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Full Length Article

Gender differences in the link between depressive symptoms and *ex vivo* inflammatory responses are associated with markers of endotoxemia

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ABSTRACT

Depressive symptoms are often linked with higher inflammation and inflammatory responses, although these associations are not always consistent. In a recent study (N = 160, 25–65 years, 67% women), our group reported gender differences relevant to this association: In men higher depressive symptoms were related to heightened *ex vivo* inflammatory responses to lipopolysaccharide (LPS), whereas in women higher depressive symptoms were related to attenuated inflammatory responses. In the present manuscript, we investigate markers of endotoxemia – i.e., markers of the presence of endotoxin in the blood, presumably due to bacterial translocation from the gut – as factors that elicit gender-dependent immune responses that may be associated with links between depressive symptoms and inflammation. We examined *ex vivo* inflammatory responses in whole blood via a composite index of LPS-stimulated cytokines. The ratio of LPS-binding protein to soluble CD14 receptor (LBP:sCD14) was quantified as an index of endotoxemia that captures the relative reliance on pro-inflammatory versus non-inflammatory pathways for bacterial clearance. Levels of endotoxemia markers in blood were found to moderate gender differences in the link between depressive symptoms and stimulated inflammation (Gender × Depressive Symptoms × Endotoxemia: $B = -0.039$, 95%CI [-0.068, 0.009], $p = 0.010$). At lower LBP:sCD14 levels, depressive symptoms and stimulated inflammation were unrelated in both men and women. However, with higher levels of LBP:sCD14, men showed an increasingly positive correlation and women showed a negative correlation between depressive symptoms and stimulated inflammation. Hence, men and women exhibited similar associations between depressive symptoms and inflammatory responses at lower endotoxin marker levels, but these associations became divergent at higher levels of endotoxin markers. This information provides a novel perspective on risk factors for depression-linked alterations in inflammation, which may help to determine susceptibility to the downstream physical consequences of depressive symptomatology.

1. Introduction

Depression is a pervasive mood disorder that affects the lives of over 320 million individuals worldwide (WHO, 2017), and is among the leading causes of disability in adults in the U.S. (Siu, 2016). Mounting evidence indicates that depressive symptoms are associated with increased and prolonged inflammatory responses to acute immune system challenges (Lopez et al., 2018) such as acute stress (Fagundes et al., 2013; Pace et al., 2006; Weinstein et al., 2010) or vaccines (Christian et al., 2010; Glaser et al., 2003). However, the link between depressive symptoms and inflammation is not always consistent, with some recent evidence suggesting that gender alters this association (Majd et al., 2018). Endotoxemia – the translocation of microbes to the blood – fuels inflammatory responses in a gender-dependent manner (Moxley et al., 2002, 2004; Marriott and Huet-Hudson, 2006; Vázquez-Martínez et al., 2018) and has been associated with altered inflammation in major depressive disorder (Maes, 2008; Kiecolt-Glaser et al., 2018). Therefore, we examined endotoxemia as a contributor to gender differences in the

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link between depressive symptoms and inflammation.

1.1. Gender differences in associations between depression and inflammation

Noted gender differences exist in the incidence and severity of depression. Women are almost twice as likely to be diagnosed with depression as men, due to an array of biological, psychological, and social factors (e.g., Nolen-Hoeksema, 2001; Salk et al., 2017). Gender differences appear to extend to the links between depressive symptoms and inflammation. In several large, cross-sectional studies, depression was predictive of increased basal interleukin (IL)-6 and C-reactive protein (CRP) levels in men but not women (Elovainio et al., 2009; Ford and Erlinger, 2014; Vogelzangs et al., 2012).

Other research has focused on inflammatory responses that are determined by exposing blood to a well-controlled mitogen challenge [typically lipopolysaccharide (LPS); see de Groot et al., 1992]. This inflammatory response to challenge appears to be distinct from basal inflammation, as the two measures often do not correlate. Recent work from our group indicates that gender differences are evident in correlations between depressive symptoms and these *ex vivo* stimulated inflammatory responses. Specifically, with increasing depressive symptomatology men mounted higher inflammatory responses to *ex vivo* immune challenge and women mounted lower responses, as determined by IL-6, TNF-α, and IL-10 levels (Majd et al., 2018). This finding is in line with earlier work that found that women with higher depressive symptoms had lower stimulated inflammatory responses (Cyranowski et al., 2007). Thus, gender differences in the associations between depression and altered inflammation appear evident in at least two distinct ways: i) Depression and low grade basal inflammation, and ii) depressive symptoms and *ex vivo* stimulated inflammation.

1.2. Responses to endotoxemia

Endotoxin levels in blood may be a contributing factor to the association between depressive symptoms and altered immune responses (Maes, 2008). The largest source of endotoxin-expressing microbes (i.e., gram-negative bacteria) is the gut, but other sources include the urinary and respiratory tracts and the oral cavity (Kiecolt-Glaser et al., 2018; de Prunder and Pruimboom, 2015). Bacterial translocation from the gut into the blood occurs at tight junctions along the gastrointestinal tract in response to normal physiological functioning and pathogenic stimuli (Odenwald and Turner, 2013, Fig. 1).

In response to endotoxin detected in the blood, the liver and intestinal epithelial cells release LPS-binding protein (LBP; Gallay et al., 1994; Wan et al., 1995; Wolk et al., 2007). LBP is a chaperone protein that binds endotoxin and catalyzes its transport to, and binding with, clusters of differentiation (CD)-14 receptors, which are either bound to the membrane of monocytes and macrophages (mCD14) or circulating in blood as a soluble form (sCD14). Recent or ongoing exposure to endotoxin or other mitogens increases sCD14 concentrations via cleavage of mCD14 from monocytes (Shive et al., 2015; Landmann et al., 1996; Hiki et al., 1998); *in vitro* pro-inflammatory cytokine exposure also increases sCD14 concentrations (Shive et al., 2015). The sCD14 receptor shuttles the endotoxin-LBP complex to high-density lipoprotein (HDL), resulting in the non-inflammatory breakdown and clearance of endotoxin, which consequently attenuates pro-inflammatory responses mediated by mCD14 (Wurfel et al., 1995; Laugerette et al., 2014). Thus, high levels of LBP or sCD14 indicate recent exposure to endotoxin (i.e., in the past 24–48 h). The ratio of LBP to sCD14 (LBP:sCD14) captures the relative reliance on the pro-inflammatory versus non-inflammatory responses to endotoxemia, with higher LBP:sCD14 levels indicating an immune system predisposed to heightened inflammation (e.g., higher CRP levels; Kiecolt-Glaser et al., 2018; Laugerette et al., 2014). Because direct measurement of endotoxin in blood is hindered by its relative instability and rapid clearance (Cohen, 2000; Novitsky, 1998; Gonzalez-Quintela et al., 2013), LBP:sCD14 has been suggested to be a clinical marker of endotoxemia (Laugerette et al., 2014).

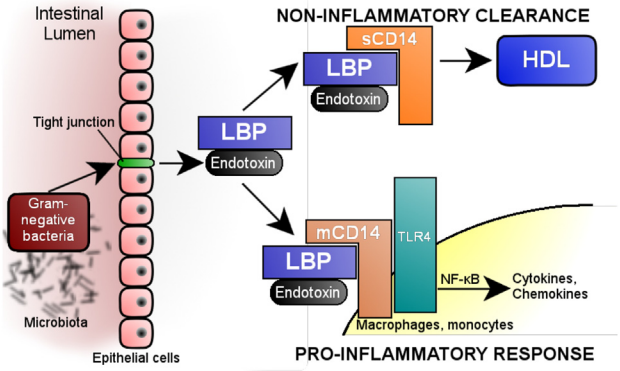

Fig. 1. Schematic of LBP and CD14 responses to bacterial translocation from the gut, including a non-inflammatory clearance pathway mediated by sCD14 and a pro-inflammatory response mediated by mCD14. Endotoxin is transported through tight junctions across the epithelium; endotoxin and other microbiota products can also pass via intracellular routes and through damage to epithelial cells and the mucosa (not pictured). Endotoxin is bound by LBP, which transports endotoxin to, and facilitates binding with, CD14 receptors. Soluble CD14 shuttles the LBP-endotoxin complex to lipoproteins, like HDL, for detoxification and non-inflammatory clearance. Membrane-bound CD14 similarly binds LBP-endotoxin complexes, which sets off a pro-inflammatory response mediated by TLR4 and the NF-κB pathway (Marriott et al., 2006). Both routes function simultaneously; the ratio of LBP to sCD14 helps determine the magnitude of inflammatory response to endotoxin. This schematic does not convey or imply causal mechanisms by which endotoxemia may associate with gender and depressive symptoms and is not drawn to scale. LBP = LPS-binding protein; sCD14 = soluble cluster of differentiation 14; mCD14 = membrane-bound CD14; TLR4 = toll-like receptor 4; NF- κB = nuclear factor kappa-light-chain-enhancer of activated B cells; HDL = high-density lipoprotein.

1.2.1. Gender differences in response to endotoxemia

Gender differences exist in immune responses to endotoxemia and other microbial challenge (Vázquez-Martínez et al., 2018). Men tend to mount heightened inflammatory responses to *in vivo* and *ex vivo* microbial challenge compared to women (Marriott and Huet-Hudson, 2006; Moxley et al., 2002, 2004; Vázquez-Martínez et al., 2018). In animal research, female rodents develop tolerance faster than males to repeated LPS exposure, such that subsequent LPS challenges induce less sickness behavior (Engeland et al., 2006). Together, these studies suggest inflammatory responses may be associated with prior exposure to endotoxin in a gender-dependent manner.

1.2.2. Depression and markers of endotoxemia

There is a growing body of evidence suggesting that depression and endotoxemia are associated. Endotoxemia markers and associated immune responses appear heightened among individuals with clinical depression (Kéri et al., 2014; Maes, 2008; Maes et al., 2008, 2012). A prior history of mood disorders (of which depression was the most prevalent) was associated with increased levels of endotoxemia markers, which in turn were associated with increased levels of circulating pro-inflammatory cytokines and CRP (Kiecolt-Glaser et al., 2018). This latter study did not find a direct association between levels of depressive symptoms and markers of endotoxemia. Overall, this past work suggests that endotoxin exposure may correlate with heightened associations between inflammation and mood disorders such as depression, but little is known about endotoxemia and the links between depressive symptoms and subsequent inflammatory responses.

1.3. Summary

For the reasons outlined above (sections 1.2.1-1.2.2), markers of endotoxemia may be associated with the previously reported gender differences in the link between depressive symptoms and inflammation (Majd et al., 2018). We hypothesized that gender-dependent associations between depressive symptoms and inflammation would be less apparent in individuals with lower levels of LBP:sCD14 – i.e., in an immune system less prone to heightened inflammation. Further, we expected that higher levels of endotoxemia might contribute to gender differences in the links between depressive symptoms and inflammation by heightening inflammatory responses in men and attenuating inflammatory responses in women.

2. Methods

2.1. Participants

As reported elsewhere (Majd et al., 2018), this study is part of "The Effects of Stress on Cognitive Aging, Physiology and Emotion" (ESCAPE) project (see Scott et al., 2015, for details on the parent study). Systematic probability sampling was used to recruit participants from the New York City Registered Voter Lists. Specifically, recruitment letters explained the study goals, which were followed by enrollment for eligible participants via telephone. Inclusion criteria included ambulatory men and women aged 25–65 who resided in Co-Op City (the Bronx, New York), were fluent in English, and who were without visual impairment.

Participants were selected from this larger study based on the following criteria: No history of inflammatory-related illness (e.g., autoimmune disorders, diabetes, cancer, HIV, chronic infections, cardiovascular disease, kidney or liver disease), no history of psychiatric disorders other than depression, and not taking immunosuppressive drugs including oral corticosteroids. Inhaled and intranasal corticosteroids were not exclusionary (see Majd et al., 2018). Of the participants in the first wave of data collection, 162 participants met these criteria and had blood samples available. This subsample consisted of a majority of women (67%) and was racially and ethnically diverse (64% African-American; 21% Latinx).

2.2. Protocol

After providing informed consent, participants completed a paper survey at home and participated in a burst of ecological momentary assessment (not reported here), returning approximately 2 weeks later for a blood draw. Participants self-reported their gender as male or female; we use the term "gender" throughout to encompass the biological and psychosocial differences between men and women (Darnall and Suarez, 2009). Female participants further self-reported their menopausal status at the blood draw. BMI was calculated via height and weight measured by trained staff.

2.3. Measures

2.3.1. Depressive symptoms

The Patient Reported Outcome Measurement Information System – Depression (PROMIS Depression) short-form scale was used to index depressive symptoms (PROMIS Health Organization, 2012). Participants responded to eight items regarding the frequency of depressive symptomology in the past seven days on a 1 (Never) to 5 (Always) scale. Per PROMIS scoring instructions, raw scores were converted to standardized T-scores, such that a score of 50 (±10) represents the mean (SD) of the US population. Cutoffs for PROMIS depressive symptom severity are described as the following: <55 (none to slight); 55.0–59.9 (mild); 60–69.9 (moderate); >70 (severe). Participants responded to the PROMIS scale in an initial appointment at the laboratory, which occurred approximately two weeks prior to the blood draw. Because the study did not involve a clinical population, PROMIS depressive symptoms were expected to be close to the US population mean. Prior work indicates that the PROMIS-Depression scale is clinically valid for major depressive disorder and other chronic health conditions (Schalet et al., 2016; Pilkonis et al., 2014). More generally, depressive symptoms predict later major depressive disorder incidence, physical health outcomes, and all-cause mortality (Moazen-Zadeh and Assari, 2016; Katon, 2003; Houle, 2013).

2.4. Bioassays

A certified phlebotomist drew blood between 7 a.m. and 11 a.m. following 12 h of fasting, at the Albert Einstein College of Medicine. Blood (5 mL) was collected in sodium heparin tubes to assess basal and stimulated cytokine levels, CRP, LBP, and sCD14.

To determine basal inflammation, CRP, LBP, and sCD14 levels, whole blood was centrifuged at 3000 g for 15 min at room temperature. The supernatant was aliquoted and stored at − 80 °C. To determine stimulated cytokine levels, 1 mL of whole blood was incubated with bacterial LPS (1 μg/mL, *E. coli* 055:B5, Sigma-100 mg) on a rotational shaker at 37 °C in 5% CO2 for 2 h. Samples were then centrifuged at 3000 g for 15 min at room temperature. The supernatant was aliquoted and stored at − 80 °C for future analysis. As described in Majd et al. (2018), basal and LPS-stimulated cytokines (IL-1β, IL-6, IL-8, IL-10, TNF-α) and CRP were quantified using multiplex magnetic bead arrays (Life Technologies, Grand Island NY). The minimum detection limit for these assays is < 0.5 pg/mL for each analyte and inter-assay CVs are 4.4%–8.6%. Confirmed values below the minimum detection limit were replaced with zeros. All cytokines were transformed via natural-log(x+1) to correct a positive skew in the distribution while maintaining a meaningful zero value. CRP was also positively skewed and was corrected with log-transformation for analysis [without the natural-log(x+1) transformation, as there were no samples at the minimum threshold].

LBP and sCD14 were determined via commercially available kits (LBP: sandwich immunoassay from Meso Scale Discovery, Rockville, MD; sCD14: ELISA from R&D Systems, Minneapolis, MN). The minimum detection limits for LBP and sCD14 were 0.038 ng/mL and 125 pg/mL, inter-assay CVs were 11.5% and 3.6%, and the intra-assay CVs were 11.6% and 2.7%, respectively. All assays were performed in duplicate.

2.4.1. Composite scores for cytokines

Given that individual cytokine levels were strongly correlated, we performed an exploratory factor analysis to determine groupings among the cytokines examined. The exploratory factor analysis revealed support for two factors (61% variance explained): one factor for basal cytokines and one for stimulated cytokines. Stimulated IL-10 weakly cross-loaded on both factors; given its biological relationship to the other stimulated cytokines (i.e., its increase in value following LPS-challenge as a compensatory response to inflammation), we included it in the stimulated cytokine composite score. Prior work has used a similar approach in order to limit repeated testing (see Fagundes et al., 2019 for further discussion). We produced composite indices of cytokine levels[1] by i) normalizing (z-score) within each individual cytokine measurement and ii) calculating the mean of these normalized values separately for basal and stimulated cytokines. These indices revealed good reliability (basal: Cronbach's $\alpha = 0.90$; stimulated: $\alpha = 0.81$). Our main analyses relied on these composite scores, but we also explored and report analyses from each individual cytokine in follow-up analyses.

2.5. Statistical analyses

All analyses were conducted in R (v.3.5.2, R-Team, 2018) using linear

[1] In our group's previous report (Majd et al., 2018), individual cytokines were examined rather than a composite index.

Table 1
Means (SDs) of biomarkers of bacterial translocation and CRP.

	Women	Men	All
Depressive Symptoms (PROMIS, standardized units)[a]	52.1 (9.4)	53.4 (8.9)	52.5 (9.2)
LBP (μg/mL)	2.99 (1.34)	2.75 (1.37)	2.91 (1.35)
sCD14 (μg/mL)	1.48 (0.297)	1.38 (0.347)	1.45 (0.316)
LBP:sCD14 Ratio (arbitrary units)	2.07 (0.982)	1.99 (0.826)	2.04 (0.932)
CRP (mg/L)	5.62 (7.38)	5.72 (9.58)	5.55 (8.14)

Note.
[a] These values were previously reported in Majd et al. (2018). See Majd et al. (2018) for means and SDs of inflammation variables.

regression. We first examined the direct associations of: i) LBP:sCD14 with inflammation levels; ii) gender with LBP:sCD14; and iii) depressive symptoms with CRP and with the LBP:sCD14 ratio. We next examined two-way interactions between gender, depressive symptoms, and endotoxemia on inflammation. Finally, we examined the three-way interaction of gender, depressive symptoms, and endotoxemia on inflammation. Significant interactions are probed and graphed using a simple-slope approach in which estimated marginal means of the association between inflammation and depression are plotted at low, medium, and high levels (i.e., at the mean and ±1 standard deviation) of LBP:sCD14 in men and women (Preacher et al., 2006).

In this context, we also examined menopausal status in women, as menopause has previously been linked to increased depressive symptoms (Judd et al., 2012) and altered inflammation (Gameiro et al., 2010). In this model, gender was treated as a two-level Helmert contrast code (Level 1: Men = −2, Pre-menopausal women = Post-menopausal women = 1; Level 2: Men = 0, Pre-menopausal women = −1, Post-menopausal women = 1) to allow us to examine i) differences between men and women, controlling for women's menopausal status; and ii) differences between pre- and post-menopausal women, controlling for gender differences.

All of our analyses utilize the LBP:sCD14 ratio as a marker of endotoxemia (Laugerette et al., 2014; Kiecolt-Glaser et al., 2018). We examined possible correlations between covariates and our composite inflammation scores and CRP, and included variables with significant correlations in all analyses. Thus, our final analyses included age, BMI, inhaled corticosteroids (i.e., self-reported *ad hoc* usage; $n = 9$), and antidepressants ($n = 8$). In a follow-up analysis, we examined the full list of covariates examined in the Majd et al. (2018) report, including household income, education, race, ethnicity, and self-reported usage of statins, non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives.[2] Gender was treated as a dichotomous categorical variable (1 = female, 0 = male).

3. Results

See Table 1 for descriptive statistics of depressive symptoms, CRP, and endotoxin levels and Table S1 for correlations among study variables. Descriptive statistics for individual cytokines can be found in our prior report (Majd et al., 2018).

3.1. Main effects

We examined basal cytokines, stimulated cytokines, and CRP regressed on the LBP:sCD14 ratio while controlling for gender, age, BMI, and medication use. These analyses indicated that the LBP:sCD14 ratio related positively to CRP levels ($B = 0.456$, *95%CI*[0.274, 0.639], $p < 0.001$). The LBP:sCD14 ratio did not significantly relate to either the basal circulating or stimulated cytokine measures (*ps* > .4; see Table S2).

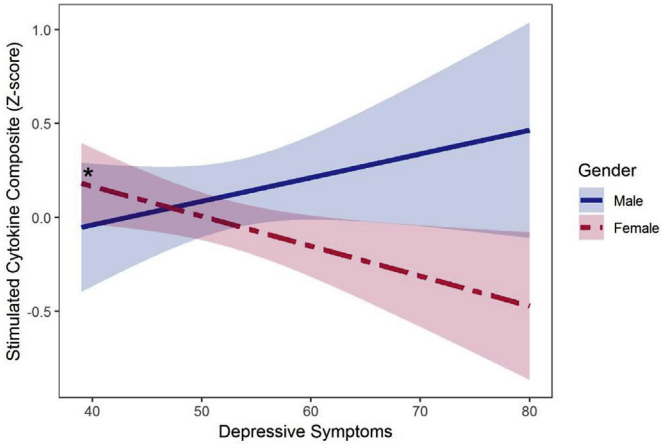

Fig. 2. Gender differences in the association between depressive symptoms and stimulated cytokine levels. Shaded regions around simple slopes represent 95% confidence intervals. Cutoffs for depressive symptom severity (PROMIS Health Organization, 2012): <55 (none to slight); 55.0–59.9 (mild); 60–69.9 (moderate); >70 (severe). *simple slope, p < 0.05.

Next, we examined the inflammation measure, CRP, and the LBP:sCD14 ratio regressed on gender, controlling for age, BMI, and medication usage. Lower composite basal cytokine scores were evident for women compared to men ($B = -0.283$, [-0.514, −0.052], $p = 0.017$). Gender differences were not evident in the LBP:sCD14 ratio[3] ($B = -0.060$, [-0.346, .225], $p = 0.676$), composite stimulated cytokine scores ($B = -0.175$, [-0.405, 0.055], $p = 0.135$), or CRP ($B = -0.051$, [-0.404, 0.302], $p = 0.775$; Tables S2 and S3; see Majd et al. (2018) for gender differences in individual cytokines).

Finally, we regressed CRP and the LBP:sCD14 ratio on depressive symptoms, controlling for gender, age, BMI, and medication use. Depressive symptom levels did not relate to the LBP:sCD14 ratio ($B = 0.002$, [-0.013, 0.017], $p = 0.790$) or CRP levels ($B = 0.005$, [-0.013, 0.024], $p = 0.553$; Table S4).

3.2. Gender and depressive symptoms: association with stimulated inflammation

Our group previously reported gender differences in the link between depressive symptoms and individual stimulated cytokine responses (Majd et al., 2018). Unsurprisingly, there was also a significant interaction for the composite measure of inflammation (Gender × Depressive Symptoms: $B = -0.029$, [-0.053, −0.004], $p = 0.021$; Fig. 2). Simple slopes revealed that men demonstrated a positive association between depressive symptoms and inflammation ($B = 0.013$, [-0.007, 0.033], $p = 0.21$), whereas women demonstrated a negative association ($B = -0.016$, [-0.029, −0.003], $p = 0.019$). An interaction between gender and depressive symptoms was not apparent for the basal cytokine composite levels ($B = -0.007$, [-0.033, 0.018], $p = 0.571$) or CRP levels ($B = -0.011$, [-0.051, 0.028], $p = 0.578$; Table S5).

3.3. Other two-way interactions

There were no significant interactions between gender and the LBP:sCD14 ratio on inflammation (Table S6), between gender and depressive symptoms on the LBP:sCD14 ratio (Table S7), or between depressive symptoms and the LBP:sCD14 ratio on inflammation (Table S8).

[2] See Supplementary methods for coding of other covariate variables.

[3] See Supplementary results for evidence of women's greater sCD14 levels compared to men.

3.4. Gender × depressive symptoms × LBP:sCD14 ratio

3.4.1. Stimulated cytokines

A significant Gender × Depressive Symptoms × LBP:sCD14 ratio interaction was found for stimulated cytokine levels ($B = -0.038$, [-0.067, −0.009], $p = 0.010$; Fig. 3, Table 2). To better understand this association, we decomposed this 3-way interaction into two 2-way interactions on the basis of gender. When the Depressive Symptoms × LBP:sCD14 interaction was examined separately for men and women, this interaction term was significant for men ($B = 0.033$, [0.012, 0.055], $p = 0.003$) but *not* significant for women ($B = -0.009$, [-0.023, 0.005], $p = 0.217$). This result suggests that markers of endotoxin levels may be a critical component of the associations between depressive symptoms and inflammatory responses in men and less critical in women.

We further deconstructed this interaction by examining the estimated simple slopes linking depressive symptoms to stimulated cytokine levels when examined at -1SD, mean, and +1SD of the LBP:sCD14 ratio in men and women. In both men and women with lower LBP:sCD14 ratios, depressive symptoms were not significantly associated with stimulated cytokine levels (Men, $B = -0.013$, [-0.043, 0.018], $p = 0.423$; Women, $B = -0.008$, [-0.025, 0.010], $p = 0.400$). However, men demonstrated increasingly positive associations between depressive symptoms and stimulated cytokine levels at mean ($B = 0.017$, [-0.003, 0.036], $p = 0.106$) and higher LBP:sCD14 ratios ($B = 0.046$, [0.012, 0.079], $p = 0.009$), whereas women demonstrated increasingly negative associations between depressive symptoms and stimulated cytokine levels at mean ($B = -0.017$, [-0.030, −0.004], $p = 0.012$) and higher LBP:sCD14 ratios ($B = -0.026$, [-0.045, −0.007], $p = 0.009$; see Fig. 3).

3.4.1.1. Other follow-up analyses. We also explored this three-way interaction for each individual stimulated cytokine. With the exception of stimulated IL-10, a significant three-way interaction was evident for each stimulated cytokine (*ps* < .025; see Table 3). For stimulated IL-10, considered an anti-inflammatory cytokine, the interaction term was non-significant and the pattern of results did not match the other stimulated, pro-inflammatory cytokines. When we re-ran the three-way interaction model predicting a composite of the four pro-inflammatory cytokines, (IL-1ß, IL-6, IL-8, TNFα), results were not substantively different from the main analyses ($B = -0.49$, [-0.081, −0.016], $p = 0.003$).

Finally, when we re-examined the model with the full list of covariates in Majd et al., (2018) approach (i.e., age, BMI, household income, educational attainment, race, ethnicity, and self-reported usage of inhaled corticosteroids, antidepressants, statins, NSAIDs, and oral contraceptives), none of the above results were changed (Table S9).

3.4.2. Basal cytokines and CRP

A three-way interaction among gender, depressive-symptoms, and the LBP:sCD14 ratio was not evident for either the basal cytokine composite or CRP levels (Table S10).

Table 2
Association of gender, depressive symptoms, and endotoxemia marker levels (LBP:sCD14) with the stimulated cytokine composite.

Predictors	Stimulated Cytokine Composite		
	Estimates	95%CI	p
Intercept	0.049	−0.145–0.243	0.620
Gender	−0.031	−0.260–0.198	0.791
LBP:sCD14	−0.241	−0.466–−0.017	**0.035**
Depressive Symptoms	0.017	−0.004–0.037	0.106
Gender x LBP:sCD14	0.359	0.101–0.616	**0.007**
Gender x Depressive Symptoms	−0.033	−0.057–−0.009	**0.007**
Depressive Symptoms x LBP:sCD14	0.029	0.003–0.055	**0.027**
Gender x Depressive Symptoms x LBP:sCD14	−0.038	−0.067–−0.009	**0.010**
Covariates			
BMI	0.061	−0.060–0.181	0.320
Age	0.061	−0.041–0.164	0.240
Inhaled Corticosteroids	0.025	−0.477–0.526	0.923
Antidepressants	0.175	−0.288–0.639	0.456
Observations	162		
R^2/adjusted R^2	0.147/0.085		

Table 3
Estimates of the gender × depressive symptoms × LBP:sCD14 interaction term for each of the individual cytokines from the basal and stimulated composites.

	Basal			Stimulated		
	B	95%CI	p	B	95%CI	p
IL-1ß	−0.0003	−0.001, 0.001	0.521	−0.068	−0.115, −0.022	**0.004**
IL-6	−0.003	−0.011, 0.005	0.508	−0.076	−0.124, −0.027	**0.003**
IL-8	−0.008	−0.021, 0.005	0.208	−0.049	−0.091, −0.007	**0.025**
IL-10	0.005	−0.01, 0.019	0.528	0.015	−0.041, 0.071	0.604
TNF-α	−0.002	−0.011, 0.008	0.759	−0.068	−0.112, −0.024	**0.003**

3.5. Menopausal status

We examined whether women's menopausal status altered the pattern of results. Approximately 33% of women reported their reproductive status as post-menopausal (n = 36). Women who were pre-versus post-menopausal did not differ on endotoxin levels or any of the inflammation measures (*ps* > .3). Controlling for menopausal status did

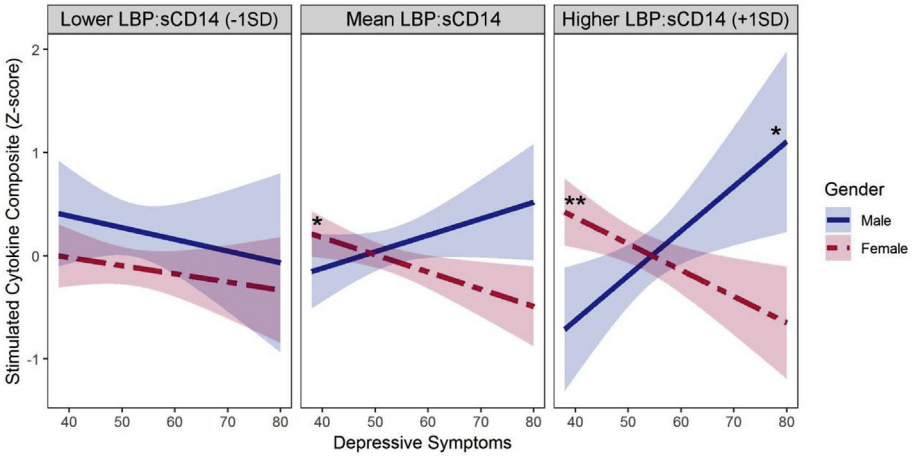

Fig. 3. Gender differences in the association between depressive symptoms and stimulated cytokine levels depended on the LBP:sCD14 ratio. Ribbons represent 95% confidence intervals. Results are plotted at −1 SD, mean, and +1 SD of the LBP:sCD14 ratio. In these analyses, the inflammatory responses of men and women with mean and higher LBP:sCD14 ratios began to significantly differ at about the midpoint of what is considered to be moderate depressive symptoms (i.e., approximately 65 on the PROMIS scale). Simple slopes, *p < 0.05; **p < 0.01.

not substantively alter the three-way interaction between gender, endotoxin levels, and depressive symptoms (Table S11).

4. Discussion

The present study investigated endotoxemia as a contributor to gender-dependent associations between depressive symptoms and *ex vivo* stimulated cytokine responses. We previously reported that men and women showed divergent patterns of association between depressive symptoms and stimulated inflammatory responses (Majd et al., 2018). Here, from the same sample, we found that these gender differences were only evident among individuals with moderate and higher levels of endotoxemia. At higher levels of the LBP:sCD14 ratio, men demonstrated positive associations and women demonstrated negative associations between depressive symptoms and *ex vivo* stimulated inflammatory responses. At lower levels of LBP:sCD14, no gender differences were evident; both men and women demonstrated similarly weak (non-significant) associations between depressive symptoms and stimulated inflammatory responses. This three-way interaction was not observed for any basal measures of inflammation (i.e., cytokines or CRP).

Our findings indicate that LBP:sCD14 was particularly related to men's associations between depressive symptoms and inflammatory responses. Several possibilities may explain the importance of endotoxemia in divergent patterns observed in men and women. Men tend to respond with more vigorous inflammatory immune responses than women to microbes in blood (Vázquez-Martínez et al., 2018). One possibility is that higher depressive symptoms heighten the association between circulating endotoxin levels and increased inflammatory responses among men. Alternatively, the positive association between depressive symptoms and inflammatory responses in men may require an inflammatory stimulus like elevated levels of LBP:sCD14. Either interpretation suggests that the association between depressive symptoms and *ex vivo* inflammation may be dependent on physical conditions like endotoxemia.

In contrast to the pronounced pattern in men, women demonstrated only slightly stronger, negative associations between higher depressive symptoms and lower inflammatory responses at higher levels of LBP:sCD14. Menopausal status did not alter these results. Prior research in rodents indicates that females desensitize more quickly than males to repeated exposures to endotoxin *in vivo* (Engeland et al., 2006). This desensitization to repeated microbial challenge might explain the relatively weaker association of LBP:sCD14 with depression and inflammatory responses in women compared to men. Our prior report speculated that endotoxemia might explain the divergent patterns observed between males and females (Majd et al., 2018), which appears accurate as gender differences were only evident at moderate and higher LBP:sCD14 levels. However, why women with higher depressive symptomatology exhibit reduced inflammatory responses (*ex vivo*) remains unclear. One possible explanation stems from the finding that depressed women show higher sensitivity to glucocorticoid's anti-inflammatory properties compared to non-depressed women at rest (Miller et al., 2005). Higher glucocorticoid sensitivity may result in relatively reduced inflammatory responses under conditions of higher depression, regardless of LBP:sCD14 level. The association between higher depressive symptoms and a lower, possibly inadequate, inflammatory response likely represents a risk for negative health outcomes in women which might be exacerbated by endotoxemia. Negative health outcomes that stem from lower than normal inflammatory responses include impaired wound healing and reduced effectiveness of vaccines (Kiecolt-Glaser et al., 1995, 1996).

4.1. Routes by which gender is associated with depression, inflammation, and endotoxemia

Future work linking depressive symptoms and inflammation should focus on gender as a factor in these processes rather than a confounder. The present results replicate prior findings of gender differences in endotoxin markers (e.g., women having higher sCD14 levels than men; Kiecolt-Glaser et al., 2018), and extend prior research by suggesting that endotoxemia levels moderate the gender difference between depressive symptomatology and *ex vivo* inflammatory responses. The present data, however, do not explain *why* this gender difference exists.

Several biological factors should be considered, including sex hormones and stress responses. Sex hormones influence immune functioning (Klein and Flanagan, 2016) and have been implicated in gender dimorphisms, such as responses to bacterial infection (Vázquez-Martínez et al., 2018). In addition, sex hormones can alter endotoxemia by influencing gut permeability (e.g., estrogens decrease permeability of the gut; Meleine and Matricon, 2014). Both depression pathogenesis and symptom severity have been associated with sex hormone levels. For example, estrogen levels at menarche are thought to relate to depression in adolescent women (Altemus et al., 2014) and testosterone in older men has been associated with lower depressive symptoms (Booth et al., 1999).

Stress response systems are another biological pathway that may be involved. Stress can be a critical precipitating factor in depression onset, in particular following severe stressful life events (Hammen, 2005). Stress also increases gut permeability, the effects of which have been demonstrated across acute and chronic stress responses via a range of biological stress response systems (reviewed in de Prunder and Pruimboom, 2015). To what extent sex hormones and/or stress responses explain the pattern of relationships observed here awaits future testing.

Psychosocial pathways that may help explain the gender differences reported here should be explored, including health behaviors. Prior work has linked obesity (Gonzalez-Quintela et al., 2013; Slyepchenko et al., 2016), overeating (Laugerette et al., 2014), and Western high-fat diets (Kiecolt-Glaser et al., 2018) to gut permeability and endotoxemia. Obesity and prandial health behaviors have been linked to depression onset and symptom severity in separate bodies of research (Faith et al., 2002; Quirk et al., 2013), with some indication of gender differences (Larsen et al., 2006). More work is necessary to determine whether these behavioral health pathways may help explain the gender differences evident among depressive symptoms, markers of endotoxemia, and inflammatory responses.

4.2. Future directions and limitations

4.2.1. The microbiome

As the present work involved circulating endotoxin levels that commonly emanate from gut sources (Kiecolt-Glaser et al., 2018; de Prunder and Pruimboom, 2015), it follows that the makeup of gut microbiota may be an important consideration. The relative proportion of different classes of bacteria – particularly vis-à-vis dysbiosis, or an imbalance of healthy to pathogenic microbiota – has been associated with both inflammatory cytokine responses (Schirmer et al., 2016) and with depressive symptoms (Foster and Neufeld, 2013). Hence, both the degree and type of bacterial translocation may influence depressive symptoms, although no work to our knowledge has investigated gender as a moderator in these domains.

4.2.2. Possible limitations to generalizability

Several aspects of the present study may limit generalizability, including reliance on cross-sectional analyses and our cohort of healthy (i.e., not clinically depressed) individuals. We also excluded participants from the larger ESCAPE project with chronic health conditions in order to examine typical inflammatory responses (see Majd et al., 2018). The study's sample and exclusion criteria may thus limit our ability to generalize these findings to clinical populations. However, sub-clinical depressive symptom scores are a critical predictor of later major depression onset and all-cause mortality (Katon, 2003; Houle, 2013). Further, clinical depression would presumably result in higher depressive symptomology, and some health conditions that we excluded (e.g., autoimmune disorders) have been related to increased gut permeability (de Prunder and Pruimboom, 2015; Meleine and Matricon, 2014). Hence, it is possible that higher depressive symptomology due to clinical

depression, and/or higher endotoxin levels due to chronic disease, could intensify the pattern of results observed here.

To better generalize these findings and inform future research, depressive symptoms, markers of endotoxemia, and inflammation need clearer resolution of the time period during which these processes associate. LBP and sCD14 are part of the acute phase response to endotoxemia (Wurfel et al., 1995), but both measures have been linked prospectively to longer-term health outcomes. For example, higher baseline measures of LBP were associated with increased cardiovascular and all-cause mortality in an eight-year follow-up period (Lepper et al., 2011). Similarly, higher levels of sCD14 have been linked to increased cardiovascular and all-cause mortality across a twenty-year follow-up (Reiner et al., 2013). These prospective associations suggest there may be trait-like qualities to LBP and sCD14 responses to endotoxemia; a one-time measure may also indicate chronic exposure to endotoxin or risk for infection. It is important to note that while either measure on its own serves as a marker of recent endotoxin exposure, the ratio index (i.e., LBP:sCD14) is indicative of the relative contribution of the non-inflammatory pathway for bacterial clearance. Hence, examining these factors in concert is critical to advance our understanding of their acute modulation of inflammatory responses, as well as their associations with gender, depression, and inflammation.

Future work that aims to infer causal associations would benefit from including biological specimens in a longitudinal measurement-burst design, consisting of multiple blood draws within short timeframes across annual or semi-annual waves in larger samples (Sliwinski, 2008). Such a longitudinal approach will improve our understanding of the time scale in which endotoxemia links to depressive symptoms and inflammation, and help to determine the reliability and variability of these physical processes. Combining a longitudinal design with populations that are at higher risk for clinical depression would help to further delineate the associations among depressive symptoms, markers of endotoxemia, and inflammation, as well as the impact of anti-depression treatments on these patterns.

5. Conclusion

This work offers insights that may be important for understanding and treating comorbid physical and mental health conditions. Depressive symptoms are risk factors for poor physical health due to dysregulated (i.e., heightened or attenuated) inflammatory responses (Kiecolt-Glaser and Glaser, 2002). Heightened inflammation has been linked to a large number of health conditions, including increased risk for incident coronary heart disease in cases of major depressive disorder (Carney and Freedland, 2017); attenuated inflammatory responses have similarly been linked to negative health outcomes, such as impaired wound healing (Kiecolt-Glaser et al., 1995) and reduced vaccine efficacy (Kiecolt-Glaser et al., 1996). The present findings suggest that endotoxemia may play a role in the association between depressive symptoms and altered inflammation. Further research is needed to better understand the timing and causal associations among these variables, and to determine the extent to which treating or reducing endotoxemia might impact the link between depressive symptoms and inflammation. Knowing who is at risk for altered immunity, and understanding the factors that contribute to these alterations, may help clinicians identify individuals who are susceptible to downstream physical consequences associated with depressive symptoms. Our results indicate that endotoxemia coupled with moderate or higher depressive symptomatology may result in more robust inflammatory responses in men, and attenuated responses in women. In turn, these altered responses may increase risk for, or worsen the severity of, physical health conditions.

Declaration of competing interest

All authors have approved this submission and declare no conflicts of interest.

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Appendix A. Supplementary data

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