

# Romantic relationship distress, gender, socioeconomic status, and inflammation: A preregistered report

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## Abstract

Poor quality romantic relationships increase risk for health problems; elevated systemic inflammation is one promising underlying mechanism. This registered report utilized data from three publicly available data sets with large sample sizes (Add Health, MIDUS, NSHAP) to test this possibility. An internal meta-analysis across all three studies determined that romantic relationship distress was unrelated to inflammation (assessed via C-reactive protein levels). In addition, this link was not moderated by gender, socioeconomic status (SES), or the combination of gender and SES.

## KEYWORDS

gender, health, inflammation, romantic relationship quality, socioeconomic status

## 1 | INTRODUCTION

One of the most robust findings in health psychology is that people in distressed romantic relationships are at higher risk for health problems (Kiecolt-Glaser & Newton, 2001; Robles,

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Slatcher, Trombello, & McGinn, 2014). For example, a meta-analysis concluded that people in lower quality marriages had worse self-rated health than those in higher quality marriages (Robles et al., 2014). Among women with coronary heart disease, those with more marital stress had a worse prognosis relative to those with less marital stress (Orth-Gomér et al., 2000). In addition, people in lower quality romantic relationships were more likely to experience depression than their counterparts in higher quality romantic relationships (Kurdek, 1998). Importantly, the size of the meta-analytic link between relationship quality and health is similar to the effects of negative health behaviors like a poor diet, and the relationship persists after controlling for health-relevant risk factors (e.g., age; Robles et al., 2014). Because the link between romantic relationship quality and health is so robust, researchers are keenly interested in understanding the underlying physiological mechanisms. Growing evidence suggests that inflammation is a potential mechanism explaining how distressed relationships increase risk for health problems (see Jaremka, Derry, & Kiecolt-Glaser, 2014 for a review). In order to understand this potential mechanism, we begin by describing inflammation and its health relevance.

## 2 | INFLAMMATION

Inflammation is a critical response to injury or pathogen exposure (e.g., bacterial or viral infection; see Sompayrac, 2015 for an in-depth discussion). When a person is injured or exposed to a pathogen, the innate immune system provides the first line of defense, helping to repair damaged tissue or fight the pathogen. As part of this response, macrophages and other resident immune cells produce inflammatory cytokines, like tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-6 (IL-6), which then elevate other downstream inflammatory markers (e.g., C-reactive protein [CRP]). Inflammatory cytokines largely act as immune messengers, signaling to other immune cells and helping to coordinate an organized immune response. If the innate immune response is unable to effectively resolve the issue, the adaptive immune system provides a second line of defense. As part of the adaptive immune response, helper T-cells and other immune cells also produce inflammatory cytokines, which help further coordinate the immune response. For example, interleukin-4 (IL-4) is produced by helper T-cells, which then stimulates the proliferation of B-cells, among other functions. Accordingly, throughout the innate and adaptive immune response, inflammatory cytokines are produced (leading to elevated inflammation), and they are a necessary component of this response. Once an injury has healed or an infection has resolved, immune cells reduce or stop their production of inflammatory cytokines, and thus inflammation levels throughout the body subside under normative conditions.

Inflammation can also become systemically elevated, even when people are not injured or exposed to a pathogen. For example, psychological stress activates the sympathetic nervous system (SNS), which causes the release of norepinephrine. In turn, norepinephrine binds to adrenergic receptors (ARs) on immune cells (see Sanders, Kasprovicz, Kohm, & Swanson, 2001 for an empirical review), and AR activation leads to increased inflammation (Grisanti et al., 2010; Tan et al., 2007). Stress also activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in the release of the hormone cortisol (see Dickerson & Kemeny, 2004 for a meta-analysis). Under normal conditions, cortisol has strong anti-inflammatory effects. However, chronic stress can lead to glucocorticoid resistance, whereby immune cells become insensitive to cortisol's anti-inflammatory effects (Miller, Cohen, & Ritchey, 2002). People experiencing chronic stress

also have an upregulation of proinflammatory genes and a downregulation of anti-inflammatory genes (Cole et al., 2007). Thus, people experiencing psychological stress may have elevated inflammation even in the absence of injury or pathogen exposure.

Higher systemic inflammation in the absence of injury or pathogen exposure increases risk for a variety of health problems. For example, systemic inflammation increases risk for premature all-cause mortality, Type II diabetes, metabolic syndrome, and neurodegenerative disorders (see Ershler & Keller, 2000; Hansson, 2005; Hotamisligil, 2006 for reviews of the empirical evidence). Elevated inflammation is also critical in the development of atherosclerosis (see Libby, 2012 for a mechanistic explanation), and inflammatory markers can be used to evaluate the risk of heart attack or stroke (Ridker, 2003). Furthermore, systemic inflammation is implicated in the development of depression. Specifically, inflammation induces “sickness behaviors,” such as anhedonia and social withdrawal, which theoretically contribute to the development of depression (Dantzer, O’Connor, Freund, Johnson, & Kelley, 2008; also see Slavich & Irwin, 2014 for a theoretical model linking inflammation and depression). Accordingly, if poor quality relationships increase systemic inflammation, we can infer that inflammation is a mechanism explaining how poor quality relationships affect long-term health.

### 3 | ROMANTIC RELATIONSHIP DISTRESS AND INFLAMMATION

Theoretically, people in distressed romantic relationships—people with global negative thoughts and feelings about their relationship, low satisfaction, and/or high levels of hostility and other negative behaviors—may have elevated inflammation for a few reasons. First, stress activates the SNS and HPA-axis, and up-regulates proinflammatory genes, as described above.

Second, people who are in distressed relationships are more likely to engage in poor health behaviors that elevate inflammation. For example, the smoking habits of those with less responsive spouses remained the same over time, whereas smokers with highly responsive spouses smoked less over time (Derrick, Leonard, & Homish, 2013). In addition, women with more negative interactions with their romantic partner experienced worse sleep quality than those with less negative interactions (Hasler & Troxel, 2010). Both smoking and poor quality sleep cause elevated inflammation (see Arnson, Shoenfeld, & Amital, 2010 and Irwin, Olmstead, & Carroll, 2016 for reviews). Thus, distressed romantic relationships may also lead to elevated inflammation via poor health behaviors.

Finally, people in distressed romantic relationships may have elevated inflammation because distressed relationships dysregulate immune function more broadly, with effects that are not specific to inflammation. Indeed, there is a long history of psychoneuroimmunology work focused on romantic relationships. Using a wide variety of immune measures (e.g., antibody titers to latent herpesviruses), this research consistently demonstrated that people in distressed romantic relationships are more likely to experience immune dysregulation than their counterparts in higher quality relationships (see Jaremka et al., 2014 for a review).

Relatively recently within psychoneuroimmunology, inflammation gained popularity as a marker of health risk, and thus only a small body of research has directly tested whether romantic relationship distress is linked to elevated inflammation (e.g., Shen, Farrell, Penedo, Schneiderman, & Orth-Gomer, 2010). One of the first studies in this area had couples complete conflict and support discussions and coded their behavior during both interactions as an observable index of relationship distress (Kiecolt-Glaser et al., 2005). Couples who displayed more

hostile behavior had higher systemic inflammation following the conflict than the support discussion. On the other hand, those who displayed less hostile behavior had similar levels of inflammation across both discussions. Thus, being in a hostile relationship was linked to elevated inflammation in contexts that primed relationship distress (a conflict discussion). In a separate study, people who reported having a less supportive spouse had more inflammation than their more supported counterparts, although the effects were inconsistent across the inflammatory markers (Yang, Schorpp, & Harris, 2014). Similarly, people with spouses who were less supportive or more negative towards them had higher scores on an allostatic load composite that included inflammation relative to those with more supportive or less negative spouses, respectively (Brooks et al., 2014).

These initial findings support the argument that romantic relationship distress is linked to inflammation. However, there are relatively few studies on this topic and the existing work is methodologically limited. For example, some studies had small sample sizes (e.g., 42 couples), others had inconsistent findings, and none of the analytic plans were preregistered. Accordingly, one goal of this paper was to replicate the link between romantic relationship distress and inflammation using a preregistered analytic plan with multiple large samples.

#### **4 | GENDER, ROMANTIC RELATIONSHIP DISTRESS, AND INFLAMMATION**

Researchers investigating the link between relationship distress and inflammation have examined gender as a theoretically plausible moderator. Identifying who is most vulnerable to the negative inflammatory consequences of romantic relationship distress will allow researchers and allied health professionals to target intervention resources to those who need them the most.

The link between romantic relationship distress and inflammation may be stronger among women than men. Women have higher levels of inflammation than men (Khera et al., 2005). In addition, women's identities are more strongly linked to their close relationships, and thus women may be more strongly affected by the quality of those relationships (Gabriel & Gardner, 1999). Empirical work testing this possibility is mixed. For example, systemic inflammation was higher among women (but not men) with less supportive marriages relative to those in more supportive marriages (Donoho, Crimmins, & Seeman, 2013). Similarly, younger women (but not men) with low marital adjustment scores had higher inflammation than those with better marital adjustment scores (Whisman & Sbarra, 2012). On the other hand, inflammation was higher among men (but not women) with more marital strain relative to those with less marital strain in another study (Liu & Waite, 2014). Importantly, a recent meta-analysis demonstrated that gender did not moderate the link between marital distress and health (which included but was not limited to inflammation), suggesting that gender differences may not exist at all (Robles et al., 2014). Because the gender effects are inconsistent across studies, a second goal of this paper was to systematically test moderation by gender across multiple large samples.

#### **5 | SOCIOECONOMIC STATUS, ROMANTIC RELATIONSHIP DISTRESS, AND INFLAMMATION**

The existing literature is heavily focused on gender as a potential moderator of the link between romantic relationship distress and inflammation, as reviewed above. Identifying alternative

moderators will help further identify who is most in need of intervention resources. Accordingly, a third goal of this paper was to examine socioeconomic status (SES) as a theoretically driven moderator of the link between romantic relationship distress and inflammation.

A wealth of research has demonstrated that people with a lower SES have worse health outcomes than their higher SES counterparts, including elevated inflammation (Jousilahti, Salomaa, Rasi, Vahtera, & Palosuo, 2003; Singh-Manoux, Marmot, & Adler, 2005). The reserve capacity model offers a theoretical framework for understanding these SES disparities (Gallo & Matthews, 2003). According to the model, people with a lower SES are disproportionately exposed to stressful or dangerous environments, such as low-paying jobs and violent neighborhoods. Being in these situations causes people with a lower SES to have a reduced “reserve capacity” (i.e., reduced interpersonal or intrapersonal resources) to cope with stress (Gallo & Matthews, 2003). Consistent with this argument, people with a lower SES have smaller social networks (an interpersonal resource) than their higher SES counterparts (Ajrouch, Blandon, & Antonucci, 2005). Similarly, a meta-analysis demonstrated that people with a lower SES have lower self-esteem (an intrapersonal resource) than those with a higher SES (Twenge & Campbell, 2002). Being a person with low SES and a reduced reserve capacity then leads to increased negative emotions and cognitions, including depression, hopelessness, anxiety, and hostility (Gallo & Matthews, 2003).

Based on the reserve capacity model, people with a lower SES are more reactive to stress because they have a reduced reserve capacity (Gallo & Matthews, 2003). For instance, women in lower status jobs had stronger blood pressure reactivity to high job demands relative to those in higher status jobs (Gallo, Bogart, Vranceanu, & Walt, 2004). This reactivity may be driven by a lack of reserve capacity all together (e.g., they grew up in an environment where their psychosocial resources were not fully developed) or by a depletion of an existing reserve capacity (e.g., living in an environment where they continually have to expend psychosocial resources; Gallo & Matthews, 2003). Either way, a reduced reserve capacity offers one theoretical explanation as to why people with a lower SES are highly reactive to stress. Based on the reserve capacity model, people with a lower SES should be particularly reactive to the stress of a poor quality relationship. The link between relationship distress and elevated inflammation should therefore be stronger among those with a lower relative to a higher SES, an unexplored possibility.

## 6 | STUDY OVERVIEWS AND HYPOTHESES

The current manuscript had three goals, plus a fourth exploratory goal, building upon existing work.

Goal 1: Attempt to replicate existing work linking distressed romantic relationships with inflammation using multiple studies with large sample sizes. We hypothesized that people in more distressed romantic relationships would have higher inflammation than those in less distressed relationships.

Goal 2: Test gender as a potential moderator of the link between relationship distress and inflammation. There are multiple competing hypotheses related to this goal, supported by the literature reviewed above. On one hand, the link between distressed relationships and inflammation maybe stronger among women than men (or among men than women). On the other hand, the link between relationship distress and inflammation may be similar for women and men.

Goal 3: Investigate SES as a second theoretically plausible moderator of the link between distressed relationships and inflammation. We hypothesized that the link between distressed relationships and inflammation would be stronger among those with a lower SES relative to those with a higher SES.

Exploratory Goal 4: Test the combination of SES and gender as moderators in exploratory analyses. We did not have an *a priori* hypothesis about the three-way interaction between relationship distress, gender, and SES because there is no clear indication in the literature about whether the combination of SES and gender would be greater than each effect on their own. However, given the large sample sizes available across our three studies, we explored the three-way interaction as a possibility.

To accomplish our goals, we used existing data from the Add Health (National Longitudinal Study of Adolescent to Adult Health), MIDUS (Mid-Life in the United States), and NSHAP (National Social Life Health and Aging Project) studies. The first two studies provided cross-sectional data, whereas the third provided both cross-sectional and longitudinal data. We also conducted an internal meta-analysis of the cross-sectional effects. These data sets were chosen because they were publicly available, had data on all of the variables of interest, and had large enough sample sizes to adequately test our proposed hypotheses. The data sets were also selected because the samples covered a wide range of ages, SESs, races, and other demographic characteristics, thus improving the generalizability of the results.

We used an inclusive approach when selecting relationship distress items, creating an omnibus relationship distress composite. In doing so, we used any item tapping into our broad definition of relationship distress, preventing us from having to cherry-pick among inter-related items.

Educational attainment was used as the SES index because stay-at-home parents in these samples did not work outside of the home, and education is less vulnerable to current economic conditions than other measures of SES.<sup>1</sup> We used five levels of educational attainment (no degree, high school or equivalent, associates or vocational training, bachelors, masters, and terminal degree) for two primary reasons. First, these levels reflect actual degrees earned (rather than partial completion of a degree), and earning a degree is strongly predictive of income (<https://www.bls.gov/careeroutlook/2016/data-on-display/education-matters.htm>), another measure of SES. Second, these levels were available across all three data sets, allowing us to use a consistent coding strategy across studies.

We used CRP, a downstream marker of inflammation, as the inflammation measure because it is a commonly used index, the assay for CRP is highly standardized, and all three studies provided CRP data. Importantly, our conceptual argument (as discussed in the introduction) is about inflammation rather than any one specific inflammatory measure. Thus, we are arguing that inflammation is a mechanism linking relationship distress to health, and not CRP per se. This approach is consistent with other discussions in psychoneuroimmunology about inflammation as a mechanism underlying long-term health problems, with inflammation being assessed by a variety of different inflammatory markers (Robles et al., 2014).

A primary analytic goal was to use a consistent analytic strategy across studies. Accordingly, we structured our models identically across studies as much as possible. In all three studies, the primary analyses tested an unadjusted model. We also conducted two sets of sensitivity analyses. Sensitivity analysis #1 added covariates to each model, to determine whether the links were robust to potential confounds. We selected the covariates *a priori* based on their theoretical and empirical links to relationship distress and/or inflammation. We only selected covariates that were available in all three studies, and when multiple possible measures of the same covariate were available in a single study, we selected the one that was most similar to the

other studies. Each adjusted model included age, body mass index (BMI; kg/m<sup>2</sup>), number of comorbid medical conditions, anti-inflammatory medication use, depressive symptoms, current smoking status (yes vs. no), exercise, and sleep duration. A detailed description of how the covariates were selected, along with a justification for each covariate, is in the supplemental material. The goal of sensitivity analysis #2 was to parse out the predictor into separate positive relationship quality versus negative relationship distress subcomponents of the omnibus relationship distress composite.

The data analytic plan and syntax for all three studies and the internal meta-analysis was preregistered on the Open Science Framework (OSF) after this manuscript received an “in principle acceptance” by the action editor and prior to data analysis (<https://osf.io/eh57w/>). We do not interpret marginally significant results ( $p > .05$  and  $< .10$ ) for any of the primary analyses, since the results are from large sample studies, and the conclusions are heavily based on the internal meta-analysis. The results from the primary and sensitivity analyses are described below. Full supporting statistics are in Supplemental eTables 4–15.

## 7 | STUDY 1: ADD HEALTH

### 7.1 | Overview

The National Longitudinal Study of Adolescent to Adult Health (Add Health) is a longitudinal study of adolescents and adults from the United States. We used Wave IV of Add Health (at which time the participants were adults) since inflammation data were only available in this wave.

### 7.2 | Participants

A detailed description of the recruitment and sampling techniques used for the Add Health study is available in existing study documentation ([https://www.cpc.unc.edu/projects/addhealth/documentation/guides/DesignPaperWave\\_IIV.pdf](https://www.cpc.unc.edu/projects/addhealth/documentation/guides/DesignPaperWave_IIV.pdf)). A total of 15,701 people participated in Wave IV. The final analytic sample included people who were in a romantic relationship during Wave IV and who had CRP data ( $n = 11,130$ ). Participants' average age was 28.5 years ( $SD = 1.77$ ). Around half of participants were White (57.5%), female (55.5%), or had a high school degree or less (55.6%). Additional sample characteristics are listed in eTable 1.

### 7.3 | Procedure

Participants filled out questionnaires assessing romantic relationship distress, SES, and various other constructs at home during an in-home interview with a study experimenter. Participants also provided a dried blood spot via finger prick to assess CRP.

### 7.4 | Measures

Participants answered questions about their gender and highest degree earned (no degree, high school or equivalent, associates or vocational training, bachelors, masters, terminal degree).

Participants also completed a 12-item measure of romantic relationship distress ( $\alpha = .93$ ). Example items include “We enjoy doing even ordinary, day-to-day things together,” “I am satisfied with the way we handle our problems and disagreements,” and “My partner listens to me when I need someone to talk to.” Items were recoded so that higher numbers reflected more relationship distress. Because some items had different scales than others, we z-scored each item and then created the relationship distress composite by averaging those z-scores. See the supplemental material for the wording of all 12 questions.

The dried blood spots for assessing CRP were mailed to the University of Washington Medical Center Immunology Lab, in Seattle WA for processing. The intra-assay coefficient of variation (CV) was 8.1 and the interassay CV was 11.0. A detailed description of the assay process is available in existing study documentation: [https://www.cpc.unc.edu/projects/addhealth/documentation/guides/Wave\\_IV\\_hsCRP\\_EBV\\_Documentation.pdf](https://www.cpc.unc.edu/projects/addhealth/documentation/guides/Wave_IV_hsCRP_EBV_Documentation.pdf). See the supplemental material for a description of how each covariate (age, BMI, number of comorbid medical conditions, anti-inflammatory medication use, depressive symptoms, current smoking status, exercise, and sleep duration) was measured for the adjusted analyses.

## 7.5 | Data analytic strategy

CRP outliers  $>4$  *SD* above the sample mean were excluded from analyses (1.2% of all samples), following prior research from the first author's lab (Jaremka et al., 2013). The distributions of the remaining samples were highly skewed and were thus  $\log_{10}$  transformed in preparation for analysis.

The Add Health data was collected using a complex sampling design with clustered samples that had unequal selection probability. In addition, certain demographic characteristics were purposefully oversampled to obtain adequate representation of the population. Based on recommendations by the Add Health research team (<https://www.cpc.unc.edu/projects/addhealth/documentation/guides>), we used a design-based analysis that accounted for these design parameters. Specifically, we used the general linear model (GLM) option within the Complex Samples (CS) command in SPSS 25.0 (IBM). We used the Wave IV grand sampling weights, along with the cluster and strata variables, as recommended. Accounting for the complex sampling design, the degrees of freedom are no longer based on the total number of participants, since the sampling design has both clusters and strata. The CSGLM command in SPSS handles missing data by dropping any case involved in the analysis with missing data.

The primary analyses were completely unadjusted. Across studies, we also conducted two sets of sensitivity analyses, as described in the study overview. However, the Add Health data only had information about positive relationship quality components, and thus sensitivity analysis #2 separating positive and negative components was not possible. We analyzed four models for both the primary and sensitivity analyses, corresponding to the four goals of this paper.

Goal 1: We constructed a GLM with romantic relationship distress as the predictor and CRP as the outcome.

Goal 2: We constructed a GLM that included the main effect of romantic relationship distress (centered), the main effect of gender (effects coded), and an interaction between relationship distress and gender predicting CRP. Significant relationship distress by gender interactions were decomposed in two ways, consistent with recommendations (Aiken & West, 1991). First, we examined the simple slope of relationship distress predicting CRP for women versus men.



Second, we tested the simple contrast of gender predicting CRP at lower ( $-1SD$ ) and higher ( $+1SD$ ) relationship distress.

Goal 3: We constructed a GLM that included the main effect of romantic relationship distress (centered), the main effect of SES (centered at associate's degree), and an interaction between relationship distress and SES predicting CRP. Significant relationship distress by SES interactions were decomposed by examining the simple slope of relationship distress predicting CRP at low (no degree) and high (terminal degree) levels of education. In addition, we tested the simple slope of education predicting CRP at lower ( $-1SD$ ) and higher ( $+1SD$ ) relationship distress.

Exploratory Goal 4: We constructed a GLM with the three-way interaction between relationship distress, gender, and SES, along with all corresponding two-way interactions and main effects.

## 8 | RESULTS

### 8.1 | Goal 1: Main effect of relationship distress

The main effect of relationship distress predicting CRP was nonsignificant in the primary analysis,  $b = -0.001$ ,  $t(128) = -0.16$ ,  $p = .874$ . The main effect remained nonsignificant in sensitivity analysis #1,  $b = -0.01$ ,  $t(128) = -1.41$ ,  $p = .161$ .

### 8.2 | Goal 2: Gender by relationship distress interaction

The interaction between gender and relationship distress predicting CRP was nonsignificant in the primary analysis,  $F(1, 128) = 3.28$ ,  $p = .073$ . This interaction became significant in sensitivity analysis #1,  $F(1, 128) = 4.87$ ,  $p = .029$ . Follow-up tests for the sensitivity analysis showed that women had higher CRP than men, both among those with lower and higher relationship distress,  $b = 0.081$ ,  $t(128) = 13.08$ ,  $p < .001$  and  $b = 0.06$ ,  $t(128) = 7.93$ ,  $p < .001$ . However, the difference between men and women was stronger among those with lower relationship distress. Among men, CRP levels were unrelated to relationship distress,  $b = 0.01$ ,  $t(128) = 0.87$ ,  $p = .388$ . However, among women, higher relationship distress predicted lower CRP levels,  $b = -0.02$ ,  $t(128) = -2.36$ ,  $p = .020$ .

### 8.3 | Goal 3: SES By relationship distress interaction

There was a significant SES by relationship distress interaction predicting CRP for the primary analysis,  $F(1, 128) = 4.08$ ,  $p = .046$ . Follow-up tests revealed that people with less education had higher CRP than people with more education, both among those with lower and higher relationship distress,  $b = -0.02$ ,  $t(128) = -3.31$ ,  $p = .001$  and  $b = -0.04$ ,  $t(128) = -5.75$ ,  $p < .001$ . However, the magnitude of this relationship was stronger among those with higher relationship distress. Among those with less education, the association between relationship distress and CRP was nonsignificant,  $b = 0.01$ ,  $t(128) = 1.09$ ,  $p = .280$ . Among those with more education, people with more relationship distress had lower CRP than people with less relationship distress,  $b = -0.05$ ,  $t(128) = -2.21$ ,  $p = .029$ . The interaction between SES and relationship

distress became nonsignificant in sensitivity analysis #1,  $F(1, 128) = 3.50$ ,  $p = .064$ , although the pattern of results was in the same direction.

## 8.4 | Exploratory goal 4: Gender, SES, and relationship distress interaction

The gender by SES by relationship distress interaction predicting CRP was nonsignificant in the primary analysis,  $F(1, 128) = 3.91$ ,  $p = .050$ . The interaction remained nonsignificant in the sensitivity analysis,  $F(1, 128) = 2.89$ ,  $p = .092$ .

## 9 | STUDY 2: MIDUS

### 9.1 | Overview

The MIDUS study is a longitudinal study of adults. Data for the present analyses are from the second wave (MIDUS II, 2004–2006). Only participants who completed MIDUS II and the MIDUS II Biomarker subproject were included in the present sample; inflammation data were only measured in the Biomarker subproject. Participants completed the Biomarker project 25.32 months ( $SD = 14.22$ ; Range: 0–62) after the MIDUS II study self-administered questionnaire.

### 9.2 | Participants

MIDUS II included 4,963 participants from MIDUS I, plus an additional 592 Black/African American people from Milwaukee who were recruited to increase racial diversity. A subsample of the MIDUS II participants ( $n = 1,255$ ) participated in the Biomarker subproject. A detailed description of the recruitment techniques used for the MIDUS II and Biomarker samples can be found in existing study documentation: <https://www.icpsr.umich.edu/icpsrweb/NACDA/studies/29282/versions/V9>, <https://www.icpsr.umich.edu/icpsrweb/NACDA/studies/22840/versions/V5>, and <https://www.icpsr.umich.edu/icpsrweb/NACDA/studies/29282/versions/V9>.

The final analytic sample included people who were married or living with a romantic partner during both MIDUS II and the Biomarker subproject and who had CRP data ( $n = 781$ ). Participants' average age was 57.70 ( $SD = 11.25$ ) and the majority of participants were White (89.1%). Around half of participants were female (48.7%) and half had a high school degree or less (46.5%). Additional sample characteristics are listed in eTable 2.

### 9.3 | Procedure

The Biomarker subproject consisted of an overnight hospital visit which included detailed physical health examinations, interviews, and a blood draw. The blood sample was used to assess CRP. Participants also answered a variety of questions via phone or computer assessing behavioral, psychological, and social processes. These questionnaires were completed during the Biomarker subproject and the larger MIDUS II study.

## 9.4 | Measures

During a phone interview in MIDUS II, participants reported their highest degree earned (no degree, high school or equivalent, associates or vocational training, bachelors, masters, terminal degree). Using a self-administered questionnaire during MIDUS II, participants also completed a 21-item scale assessing romantic relationship distress ( $\alpha = .94$ ). Example items include “During the past year, how often have you thought your relationship might be in trouble?” “How much does your spouse or partner really care about you?” and “How often does he or she get on your nerves?” Items were recoded so that higher numbers reflected more relationship distress. Because some of the items had different scales, all items were first z-scored and then averaged together to form a relationship distress composite. See the supplemental material for additional information about the 21 questions.

CRP was measured using particle enhanced immunonephelometric assays and immunoelectrochemiluminescence high-sensitivity assays. The intra-assay CV was 2.3–4.4 and the interassay CV was 2.1–5.7. More information regarding the collection of the blood sample and the CRP assays can be found in published documentation (Dienberg-Love, Seeman, Weinstein, & Ryff, 2010). See the supplemental material for a description of how each covariate (age, BMI, number of comorbid medical conditions, anti-inflammatory medication use, depressive symptoms, current smoking status, exercise, and sleep duration) was measured for the adjusted analyses.

## 9.5 | Data analytic strategy

CRP outliers were excluded using the same strategy as Study 1 (1.7% of all samples). The distribution of the remaining samples was highly skewed and was thus  $\log_{10}$  transformed. Unlike Study 1, the MIDUS Biomarker Project does not incorporate sampling weights. Accordingly, we used linear regression analyses in SPSS 25.0 (IBM) for these analyses (which handles missing data by dropping any case with missing data involved in the analysis, by default), rather than the design-based GLM analysis from Study 1.<sup>2</sup> Otherwise, we constructed identical models as described for Study 1 Goals 1–4. We conducted primary analyses and two sets of sensitivity analyses, identical to Study 1.

# 10 | RESULTS

## 10.1 | Goal 1: Main effect of relationship distress

The main effect of relationship distress predicting CRP was nonsignificant in the primary analysis,  $b = 0.001$ ,  $t(763) = 0.09$ ,  $p = .930$ . The main effect remained nonsignificant in both sensitivity analyses ( $ps > .05$ ).

## 10.2 | Goal 2: Gender by relationship distress interaction

There was a significant gender by relationship distress interaction predicting CRP for the primary analyses,  $F(1, 761) = 3.90$ ,  $p = .049$ . Follow-up tests revealed no gender differences in

CRP among those with lower relationship distress,  $b = 0.02$ ,  $t(761) = 1.10$ ,  $p = .271$ . However, women had higher CRP levels than men among those with higher relationship distress,  $b = 0.05$ ,  $t(761) = 3.89$ ,  $p < .001$ . Furthermore, CRP was not related to relationship distress among men,  $b = -0.04$ ,  $t(761) = -1.60$ ,  $p = .111$ , or among women,  $b = 0.02$ ,  $t(761) = 1.18$ ,  $p = .240$ .

The gender by relationship distress interaction predicting CRP became nonsignificant in sensitivity analysis #1,  $b = 0.02$ ,  $t(679) = 1.67$ ,  $p = .095$ , although the patterns of results was similar to the primary analysis.

For sensitivity analysis #2, the two-way interaction comprised of gender and negative relationship distress predicting CRP was nonsignificant,  $b = 0.03$ ,  $t(758) = 1.85$ ,  $p = .065$ , although the patterns of results were similar to the primary results. The two-way gender by positive relationship quality interaction predicting CRP was also nonsignificant,  $b = -0.02$ ,  $t(758) = -1.59$ ,  $p = .112$ .

### 10.3 | Goal 3: SES By relationship distress interaction

The interaction between SES and relationship distress predicting CRP was nonsignificant in the primary analyses,  $F(1, 759) = 0.27$ ,  $p = .606$ . The interaction remained nonsignificant in both sensitivity analyses as well,  $ps > .05$ .

### 10.4 | Exploratory goal 4: Gender, SES, and relationship distress interaction

The gender by SES by relationship distress interaction predicting CRP was nonsignificant in the primary analysis,  $F(1, 755) = 0.01$ ,  $p = .912$ . The interaction remained nonsignificant in both sensitivity analyses,  $ps > .05$ .

## 11 | STUDY 3: NSHAP

### 11.1 | Overview

The National Social Life Health and Aging Project (NSHAP) is a longitudinal study using a national area probability sample of community-dwelling adults, ages 57+. Inflammation data are only available in Waves 1 and 2 (around 5 years apart), and thus only those waves were used in these analyses.

### 11.2 | Participants

A description of the recruitment techniques for NSHAP is available in existing published papers (O'Muirheartaigh, Eckman, & Smith, 2009). Community-dwelling adults ages 57 to 85 at the time of Wave 1 were eligible to participate. From 2005 to 2006, 3,005 people participated in Wave 1. The final analytic sample included people who were in a romantic relationship during Wave I and who had CRP data ( $n = 1,279$ ). Participants' average age was 67.99 years

( $SD = 7.48$ ), and the majority of participants were White (83.2%). A little over half of participants were male (60.1%) or had a high school degree or less (58.7%).

The Wave 2 sample consisted of people who participated in Wave 1 plus those who were initially eligible but did not participate in Wave 1.<sup>3</sup> From 2010 to 2011, 2,422 people participated in Wave 2. The final analytic sample included people who were in a romantic relationship during Wave 2 and who had CRP data ( $n = 1,379$ ). Participants' average age was 71.87 years ( $SD = 6.88$ ) and the majority of participants were White (79.8%). A little over half of participants were male (61.4%) or had a high school degree or less (54.8%). A total of 832 people participated in both Waves 1 and 2 that had both relationship distress and inflammation data. Additional sample characteristics for Waves 1 and 2 are listed in eTable 3.

### 11.3 | Procedure

Both Wave 1 and Wave 2 data collection were completed during in-home interviews by a trained experimenter. Participants also provided a dried blood spot via finger prick to assess CRP.

### 11.4 | Measures

Participants answered questions about their gender and highest degree earned at both Wave 1 and Wave 2 (no degree, high school or equivalent, associates, bachelors, masters, terminal degree).<sup>4</sup> Participants also completed the same seven-item measure of romantic relationship distress at both Wave 1 ( $\alpha = .71$ ) and Wave 2 ( $\alpha = .68$ ). Example items include “How often does your partner criticize you?” “How often can you open up to your partner if you need to talk about your worries?” and “How often can you rely on your partner for help if you have a problem?” Items were recoded such that higher numbers reflected higher relationship distress. Because some items had different scales than others, we first created z-scores for each item within each wave. Then we created a relationship distress composite for each wave by averaging those z-scores. See the supplemental material for the wording of all items.

The dried blood spots used to assess CRP were mailed to the Laboratory for Human Biology Research in the Department of Anthropology at Northwestern University for processing. The intra-assay CV was 5.1–9.5 and the interassay CV was not reported. A detailed description of the assay process can be found in existing study documentation <https://www.icpsr.umich.edu/icpsrweb/NACDA/studies/20541>. See the supplemental material for a description of how each covariate (age, BMI, number of comorbid medical conditions, anti-inflammatory medication use, depressive symptoms, current smoking status, exercise, and sleep duration) was measured for the adjusted analyses.

### 11.5 | Data analytic strategy

CRP outliers were excluded using the same strategy as Study 1 and Study 2 (<1.1% of all samples). The distribution of the remaining samples was highly skewed and was thus  $\log_{10}$  transformed.

The NSHAP data was collected using a standard multistage area probability design. Based on published recommendations (O'Muircheartaigh et al., 2009), we used a design-based analysis that accounts for these design parameters. Similar to Study 1, we used the GLM option within the CS command in SPSS 25.0 (IBM). We used the nonresponse-adjusted sampling weights, along with cluster and stratum information for each wave (O'Muircheartaigh et al., 2009). After accounting for these design parameters, we constructed identical models as described for Goals 1–4 in Study 1 and Study 2, examining each wave separately for the primary analyses and both sensitivity analyses.

Because NSHAP provides a unique opportunity to examine longitudinal effects, we also examined whether Wave 1 predictors are associated with changes in CRP from Wave 1 to Wave 2. Thus, for each goal, we used the predictor variables of interest at Wave 1 predicting CRP at Wave 2, controlling for CRP at Wave 1.

## 12 | RESULTS

### 12.1 | Goal 1: Main effect of relationship distress

The main effect of relationship distress predicting CRP was nonsignificant in the primary analysis for both Waves 1 and 2, along with the prospective analyses looking at changes from Waves 1 to 2,  $b = 0.002$ ,  $t(48) = 0.13$ ,  $p = .896$ ;  $b = 0.02$ ,  $t(50) = 1.09$ ,  $p = .281$ ;  $b = -0.01$ ,  $t(46) = -0.64$ ,  $p = .524$ .

The main effect remained nonsignificant for both sensitivity analyses across the cross-sectional models and the prospective model ( $ps > .05$ ).

### 12.2 | Goal 2: Gender by relationship distress interaction

The interaction between gender and relationship distress predicting CRP was nonsignificant in the primary analyses for both Waves 1 and 2 along with the Waves 1–2 prospective analyses,  $F(1, 48) = 1.93$ ,  $p = .172$ ;  $F(1, 50) = 0.42$ ,  $p = .519$ ;  $F(1, 46) = 0.14$ ,  $p = .713$ .

The interaction remained nonsignificant for sensitivity analysis #1 across the cross-sectional models and the prospective model ( $ps > .05$ ). The interaction also remained nonsignificant for sensitivity analysis #2 for the Wave 2 cross-sectional and Waves 1–2 prospective models ( $ps > .05$ ). The interaction between gender and relationship distress predicting CRP was significant for sensitivity analysis #2 for Wave 1 only, and only for the model focused on negative relationship distress components,  $F(1, 48) = 4.41$ ,  $p = .041$ . Because this interaction did not replicate for the other waves of data collection or the primary analyses, we do not interpret it further. Follow-up tests are available in the supplemental material for the interested reader.

### 12.3 | Goal 3: SES by relationship distress interaction

The interaction between SES and relationship distress predicting CRP was nonsignificant in the primary analyses for both Waves 1 and 2 along with the Waves 1–2 prospective analyses,  $F(1, 48) = 0.41$ ,  $p = .528$ ;  $F(1, 50) = 2.05$ ,  $p = .158$ ;  $F(1, 46) = 0.04$ ,  $p = .850$ .

The interaction remained nonsignificant for sensitivity analysis #1 across the cross-sectional models and the prospective model ( $ps > .05$ ). The interaction also remained nonsignificant for sensitivity analysis #2 for the Wave 1 cross-sectional and Waves 1–2 prospective models ( $ps > .05$ ). The interaction between SES and relationship distress predicting CRP was significant for sensitivity analysis #2 for Wave 2 only, and only for the model focused on negative relationship distress components,  $F(1, 50) = 6.49, p = .014$ . Because this interaction did not replicate for the other waves of data collection or the primary analyses, we do not interpret it further. Follow-up tests are available in the supplemental material for the interested reader.

## 12.4 | Exploratory goal 4: Gender, SES, and relationship distress interaction

The gender by SES by relationship distress interaction predicting CRP was nonsignificant in the primary analysis for both Waves 1 and 2 along with the Waves 1–2 prospective analyses,  $F(1, 48) = 0.05, p = .825$ ;  $F(1, 50) = 2.15, p = .149$ ;  $F(1, 46) = 2.94, p = .093$ .

The interaction remained nonsignificant for sensitivity analysis #1 in both cross-sectional models ( $ps > .05$ ). The three-way interaction became significant for sensitivity analysis #1 for the Waves 1–2 prospective model,  $F(1, 46) = 4.35, p = .042$ . Because this interaction did not replicate for the other waves of data collection or the primary analyses, we do not interpret it further. The three-way interaction between gender, SES, and relationship distress was nonsignificant for all sensitivity #2 analyses ( $ps > .05$ ).

## 13 | STUDY 4: INTERNAL META-ANALYSIS

To aggregate the results of the cross-sectional primary analyses for Study 1 to Study 3, we conducted an internal meta-analysis using the *metafor* R package (Viechtbauer, 2019). This package is designed to estimate an aggregated effect size from multiple effect sizes (in this case using the slope coefficients and standard errors across studies). We used a fixed-model approach since we only had three studies and were unable to estimate heterogeneity across studies. We used standardized regression coefficients as the effect sizes, and standard errors as the variation associated with the effect sizes, following previous recommendations (Cooper, 2016). Since the outcome and predictors were measured similarly across studies, a meta-analysis using regression slopes is appropriate (Becker & Wu, 2007). We ran four separate sets of meta-analyses, one corresponding to the primary analysis for each study goal. Each marginal main effect is centered or effects-coded consistently across studies, ensuring the interpretation of the meta-analytic effect size for the marginal main effects is meaningful.

Goal 1: We estimated the meta-analytic effect size for the slope of relationship distress predicting CRP.

Goal 2: We estimated the marginal main effect of relationship distress, the marginal main effect of gender, and the interaction between relationship distress and gender predicting CRP.

Goal 3: We estimated the marginal main effect of relationship distress, the marginal main effect of SES, and the interaction between relationship distress and SES predicting CRP.

Exploratory Goal 4: We estimated the marginal main effect of relationship distress, the marginal main effect of gender, the marginal main effect of SES, the interaction between relationship distress and gender, the interaction between relationship distress and SES, the interaction

between gender and SES, and the three-way interaction among relationship distress, gender, and SES predicting CRP.

### 13.1 | Results

Below we report the meta-analytic results that test our hypotheses. The other terms for each model, and corresponding forest plots, are available in the supplemental materials.

Goal 1: The meta-analytic main effect of relationship distress predicting CRP was nonsignificant,  $\beta = 0.00$ ,  $SE = 0.01$ , 95%CI [-0.02, 0.03].

Goal 2: The meta-analytic interaction term between gender and relationship distress predicting CRP was nonsignificant,  $\beta = -0.02$ ,  $SE = 0.01$ , 95%CI [-0.04, 0.01].

Goal 3: The meta-analytic interaction term between SES and relationship distress predicting CRP was nonsignificant,  $\beta = -0.02$ ,  $SE = 0.01$ , 95%CI [-0.04, 0.00].

Exploratory Goal 4: The meta-analytic gender by SES by relationship distress interaction predicting CRP was nonsignificant,  $\beta = 0.02$ ,  $SE = 0.01$ , 95%CI [-0.01, 0.04].

### 13.2 | Discussion

Contrary to hypotheses, the internal meta-analysis demonstrated that romantic relationship distress was unrelated to CRP levels across three studies. In addition, the meta-analytic relationship between romantic relationship distress and CRP was not moderated by gender, SES, or the combination of gender and SES.

There were some significant effects in the expected direction within specific studies. However, the effects did not replicate across studies (with the effects being either null or in the opposite direction), and they varied within studies based on whether the model was from the primary analyses (the unadjusted models), sensitivity analyses #1 (the adjusted models), or sensitivity analyses #2 (the models separating negative and positive relationship characteristics into separate composites). Thus, each individual result should be interpreted with caution.

There are multiple interpretations of the null findings. One possibility is that the effects of interest are indeed null. The meta-analytic results are from three studies with a combined sample size of over 13,000 people, and the data-analytic plan was preregistered. Thus, it is reasonable to conclude that romantic relationship distress is unrelated to CRP, and that this relationship is not moderated by gender, SES, or the combination of gender and SES. If this conclusion is accurate, what implications does it have for understanding romantic relationship distress and inflammation? Or the broader link between relationship distress and immune dysregulation? At one extreme, these findings may suggest that romantic relationship distress is unrelated to immune function of any kind. However, inflammation is only one immune measure, and thus it is unclear whether the current findings extend to other immune measures, an important direction for future research. A more tempered interpretation of the results is that romantic relationship distress is unrelated to inflammation specifically. From this perspective, inflammation may not be a mechanism linking relationship distress and long-term health. Caution is also warranted in interpreting the results in this way; CRP is only one potential inflammation measure, and it is a downstream marker of inflammation. Thus, it is possible that romantic relationship distress is related to more upstream markers of inflammation, like IL-6.



Another critical next step for additional research is to examine this possibility. For example, one study (using MIDUS data) demonstrated that support and strain from family members predicted IL-6 levels, but not CRP (Yang et al., 2014).

Another interpretation of null findings is that they are driven by measurement issues. On one hand, this potential problem should be minimal. Specifically, we used consistent operational definitions across studies, and educational attainment is a common measure of SES. In addition, the CRP intra- and inter-assay CVs were within acceptable limits across all studies. Further bolstering our confidence in the SES and CRP measures, there was a robust relationship between SES and CRP across all studies and all analyses (see eTables 10–12). The current findings are thus consistent with a large published literature demonstrating that people with a higher SES have lower inflammation than those with a lower SES (Jousilahti et al., 2003). The relationship distress composite also had acceptable internal consistency ( $\alpha$ ) across all studies. We purposefully selected any relationship items tapping into our broad definition of relationship distress, preventing us from having to cherry-pick among inter-related items. Although this is a strength on one hand, it also limits our ability to make conclusions about more specific types of relationship function (e.g., amount of conflict). Thus, it is possible that specific components of relationship quality are related to CRP, or inflammation more broadly. In addition, behavioral measures of relationship distress may predict CRP or inflammation better or differently than self-report.

Another interpretation of null findings is that they are driven by “hidden” moderators (Van Bavel, Mende-Siedlecki, Brady, & Reinero, 2016). We attempted to preemptively address this issue by testing an empirically supported moderator (gender), along with a theoretically supported moderator (SES). We did not find support for either moderator. The current results also indirectly suggest that age is not a moderator; the three samples were comprised of different age groups, ranging from young adult to the elderly, but we do not see any clear patterns across studies. However, there are other potential unexplored moderators. For example, perhaps the impact of a distressed romantic relationship is attenuated among those with highly supportive friend and family networks.

To address the ambiguity inherent in null findings, more research is needed. An important first step is to test the link between romantic relationship distress, other inflammatory markers (e.g., IL-6), and noninflammatory immune markers in studies with large sample sizes. Expanding upon the relationship distress measures is also a critical next step, both in terms of assessing specific components of relationship functioning (e.g., amount of conflict) and adding behavioral measures. The inclusion of behavioral measures is important because the extant literature suggests they provide critical prognostic information about long-term health (Kiecolt-Glaser & Newton, 2001). Finally, the current results are largely focused on cross-sectional findings. In addition, the nature of the relationship distress items does not allow researchers to disentangle people who feel chronically distressed or not versus those who fluctuate between distressed and not distressed. It is possible that CRP and/or inflammation are linked to specific patterns of relationship distress and not others.

In conclusion, an internal meta-analysis of three large sample size studies determined that romantic relationship distress was unrelated to CRP. Moreover, this link was not moderated by gender, SES, or the combination of gender and SES. Although there were significant effects within each study, the results did not replicate across studies and they were not robust to the sensitivity analyses. Although there are multiple interpretations of null findings, the preregistered nature of the data analytic plan, along with the large sample sizes, strongly suggest that romantic relationship distress is not related to CRP levels. These results may or may

not extend to other measures of inflammation, and other noninflammatory immune markers, an important direction for future research.

## DATA AVAILABILITY STATEMENT

As part of IARR's encouragement of open research practices, the authors have provided the following information:

The studies reports in this manuscript were preregistered after data collection was complete and before data analyses were conducted. The preregistration, along with all relevant statistical syntax, can be found at <https://osf.io/eh57w/>.

The data from the three studies used in this paper are all available publicly, although two of the three require special permission to use, along with written security contracts through their respective data management sources. The study codebooks and other materials are also available online.

Add Health: <https://www.cpc.unc.edu/projects/addhealth>, <https://data.cpc.unc.edu/projects/2/view>

MIDUS: <http://midus.wisc.edu/>, <https://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/4652>, <https://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/29282>

NSHAP: <http://www.norc.org/Research/Projects/Pages/national-social-life-health-and-aging-project.aspx>, <https://www.icpsr.umich.edu/icpsrweb/NACDA/studies/20541>, <http://www.icpsr.umich.edu/icpsrweb/NACDA/studies/34921>

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## ENDNOTES

- <sup>1</sup> We considered examining income as a secondary SES measure. However, there is a relatively large proportion of missing data in Study 3 for household income (25% of the sample). In addition, all of the participants in Study 3 were past retirement age, along with a proportion of participants from Study 2. The instructions for the household income question specifically excluded retirement savings in both studies. Thus, if we relied on this question as a measure of SES, some people would have a low household income (and thus be considered low SES) even though they had substantial retirement savings.
- <sup>2</sup> In our MIDUS analytic sample, there were 93 twin and sibling pairs, and one family of 4 siblings. We examined potential dependency in the data by computing an intra-class correlation coefficient (ICC) from the output of a hierarchical linear modeling analysis that used an empty model, family as the grouping variable, and CRP as the dependent variable. The ICC was .018 (1.8%), indicating virtually no dependence between twins/siblings in their CRP values. Thus, there was no statistical need to account for dependency among family units for this dependent measure (since it virtually did not exist).
- <sup>3</sup> An additional 915 romantic partners of the target participants also provided data at this assessment, bringing the total initial sample size to 3,337. We do not discuss the partners further since they are not the focus of these analyses.
- <sup>4</sup> The NSHAP dataset did not include vocational training anywhere within their list of highest degree earned, whereas Add Health and MIDUS both listed vocational training at the level of associates.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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