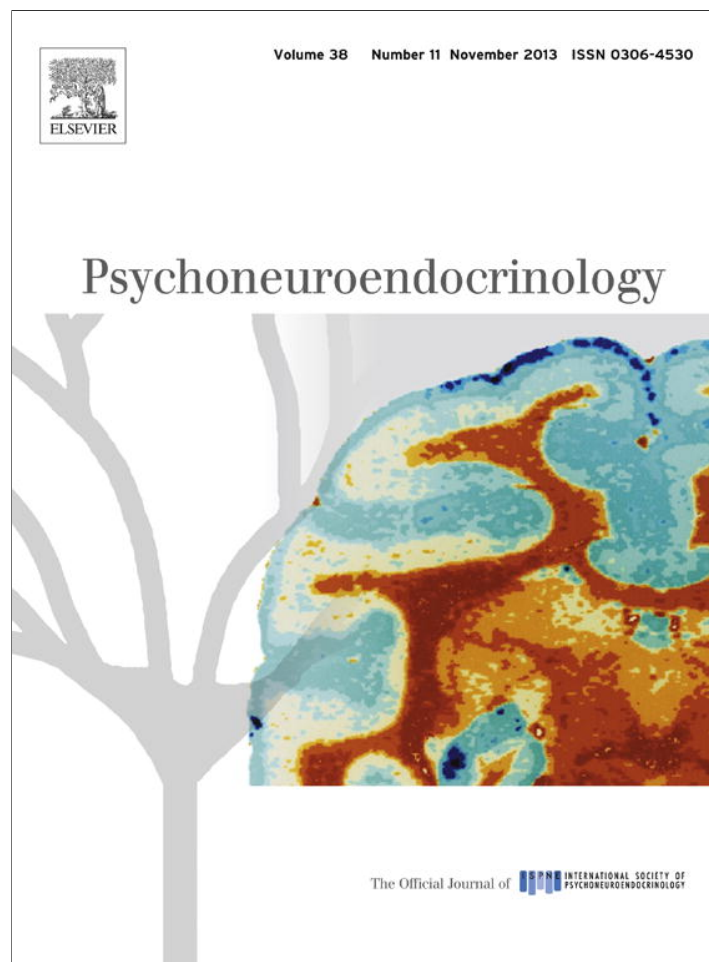


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Marital distress prospectively predicts poorer cellular immune function



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Summary

Objective: Distressed marriages enhance risk for a variety of health problems. Immune dysregulation is one potential mechanism; cross-sectional studies have demonstrated that marital distress is linked to maladaptive immune alterations. The current study filled an important gap in the literature by examining the ability of marital distress to prospectively predict immune alterations over a two-year period.

Method: Participants were 90 couples ($N = 180$ individuals; $M_{\text{age}} = 25.67$) married less than a year at the time of their first study visit. Both members of a couple completed a baseline assessment of marital quality and provided blood samples at baseline and two years later. 63 couples ($N = 123$ individuals) completed the follow-up assessment.

Results: Spouses in more distressed marriages had larger declines in cellular immune function over time than spouses in less distressed marriages. Furthermore, the results were highly consistent across two different indices, proliferative responses to two mitogens, concanavalin A (Con A) and phytohemagglutinin (PHA).

Conclusions: Marital distress has a variety of negative health consequences. The current study provided important evidence that marital distress has longer-term immune consequences. Accordingly, the present results provide a glimpse into the pathways through which marital distress may impact health over time.

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Being married confers health benefits. For example, married people had lower premature all-cause mortality rates, higher 5-year cancer survival rates, and fewer chronic health conditions than their non-married counterparts (Johnson et al., 2000; Schoenborn, 2004; Sprehn et al., 2009). On the other hand, distressed marriages enhance risk for a variety of health problems, such as coronary heart disease, delayed wound healing, metabolic syndrome, and premature all-cause mortality (Orth-Gomér et al., 2000; Kiecolt-Glaser and Newton, 2001; Kiecolt-Glaser et al., 2005; Troxel et al., 2005; Holt-Lunstad et al., 2010). Importantly, the links between distressed marriages and health remain after controlling for sociodemographic and health-relevant risk factors. Furthermore, a recent meta-analysis concluded that the link between distressed marriages and health was on par with the negative effects of health behaviors like a poor diet (Robles et al., in press).

Because marital distress is a chronic interpersonal stressor, stress-relevant physiological mechanisms may provide insight into the link between marital distress and health. Immune dysregulation may be one mechanistic pathway because stress alters immune function and the immune system is essential to health (Robles et al., in press; Robles and Kiecolt-Glaser, 2003). For example, inflammation and other forms of immune dysregulation increase risk for premature all-cause mortality and a variety of diseases including cardiovascular disease, cancer, and metabolic syndrome (Ershler and Keller, 2000; Hansson, 2005; Hotamisligil, 2006; Nabipour et al., 2006; Parkin, 2006).

A growing body of works demonstrates cross-sectional links between distressed marriages and immune dysregulation. For example, people in more distressed marriages had smaller antibody responses to an influenza virus vaccine than people in less distressed marriages (Phillips et al., 2006). Compared to more happily married people, spouses in more distressed marriages had poorer cellular immune function, as indexed by lower proliferative responses to two mitogens, concanavalin A (Con A) and phytohemagglutinin (PHA; Kiecolt-Glaser et al., 1987). Furthermore, individuals in more distressed marriages had higher Epstein–Barr virus (EBV) antibody titers than those in less distressed marriages (Kiecolt-Glaser et al., 1987, 1988). Because herpesviruses such as EBV are better able to reactivate and replicate when the cellular immune system is compromised, higher antibody titers to a latent herpesvirus reflect poorer cellular immune system control over viral latency (Glaser and Jones, 1994).

Observational studies of marital conflict discussions provide another window into marital distress; behavioral coding systems assess relationship behaviors between romantic partners as an index of relationship quality. A provocative study using this paradigm demonstrated that wound healing, an immune-mediated event, was slower after a marital disagreement than a socially supportive discussion (Kiecolt-Glaser et al., 2005). In addition, production of inflammatory cytokines at the wound site was lower following the conflict than the support discussion. In contrast to heightened systemic inflammation, which is linked to a variety of age-related diseases (Harris et al., 1999; Ershler and Keller, 2000; Hansson, 2005; Hotamisligil, 2006), local inflammation at the wound site is adaptive and critical to effective wound healing.

Negative and hostile behaviors during a conflict discussion, such as blaming or interrupting the partner, appear to

be particularly detrimental. A conflict discussion led to slower wound healing among couples displaying more hostile behaviors compared with their less hostile counterparts (Kiecolt-Glaser et al., 2005). Furthermore, whereas hostile couples had higher systemic inflammation following a conflict discussion compared to a social support discussion, low hostile couples had similar levels of inflammation across both discussions (Kiecolt-Glaser et al., 2005). Other studies using the marital disagreement paradigm provide evidence for additional immune alterations. For example, spouses whose discussions were more hostile had higher serum antibody titers to latent EBV than spouses whose discussions were less hostile (Kiecolt-Glaser et al., 1993). The cellular immune response plays an important role in controlling the expression of latent EBV, and thus these data are consistent with greater EBV reactivation among distressed individuals (Glaser et al., 1994). Compared to their less hostile counterparts, more hostile couples also had larger declines in two different indices of cellular immune function during the 24 h following the disagreement (Kiecolt-Glaser et al., 1993).

The immunological consequences of marital distress may be particularly strong for women compared with men (Kiecolt-Glaser and Newton, 2001). For example, marital stress was associated with heightened systemic inflammation in young women but not young men (Whisman and Sbarra, 2012). A marital conflict discussion led to greater immune dysregulation among women compared with men (Kiecolt-Glaser et al., 1993; Mayne et al., 1997).

1. The current study

Taken together, prior research suggests a reliable link between marital distress and concurrent immune dysregulation, particularly cellular immunity. *To date, little to no work has addressed whether marital distress alters the trajectory of immune function over time (Robles et al., in press). Longitudinal studies are needed to understand the directional nature of the link between marriage and immune function in a naturalistic context.* Accordingly, the current study, which followed newlywed married couples over a two-year period, fills an important gap in the literature.

We selected three measures of cellular immune function, EBV antibody titers and T-cell proliferation in response to Con A and PHA, because previous studies have shown that cellular immunity is modulated by interpersonal stress (Kiecolt-Glaser et al., 1987, 1993). In addition, proliferative responses to Con A and PHA may index the immune system's response to bacterial and viral challenges. Indeed, the cellular immune response is critical to the effective resolution of viral and bacterial infections, among other functions. Proliferative responses also decrease with age (Antel et al., 1980; Wayne et al., 1990); decreased T-cell proliferation is part of immunosenescence, the aging of the immune system that is linked to age-related diseases (Malaguarnera et al., 2001).

We hypothesized that, compared to spouses in less distressed marriages, those who were more distressed would exhibit greater immune dysregulation over time, as evidenced by higher EBV antibody titers and decreased proliferative responses. Based on prior research suggesting possible immune-related gender differences, we also explored whether gender moderated the relationship between marital distress and immune function over time.

2. Method

2.1. Participant selection procedure

We used a stringent 3-stage selection process to recruit newlywed couples. First, we sent letters to couples who obtained their first marriage license within the previous 4–6 months. Couples who responded then completed two sets of phone interviews assessing their mental and physical health.

Individuals were ineligible for the study if they were pregnant, drank excessive amounts of alcohol or caffeine, smoked, used any type of medication other than birth control, had health problems that had immunological consequences (e.g., cancer, diabetes), or if they were not within 20% of their ideal weight for their height. We also excluded people who met DSM-III-R criteria for any psychotic diagnosis, a depressive or anxiety disorder other than simple phobia, or a substance abuse disorder, which eliminated individuals whose psychopathology might produce marital discord or immunological alterations (Johnson and Jacob, 1997). Couples who told us they were planning to move or have children within the next two years were also ineligible, since they might be lost to follow-up. Aside from our stringent mental and physical health criteria, couples were eliminated if they reported any needle or hospital phobias or if they could not be scheduled for their first study visit within 14 months of their marriage. Anyone who developed an immunological disorder prior to the follow-up visit was excluded from the study ($n = 0$). The project was approved by The Ohio State University Institutional Review Board; participants provided written informed consent before participating.

2.2. Study procedure

Couples completed 2 study visits that were 2 years apart. At both visits, couples were admitted to the Clinical Research Center (CRC), a hospital research facility, at 7:00 a.m. for a 24-h visit. Participants provided their first blood sample shortly after arrival and their second sample around the same time the following morning. During the remainder of the visit, couples engaged in a marital problem solving task which is discussed elsewhere and is not the focus of the current study (Kiecolt-Glaser et al., 1993, 1996).

2.3. Questionnaires

The Marital Adjustment Test (MAT) is a widely used measure of marital quality. The MAT can discriminate between satisfied and dissatisfied couples and demonstrates adequate reliability and good criterion validity (Locke and Wallace, 1959; Freeston and Plechaty, 1997). Participants completed the MAT assessing baseline marital distress during their first telephone screening interview. Lower scores on the MAT indicate more marital distress.

The Structured Clinical Interview for DSM-III-R Axis I disorders – Nonpatient version (SCID-NP) measured current mood, anxiety, substance abuse, and psychotic disorders. The SCID-NP is a reliable and valid method for evaluating psychopathology (First et al., 1997). Interviews were completed by advanced clinical psychology graduate students or

clinically supervised staff. At least three trained personnel then arrived at a diagnosis during a consensus meeting. The SCID-NP was used to screen people with a mental disorder from the study. We also re-administered the SCID-NP at the follow-up to account for potential changes in mental health status over time.

2.4. Immunological assays

The EBV VCA serum antibody titers (IgG) were measured by the indirect immunofluorescence (IF) test using HR-1 cells by previously described procedures (Kiecolt-Glaser et al., 1991). Proliferative responses to Con A and PHA provided data on functional in vitro cellular immune changes. The concentrations for PHA and Con A were 2.5, 5.0, 10.0, and 20.0 $\mu\text{g/ml}$. Cells, 1×10^5 /well, were incubated for 92 h at 37 °C in 96-well round-bottom plates, then pulsed for 4 h with $^3\text{H TdR}$ (0.5 $\mu\text{Ci/well}$, specific activity 1 mCi/ml). All samples were run in triplicate (Kiecolt-Glaser et al., 1991).

2.5. Data analytic strategy

The immune assay scores were highly skewed. Accordingly, each measure was \log_{10} transformed prior to analyses. Because the Con A and PHA data had 5 levels (i.e., couple, subject, visit, sample time, and dilution) and only 63 couples completed the follow-up visit, scores were averaged across dilutions, simplifying the complex model. The EBV data only had 3 levels; the assay does not require different dilutions and we only measured IgG EBV antibody titers once at each visit (because the half-life of IgG antibodies is at least one week).

Mixed models were utilized to account for the correlations within couples and subjects. All models were analyzed with SPSS version 19.0 (IBM, New York) using random effects for couple and subject. The random couple effect accounted for dependency between husbands and wives and the random subject statement accounted for the repeated effects of visit (first vs. second) and sample time (CRC entry vs. CRC exit, when applicable). An identity variance–covariance matrix was fitted to estimate the error variance.

To test the hypothesis that marital distress predicts the trajectory of immune function over time, we tested whether marital distress at the first study visit predicted changes in immune function between the first and second visit, two-years later. Specifically, we were interested in whether the marital distress by visit interaction predicted EBV antibody titer levels, Con A responses, and PHA responses, separately. Although our hypothesis was about the marital distress and visit interaction, we included fixed effects for the 3-way marital distress by visit by sample time interaction predicting Con A and PHA responses, and all corresponding 2-way interactions. This allowed us to test whether sample time (CRC entry vs. CRC exit) affected our results. Significant interactions were decomposed using simple slopes tests that examined the hypotheses of interest.

Potential confounds were selected based on their theoretical and empirical relationships to marital distress and cellular immune function. Every model adjusted for age, gender, and body mass index (BMI: kg/m^2) using time-varying covariates. We also conducted a series of ancillary analyses

to test whether the effects held when controlling for health behaviors. Specifically, we adjusted for participants' typical number of alcoholic drinks per week, cups of caffeinated drinks per day, and hours of exercise per week. We conducted a second set of auxiliary analyses that excluded anyone who had a mental disorder ($n = 3$) or was pregnant ($n = 4$) at the time of the follow-up visit.

We initially included all possible gender interactions in each model. None of the interactions involving gender were significant and thus the gender interaction terms were omitted from all analyses.

3. Results

3.1. Participant information

Participants were 90 newlywed couples ($N = 180$ individuals) married an average of 10.45 months ($SD = 2.08$, range 6–15) prior to their first study visit. Husbands' and wives' average age was 25.67 years ($SD = 3.06$, range 20–37) and the majority of participants were White ($N = 171$ individuals). All couples were in their first marriage and had no children at the time of their first study visit. Additional sample characteristics are listed in Table 1.

A total of 63 couples ($N = 126$ individuals) completed the two-year follow-up visit, consistent with the average 31%

attrition rate in longitudinal marital studies (Karney and Bradbury, 1995). Of the 27 couples who did not return for the follow-up, 8 separated or divorced in the interim, 10 either moved out of town or could not be contacted, and 9 declined to participate. In addition, couples who returned for the follow-up had higher marital quality at baseline ($M = 129.81$, $SD = 13.67$) than couples who did not return ($M = 124.72$, $SD = 16.15$), $t(178) = 2.16$, $p = .032$. All reported coefficients are unstandardized (Table 2).

3.2. Primary analyses

Contrary to expectations, the interaction between marital distress and visit predicting EBV antibody titers was non-significant ($b = .002$, $F(1,121) = 1.826$, $p = .179$). However, there was a significant main effect of visit ($b = -.10$, $F(1,364) = 21.29$, $p < .001$), and a significant marital distress by visit interaction ($b = .003$, $F(1,346) = 5.60$, $p = .019$) predicting Con A responses. Specifically, proliferative responses to Con A decreased on average from the first to the second visit. This relationship was stronger for spouses in more distressed marriages (see Fig. 1). None of the interactions with sample time were significant, indicating that the link between visit and Con A, marital distress and Con A, or the combination of the two did not differ whether the serum sample was collected at the beginning of the CRC visit or 24-h later.

Table 1 Study sample characteristics.

Characteristic	Category	Number (%) or mean (SD)
Race	White	171(95)
	Non-white	9(5)
Gender	Female	90(50)
	Male	90(50)
Education	High school or below	11(6.1)
	Some college or college graduate	138(76.6)
	Graduate or professional training	31(17.2)
Age (years)	N/A – numbers are mean (SD)	25.67(3.06)
Body mass index (kg/m ²)	N/A – numbers are mean (SD)	22.64(2.44)
Time dated before marriage (months)	N/A – numbers are mean (SD)	36.56(25.32)
Length of marriage (months)	N/A – numbers are mean (SD)	10.45(2.08)

Table 2 Raw means and standard errors of the mean for the outcome variables broken down by marital quality.

Outcome	Marital quality	T1 Mean (SE)	T2 Mean (SE)	<i>b</i>	<i>p</i>
Con A responses	Low marital quality (–1 SD)	6291(931)	3273(1135)	–.15	<.001
	High marital quality (+1 SD)	6491(932)	4438(1049)	–.05	.052
PHA responses	Low marital quality (–1 SD)	56,130(2156)	30,106(2802)	–.14	<.001
	High marital quality (+1 SD)	50,753(2163)	37,255(2519)	–.08	<.001
EBV antibody titers	Low marital quality (–1 SD)	405(36)	267(46)	–	–
	High marital quality (+1 SD)	359(37)	335(42)	–	–

Note. Raw sample means and standard deviations were estimated using a model adjusted for BMI, age, and gender. *b* refers the unstandardized slope of the outcome from T1 to T2 either for the lower or higher marital quality group. Simple slopes tests were calculated using log transformed data. The simple slopes for the analysis predicting EBV antibody titers are not reported because the marital quality by visit interaction was not significant.

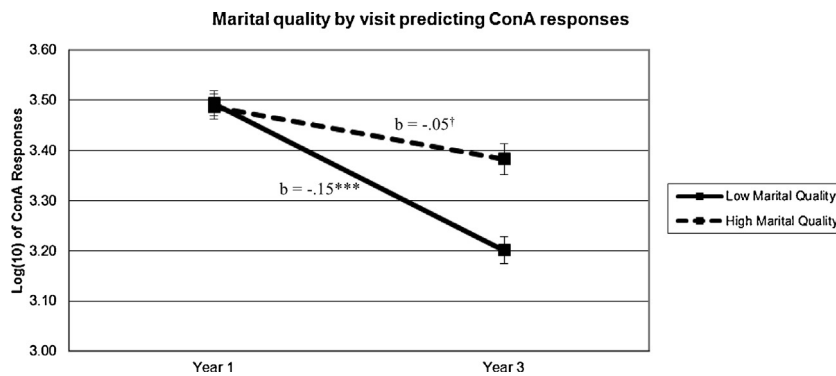


Figure 1 To illustrate the relationship between marital quality and Con A responses over time, Con A average values were graphed for participants 1 standard deviation above (high marital quality) and below (low marital quality) the mean of marital quality. Sample means were estimated using a model adjusted for BMI, age, and gender. † $p \leq .10$ and *** $p \leq .001$.

Next, we examined functional immune responses to PHA. There was a significant main effect of visit ($b = -.11$, $F(1,368) = 61.60$, $p < .001$), and a significant marital distress by visit interaction ($b = .002$, $F(1,348) = 4.87$, $p = .028$). Specifically, proliferative responses to PHA decreased on average from the first to the second visit. Furthermore, this link was stronger for spouses in more distressed marriages (see Fig. 2). None of the interactions with sample time were significant, indicating that the link between visit and PHA, marital distress and PHA, or the combination of the two did not differ whether the serum sample was collected at the beginning of the CRC visit or 24-h later.

In accord with prior work, we were also interested in testing potential differences between spouses who showed patterns of higher versus lower immune responses across our three immunological measures (Kiecolt-Glaser et al., 1997). Accordingly, participants whose values were above the median for their gender on at least two of the three assays were designated "high responders" and remaining participants were deemed "low responders." A logistic generalized estimating equations analysis revealed a significant main effect of visit ($b = -2.45$, $\chi^2(1, N = 180) = 4.71$, $p = .030$), and a marginally significant marital distress by visit interaction ($b = .01$, $\chi^2(1, N = 180) = 2.75$, $p = .097$). Specifically, the likelihood of being a high responder decreased on average from the first to the second visit. Follow-up tests

demonstrated that this relationship was stronger for spouses in more distressed marriages.

3.3. Ancillary analyses

Ancillary analyses tested whether the Con A and PHA effects held when controlling for health behaviors. The results were unchanged after adjusting for participants' typical number of alcoholic drinks per week, cups of caffeinated drinks per day, and hours of exercise per week. The results also remained the same when we excluded participants who had a mental disorder ($n = 3$) or were pregnant ($n = 4$) at the time of the follow-up visit.

4. Discussion

The current study demonstrated that spouses in more distressed marriages had larger declines in cellular immune function over a two-year period than spouses in less distressed marriages. Contrary to expectations, latent EBV reactivation was unrelated to marital quality. However, the results were highly consistent across two different indices of cellular immune function, proliferative responses to Con A and PHA. In addition, spouses in more distressed marriages had relatively larger immunological declines

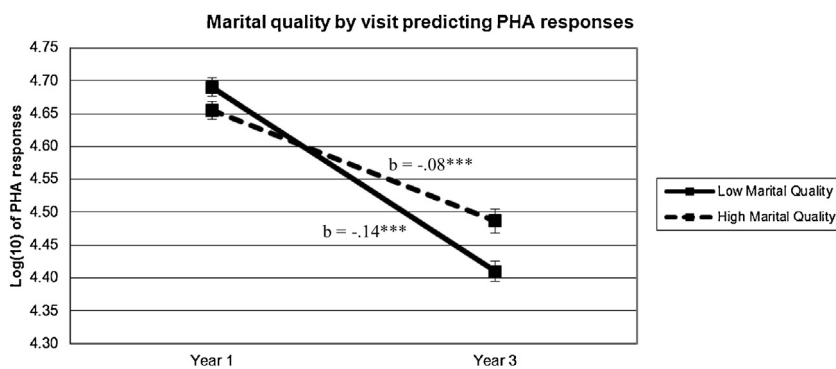


Figure 2 To illustrate the relationship between marital quality and PHA responses over time, PHA average values were graphed for participants 1 standard deviation above (high marital quality) and below (low marital quality) the mean of marital quality. Sample means were estimated using a model adjusted for BMI, age, and gender. *** $p \leq .001$.

across our three immune measures than spouses who were more happily married.

A growing body of cross-sectional studies have demonstrated that poorer marital quality is related to greater immune dysregulation (e.g., Kiecolt-Glaser et al., 1987, 1988, 2005; Phillips et al., 2006). The present results extend these findings in an important new direction by investigating immune alterations over a two-year period, an important first step in establishing a causal pathway. Furthermore, the stringent mental and physical health criteria used in this study helped rule out potential confounding factors that might explain the link between marital quality and immune function. Accordingly, the present findings provide robust evidence that marital quality is related to changes in cellular immune function over time.

The current results suggest that marital quality may influence health through long-term alterations in cellular immunity; the cellular immune response is critical to the effective resolution of viral and bacterial infections, among other functions. Furthermore, proliferative responses decrease with age, one characteristic of immunosenescence (Antel et al., 1980; Wayne et al., 1990). In the current study, age-related proliferative declines were accelerated among spouses in more distressed marriages.

Other physiological mechanisms may work independently or in tandem with changes in cellular immunity to influence health (Robles et al., in press; Robles and Kiecolt-Glaser, 2003). For example, hostile marital interactions were related to maladaptive alterations in cardiovascular activity (Smith et al., 2009) and increased catecholamine levels among newlywed and older adult couples (Malarkey et al., 1994; Kiecolt-Glaser et al., 1997). Accordingly, research incorporating the autonomic, neuroendocrine, and immune consequences of marital distress would help provide a more complete picture about the ways that these physiological systems influence each other to affect health.

Mental health and health behaviors may also contribute to the link between marital distress and health. For instance, recurrent depressive episodes have been linked to chronic interpersonal troubles; depression enhances risk for immune dysregulation (Herbert and Cohen, 1993; Monroe et al., 2007). In addition, people in more distressed marriages have a greater risk of developing alcohol problems than people in less distressed marriages (Whisman et al., 2006); alcohol abuse has deleterious effects on immune function (Cook, 1998). The current study used stringent selection criteria that excluded people with mental or physical health problems; as a result, our participants had exceptional health habits (e.g., commitment to regular exercise). By admitting couples to the CRC for 24 h, we were able to control factors like physical activity, diet, and caffeine intake that could influence immune function (Kiecolt-Glaser et al., 2010), while simultaneously providing a uniform environment across couples. In addition, ancillary analyses demonstrated that our results were unchanged after accounting for participants' typical number of alcoholic drinks per week, cups of caffeinated drinks per day, and hours of exercise per week. Accordingly, the current data suggest that marital distress affects cellular immune function independent of spouses' health behaviors and mental and physical comorbidities.

In sum, spouses in more distressed marriages had larger declines in cellular immune function over a two-year period

than spouses in less distressed marriages. These results are particularly notable in light of the sample under investigation; only healthy couples were allowed to participate and the marital distress scores were on the lower end of the spectrum. Thus, the cellular immune alterations evident in this sample likely underestimate the true effects. Accordingly, the current study demonstrates that marital distress has longer-term physiological costs and provides a glimpse into the pathways through which social relationships can impact health.

Role of the funding sources

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Conflicts of interest

None declared.

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