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Full-length Article

The gut connection: Intestinal permeability as a pathway from breast cancer survivors' relationship satisfaction to inflammation across treatment

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ABSTRACT

Background: Breast cancer survivors are prone to weakened gut barriers, allowing bacteria to migrate into the blood stream. Gut permeability fuels inflammation, which, among survivors, can elevate risk for comorbid disease development, cancer recurrence, and a poor quality of life; however, survivors' satisfying relationships can provide health benefits. This longitudinal study used a conceptual model addressing how intimate relationships is associated with health through changes in gut permeability and inflammation.

Method: Breast cancer survivors (n = 139, stages 0–IIIC) completed a baseline visit before treatment and two follow-up visits 6 and 18 months after treatment ended. Women who had an abnormal breast cancer test followed by a benign diagnosis completed visits within a comparable timeframe (noncancer patient controls; n = 69). All women completed questionnaires assessing their relationship satisfaction and provided blood samples to assess two bacterial endotoxin biomarkers, lipopolysaccharide-binding protein (LBP) and soluble CD14 (sCD14), as well as C-reactive protein (CRP) and interleukin 6 (IL-6).

Results: Within-person multilevel mediation analyses showed that when a survivor's relationship satisfaction was higher than usual, her own LBP and LBP/sCD14 were lower, which was associated with lower than her own average CRP and IL-6 (95% CIs [−0.0104, −0.0002]). IL-6 was also higher when older survivors, but not younger survivors, experienced higher than usual intestinal permeability (p = .001). These effects of satisfying relationships held after accounting for cancer-related and behavioral factors. Post-hoc analyses showed LBP, sCD14, and LBP/sCD14 were associated with CRP for the cancer survivors, but only LBP and LBP/sCD14 were linked to CRP among the noncancer control patients.

Conclusion: The gut environment is a new promising candidate for understanding a relationship's long-term health impact, particularly among those with elevated health risks. Survivors may reap multiple physiological benefits from satisfying relationships.

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1. Introduction

A weakened gut barrier and its inflammatory consequences pose risks to breast cancer survivors' long-term health. Cancer treatment can disrupt gut barrier integrity, allowing bacteria to migrate into the blood stream—referred to as gut or intestinal permeability (Bajic et al., 2018; Jordan et al., 2018). Even among healthy adults, gut permeability is associated with poorer psychological and physical function (Kiecolt-Glaser and Wilson et al., 2021; Madison et al., 2020; Stehle et al., 2012), and cancer survivors' heightened risks for a weakened gut barrier carries additional health consequences (Bajic et al., 2018; Jordan et al., 2018). Indeed, the body's inflammatory response to intestinal permeability can promote inflamm-aging, or chronic low-grade inflammation that accelerates biological aging and age-related frailty, morbidity, and mortality (Kiecolt-Glaser et al., 2019; Stehle et al., 2012). Both gut permeability and inflammation may fuel serious chronic health conditions, including atherosclerosis, cardiovascular disease, and diabetes, each of which occurs at higher rates in breast cancer survivors than women without a cancer history (Ganz, 2001; Pussinen et al., 2011; Stoll et al., 2004).

However, breast cancer survivors' strong and satisfying intimate relationships can offer broad health benefits across the cancer trajectory. Having a close and supportive partner is associated with better emotional and physical adjustment to receiving a potentially life-threatening breast cancer diagnosis (Kayser and Scott, 2008). When sharing their cancer-related concerns during treatment, survivors who felt understood and validated by their partners reported lower stress levels and higher intimacy than those who felt less understood and validated (Manne et al., 2004a, 2004b). A satisfying relationship can help survivors recover their health more quickly after finishing treatment, with satisfied women reporting better psychological and physical health than women in dissatisfying marriages or who were unmarried (Shrout et al., 2021). Likewise, survivors in non-distressed relationships had fewer cancer-related symptoms and treatment side effects in the years following their diagnosis and treatment than those in distressed relationships (Yang and Schuler, 2009). These findings illustrate how strong, satisfying relationships are associated with better health across the cancer trajectory.

A conceptual model addressing intimate relationships' health implications through changes in the gut environment and inflammation may lend mechanistic insight into how breast cancer survivors' relationships impact health. The model suggests that partners' relationship satisfaction is associated with healthy aging through changes in intestinal permeability and associated inflammation (Kiecolt-Glaser et al., 2019). That is, the quality of a relationship may modify the gut barrier's structure and function and, in turn, inflammation—a physiological cascade that can lead to changes in health status and biological aging. For example, partners' relationship satisfaction and interactions have been linked to the autonomic nervous system (Wilson et al., 2018), a key regulator of gastrointestinal functioning and a route to gut structure and function changes (Sandhu et al., 2017). Furthermore, aging theories such as socioemotional selectivity theory suggest adults value intimate relationships more as they age (Carstensen, 1995). Accordingly, older survivors' relationships may have even stronger health effects relative to younger survivors. Older adults also experience age-related gut barrier and immune system weakening; gut bacteria in circulation can elicit inflammatory responses, while aging is associated with enhanced inflammatory responses to these stimuli (Franceschi et al., 2006; Stehle et al., 2012). Thus, this physiological cascade may be even stronger with age, heightening inflammatory risks.

Previous research on middle-aged couples showed that lower quality marital interactions were associated with markers related to intestinal permeability and, in turn, inflammation (Kiecolt-Glaser et al., 2018). Partners who were more hostile when discussing a marital problem had higher lipopolysaccharide-binding protein (LBP) and LBP/soluble CD14 (sCD14) ratio levels, while their less hostile counterparts had lower LBP and LBP/sCD14 ratios, two bacterial endotoxin biomarkers reflecting greater gut permeability (Keane et al., 2021; Kelly et al., 2016; Stehle et al., 2012). LBP and sCD14 are produced in response to bacterial translocation of endotoxin (lipopolysaccharide; LPS) from the gut microbiota to blood circulation (Amar et al., 2003; Stehle et al., 2012). Higher LBP levels reflect LPS (found in the Gram-negative bacterial cell envelope) leakage out of the gut and into the bloodstream (Schumann, 2011), and sCD14 helps clear the circulating LPS (Wurfel et al., 1995). The relative balance of LBP and sCD14 is important because high LBP and low sCD14 suggest that the body is not clearing the circulating LPS; thus, a high LBP/sCD14 ratio is pro-inflammatory. Indeed, Kiecolt-Glaser and colleagues (2018) found that partners with higher LBP and LBP/sCD14 ratios had higher inflammation that day compared to those with lower LBP and LBP/sCD14 ratios. These gut permeability markers are also associated with poorer physical function and serious health problems such as immune and gastrointestinal disorders (Stehle et al., 2012). Despite breast cancer survivors' heightened risk for a weakened gut barrier and inflammatory health conditions (Jordan et al., 2018), research has not examined the ties between their relationships and intestinal permeability. However, breast cancer survivors' satisfying relationships have been linked indirectly to lower inflammation (Shrout et al., 2020). The gut environment may serve as a mechanistic pathway from their strong relationships to lower inflammation and better health (Kiecolt-Glaser et al., 2019).

This longitudinal study examined the associations among survivors' intimate relationship satisfaction, gut permeability, and inflammation before treatment and 6 and 18 months after treatment, providing insight into the physiological pathways connecting survivors' relationships to health across early survivorship. Survivors' satisfying relationships are associated with better psychological, physical, and immune functioning (Shrout et al., 2021; Shrout et al., 2020); however, a breast cancer diagnosis and cancer treatment can create challenges for survivors' relationships (Manne et al., 2004a, 2004b). Therefore, in addition to comparing average associations among survivors' relationship satisfaction, gut permeability, and inflammation throughout the study (between-person effects), we examined how changes in a survivor's own relationship satisfaction from visit to visit were associated with changes in her own gut permeability and, in turn, inflammation (within-person effects). This within-person approach is important for understanding how a survivor's own relationship satisfaction changes throughout treatment, and how those changes may be associated with her own gut permeability and inflammation.

Consistent with Kiecolt-Glaser and colleagues' (2019) model linking intimate relationships with the gut environment and inflammation, we expected that higher relationship satisfaction would be associated with lower gut permeability, and gut permeability would be associated with greater inflammation at both the within- and between-person level. In addition to these direct effects, we expected that relationship satisfaction would have indirect effects on inflammation through gut permeability. At the within-person level, we hypothesized that at visits in which survivors were more satisfied with their relationships, they would also have lower gut permeability, and, in turn, lower inflammation levels than usual. Between survivors, we hypothesized that survivors who were satisfied with their relationships throughout the study would have lower average gut permeability and, in turn, lower average inflammation. We also expected that associations among relationship satisfaction, gut permeability, and inflammation would be stronger for older survivors compared to younger survivors, given older adults' focus on relationships and gut barrier and immune system weakening (Carstensen, 1995; Stehle et al., 2012). Specifically, we hypothesized that older survivors' within- and between-person relationship satisfaction would be more strongly associated with gut permeability than younger survivors, and that older survivors within- and between-person gut permeability would have stronger effects on inflammation than younger survivors. Lastly, post-hoc analyses examined the clinical significance of these findings and assessed how associations among relationship satisfaction, gut permeability, and inflammation differed between cancer

survivors and those with an abnormal breast cancer test followed by a benign diagnosis.

2. Method

2.1. Participants and procedure

Participants were women who were married/domestic partners with an initial suggestive test of cancer identified at cancer clinics for a larger longitudinal study on fatigue and immune function. After follow-up testing, women received either a malignant diagnosis (cancer survivors; $n = 139$, stages 0–IIIC) or benign diagnosis (noncancer patient controls; $n = 69$). Breast cancer survivors completed a baseline visit prior to beginning cancer treatment and two follow-up visits 6 and 18 months after treatment ended (surgery, radiation, or chemotherapy, whichever came last); noncancer patient controls completed visits within a comparable timeframe. All women completed self-report questionnaires and provided a blood sample at each visit. Fasting blood samples were collected between 7:00 and 9:00 AM to control for diurnal variation. Exclusion criteria included a history of cancer except basal or squamous cell skin carcinomas, and significant visual, auditory, or cognitive impairments that would interfere with study completion. Women were on average 55 years old ($SD = 9.65$, range 32–78) and primarily White (86%). Table 1 provides additional sample characteristics. All study procedures were approved by the Ohio State University Institutional Review Board, and all women gave written informed consent prior to participation.

Table 1
Baseline Characteristics.

	Breast Cancer Survivors		Noncancer Patient Controls	
	Mean (*SD*)	Number (%)	Mean (*SD*)	Number (%)
Age	54.60 (9.65)		55.59 (9.77)	
Body mass index	28.05 (6.84)		27.60 (6.45)	
Physical comorbidities	0.70 (1.24)		0.30 (0.63)	
Physical activity	18.56 (19.43)		20.59 (21.81)	
Insomnia	8.85 (5.38)		1.95 (0.83)	
Alcoholic beverages per week	1.80 (2.81)		2.28 (3.92)	
Depressive symptoms	16.19 (10.25)		13.35 (11.23)	
Smoking status (% yes)		14 (10%)		1 (1.4%)
Race				
White		120 (86%)		62 (90%)
Black		10 (7%)		3 (4%)
Other		9 (7%)		4 (4%)
Education				1 (1%)
< College		62 (44%)		26 (38%)
≥ College		77 (56%)		43 (62%)
Cancer stage				
0		29 (21%)		
I		53 (38%)		
II		40 (29%)		
IIIA-C		16 (12%)		
Chemotherapy treatment (% yes)		62 (45%)		
Radiation treatment (% yes)		75 (53%)		
Postmenopausal (% yes)		83 (60%)		20 (30%)

Note: The reported data reflect information obtained at the first visit.

2.2. Measures

2.2.1. Relationship satisfaction

The 4-item Couples Satisfaction Index (CSI-4) assessed relationship satisfaction (Funk and Rogge, 2007). Developed using item response theory, the short version of the CSI distinguishes between satisfied and dissatisfied partners with greater precision than most commonly used relationship satisfaction scales, and has a cut-score of 13.5 to identify notable marital dissatisfaction (Funk and Rogge, 2007). Cronbach's α for the CSI-4 ranged from 0.92 to 0.95 across the three visits.

2.2.2. Intestinal permeability biomarkers

At each visit, the fasting blood samples provided data on LBP and soluble CD14 (sCD14), two intestinal permeability biomarkers (Keane et al., 2021; Stehle et al., 2012). Serum LBP was multiplexed and measured using an electrochemiluminescence method with Meso Scale Diagnostics kits, and plates were read using the MSD Sector Imager 2400. Serum sCD14 levels were measured using a Quantikine ELISA kit, and plates were read using a Fisher Scientific Labsystems Multiskan MCC/340 plate reader. Sensitivity was 0.038 ng/mL for LBP and 125 pg/mL for sCD14. The intra- and inter-assay coefficients of variation (CV) for LBP were 2.74% and 8.33%, respectively; corresponding coefficients for sCD14 were 5.5% and 6.3%.

2.2.3. Inflammatory markers

Fasting blood samples at each visit also provided data on serum C-reactive protein (CRP) and interleukin-6 (IL-6), two key inflammatory biomarkers implicated in morbidity and mortality (Kiecolt-Glaser et al., 2002; Liu et al., 2017). IL-6 and CRP underly poor physical functioning and age-related health declines, and elevated levels reflect functional disability among healthy adults and post-treatment immune risks for cancer survivors (Lambert et al., 2020; Willeit et al., 2016). CRP was measured using a chemilluminescence methodology via the Immulite 1000 (Siemens Healthcare Diagnostics, Inc., Deerfield, IL). Sensitivity for the assay was 0.3 mg/L. The intra-assay coefficient of variation (CV) was 3.1%, and the inter-assay CV was 7.3%. IL-6 was measured using an electrochemiluminescence method with Meso Scale Discovery kits, and read using the Meso Scale Discovery Sector Imager 2400 (Meso Scale Discovery, Rockville, MD). Sensitivity was 0.3 pg/mL, and the intra-assay and inter-assay CVs were 1.43% and 4.42%, respectively. Each woman's frozen samples were assayed for all inflammatory markers at once, using the same controls for all time points for each person. Inflammatory measurements were log transformed prior to analyses to better approximate normality of residuals. Inflammation data in Table 2 and Fig. 3 represent back transformed geometric numbers (anti-log10) to enhance interpretability.

2.2.4. Covariates

To account for the effects of cancer-related variables on gut permeability (Sampsell et al., 2020), models adjusted for cancer treatment (chemotherapy and radiation treatment), cancer stage, age, physical

Table 2
Estimated Marginal Means and Standard Errors of Survivors' Primary Study Variables by Visit.

	Visit 1	Visit 2	Visit 3
Relationship satisfaction	16.08^{a} (0.54)	14.68^{b} (0.42)	15.13^{b} (0.42)
LBP (ng/mL)	4872 (188)	5202 (267)	5073 (236)
sCD14 (pg/mL)	2058 (43)	2196 (56)	2134 (52)
LBP/sCD14	2.42 (0.08)	2.35 (0.09)	2.38 (0.09)
CRP (mg/L)	1.12 (1.12)	1.10 (1.12)	1.35 (1.15)
IL-6 (pg/mL)	1.35^{a} (1.07)	1.70^{b} (1.07)	0.86^{b} (1.10)

Note. LBP = lipopolysaccharide-binding protein. sCD14 = soluble CD14. CRP = C-reactive protein. IL-6 = Interleukin-6. CRP and IL-6 data represent back transformed geometric numbers (anti-log10). Standard errors are shown in parentheses. Means that do not share the same superscript differ at $p < .05$.

comorbidities (Charlson Comorbidity Index; Charlson et al., 1987), BMI, menopause status, and visit; cancer treatment and stage were obtained from medical records. In addition, several behavioral factors have been associated with gut permeability (Conlon and Bird, 2015); thus behavioral covariates included physical activity level (Godin and Shephard, 1985), diet quality (Alternative Healthy Eating Index from 24-hour dietary recall interviews; McCullough and Willett, 2006), insomnia (Insomnia Sleep Index; Bastien et al., 2001), alcoholic beverage consumption, smoking status, and depressive symptoms (Center for Epidemiologic Studies Depression scale; Radloff, 1977).

2.3. Analysis plan

The sample size for this study was determined by an a priori power analysis conducted for the parent study, which yielded a recommended sample size of 118 survivors to detect longitudinal associations with small effects and an alpha of 0.05 at 80% power. Preliminary analyses examined bivariate correlations, as well as changes in study variables over time. We then used the MIXED MODELS procedure in SPSS version 27 to test the effects of between- and within-person relationship satisfaction on gut permeability (LBP, sCD14, and LBP/sCD14), as well as within- and between-person effects of relationship satisfaction and gut permeability on inflammation (CRP, IL-6). This modeling approach accounted for the non-independence in participants' data (i.e., an individual's scores on the same variable over time) and maximized the use of existing data by including all participants in the analyses, regardless of missing data points (Brauer and Curtin, 2018); the mixed models used restricted maximum likelihood estimation, and a subject-specific random effect captured the within-subject correlation. We separated out the within- and between-person effects by including the person-centered variable at level 1 and the between-person mean across the study at level 2. For example, within-person scores reflected how much higher or lower women's satisfaction deviated from their own average across the study; in contrast, between-person scores reflected a woman's average relationship satisfaction throughout the study. Thus, a woman's between-person score was the same at each visit, whereas the within-person score changed from visit to visit and compared how much higher or lower her score was at that visit compared to her own between-person average across the study.

Models were tested using a two-step approach to first include cancer-related covariates, and then behavioral covariates. The first models adjusted for visit, cancer treatment (chemo and radiation treatment), cancer stage, age, physical comorbidities, BMI, and menopause status. The second models added behavioral covariates, including physical activity, insomnia, alcohol use, smoking status, and depressive symptoms; diet was not significantly correlated with gut permeability and thus was not included in the subsequent analyses. The continuous covariates (age, BMI, comorbidities, physical activity, insomnia, alcohol use, and depressive symptoms) were grand mean-centered to improve the interpretability of the intercepts. In the fully adjusted models with behavioral covariates, interactions with age addressed moderation hypotheses. Significant interactions were investigated using simple slopes at 45 (-1SD), 55 (mean), and 65 (+1SD) years of age, which also correspond to typical benchmarks across adulthood.

The MLmed macro for SPSS (Rockwood and Hayes, 2017) was used to test the indirect effects of relationship satisfaction on inflammation through gut permeability at the within- and between-person levels. The macro used robust standard errors (REM estimation) to simultaneously account for within-person and between-person variability (Bauer et al., 2006). Moderated mediation analyses addressed hypotheses for the moderating effects of age. Conditional and indirect effects were tested with Monte Carlo simulations generating 95% confidence intervals (CIs) using 10,000 resamples and were significant if the CIs did not include zero (Rockwood and Hayes, 2017).

Post-hoc mixed models were conducted to assess the clinical significance of these findings. We examined the effects of within-and between-person relationship satisfaction on clinically relevant covariates, including comorbidities, physical activity, insomnia, alcohol use, and depressive symptoms. Then we assessed how key study variables changed over time by survivors and noncancer patient controls, as well as how associations between satisfaction, gut permeability, and inflammation differed by breast cancer survivors and noncancer patient controls.

3. Results

3.1. Descriptives

Table 2 provides summary statistics for key study variables. The intraclass correlations were 0.66 for relationship satisfaction, 0.53 for LBP, 0.33 for sCD14, 0.68 for LBP/sCD14, 0.67 for IL-6, 0.73 for and CRP. Correlations within study variables showed that relationship satisfaction scores were positively correlated across the visits (rs = 0.52–0.82, $ps < 0.001$), as were LBP (rs = 0.50–0.60, $ps < 0.001$), sCD14 (rs = 0.24–0.36, $ps < 0.035$, and LBP/sCD14 levels (rs = 0.64–0.70, $ps <$ 0.001). The gut permeability biomarkers were associated across the study, with higher LBP correlating with higher sCD14 (rs = 0.33–0.55, $ps < 0.001$). In addition, the inflammatory markers CRP and IL-6 were positively correlated across the visits (rs = 0.32–0.37, $ps < 0.005$).

Mixed models demonstrated that relationship satisfaction changed over time $F(2, 106) = 5.20$, $p = .007$; the boxplots in Fig. 1 depict satisfaction scores across the visits. Relationship satisfaction was higher at the first visit (before treatment) compared to the second visit (6 months posttreatment; $b = 1.40$, $SE = 0.45$, $p = .002$) and third visit (18 months posttreatment; $b = 0.95$, $SE = 0.45$, p=.035); there were no differences in relationship satisfaction at the second and third visits (p = .107). Although the CSI does not have normative data, the pre-treatment satisfaction mean was consistent with the average in previous research (e.g., m = 16; Funk and Rogge, 2007), while the two post-treatment visits were numerically lower than averages in prior work. Using the CSI cut-score, the number of women in satisfying (ns = 60, 69, and 81) and notably dissatisfying (ns = 25, 41, and 29) relationships varied across the three visits; however, chi-square tests of independence showed no association between the study visit and women's satisfaction classification ($p = 0.20$).

LBP, (p=.344), sCD14 ($p = .071$), and LBP/sCD14 ratio ($p = .682$) levels did not change over time. CRP levels did not change over time (ps > 0.063). IL-6 was lower at the first visit (before treatment) compared to the second visit (6 months posttreatment; $b = -0.10$, $SE = 0.02$, $p <$ .001) and third visit (18 months posttreatment; $b = -0.14$, $SE = 0.03$, p<.001); there were no differences in IL-6 at the second and third visits ($p = .186$).

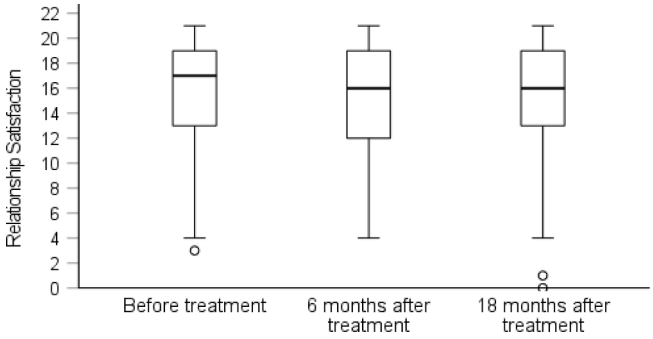

Fig. 1. Boxplots of relationship satisfaction scores across the three visits, illustrating that survivors' satisfaction was higher at the pre-treatment visit compared to the two post-treatment visits. Satisfaction scores range from 0 to 21, and those below 13.5 indicate notable dissatisfaction (Funk and Rogge, 2007).

3.2. Relationship satisfaction and gut permeability

Results from the models without the behavioral covariates (Table 3, model a) demonstrated that women's within-person, but not between-person, relationship satisfaction was associated with lower LBP ($p_{within} = 0.032$, $p_{between} = 0.539$) and LBP/sCD14 levels ($p_{within} = 0.026$, $p_{between} = 0.259$). That is, when a woman's relationship satisfaction was higher than usual, she also had lower LBP and LBP/sCD14 levels, but her average relationship satisfaction across the study was not significantly associated with her average LBP or LBP/sCD14 levels. Within- and between-person relationship satisfaction were not related to sCD14 ($p_{within} = 0.404$, $p_{between} = 0.646$).

These effects were consistent with the behavioral covariates added to the models (Table 3, model b), indicating that visits at which a woman was more satisfied with her relationship than she typically was throughout the study, the lower her own LBP ($p_{within} = 0.029$) and LBP/sCD14 ($p_{within} = 0.029$). As with the first models, the effects of within- and between-person relationship satisfaction on sCD14 were not significant ($p_{within} = 0.352$, $p_{between} = 0.516$), nor were the effects of between-person relationship satisfaction on LBP ($p_{between} = 0.804$) and LBP/sCD14 ($p_{between} = 0.329$). Significant covariates indicated that women with a higher average BMI also had higher LBP ($b = 152.87$, $SE = 28.21$, $p < .001$). In addition, women with lower alcohol consumption ($b = -0.04$, $SE = 0.02$, $p = .046$) and higher BMIs ($b = 0.07$, $SE = 0.01$, $p < .001$) had higher average LBP/sCD14 levels. Soluble CD14 was higher among women with greater depressive symptoms ($b = 10.17$, $SE = 4.13$, $p = .015$), greater insomnia ($b = 15.40$, $SE = 12.88$, $p = .032$), and those who were postmenopausal ($b = 222.34$, $SE = 102.50$, $p = .030$). We also examined if the effects of relationship satisfaction on LBP, sCD14, and LBP/sCD14 differed by age; these interactions were not significant at the within- or between-person level ($ps > 0.113$).

In addition to examining the within- and between-person effects of relationship satisfaction on the gut permeability biomarkers, secondary analyses assessed whether women with notable relationship dissatisfaction, as indicated by the CSI cut-score, had greater gut permeability. In the fully adjusted models with behavioral covariates, women in satisfying relationships had lower LBP ($b = -705.19$, $SE = 345.22$, $p = .042$) and LBP/sCD14 ($b = -705.19$, $SE = 345.22$, $p = .002$) levels than those in dissatisfying relationship (see Fig. 2). Soluble CD14 was not significantly different among satisfied and dissatisfied women ($p = .657$). Consistent with the between- and within-person analyses, age did not moderate the effects of the relationship satisfaction cut-score on LBP, sCD14, or LBP/sCD14 ($ps > 0.145$).

3.3. Gut permeability and inflammation

3.3.1. Models predicting CRP

We examined within- and between-person effects of the gut permeability biomarkers and relationship satisfaction on CRP without the behavioral covariates (Table 4, model a). Results showed that within- and between-person LBP ($p_{within} = 0.001$, $p_{between} < 0.001$), sCD14 ($p_{within} = 0.027$, $p_{between} = 0.024$), and LBP/sCD14 ($p_{within} = 0.010$, $p_{between} = 0.002$) were associated with higher CRP. Relationship satisfaction at the within- and between-person levels were not associated with CRP ($ps_{within} > 0.151$, $ps_{between} > 0.314$).

The findings were similar when the behavioral covariates were included (Table 4, model b), except within-person sCD14 no longer predicted CRP ($p_{within} = 0.065$). Thus, women had higher CRP at visits in which their LBP ($p_{within} < 0.001$) and LBP/sCD14 ($p_{within} = 0.008$) were higher than usual (within-person), and when their average LBP ($p_{between} = 0.001$), sCD14 ($p_{between} = 0.026$), and LBP/sCD14 ($p_{between} = 0.004$) were higher across the study (between-person). In addition, CRP was higher among those with a higher BMI across the models ($bs = 0.03–0.04$, $SEs = 0.01$, $ps < 0.001$). The interactions between age and within- and between-person LBP, sCD14, and LBP/sCD14 were not significant ($ps_{between} > 0.175$).

3.3.2. Models predicting IL-6

Next, we examined the models predicting IL-6 without the behavioral covariates (Table 4, model a). Within- and between-person LBP ($p_{within} < 0.001$, $p_{between} = 0.003$) and LBP/sCD14 ($p_{within} < 0.001$, $p_{between} < 0.001$) were related to higher IL-6 levels. Within-person, but not between-person, sCD14 was related to IL-6 ($p_{within} = 0.019$, $p_{between} = 0.544$). Relationship satisfaction at the within- and between-person levels were not associated with IL-6 ($ps_{within} > 0.571$, $ps_{between} > 0.617$).

Results were robust to behavioral covariates (Table 4, model b). Thus, women had higher IL-6 when their LBP ($p_{within} < 0.001$), sCD14 ($p_{within} = 0.034$), and LBP/sCD14 ($p_{within} < 0.001$) were higher than usual (within-person), and when their average LBP ($p_{between} = 0.003$) and LBP/sCD14 ($p_{between} < 0.001$) were higher across the study (between-person). In addition, consistent with the descriptive analyses, women's IL-6 was lower at the pre-treatment visit compared to visits 6 ($bs = -0.10$ to -0.06, $SEs = 0.03$, $ps = 0.001$ to 0.048) and 18 months after treatment ($bs = -0.14$ to -0.11, $SEs = 0.04$, $ps = 0.001$ to 0.008). These results were similar to those of CRP except for the non-significant between-person effects of sCD14 on IL-6.

Age moderated the effects of within-person LBP ($b = 0.000001$, $SE = 0.0000004$, $p = .001$), sCD14 ($b = 0.00001$, $SE = 0.000003$, $p < .001$), and LBP/sCD14 $b = 0.01$, $SE = 0.002$, $p < .001$) on IL-6 in the fully adjusted models with behavioral covariates. As shown in Fig. 3, simple slopes analyses showed that 55 (mean) and 65 (+1SD) year-old women experienced higher IL-6 when their LBP ($ps < 0.001$), sCD14 ($ps < 0.031$), and LBP/sCD14 ($ps < 0.001$) levels were higher than usual. In contrast, 45 (-1SD) year-old women's within-person LBP, sCD14, and LBP/sCD14 were not related to their IL-6 levels ($ps > 0.152$). The interactions between age and between-person LBP, sCD14, and LBP/sCD14 were not significant ($ps_{between} > 0.126$).

3.4. Indirect effects of relationship satisfaction on inflammation through gut permeability

Given the significant effects of relationship satisfaction on LBP and LBP/sCD14, as well as LBP and LBP/sCD14 on CRP and IL-6, we tested multilevel mediation models to assess whether relationship satisfaction was linked indirectly to inflammation through gut permeability at the within- and between-person levels. The MLmed macro allows for six

Table 3
Relationship Satisfaction Coefficients (and Standard Errors) on Survivors' Gut Permeability.

	LBP		sCD14		LBP/sCD14	
	Model a	Model b	Model a	Model b	Model a	Model b
Predictors						
Rel. satisfaction (WI)	−113.20(52.11)*	−118.69(53.77)*	−10.88(13.00)	−12.42(13.28)	−0.038(0.017)*	−0.039(0.018)*
Rel. satisfaction (BW)	−28.86(46.86)	−12.14(48.67)	4.81(10.46)	6.97(10.69)	−0.021(0.018)	−0.016(0.019)

Note. Rel. = relationship. WI = within. BW = between. LBP = lipopolysaccharide-binding protein. sCD14 = soluble CD14. Model a controls for visit, cancer stage, chemotherapy, radiation, comorbidities, age, BMI, and menopause. Model b additionally controls for insomnia, physical activity, alcohol use, and smoking status. Within-person effects demonstrate fluctuations from visit to visit. Between-person effects demonstrate average effects across the study.
*$p < .05$. **$p < .01$. ***$p < .001$.

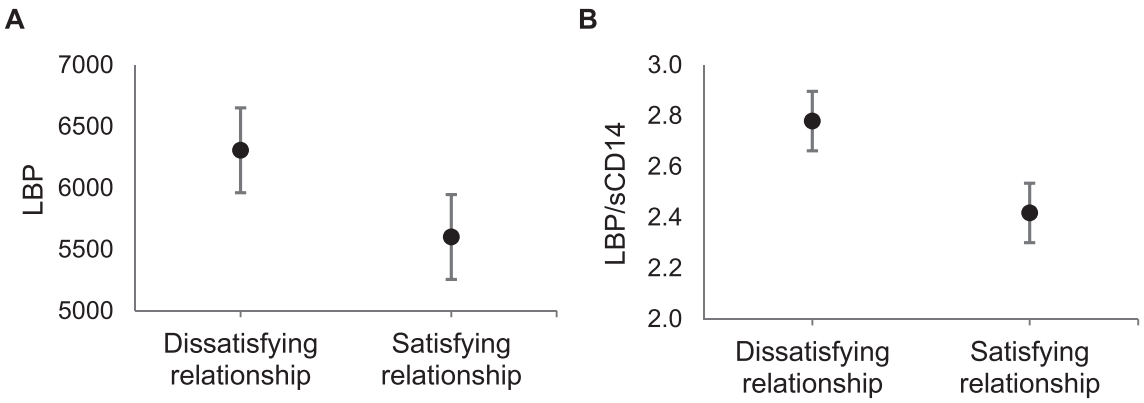

Fig. 2. LBP = lipopolysaccharide-binding protein. sCD14 = soluble CD14. Average estimated marginal means of gut permeability among survivors with notable relationship dissatisfaction and those in satisfying relationships across the study.

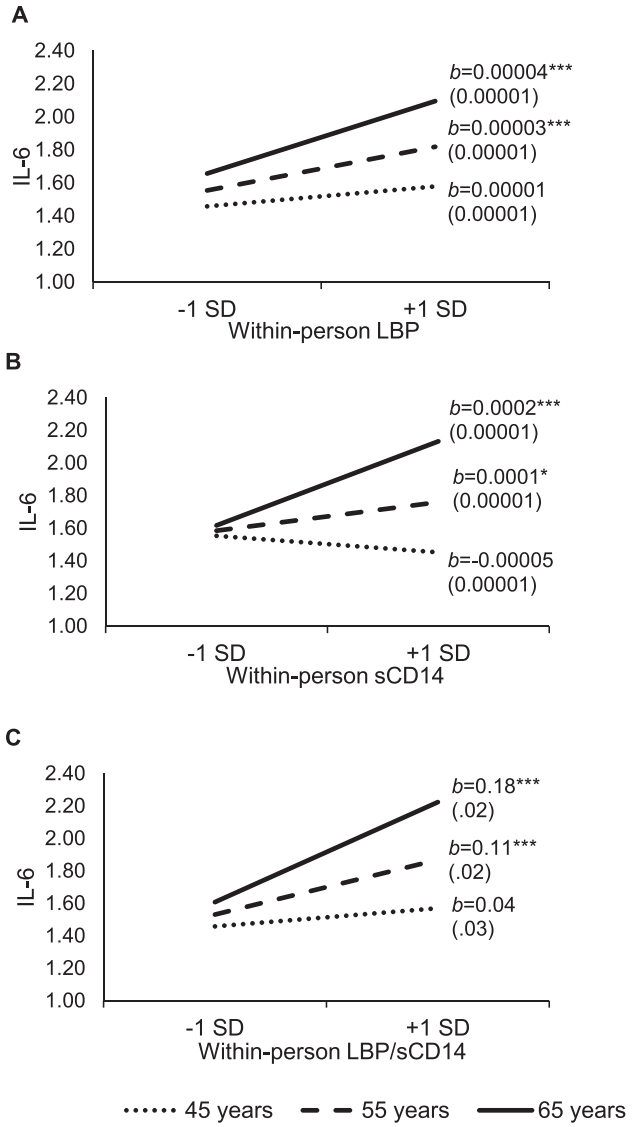

Fig. 3. LBP = lipopolysaccharide-binding protein. sCD14 = soluble CD14. IL-6 = Interleukin-6. Estimated slopes (and standard errors) in IL-6 as a function of survivors' age and within person (A) LBP, (B), sCD14, and (C) LBP/sCD14. IL-6 data represent back transformed geometric numbers (anti-log10). Slopes are shown for ages 45 (-1SD), 55 (mean), and 65 (+1SD), which also correspond to typical benchmarks across adulthood. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 4
Relationship Satisfaction and Gut Permeability Coefficients (and Standard Errors) on Survivors' Inflammation.

	CRP		IL-6	
	Model a	Model b	Model a	Model b
Predictors				
Rel. satisfaction (WI)	−0.01(0.01)	−0.01(0.01)	−0.0007 (0.005)	−0.000002 (0.005)
Rel. satisfaction (BW)	0.01(0.01)	0.01(0.01)	−0.001 (0.007)	−0.002 (0.008)
LBP (WI)	0.0001 (0.00002)**	0.0001 (0.00002)**	0.00004 (0.00001) ***	0.00004 (0.000006) ***
LBP (BW)	0.0001 (0.00002) ***	0.00002 (0.00002) ***	0.00004 (0.00001)**	0.000002 (0.00002)**
Predictors				
Rel. satisfaction (WI)	−0.02(0.01)	−0.01(0.01)	−0.003 (0.005)	−0.003 (0.006)
Rel. satisfaction (BW)	0.01(0.01)	0.01(0.01)	−0.004 (0.007)	−0.005 (0.008)
sCD14 (WI)	0.0002 (0.0001)*	0.0001 (0.0001)	0.0001 (0.00004)*	0.0001 (0.00004)*
sCD14 (BW)	0.0002 (0.0001)*	0.0002 (0.0001)*	0.00004 (0.0001)	0.00003 (0.00007)
Predictors				
Rel. satisfaction (WI)	−0.01(0.01)	−0.01(0.01)	−0.001 (0.005)	−0.0004 (0.005)
Rel. satisfaction (BW)	0.01(0.01)	0.01(0.01)	−0.001 (0.007)	−0.001 (0.007)
LBP/sCD14 (WI)	0.16(0.04) ***	0.15(0.05)**	0.11(0.02) ***	0.11(0.02)***
LBP/sCD14 (BW)	0.17(0.04) ***	0.15(0.05)**	0.13(0.04) ***.	0.14(0.04)***

Note. Rel. = relationship. WI = within. BW = between. LBP = lipopolysaccharide-binding protein. sCD14 = soluble CD14. CRP = C-reactive protein. IL-6 = Interleukin-6. Model a controls for visit, cancer stage, chemotherapy, radiation, comorbidities, age, BMI, and menopause. Model b additionally control for insomnia, physical activity, alcohol use, smoking status, and relationship satisfaction. Within-person effects demonstrate fluctuations from visit to visit. Between-person effects demonstrate average effects across the study. *$p < .05$. **$p < .01$. ***$p < .001$.

covariates; therefore, we adjusted for the covariates significantly associated with LBP, LBP/sCD14, CRP, and IL-6 in the previous models (i.e., BMI, alcohol use), along with cancer variables including chemotherapy,

radiation, comorbidities, and cancer stage.

As shown in Fig. 4, the indirect effects of relationship satisfaction on CRP and IL-6 through LBP were significant at the within-person level (CRP 95% CI [−0.0176, −0.0002]; IL-6 95% CI [−0.0104, −0.0001]), but not between-person level (CRP 95% CI [−0.0101, 0.0069]; IL-6 95% CI [−0.0044, 0.0029]). Thus, when women were more satisfied with their relationships than usual, they had lower LBP than usual, which, in turn, was associated with lower than their own average CRP and IL-6 levels. The indirect effects of within- and between-person relationship satisfaction on CRP and IL-6 through LBP/sCD14 were not significant (CRP_{within} 95% CI [−0.0093, 0.0008], $CRP_{between}$ 95% CI [−0.0113, 0.0024]; $IL\text{-}6_{within}$ 95% CI [−0.0074, 0.0005], $IL\text{-}6_{between}$ 95% CI [−0.0068, 0.0013). We also tested age as a moderator, given the significant interactions between age and within-person LBP and LBP/sCD14 on IL-6; moderated mediation analyses showed that age did not alter the indirect effects of relationship satisfaction on IL-6 through LBP (index of moderated mediation = −0.0001, 95% CI [−0.0003, 0.0000]) or LBP/sCD14 (index of moderated mediation = −0.0001, 9% CI [−0.0004, 0.0000]).

3.5. Post-Hoc analyses

3.5.1. Relationship satisfaction and clinically relevant covariates

At the within-person level, survivors reported lower insomnia when they were more satisfied with their relationships than usual ($b = -0.03$, $SE = 0.01$, p=.03). At the between-person level, survivors had lower depressive symptoms when their average relationship satisfaction was higher across the study compared to those with lower average satisfaction ($b = -0.24$, $SE = 0.11$, p=.03). There were no other significant associations with covariates ($ps > 0.08$).

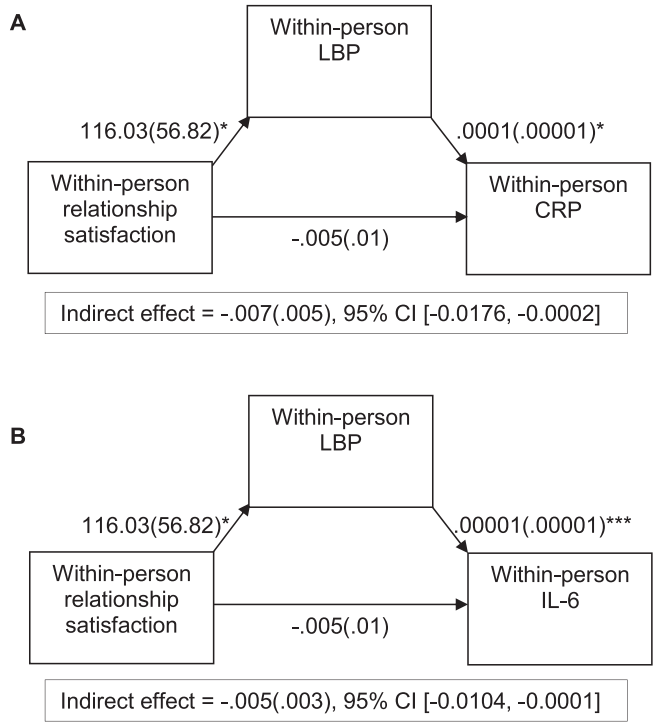

Fig. 4. LBP = lipopolysaccharide-binding protein. CRP = C-reactive protein. IL-6 = Interleukin-6. Coefficients (and standard errors) for the within-person (1-1-1) multilevel mediation models on survivors' CRP and IL-6. Within-person analyses demonstrate associations among fluctuations in relationship satisfaction, LBP, and inflammation (CRP, IL-6) from visit to visit. *p < 0.05; **p < 0.01; ***p < 0.001.

3.5.2. Differences between cancer and noncancer patient controls

Preliminary mixed models showed sCD14 changed over time by group, $F(2, 191) = 3.27$, $p = .04$. Cancer survivors' sCD14 was higher than that of noncancer patient controls at the first visit (survivors: $b = 2054$, $SE = 39.76$; controls: $b = 1859$, $SE = 57.13$; p=.005); there were no differences in cancer survivors' and noncancer patient controls' sCD14 at the second and third visits ($ps > 0.75$). There were no group differences in relationship satisfaction, LBP, LBP/sCD14, CRP, or IL-6 ($ps > 0.21$), nor did group alter how these variables changed over time ($ps > 0.10$).

Preliminary analyses on the covariates showed breast cancer survivors, but not the noncancer patient controls, had lower insomnia when they were more satisfied with their relationships than usual (i.e., within-person effects; survivors: $b = -0.04$, $SE = 0.01$, $p = .004$; controls: $b = 0.02$, $SE = 0.02$, $p = .50$); also, when satisfaction was lower than usual, survivors had greater insomnia than noncancer patient controls ($b = 0.28$, $SE = 0.12$, $p = .02$). Cancer survivors reported greater depressive symptoms than noncancer patient controls at the pre-treatment visit ($b = 3.38$, $SE = 1.57$, $p = .03$); cancer survivors' depressive symptoms also decreased over time and were higher before treatment than at the 6- and 18-month post-treatment visits (6 month: $b = 6.58$, $SE = 0.94$, $p < .001$; 18 month: $b = 7.32$, $SE = 0.98$, $p < .001$). There were no other significant group differences on covariates ($ps > 0.09$).

When looking at group differences in the main analyses, group did not moderate the links between relationship satisfaction and gut permeability ($ps > 0.08$), or the effects of relationship satisfaction and gut permeability on IL-6 ($ps > 0.08$). However, group moderated the effects of each gut permeability marker on CRP. At the between-person level, cancer survivors had higher CRP when their average sCD14 was higher across the study ($b = 0.0002$, $SE = 0.0001$, $p = .01$); these between-person effects were not significant for the noncancer patient controls ($b = -0.0001$, $SE = 0.0001$, $p = .40$). At the within-person level, CRP was higher when survivors and noncancer patient controls had higher LBP (survivors: $b = -0.0001$, $SE = 0.00002$, $p < .001$; controls: $b = 0.00002$, $SE = 0.02$, $p < .001$) and LBP/sCD14 (survivors: $b = 0.15$, $SE = 0.05$, $p = .004$; controls: $b = 0.35$, $SE = 0.07$, $p < .001$) than usual. Given the nonsignificant group effects on links between relationship satisfaction and gut permeability, we did not test group differences in the indirect effects of relationship satisfaction on inflammation through gut permeability.

4. Discussion

In accord with Kiecolt-Glaser and colleagues' (2019) conceptual model on intimate relationships, the gut environment, and inflammation, this longitudinal study demonstrated that breast cancer survivors in satisfying relationships had lower gut permeability and, in turn, lower inflammation than survivors in dissatisfying relationships. These associations were significant at the within-person level: at visits in which a survivor's relationship satisfaction was higher than usual, her own gut permeability was also lower than usual, which ultimately was associated with lower than her own average inflammation levels. In addition, as indicated by the CSI cut-score, survivors in satisfying relationships had lower average gut permeability across the study, whereas survivors with notable relationship dissatisfaction had higher average gut permeability. Likewise, greater gut permeability on average was associated with higher inflammation. In addition to considering average associations across time, these findings highlight the value of taking a within-person approach to capture how changes in a breast cancer survivor's relationship satisfaction are connected to her own gut permeability and inflammation across early survivorship. From cancer diagnosis to nearly two years after finishing cancer treatment, satisfying relationships may provide physiological health benefits.

When examining specific gut permeability and inflammatory markers, the results showed that when survivors were more satisfied with their relationships than usual, their LBP and LBP/sCD14 levels

were lower. These findings are similar to prior work demonstrating that LBP and the LBP/sCD14 ratio were key leaky gut biomarkers associated with relationship interactions in healthy adults (Kiecolt-Glaser et al., 2018). The relative balance of LBP and sCD14, rather than sCD14 alone, may be particularly important. High LBP and low sCD14 suggest that the body is not clearing circulating endotoxin, posing additional inflammatory risks. Indeed, our results showed that greater LBP, sCD14, and LBP/sCD14 levels were associated with higher CRP and IL-6. Relationship satisfaction was indirectly, but not directly, associated with CRP and IL-6 through LBP. These findings demonstrate LBP's mechanistic utility in connecting satisfying relationships to lower inflammation across two important inflammatory markers.

Additionally, age moderated the effects of each gut permeability biomarker on inflammation; IL-6 was higher when older survivors experienced higher than usual LBP, sCD14, and LBP/sCD14, but not when younger survivors experienced higher than usual gut permeability. These results suggest intestinal permeability is particularly pro-inflammatory for older breast cancer survivors. Older survivors' greater gut-related inflammatory consequences might indicate inflamm-aging, or accelerated aging of the immune system (Franceschi et al., 2006; Stehle et al., 2012). That is, older survivors' age-related gut barrier and immune system weakening might have primed stronger proinflammatory responses to their higher than typical gut permeability. Therefore, inflammation may accompany heightened gut permeability, especially among older survivors, with implications for age-related frailty, morbidity, and mortality (Kiecolt-Glaser, Wilson, and Madison, 2019; Stehle et al., 2012). Age did not moderate the effects of relationship satisfaction on gut permeability, suggesting that a survivors' relationship may impact gut permeability for survivors of all ages.

These findings contribute to theoretical conceptualization on the physiological pathways connecting relationships to health (Kiecolt-Glaser, Wilson, and Madison, 2019; Robles et al., 2014; Shrout and Kiecolt-Glaser, 2020; Shrout, 2021). Kiecolt-Glaser and colleagues' (2019) conceptual model addressing relationships and the gut environment suggests that partners' relationship satisfaction can influence healthy or unhealthy aging through changes in intestinal permeability and inflammation. The current results provide new evidence for the conceptual model by demonstrating that survivors' satisfying relationships were associated with lower gut permeability, and that their relationships' protective effects on inflammation were indirect through lower gut permeability. These findings correspond with previous research showing marital satisfaction was not directly associated with inflammation (Shrout et al., 2020; Uchino et al., 2018), and that gut permeability may be a mechanistic pathway connecting marital interactions to inflammation (Kiecolt-Glaser, Wilson, and Madison, 2019). The gut environment is a new promising candidate for understanding a relationship's long-term health impact.

The present study also contributes to the literature on health benefits of breast cancer survivors' relationships—a group with elevated gut- and immune-related health consequences. Cancer survivors have heightened risks for a weakened gut barrier and thus greater intestinal permeability (Bajic et al., 2018; Jordan et al., 2018). Moreover, a leaky gut and its inflammatory consequences are associated with greater depression, accelerated aging, and chronic disease development (Gonzalez-Quintela et al., 2013; Madison et al., 2020). The current findings show that survivors' strong relationships across early survivorship may be associated with lower gut permeability and inflammation, potentially altering their long-term health risks (Aggarwal et al., 2006; Pierce et al., 2009). Survivors' satisfying relationships were also associated with lower insomnia and depressive symptoms, each of which as been linked to poorer physical functioning, psychiatric diagnoses, and quality of life (Croyle and Rowland, 2003; Karakoyun-Celik et al., 2010; Reyes-Gibby et al., 2012). Survivors' relationship may therefore have clinical implications for their psychological and physical functioning. In accordance with national guidance from the American Society of Clinical Oncology (Andersen et al., 2014) to screen for distress, these results underscore the importance of screening survivors' relationships satisfaction throughout treatment and referring dissatisfied couples to counseling when appropriate.

This study has several notable strengths. The assessment of survivors from cancer diagnosis to 6 and 18 months after cancer treatment provided novel insight into the connections among survivors' relationships, gut permeability, and inflammation during early survivorship. This longitudinal design also allowed for within-person examination, which demonstrated that changes in a survivor's relationship satisfaction from visit to visit, rather than how her relationship satisfaction compared to other survivors, was important for how her gut permeability and inflammation changed throughout the study. These findings show the importance of disaggregating between- and within-person effects and assessing intraindividual differences in connections between relationship satisfaction, gut permeability, and inflammation. In addition, gut permeability also was identified as a physiological pathway linking survivors' relationships to their inflammation across early survivorship. These findings pave a new way for future research to address how relationships can "get under the skin" to influence health. Including cancer survivors and women with an initial suggestive test of cancer followed by a benign diagnosis allowed us to examine potential differences in relationship and health links. Cancer survivors, but not women with a benign diagnosis, had lower insomnia when they were more satisfied with their relationships than usual. Likewise, each gut permeability marker was associated with CRP for the cancer survivors, but only LBP and LBP/sCD14 were linked to CRP among the women with a benign diagnosis. Though these findings were exploratory and additional research with larger group sizes is needed, they provide initial evidence that fluctuations in intestinal permeability and the gut environment carry inflammatory consequences for women with and without a cancer history.

Though the current study adjusted for important cancer and behavioral covariates, one limitation is that our sample's demographic characteristics were fairly homogeneous. It is important to address how relationship satisfaction contributes to survivors' gut permeability and inflammation in more diverse samples. In addition, survivors' BMI, alcohol consumption, depressive symptoms, insomnia, and menopausal status were linked to gut permeability in the full models, and may be particularly important for the gut environment; although diet was not associated with these gut biomarkers, their effects should be examined on other aspects of gut health, such as diversity and richness, and across the survivorship trajectory. The current study focused on survivors' relationships, gut permeability, and inflammation before treatment and during early survivorship, and thus we did not obtain longer-term follow-up measurements. Examining how changes in survivors' relationships are linked to changes in their gut permeability and inflammation throughout survivorship may further our understanding on the long-term health benefits of a satisfying relationships. Moreover, recent work has demonstrated how individuals' relationship satisfaction is associated with their own and their partners' physiological functioning and long-term health (Shrout, 2021). Future research should address connections between each partner's satisfaction, gut permeability, and inflammation, and whether these physiological mechanisms promote health as they age. Also, work is needed to understand gut- and immune-related health consequences among women who are not in relationships. Close relationships with family and friends may instead provide protective health effects across the cancer trajectory.

This longitudinal study demonstrated significant ties between survivors' satisfying relationships and lower gut permeability and inflammation across early survivorship. Survivors who were satisfied across the study had lower average gut permeability, while their counterparts in notably dissatisfying relationships had higher average gut permeability. At the within-person level, visits in which a survivor was more satisfied with her relationship than usual, her own gut permeability and, in turn, inflammation were lower at that visit than at a different visit when she was less satisfied. These associations held even after adjusting

for important cancer-related and behavioral covariates, suggesting that breast cancer survivors' relationship satisfaction has unique implications for gut permeability and inflammation across early survivorship. This research identifies gut permeability and its associated inflammation as pathways through which breast cancer survivors' relationships may influence long-term health.

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