Psychoneuroendocrinology 98 (2018) 52–60

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Marital distress, depression, and a leaky gut: Translocation of bacterial endotoxin as a pathway to inflammation

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ARTICLE INFO

Keywords:
Marriage
Depression
Inflammation
Microbiome
Leaky gut
Intestinal permeability

ABSTRACT

Background: Marital distress and depression work in tandem to escalate risks for inflammation-related disorders. Translocation of bacterial endotoxin (lipopolysaccharide, LPS) from the gut microbiota to blood circulation stimulates systemic inflammatory responses.

Methods: To investigate increased gut permeability (a "leaky gut") as one potential mechanistic pathway from marital distress and depression to heightened inflammation, this secondary analysis of a double-blind, randomized crossover study examined serial assessments of two endotoxin biomarkers, LPS-binding protein (LBP) and soluble CD14 (sCD14), as well as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α) during two separate 9.5 h visits. The 43 (N = 86) healthy married couples, ages 24–61 (mean = 38.22), discussed a marital disagreement during both visits; behavioral coding of these interactions provided data on hostile marital behaviors, a hallmark of marital distress. The Structured Diagnostic Interview for DSM-IV assessed participants' mood disorder history.

Results: Participants with more hostile marital interactions had higher LBP than those who were less hostile. Additionally, the combination of more hostile marital interactions with a mood disorder history was associated with higher LBP/sCD14 ratios. Higher LBP and LBP/sCD14 were associated with greater CRP production; for example, only 21% of low LBP participants (lowest quartile) had average CRP across the day > 3, compared to 79% of those in the highest quartile. Higher sCD14 was associated with higher IL-6.

Conclusions: These bacterial LPS translocation data illustrate how a distressed marriage and a mood disorder history can promote a proinflammatory milieu through increased gut permeability, thus fueling inflammation-related disorders.

1. Introduction

Unhappy marriages take a toll on mental and physical health. For example, marital stress worsened the prognosis for recurrent coronary events three-fold (Orth-Gomer et al., 2000). Among patients with congestive heart failure, marital quality was as strong a predictor of four-year survival as well as patients' illness severity (Coyne et al., 2001). A meta-analysis reported that the relationships between marital quality and clinical health endpoints had statistical effect sizes similar in magnitude to the health effects of diet and exercise (Robles et al.,

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https://doi.org/10.1016/j.psyneuen.2018.08.007
Received 20 April 2018; Received in revised form 3 July 2018; Accepted 2 August 2018

2014).

In work from our lab, proinflammatory cytokine production increased following marital disagreements characterized by high rates of negative or punishing behaviors (e.g., hostility, sarcasm, withdrawal/disengagement), the hallmarks of marital distress (Kiecolt-Glaser et al., 2005); other studies have linked troubled marriages with chronically heightened inflammation (Shen et al., 2010; Whisman and Sbarra, 2012; Donoho et al., 2013; Kiecolt-Glaser et al., 2015c). Marital discord's notable consequences include an amplified risk for inflammation-related diseases and disorders including depression, cardiovascular disease, metabolic syndrome, diabetes, and slower wound healing (Orth-Gomer et al., 2000; Gallo et al., 2003; Kiecolt-Glaser et al., 2005; Troxel et al., 2005; Beach, 2014; Joseph et al., 2014; Whisman et al., 2014). The gut microbiota can fuel inflammation (Rogers et al., 2016), providing a potential mechanistic pathway linking marital distress to inflammation and inflammation-related diseases.

Translocation of bacterial endotoxin (lipopolysaccharide, LPS) from the gut microbiota to blood circulation – the result of a "leaky gut"– stimulates systemic inflammatory responses (Kelly et al., 2012; Stehle et al., 2012). Hepatocytes and intestinal epithelial cells can be induced to release LBP through LPS stimulation, as well as by stimulation with inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α, and IL-22) (Wan et al., 1995; Wolk et al., 2007). LPS-binding protein (LBP) and soluble CD14 (sCD14) are produced in response to bacterial translocation of endotoxin (Amar et al., 2003; Stehle et al., 2012). LBP binds LPS and presents LPS to CD14, the receptor for LPS-LBP complexes (Wright et al., 1990; Ulevitch and Tobias, 1995; Stehle et al., 2012). The endotoxin receptor sCD14 facilitates proinflammatory signaling following endotoxin exposure (Wright et al., 1990). CD14 presents LPS to Toll-like receptor (TLR)-4, a process that leads to NF-κB activation and proinflammatory cytokine production. The relative balance of LBP and sCD14 is also important; higher LBP/sCD14 ratios promote heightened inflammation (Laugerette et al., 2012, 2014).

Rodent models have shown that stress-induced changes in the gut microbiota can provoke bacterial translocation (Bailey et al., 2011; Ait-Belgnaoui et al., 2012), and that intestinal bacteria contribute to stress-induced immunopotentiation (Bailey et al., 2011; Maslanik et al., 2012). Although human data are sparse, one study demonstrated that both the prevalence and median values of serum antibodies against the LPS of six enterobacteria were greater in depressed patients than controls (Maes et al., 2008). In another study, major depressive disorder (MDD) patients had elevated expression of bacterial DNA, indicative of bacterial translocation, compared to nondepressed controls, and the magnitude was correlated with depressive symptom severity (Keri et al., 2014). These depression-related findings are relevant to the current study: unhappy marriages are a potent risk factor for depression (Beach, 2014).

The gut microbiota can impact energy balance, glucose metabolism, and obesity-related inflammation, in part through gut leakiness (Newsholme and Homem de Bittencourt, 2016). Recent work from our lab has shown that stress and a mood disorder history alter metabolic responses to high-fat meals (Kiecolt-Glaser et al., 2015b,c, 2017). In a double-blind, randomized crossover study, couples ate a high-fat meal and then discussed a marital disagreement during each of two visits (Kiecolt-Glaser et al., 2015c). When combined with a mood disorder history, men and women who had more hostile marital interactions had lower post-meal energy expenditure: 128 kcal, a difference that could add ~7.7 pounds/year. Furthermore, higher levels of hostile behaviors among those who had a mood disorder history were also associated with higher post-meal insulin compared with other participants. Higher insulin levels stimulate food intake and visceral fat accumulation (Dallman, 2010), and thus would act in tandem with lower energy expenditure to promote obesity.

In this secondary analysis of the same couples, we hypothesized that higher levels of hostile behavior and a mood disorder history would be associated with higher LBP, sCD14, and a higher LBP/sCD14 ratio. We also expected that higher LBP, sCD14, and a higher LBP/sCD14 ratio would be associated with greater systemic inflammation: C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α). Our endotoxin biomarkers have relatively slow response times (Hudgins et al., 2003), and thus we did not expect them to acutely change in response to the marital conflict or the meals.

2. Methods and materials

2.1. Design and overview

This double-blind, randomized crossover study assessed metabolic responses following high-fat meals; detailed methods have been described previously (Kiecolt-Glaser et al., 2015c). Couples completed an online screening questionnaire and an in-person screening visit. During two separate full-day visits to a hospital research unit, couples received either a high saturated fat meal or a high oleic sunflower oil meal (order randomized) after fasting for 12 h.

A 25-min baseline followed catheter insertion, and then couples ate their meals. The marital problem discussion was introduced two hours post-meal. Couples remained on the unit for ~7 h after meal completion without further food, only water. Serum LBP, sCD14, CRP, IL-6 and TNF-α were assessed following the resting baseline, and then every 2 h post-meal. Body composition was assessed by dual X-ray absorptiometry (DXA).

Visits occurred 1–25 weeks apart (mean = 4.45, SD = 4.76). Although 55% of visits occurred within 3 weeks, some were more widely spaced due to participants' work schedules.

2.2. Participants

Using print and web-based announcements, we recruited 43 healthy couples (N = 86), ages 24–61, who had been married at least 3 years. Individuals were ineligible if they or their partner had any notable chronic health problems, including gut-related disorders such as ulcerative colitis, Crohn's disease, and celiac disease. Other exclusions included smoking, alcohol/drug abuse, diabetes, anemia, and any prescription medications except birth control pills (N = 5) and levothyroxine (N = 3). We prioritized recruitment of heavier sedentary individuals to maximize the likelihood of stress-related metabolic responses, and thus our inclusion criteria specified a maximum of 2 h of vigorous activity per week for BMI $<$ 25 and 5 h per week for BMI $\geq$ 25. Table 1 lists additional sample characteristics. The institutional review board approved this study, and each participant provided written informed consent before participation.

2.3. Standardized pre-study meals

On the day before each study visit, couples received three standardized meals to reduce the variability associated with recent food intake, as previously described (Kiecolt-Glaser et al., 2015c). Participants' last meals, eaten no later than 7:30 PM the night before admission, were light and low in fat.

2.4. Research meals

Both research meals during the visit included 930 kcals, with 60 g fat, 59 g carbohydrate, and 36 g protein (percent of total kcals = 60, 25, 15, respectively). However, to address the parent study's metabolic questions (Kiecolt-Glaser et al., 2015c), the high saturated fat meal contained 16.84 g palmitic and 13.5 g oleic, compared to 8.64 g palmitic and 31.21 g oleic for the high oleic sunflower oil meal. Compliance was good: participants consumed 91.18 $\pm$ 8.62% of these meals.

Table 1
Participant Characteristics.

	Men (N = 43)	Women (n = 43)	Overall Sample (n = 86)
Age, years	39.25 (9.17)	37.19 (7.00)	38.22 (8.18)
BMI, kg/m^2	31.96 (5.06)	32.17 (6.58)	32.07 (5.83)
Waist, cm	106.71 (14.72)	99.14 (13.63)	102.93 (14.61)
Trunk fat, g	19502.14 (7761.57)	19,375.02 (7382.91)	19,438.58 (7530.19)
Activity, hours per week	3.52 (5.09)	1.86 (2.00)	2.70 (3.95)
Systolic blood pressure, mmHg	127.12 (12.18)	111.67 (12.30)	119.40 (14.44)
Diastolic blood pressure, mmHg	76.00 (7.21)	67.72 (8.22)	71.85 (8.74)
Years married			11.49 (6.64)
Race			
White	35 (81%)	35 (81%)	70 (81%)
Black	8 (19%)	8 (19%)	16 (19%)
Education			
Graduate degree	17 (40%)	20 (47%)	37 (43%)
College graduate	13 (30%)	8 (19%)	21 (24%)
Partial college	6 (14%)	10 (23%)	16 (19%)
High school graduate	5 (12%)	5 (12%)	10 (12%)
≤ 11 years high school	2 (5%)	0 (0%)	2 (2%)
Hostile behavior score*			22.7 (29.1)
Couples' Satisfaction Index**			124.2 (31.6)

Data shown are mean (SD) or N (%).
* Summed across spouses and averaged across visits.
** Averaged across spouses.

2.5. Interview data

The mood disorder modules of the Structured Clinical Interview for DSM-IV, nonpatient version (SCID-NP) provided data on lifetime prevalence. Interviews were administered by trained clinical psychology graduate students or staff. Consensus meetings reviewed the recorded interviews to obtain diagnoses. SCID-NP data showed that 16 people met criteria for a past mood disorder (MDD = 13, and 1 each for depression NOS, bipolar, and dysthymia). Average time since diagnosis was 7.95 years (SD = 6.27). Two currently met criteria (1 MDD, 1 dysthymia).

2.6. Questionnaires

The 32-item Couples Satisfaction Index (CSI) assessed marital satisfaction (Funk and Rogge, 2007). Developed using item response theory, the CSI discriminates well between satisfied and dissatisfied couples with greater precision than the most commonly used marital scales (Funk and Rogge, 2007). The Pittsburgh Sleep Quality Index (PSQI) evaluated sleep quality and disturbances over a one-month interval (Buysse et al., 1989). The CHAMPS assessed the weekly frequency and duration of various physical activities (Harada et al., 2001; Stewart et al., 2001).The Center for Epidemiological Studies Depression (CES-D) Scale assessed depressive symptoms in the past week (Radloff, 1977).

2.7. Marital problem discussion

Hostile behavior, a hallmark of marital distress, has predicted couples' physiological changes more reliably than self-reports (Kiecolt-Glaser and Newton, 2001). To obtain behavioral data, the experimenter first conducted a 10–20 minute interview to identify the most conflictual topics (Kiecolt-Glaser and Newton, 2001; Kiecolt-Glaser et al., 2005), based on each spouse's Relationship Problem Inventory ratings (Knox, 1971). Couples were then asked to discuss and try to resolve one or more marital issues that the interviewer judged to be the most conflict-producing, e.g., money, communication, or in-laws. The research team remained out of sight while videotaping the subsequent 20-min discussion.

Marital interaction tapes were coded using the Rapid Marital Interaction Coding System (RMICS) which discriminates well between distressed and nondistressed couples (Heyman, 2004). Distressed marriages are characterized by negative affect, conflictual communication, and poor listening skills (Kiecolt-Glaser and Newton, 2001; Kiecolt-Glaser et al., 2005; Robles et al., 2014). Accordingly, the composite index summed each of the four following RMICS codes, which we refer to collectively as hostility: psychological abuse (e.g., disgust, contempt, belligerence, as well as nonverbal behaviors like glowering), distress-maintaining attributions (e.g., "You're only being nice so I'll have sex with you tonight" or "You were being mean on purpose"), hostility (e.g., criticism, hostile voice tone, or rolling the eyes dramatically) and withdrawal (behaviors that suggest pulling back from the interaction or not listening).

Marital behavior, as measured by the composite hostile behavior scores, was highly correlated across visits (Spearman $r = 0.77$, $p < 0.0001$) and within couples (Spearman $r = 0.81$, $p < 0.0001$), and thus the couple's hostile behavior sum was averaged across visits for use as a predictor in our analyses. Interrater agreement for the RMICS hostility composite (Holley and Guilford, 1964; Xu and Lorber, 2014) was high (Holley and Gilford's G index = 0.88). This hostility composite score shared a moderate, negative association with couples' self-reported marital satisfaction (Spearman $r = -0.33$, $p < 0.05$).

2.8. Assays

Serum IL-6, TNF-α, CRP, and LBP were multiplexed and measured using an electrochemilluminescence method with Meso Scale Discovery kits, while sCD14 levels were measured using a Quantikine ELISA kit from R&D Systems. Each couple's stored samples from both visits were assayed for each marker in one run, thus using the same controls for all time points. Sensitivity for IL-6 and TNF-α was 0.3 pg/ml, CRP was 0.7 ng/mL, LBP was 0.038 ng/mL, and sCD14 was 125 pg/mL The intra-assay coefficient of variation for IL-6 was 3.42%, and the inter-assay coefficient of variation was 8.425%; corresponding values for TNF-α were 2.59% and 8.14%, 6.28% and 7.36% for CRP, 2.74% and 8.33% for LBP, and 5.5% and 6.3% for sCD14.

2.9. Statistical methods

To summarize the repeated measurements of endotoxin and inflammatory markers, area under the curve with respect to ground (AUC_G) was calculated from baseline (pre-meal) to the last time point (7.5 h post-meal) for serum TNF-α, IL6, CRP, LBP, sCD14, and LBP/sCD14 ratio (Pruessner et al., 2003), Table 2. We used AUC_G as a summary measure since it captures the overall intensity of exposure, and we did not expect acute meal- or conflict-related changes in the endotoxin markers due to their relatively slow response times (Hudgins et al., 2003). Fig. 1 shows trajectories of all outcomes across the day; complete summary statistics are provided in eTable 1. All three endotoxin markers showed statistically significant, though small, changes, but LBP and the LBP/sCD14 ratio actually decreased across the day, and there were no meal-related differences in these slopes (ps > 0.12). These endotoxin markers also showed remarkable stability from one visit to the next (LBP, Pearson $r = 0.86$, $p < 0.0001$; sCD14, Pearson $r = 0.85$, $p < 0.0001$). Previous analyses (Kiecolt-Glaser et al., 2015b,c) showed an increase in IL-6 post-meal, but no change in TNF-α, and no meal-related differences; similar analyses showed no change in CRP post-meal and no meal effects. AUC_G for both LBP and sCD14 was rescaled by dividing values by 1000 to avoid extremely small regression coefficients. Several of the AUC_G variables had skewed distributions, thus all regression models were fit using generalized estimating equations (GEE) to relax parametric assumptions. In these models, we used

Table 2
Endotoxins and Inflammatory markers at baseline and summarized across the day (area under the curve; AUC).

Outcome		N*	Mean (SD)	Median (IQR)
LBP	Baseline	154	41876 (17,105)	39,700 (30100–50100)
(*82 subjects*)	AUC	154	334717 (128,817)	327,165 (241018–397420)
sCD14	Baseline	157	1374 (296)	1350 (1190–1560)
(*83 subjects*)	AUC	157	12113 (2441)	11,873 (10582–13445)
LBP/sCD14	Baseline	154	32 (15)	31 (21–39)
(*82 subjects*)	AUC	154	239 (110)	224 (162–305)
CRP	Baseline	160	4.3 (5.1)	2.6 (0.92–5.9)
(*86 subjects*)	AUC	160	35 (41)	20 (8.0–49)
IL-6	Baseline	159	1.5 (1.7)	1.0 (0.69–1.5)
(*86 subjects*)	AUC	159	20 (13)	17 (11–25)
TNF-a	Baseline	160	4.8 (1.1)	4.7 (3.9–5.5)
(*86 subjects*)	AUC	160	38 (8.4)	38 (33–44)

AUC = area under the curve.
* N = number of subject-visits (each participant had 2 visits).

an independent working correlation matrix and robust standard errors to account for the clustering of spouses and multiple visits per subject. Results from these models are presented as the average across visits, since the majority of outcomes did not have significant visit effects.

We tested for an interaction between mood disorder history and hostile behaviors in models predicting endotoxins, because this interaction was significant in previous analyses of other post-meal outcomes (Kiecolt-Glaser et al., 2015c). Non-significant interactions ($p > 0.1$) were removed in constructing the final models. In secondary analyses, we substituted depressive symptoms (CES-D) for mood disorder history and marital satisfaction (CSI) for hostile behavior to explore the patterns' stability.

All models controlled for age, race (white vs. African-American), trunk fat, gender, sleep (PSQI), and physical activity (average calories expended per week from the CHAMPS) to guard against potential confounding (all measured at the first visit). Models for outcomes measured at both visits (endotoxins and inflammatory markers) also controlled for visit number (first or second) and meal type to account for the study design, though these effects were not of primary interest. All analyses were conducted in SAS version 9.4 (Cary, NC).

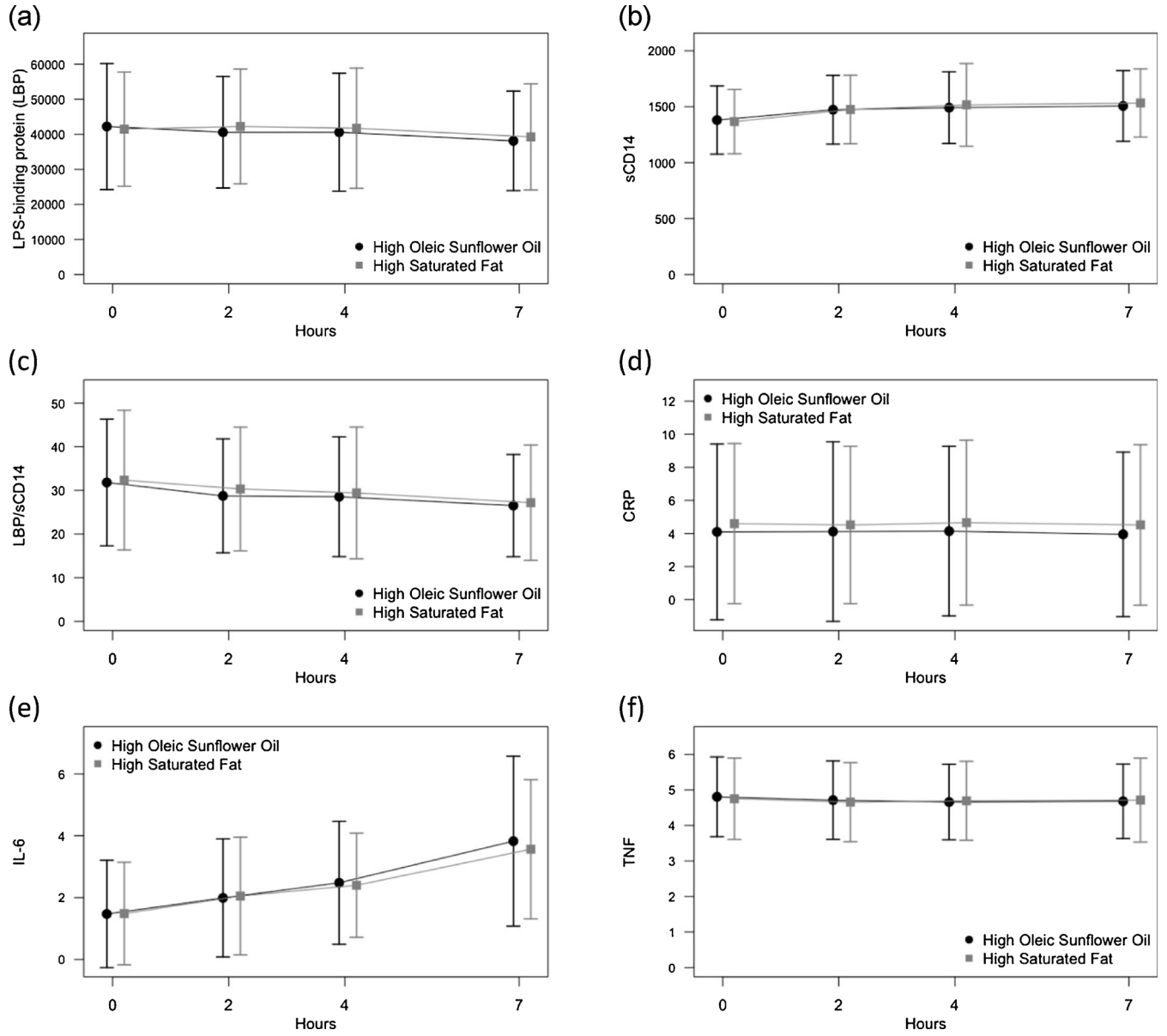

Fig. 1. Mean (a) LBP, (b) sCD14, (c) LBP/sCD14 ratio, (d) CRP, (e) IL-6, and (f) TNF across the day, separately by meal type. Error bars show +/− 1 SD.

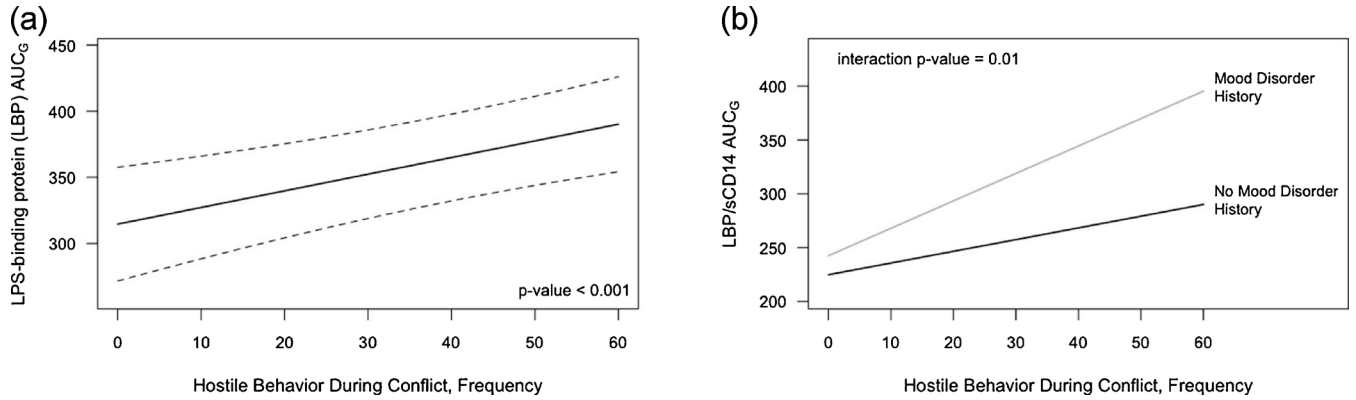

Fig. 2. Estimated (a) LBP AUC_G and (b) LBP/sCD4 ratio AUC_G as a function of couples' hostile behavior, averaged across visits. Results are from GEE models controlling for age, sex, race, trunk fat, sleep, daily activity level, meal type, and visit order. Dotted lines are a 95% confidence interval.

In the analyses there were five subjects who only contributed data for one visit: of these, two partners did not have a second visit, and three subjects' modestly elevated temperature indicated acute illness at one visit. Data from these five visits were excluded from all models, but data from these subjects' other visits were included. Additionally, there were seven subjects with one visit excluded from the CRP analyses because they were missing the last measurement of CRP and thus AUC_G could not be calculated. Data from other outcomes for these subjects' visits were available and thus they were included in the other models.

3. Results

3.1. Marital discord, past mood disorders, and endotoxin biomarkers

As shown in Fig. 2a, there was a strong, significant association between hostile behavior and LBP AUC_G ($p = 0.0005$), such that participants with more hostile marital interactions had higher LBP AUC_G (eTables 2–6 provide details for analyses**)**. Each one unit increase in hostile behavior frequency was associated with a 1.3 unit increase in LBP AUC_G (95% CI: 0.55–2.0). As a result, a participant with higher hostile behavior (75th percentile) had 7.2% higher LBP AUC_G than a participant with lower hostile behavior (25th percentile). The effect of mood disorder history was not significant ($p = 0.13$) but trended towards higher LBP AUC_G among participants with a mood disorder history. There was not a significant association between sCD14 AUC_G and either mood disorder history ($p = 0.59$) or hostile behavior ($p = 0.22$), but the trend was for more hostile behaviors to be associated with lower sCD14. There was a significant interaction of hostile behavior and mood disorder history in predicting the LBP/sCD14 ratio ($p = 0.01$, Fig. 2b). The relationship between hostile behaviors and LBP/sCD14 ratio was stronger among participants with a mood disorder history (slope = 2.5, 95% CI: 1.6–3.5, $p < 0.0001$) compared to participants without a history of mood disorder (slope = 1.1, 95% CI: 0.38–1.8, $p = 0.003$).

In secondary analyses, self-reported marital satisfaction using the couple's average CSI scores was used in place of hostile behavior frequency in the models, and patterns of results were similar. Poorer marital satisfaction (lower CSI) trended towards being associated with higher LBP AUC_G ($p = 0.055$), and there was a significant interaction between marital satisfaction and mood disorder history in predicting the LBP/sCD14 ratio ($p < 0.0001$). Poorer marital satisfaction (lower CSI) was associated with higher LBP/sCD14 ratio among participants with a mood disorder history (slope = −2.3; 95% CI: −2.8 to −1.8, $p < 0.0001$) but was not associated with LBP/sCD14 for participants without a history of mood disorder (slope = 0.060; 95% CI: −0.39 to 0.51, $p = 0.79$). Unlike the models using hostile behaviors, there was a significant interaction between marital satisfaction and mood disorder history in predicting sCD14 ($p = 0.001$); poorer marital satisfaction (lower CSI) was significantly associated with lower sCD14 for participants with a history of a mood disorder (slope = 0.030; 95% CI: 0.009 to 0.051, $p = 0.006$) but not for participants without a mood disorder history (slope = −0.011; 95% CI: −0.027 to 0.005, $p = 0.17$).

3.2. Endotoxin biomarkers and inflammation

Both LBP AUC_G ($p = 0.007$) and LBP/sCD14 ratio AUC_G ($p = 0.02$) were significantly associated with CRP AUC_G (Fig. 3). The estimated CRP AUC_G for a participant with high LBP AUC_G (75th percentile) was 80% higher than for a participant with low LBP (25th percentile),-corresponding to an average estimated CRP level across the day of

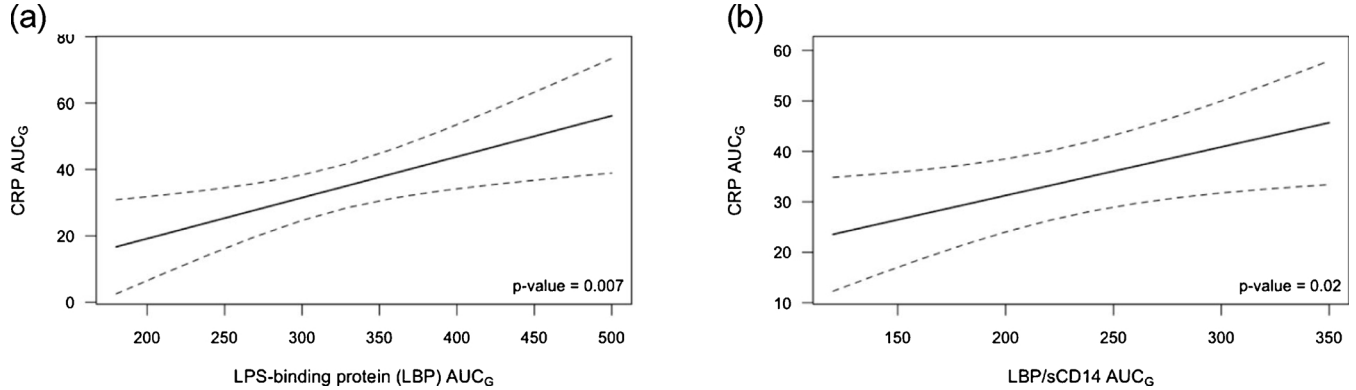

Fig. 3. Estimated CRP AUC_G as a function of (a) LBP AUC_G and (b) LBP/sCD14 AUC_G, averaged across visits. Results are from GEE models controlling for age, sex, race, sleep, daily activity level, trunk fat, meal type, and visit order. Dotted lines are a 95% confidence interval.

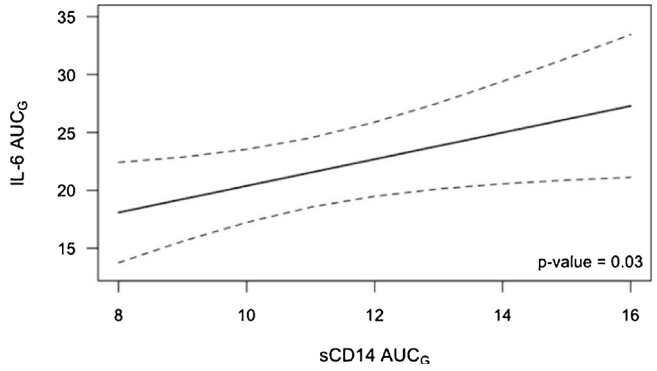

Fig. 4. Estimated IL-6 AUC_G as a function of sCD14 AUC_G, averaged across visits. Results are from GEE models controlling for age, sex, race, sleep, daily activity level, trunk fat, meal type, and visit order. Dotted lines are a 95% confidence interval.

6.21 ng/mL for a participant with high LBP AUC_G compared to 3.46 ng/mL for a participant with low LBP AUC_G. This effect was also seen when looking at the unadjusted AUC values; among values in the lowest quartile of LBP AUC_G, only 21% had an average CRP > 3 ng/mL across the day, while 79% of those in the highest quartile of LBP AUC_G had an average CRP > 3 ng/mL across the day. The effect for LBP/sCD14 ratio AUC_G was similar though smaller in magnitude. The estimated CRP AUC_G for a participant with high LBP/sCD14 AUC_G (75th percentile) was 50% higher than for a participant with low LBP/sCD14 AUC_G (25th percentile), corresponding to average estimated CRP across the day of 5.91 ng/mL compared to 3.94 ng/mL. However, sCD14 AUC_G was not associated with CRP AUC_G ($p = 0.12$), though the trend was for higher sCD14 to be associated with higher CRP AUC_G.

There was a nonsignificant trend towards higher LBP AUC_G associated with higher IL-6 AUC_G ($p = 0.12$), and higher sCD14 AUC_G was associated with higher IL-6 AUC_G ($p = 0.03$). Compared to low sCD14 participants (25th percentile), those in the 75th percentile had 15% higher IL-6 AUC_G (Fig. 4). The LBP/sCD14 ratio was not significantly associated with IL-6 AUC_G ($p = 0.35$). None of the endotoxin markers (LBP, sCD14, LBP/sCD14 ratio) were significantly associated with TNF-α AUC_G (ps > 0.4).

3.3. Covariate effects

The effects of controlling variables varied slightly depending on which other predictors were included (e.g., hostile behaviors versus marital satisfaction; LBP versus sCD14) (see eTables 2–8). In general, older age was associated with higher LBP/sCD14 AUC_G, and higher trunk fat was associated with higher LBP AUC_G, CRP AUC_G, and TNF AUC_G, with a trend towards higher IL-6 AUC_G. Men had significantly lower sCD14 AUC_G, CRP AUC_G, and IL-6 AUC_G than women, and white participants had higher sCD14 AUC_G, a lower LBP/sCD14 ratio, lower IL-6 AUC_G, and higher TNF AUC_G than African-American participants. Higher physical activity (higher average calories expended per week) was associated with lower IL-6 AUC_G. Neither sleep nor meal type were significant predictors in any model.

3.4. Ancillary analyses

To investigate the associations with current affective symptoms, mood disorder history was replaced by current depressive symptoms in all models. However, neither the main effect of CES-D nor the interactions between CES-D and hostile behavior or self-reported marital satisfaction were significant predictors of the endotoxin markers (LBP, sCD14, LBP/sCD14 ratio; ps > 0.1).

4. Discussion

Consistent with our hypotheses, participants with more hostile marital interactions had higher LBP. Additionally, partners who had more hostile marital interactions had higher LBP/sCD14 ratios, with the strongest effects among those who had a prior mood disorder. Neither hostile behavior nor mood disorder history was related to sCD14 alone, but instead predicted the relative balance of LBP and sCD14. Likewise, higher LBP and LBP/sCD14 ratios, but not sCD14, were associated with greater CRP production. Indeed, compared to participants with low LBP (25th percentile), participants with high LBP (75th percentile) had 79% higher CRP across the day. Similarly, relative to participants with lower LBP/sCD14 ratios (25th percentile), participants with higher LBP/sCD14 ratios (75th percentile) had 45% higher CRP over the study visit. Higher sCD14 was associated with higher IL-6. Mirroring our findings, LBP was associated with CRP but not IL-6 in two other studies (Stehle et al., 2012; Romani et al., 2013), while sCD14 was significantly related to IL-6 but not CRP (Stehle et al., 2012).

CRP has clinically relevant prognostic significance, discriminating among people with low, moderate and high risk of future heart attack and stroke (< 1, 1–3, and > 3 mg/L, respectively) (Ridker, 2003). Thus it is noteworthy that only 21% of low LBP participants (lowest quartile) had average CRP values > 3, compared to 79% of those in the highest quartile. The higher CRP values in this sample reflect this study's inclusion criteria that prioritized overweight and sedentary couples.

LBP has been described as a surrogate marker of microbial translocation (Stehle et al., 2012). Thus, higher levels of LBP reflect greater amounts of endotoxin from commensal microbes translocating from their niche on the body to the blood, where they stimulate LBP production by the liver. Every surface of the body can be colonized by commensal bacteria, but the vast majority of microbes reside in the gut. Many of these are Gram-negative microbes with LPS in their cell wall. Thus, high levels of LBP often reflect translocation of Gram-negative bacteria from the gut to the interior of the body. It should be noted, however, that in addition to LPS, cytokines (such as IL-6, IL-1β, TNF-α, and IL-22) can increase LBP production in hepatocytes and colonic epithelial cells (Wan et al., 1995; Wolk et al., 2007). In stressor-exposed animals, cytokine increases have been associated with bacterial translocation and influenced by the gut microbiota (Bailey et al., 2011; Maslanik et al., 2012; Lafuse et al., 2017), supporting the rationale for bacterial translocation from a leaky gut as a new mechanistic pathway among marital distress, a history of depression, and inflammation-related disorders.

In studies with MDD patients, the gut microbiota's composition has differed from that of healthy controls (Kelly et al., 2015, 2016; Rogers et al., 2016). After a disturbance, the gut microbiota community typically returns to the pre-disturbance composition. However, severe insults may produce long-term—perhaps permanent—changes in the microbiota's composition, leading to problematic alterations in the commensal gut microbiota that regulate local and systemic inflammation and immunity, as well as maintenance of gut barrier function.

In fact, the differences we found between individuals with a mood disorder history compared to those without may reflect persistent psychological and physiological vulnerabilities, in a way that past-week depressive symptoms did not capture. Indeed, impairments in marital relationships can persist for years after an acute depressive episode (Bothwell and Weissman, 1977; Levkovitz et al., 2003). People with a history of depression experience more major and minor stressors than those without a similar history, and past depression can boost emotional reactivity to daily stressors (Hammen, 1991; Gunthert et al., 2007; Husky et al., 2009). Repeated intermittent stressors also characterize distressed marriages (Story and Bradbury, 2004). For example, in a study that collected daily reports of stress and marital functioning, daily stress among hostile couples was driven in part by the prior day's marital conflict (Timmons et al., 2017). In turn, daily stress spilled over to increase the next day's marital conflict, fueling a vicious cycle.

Greater and more frequent emotional reactivity to stressors has implications for bacterial translocation; two weeks of daily 15-min stress exposures produced persistent increases in gut permeability in mice that were still evident two weeks after the last session (Rodrigues et al., 2017). Thus, it is possible that the associations in our data related to distressed marriages and past mood disorders may reflect longer-term microbiota alterations. A leaky gut may serve to maintain low-grade inflammation that could be exacerbated by stress, thereby enhancing risk for recurrent mood disorder episodes.

Just as hostile behaviors remained similar from one visit to the next, endotoxin biomarkers were very highly correlated across visits, suggesting more chronic exposure. Indeed, steady, lasting associations seem to exist between marital distress and intestinal permeability in a way that may chronically fuel inflammation. In addition to their stability across visits, the endotoxin biomarkers showed little change within each of the study visits (Fig. 1), consistent with evidence that they are relatively slow-moving. For example, in one study LBP finally peaked 12 h after an endotoxin injection (Hudgins et al., 2003), a far more substantial inflammatory stimulus than a marital discussion or a high-fat meal.

The bidirectional microbiota-gut-brain communication involves multiple depression- and stress-responsive pathways including the sympathetic nervous system (SNS), the hypothalamic-pituitary-adrenal (HPA) axis, the vagus nerve, and the immune system. For example, SNS-stimulated catecholamine production can elevate both pathogenic and commensal bacterial levels 10,000-fold while simultaneously enhancing pathogenic virulence (Freestone et al., 2002). In addition, The HPA axis activation that accompanies stress and depression can disrupt the functioning of the intestinal barrier by promoting corticotropin-releasing hormone (CRH) release, which prompts ACTH and cortisol production (Vanuytsel et al., 2014).

Heightened SNS and HPA responses have also been observed in laboratory studies with distressed couples. For example, more hostile couples produced larger and more persistent catecholamine, ACTH, and cortisol responses during and following marital problem discussions compared to their less hostile counterparts (Kiecolt-Glaser and Newton, 2001), as well as greater elevations in these hormones throughout the remainder of the day and night (Kiecolt-Glaser et al., 1996).

The vagus nerve provides neural communication between peripheral gut microbes and centrally mediated behavioral processes (Kelly et al., 2015). Lower vagal activation has been associated with poorer marital satisfaction in both cross-sectional and longitudinal studies (Smith et al., 2011; Donoho et al., 2015), and a meta-analysis showed that depression also lowers vagal activation (Kemp et al., 2010). Importantly, although antidepressant treatment reduces depressive symptoms, it does not change HRV (Kemp et al., 2010). Persistent HRV reductions could drive long-term maladaptive communication between gut microbes and behavior.

The immune system helps to maintain intestinal homeostasis, and immune dysregulation can provoke gut dysbiosis (microbial imbalance), thus promoting bacterial translocation (Bailey et al., 2011; Ait-Belgnaoui et al., 2012). Both hostile marital interactions and depression can dysregulate cellular and inflammatory immune responses (Kiecolt-Glaser and Newton, 2001; Kiecolt-Glaser et al., 2005; Robles et al., 2014; Kiecolt-Glaser et al., 2015a). Marital behavior is stable across time, as reflected in the high correlation in hostile behaviors between the two study visits, also shown in other work (Kiecolt-Glaser and Newton, 2001). Accordingly, persistent marital distress and past depression could spur gut dysbiosis and bacterial translocation through multiple routes, including heightened SNS and HPA activation in tandem with lower vagal activation and immune dysregulation.

Heightened endotoxin exposure has important health implications. Atherosclerosis, cardiovascular disease, and diabetes have all been associated with chronic bacterial endotoxin exposure (Stoll et al., 2004; Pussinen et al., 2011; Kelly et al., 2012), and each has been linked to marital discord and depression (Orth-Gomer et al., 2000; Gallo et al., 2003; Jones et al., 2003; Troxel et al., 2005; Joseph et al., 2014; Whisman et al., 2014). Furthermore, aging is accompanied by increased gut bacteria translocation as well as less diversity in the gut microbiota's bacterial composition, and both of these changes promote persistent low-grade inflammation (Stehle et al., 2012). Higher levels of LBP have been associated with poorer physical function and higher levels of inflammation even among healthy older adults independent of age, gender, BMI, aerobic fitness, and inflammatory biomarkers (Stehle et al., 2012).

Our sample's average age was 38, a feature of the study that probably underestimates the associations among middle-aged and older populations. Marital distress and depression likely interact with age-related increases in gut bacterial translocation to heighten age-associated risks. This study did not include gut microbiota assessments, another limitation. Additionally, although convergent data from two studies suggests that a mood disorder history can alter metabolic responses to high-fat meals (Kiecolt-Glaser et al., 2015b,c), the relatively small number of participants with a past mood disorder suggest that those results should be interpreted cautiously.

Both marital discord and depression have notable physiological repercussions, as documented in the poorer clinical outcomes for conditions ranging from cardiovascular disease to metabolic syndrome and diabetes (Orth-Gomer et al., 2000; Gallo et al., 2003; Jones et al., 2003; Troxel et al., 2005; Joseph et al., 2014; Whisman et al., 2014). This study illustrates novel pathways through which a troubled marriage and a mood disorder history could contribute to each of these high risk conditions. Accordingly, treatments that address marital distress and/or depression could also benefit both mental and physical health.

Our data demonstrate how a distressed marriage and a depression history can promote a proinflammatory milieu through increased gut permeability, with broad health implications. Indeed, this study shows how the gut microbiota can fuel a range of stress-associated pathologies.

Declaration of interest

All authors declare no conflicts of interest.

Acknowledgements

The study was supported in part by NIH grants R21 CA154054, K05 CA172296, R01 AG057032, T32 DE014320, K99 AG056667, and UL1TR001070. The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The authors had no potential conflicts of interest. We are grateful to Michael Di Gregorio, M.A., for his role as a key organizer and experimenter, and Susan Glaser, PhD, who conducted the interviews to identify the best topics for couples' conflict discussions.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2018.08.007.

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