; two-tailed test.

[a] Controls for age, sex, SNS activity (creatinine-adjusted epinephrine and norepinephrine levels), household income, education, BMI, current smoking status, and medications.

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