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Endotoxemia coupled with heightened inflammation predicts future depressive symptoms

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ABSTRACT

Objective: Cross-sectional data have linked gut barrier abnormalities and endotoxemia with depression, even among those without gastrointestinal symptoms. This study examined longitudinal associations between endotoxemia markers and depressive symptoms, as well as the role of inflammation in this relationship.

Design: At three annual visits, 315 women (n=209 breast cancer survivors, n = 106 non-cancer patient controls, M=55 years old) completed the Center for Epidemiological Studies Depression questionnaire (CES-D) and provided blood samples to assess inflammatory markers – interleukin-6, tumor necrosis factor-alpha, and C-reactive protein – and endotoxemia markers – lipopolysaccharide-binding protein (LBP), soluble CD14 (sCD14), and their ratio.

Results: Adjusting for key demographic variables, health behaviors, visit 1 depressive symptoms, and cancer status and treatment, women with higher visit 1 LBP and LBP/sCD14 had more depressive symptoms at the two subsequent annual visits. Illustrating the notable impact, a woman at the 75th percentile for LBP or LBP/sCD14 at visit 1 was 18 % more likely to report clinically significant depressive symptoms (CES-D $\geq$16) at follow-up than a woman in the lowest quartile. Cancer status and treatment type did not modulate this relationship. In contrast, visit 1 depressive symptoms did not predict endotoxemia at follow-up. A significant interaction between LBP/sCD14 and inflammatory burden suggested that visit 1 endotoxemia fueled depressive symptoms only in the context of elevated inflammation.

Conclusion: These results suggest that endotoxemia, combined with systemic inflammation, can drive depressive symptoms. These findings may implicate bacterial endotoxin translocation from the gut to the bloodstream in depression etiology. Interventions that reduce endotoxemia and inflammation may lessen the risk of depression.

1. Background

Gastrointestinal and psychiatric disorders are commonly comorbid (Whitehead et al., 2002). Even in the absence of gastrointestinal symptoms, cross-sectional data have linked depression and poorer gut barrier integrity (Maes et al., 2008; Slyepchenko et al., 2017; Stevens et al., 2018). For example, one cross-sectional study showed that those with depression had higher levels of circulating endotoxin, zonulin, and

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intestinal fatty acid binding protein, indicative of gut barrier damage (Stevens et al., 2018). The current study probes longitudinal associations between biomarkers of circulating endotoxin and depressive symptoms over a two-year period.

The gastrointestinal tract is the primary reservoir of endotoxin (lipopolysaccharide; LPS) in the body (Kell and Pretorius, 2015). Higher levels of circulating endotoxin (i.e., endotoxemia) likely result from LPS translocation from the gut, as illustrated by a study in which an oral antibiotic wiped out gram-negative bacteria in the feces along with circulating endotoxin (Brenchley et al., 2006). However, LPS's short half-life renders it difficult to measure (Gonzalez-Quintela et al., 2013). As an alternative, LBP reflects recent exposure to circulating LPS (Schumann, 2011). LBP can be mildly elevated even among healthy individuals, and those with more LPS-producing gut bacteria also have higher LBP (Citronberg et al., 2018). LBP tracks with LPS (Abad-Fernández et al., 2013), intestinal fatty acid binding protein, a plasma biomarker of intestinal epithelial cell damage (Uhde et al., 2016), and zonulin, a protein that regulates the tight junctions between epithelial cells (Tremellen and Pearce, 2020). LBP predicts important health outcomes like coronary artery disease (Lepper et al., 2011), and therefore LBP has been called a clinical marker of "effective endotoxemia" (Gonzalez-Quintela et al., 2013). Indeed, LBP is a multi-informative biomarker underlying aging, inflammation, metabolic syndrome, and gastrointestinal disorders (Gonzalez-Quintela et al., 2013; Lakatos et al., 2010). Soluble CD14 (sCD14) facilitates clearance of LPS via high-density lipoproteins (Wurfel et al., 1995). Therefore, the combination of high LBP and low sCD14 suggests that the body is not responding effectively to circulating LPS (Kiecolt-Glaser et al., 2018; Laugerette et al., 2014).

Depression-induced psychosocial and physiological changes may erode the gut barrier, increasing endotoxemia, one possibility. For example, depression increases stress exposure (Hammen, 2006) and reactivity (Hu et al., 2016), and may change the gut environment through this pathway (Vanuytsel et al., 2014). One study from our lab showed that the combination of a past depressive disorder and the stress of a hostile marital relationship was associated with greater intestinal permeability (Kiecolt-Glaser et al., 2018). Depression also fuels poor health behaviors, such as low physical activity, which is linked to a lower abundance of health-promoting gut microbiota species (Bressa et al., 2017). Additionally, 30–50 % of clinically depressed individuals have elevated inflammation (Raison and Miller, 2011), which can weaken the gut barrier (Neurath, 2014).

Alternatively, another possibility is that endotoxemia promotes depression (Slyepchenko et al., 2017). Stress-induced intestinal permeability led to depressive-like behavior in rodents (Gárate et al., 2011). In humans, endotoxin injections increased depressive symptoms and reduced neural responding to reward, a correlate of anhedonia (Eisenberger et al., 2010). However, it is unknown whether basal endotoxemia – without endotoxin administration – precedes later depressive symptoms. Heightened endotoxemia could be especially depressogenic when coupled with elevated systemic inflammation. Inflammation can fuel depression (Kiecolt-Glaser et al., 2015), and therefore those with both heightened endotoxemia *and* elevated inflammation may have the greatest increases in depressive symptoms over time.

1.1. The current study

The current study probed the directional flow of the gut-mood connection by examining longitudinal relationships between endotoxemia and depressive symptoms. It also probed whether cancer status and treatment type, significant psychosocial and physiological challenges, modulated these longitudinal relationships. Lastly, post-hoc analyses addressed the clinical significance of the findings, as well as the role of inflammation.

2. Methods and materials

As part of a longitudinal parent study addressing fatigue in breast cancer survivors and non-cancer patient controls, 315 women were identified from cancer clinics at The Ohio State University shortly after an initial test suggestive of cancer. Upon follow-up testing, participants received either a benign (noncancer patient controls) or malignant (cancer survivors) diagnosis. Noncancer patient controls were recruited before they received their benign diagnosis, and cancer survivors were recruited after their diagnosis. Among the cancer survivors, 63 % were Stage I, 27 % were Stage II, and 10 % were Stage III at diagnosis. Prior to cancer treatment (visit 1), all participants completed questionnaires and provided blood samples. Breast cancer survivors returned for visits 2 and 3 an average of 13.8 (± 5.6) months and 25.6 (± 6.4) months after visit 1, respectively. Non-cancer patient controls returned for follow-up visits within a comparable timeframe. Overall, 281 women ($n = 187$ breast cancer survivors; $n = 94$ controls) returned for the first follow-up visit and 260 ($n = 171$ breast cancer survivors; $n = 89$ controls) returned for the second. At each follow-up visit, all participants completed self-report measures and provided blood draws. Women with stage IV cancer, a prior history of cancer (excluding basal or squamous cell skin carcinomas), or significant visual, auditory, or cognitive impairments were excluded. The Ohio State University Institutional Review Board approved the study, and all participants provided written consent. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

2.1. Depression

Women completed the widely-used Center for Epidemiological Society's Depression (CES-D) scale (Radloff, 1977) at each visit. At visit 1, 47 % of women scored at or above the CES-D cut-off score of 16, indicating clinically significant depressive symptoms (Weissman et al., 1977). Cancer survivors and non-cancer patient controls did not differ in rates of clinically significant depressive symptoms at any visit ($ps > 0.11$).

2.2. Endotoxemia

Serum LBP was multiplexed and measured using an electrochemiluminescence method with Meso Scale Diagnostics kits (Rockville, MD) following kit instructions. Plates were read using the MSD Sector Imager 2400. Soluble CD14 levels were ascertained via a Quantikine ELISA kit (R&D Systems, Minneapolis, MN). Plates were read using a Fisher Scientific Labsystems Multiskan MCC/340 plate reader. Sensitivity was 125 pg/mL for sCD14 and 0.038 ng/mL for LBP. The intra-assay coefficient of variation (CV) for sCD14 was 5.5 %, and the inter-assay CV was 6.3 %; corresponding coefficients for LBP were 2.74 % and 8.33 %, respectively.

2.3. IL-6, CRP, and TNF-α

To control for diurnal variation, fasting blood samples were collected between 7:00 and 10:00 AM. CRP was measured using a chemilluminescence methodology via the Immulite 1000 (Siemens Healthcare Diagnostics, Inc., Deerfield, IL). The assay's sensitivity was 0.3 mg/L. The intra-assay CV was 3.1 % and the inter-assay CV was 7.3 %. Serum IL-6 and TNF-α were measured using MSD Human ProInflammatory 2 Ultra-Sensitive Kits and an MSD Imager 2400 (Meso Scale Discovery, Rockville, MD), following kit instructions. The intra-assay and inter-assay CVs for IL-6 were 1.43 and 4.42 %, respectively, and for TNF-α they were 4.32 and 5.30 %, respectively. The average lower limits of detection for IL-6 and TNF-α were 0.26 pg/mL and 0.37 pg/mL, respectively.

Table 1
Sample Information at Visit 1 (N=315).

	Breast Cancer Survivors (n=209)			Non-cancer patient controls (n=106)		
Measure	M (SD)	N (%)	Range	M (SD)	N (%)	Range
Age	55.7(11.5)		26.0–88.0	55.4(11.0)		34.0–83.0
Body mass index (kg/m^2)	28.7(7.3)		15.8–58.7	28.6(7.5)		17.9–55.0
Race (% Caucasian)		156(78 %)			79(81 %)	
Comorbidities	0.8(1.3)*		0.0–7.1	0.5(0.9)*		0.0–5.0
AHEI at Visit 2	34.8(14.0)		8.0–77.0	35.0(12.3)		10.0–68.0
PSQI at Visit 2	7.4(3.8)		0.0–17.0	6.7(3.9)		0.0–18.0
Godin Activity Scale	17.9(18.7)		0.0–119.0	21.6(23.7)		0.0–119.0
Smoker (% yes)		27(13 %)			8(8%)	
Number of Alcoholic Beverages per Week	1.9(3.6)		0.0–35.0	2.3(4.1)		0.0–19.0
Anti-Depressant Usage (% Taking)		48(23 %)			25(24 %)	
Depression (CES-D)	16.5(10.5)		0.0–49.0	13.6(9.9)		0.0–48.0
sCD14 (pg/mL)	2060(524)*		1070–3960	1915(403)*		1290–3810
LBP (ng/mL)	4979(2178)		221–13310	4801(2251)		353–12702
LBP/sCD14	2.5(1.0)		0.1–6.3	2.6(1.3)		0.3–7.0
Interleukin-6 (pg/mL)	2.0(2.3)		0.3–21.8	3.0(6.2)		0.2–59.0
CRP (mg/L)	2.7(4.0)		0.2–25.6	3.0(4.3)		0.2–24.1
TNF-alpha (pg/mL)	6.9(3.7)*		1.4–28.4	8.8(6.6)*		1.8–35.2
Chemotherapy treatment		89(43 %)				
Radiation treatment		110(52 %)				
Stage 0–1		131(63 %)				
Stage II		55(27 %)				
Stage III		21(10 %)				

PSQI and AHEI were not measured at Visit 1; *$p < 0.05$.

2.4. Covariates

The Charlson Comorbidity Index provided data on medical comorbidities (Charlson et al., 1987). The Charlson Index is well-validated and predicts short- and long-term mortality and disability (De Groot et al., 2003).

At each follow-up visit, trained researchers conducted a 24 -h dietary recall with each participant using the gold-standard USDA Multiple Pass Approach method (Blanton et al., 2006; Moshfegh et al., 2008). The Alternative Health Eating Index (aHEI) (McCullough and Willett, 2006), a common dietary quality index, was calculated.

The Pittsburgh Sleep Quality Index (PSQI) evaluated sleep quality over the past month (Buysse et al., 1989). The Godin Leisure-Time Exercise Questionnaire measured light, moderate, and vigorous activity over the previous week (Godin and Shephard, 1985), and an index of aerobic exercise accounting for the frequency and duration of moderate and vigorous activity was calculated for each participant (Amireault et al., 2015). Women self-reported smoking history and alcohol use. Medical records provided data on cancer treatment type and medication usage.

2.5. Statistical analysis

To calculate a composite index of inflammatory burden, each inflammatory marker (IL-6, CRP, and TNF-α) was z-standardized and then these z-scores were averaged (Murdock et al., 2016). Cross-sectional, bivariate associations between all study variables were assessed using Pearson correlations.

To test longitudinal correlations between endotoxemia and depressive symptoms, a four-step modeling approach was used. Using hierarchical linear models with an unstructured covariance matrix, depressive symptoms at visits 2 and 3 were modeled as outcomes, with visit 1 endotoxemia markers (LBP, sCD14, LBP/sCD14) as the predictors, in separate models. The first step (i.e., most basic model) adjusted for visit, cancer status, visit 1 depressive symptoms, and the visit 1 value of the predictor as covariates. The second step added demographic covariates measured at visit 1 (age, comorbidities, BMI) as well as antidepressant usage at the follow-up visits. In the third step, the following health behaviors, measured at the follow-up visits, were added as covariates: diet quality, sleep quality, self-reported physical activity level, alcoholic beverages consumed per week, and current smoking status. The final step adjusted for cancer treatment type using indicator variables for chemotherapy and radiation. The four-step modeling approach was repeated with visit 1 depressive symptoms predicting visit 2 and 3 endotoxemia markers. In full models, cancer status and cancer treatment type were tested as moderators but not retained due to lack of significance. Thus, breast cancer survivors and non-cancer patient controls were combined in all models.

Post-hoc analyses were conducted to determine the clinical significance of the endotoxemia-to-depression pathway as well as the role of inflammation. To test clinical significance, post-hoc regression models were constructed with visit 1 endotoxemia measures predicting whether women were at or above the CES-D clinical cut score at each follow-up visit. For this binary outcome, generalized estimating equations with a log link, unstructured covariance matrix, and robust standard errors were used to produce estimates of relative risk (Zou, 2004). In these models, group, visit, and CES-D cut score at visit 1 were the only covariates. To examine the role of inflammation, we added the interaction term of visit 1 endotoxemia and visit 1 inflammatory burden to the full hierarchical linear model of depressive symptoms described in the prior paragraph.

All analyses were performed in SAS Version 9.4 (Cary, NC). Two-tailed tests were performed, and the alpha level for all analyses was set at 0.05. Visual inspection of residual plots revealed two potentially influential observations (one observation of LBP > 20,000 ng/mL; one observation of inflammatory burden>6), which were excluded from relevant models.

3. Results

Table 1 provides the sample's demographic information. Breast cancer survivors and non-cancer patient controls were equivalent on all variables of interest except survivors had more comorbidities (p=0.050) and higher sCD14 at visit 1 (p = 0.009) (Table 1). Among the cancer survivors, 30 % did not receive radiation or chemotherapy, 26 % received radiation only, 16 % received chemotherapy only, 26 % received both, and 2% were missing treatment information. Cancer survivors were an average of 8.4 months and 20.2 months post-primary cancer treatment at visit 2 and visit 3, respectively. Overall, women were mostly White (79 %), with an average age of 55 years.

Table 2
Correlation matrix for key study variables at Visit 1 (N = 315).

Variable	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
1. CES-D																	
2. LBP	.111																
3. sCD14	.051	**.285**															
4. LBP/sCD14	.076	**.840**	**−.230**														
5. IL-6*	.106	**.232**	−.009	**.224**													
6. CRP*	**.168**	**.527**	.076	**.482**	**.384**												
7. TNF-α*	.036	.111	−.052	**.145**	**.628**	**.161**											
8. Inflam. Burden	**.135**	**.311**	−.024	**.309**	**.772**	**.539**	**.737**										
9. Group	**.117**	.038	**.138**	−.053	−.086	−.045	**−.119**	**−.139**									
10. Age	**−.285**	**.114**	**.164**	−.017	−.077	−.008	−.003	−.060	.024								
11. Comorbidities	.093	.048	.039	−.010	.066	.058	.005	.044	**.112**	**.211**							
12. Antidepressant	**.193**	.103	.061	.029	−.020	.063	−.049	.019	−.006	−.003	.063						
13. BMI	**.163**	**.383**	−.064	**.418**	**.259**	**.544**	**.114**	**.358**	.018	.021	.093	.027					
14. Smoker	**.140**	.038	−.026	.053	**.147**	**.143**	.013	**.126**	.063	**−.200**	.013	**.112**	.093				
15. Alcohol use	.010	**−.151**	.112	**−.198**	−.001	**−.120**	−.061	**−.130**	−.064	−.090	−.077	−.028	**−.174**	.047			
16. Godin	**−.183**	**−.211**	−.001	**−.207**	−.021	**−.252**	.049	−.069	−.075	−.011	**−.139**	−.089	**−.261**	−.070	.031		
17. aHEI+	**−.160**	−.122	−.070	−.096	−.076	**−.160**	−.068	**−.136**	−.046	−.013	**−.138**	**−.137**	**−.163**	**−.142**	.086	**.214**	
18. PSQI+	**.538**	.050	−.017	.029	−.021	.102	−.047	.000	.078	−.079	**.134**	**.162**	.100	.115	−.005	**−.204**	−.123

* IL-6, CRP, and TNF-α are natural-log transformed; +aHEI and PSQI are Visit 2 measures and are correlated with Visit 2 values of other variables; **p < 0.05**.

Table 3
Estimated effects of baseline endotoxemia measures on CES-D total scores at follow-up.

Predictor	Model	Slope	(SE)	95 % CI	F statistic	P-value
sCD14	Step 1	−0.00068	(0.00093)	−0.0025 to 0.0011	F(1, 249) = 0.55	0.46
	Step 2	−0.00045	(0.00092)	−0.0023 to 0.0014	F(1, 243) = 0.24	0.62
	Step 3	−0.00023	(0.00088)	−0.0020 to 0.0015	F(1, 212) = 0.07	0.80
	Step 4	−0.00016	(0.00088)	−0.0019 to 0.0016	F(1, 208) = 0.03	0.85
LBP	Step 1	0.00052	(0.00022)	0.0001 to 0.0009	F(1, 252) = 5.67	**0.02**
	Step 2	0.00042	(0.00023)	0.0000 to 0.0009	F(1, 249) = 3.25	0.07
	Step 3	0.00057	(0.00023)	0.0001 to 0.0010	F(1, 222) = 5.87	**0.02**
	Step 4	0.00059	(0.00023)	0.0001 to 0.0010	F(1, 217) = 6.33	**0.01**
LBP/sCD14	Step 1	1.13	(0.43)	0.28 to 1.98	F(1, 247) = 6.85	**0.01**
	Step 2	1.02	(0.47)	0.09 to 1.95	F(1, 246) = 4.63	**0.03**
	Step 3	1.25	(0.47)	0.32 to 2.17	F(1, 217) = 7.04	**0.01**
	Step 4	1.28	(0.47)	0.35 to 2.20	F(1, 211) = 7.41	**0.01**

Step 1: Controlling for group (cancer vs. control), visit, and baseline CES-D total score.
Step 2: Additionally controlling for age, comorbidities, BMI, and antidepressant use.
Step 3: Additionally controlling for diet quality, sleep quality, self-reported physical activity level, alcoholic beverages consumed per week, and current smoking status.
Step 4: Additionally controlling for cancer treatment type.

Cross-sectionally at visit 1, women with greater LBP had elevated serum IL-6 (r=0.232, p<0.001), CRP (r=0.527, p < 0.001), and a greater inflammatory burden as measured by the standardized composite score described above (r=0.311, p < 0.001). Similarly, women with higher LBP/sCD14 had greater serum IL-6 (r=0.224, p<0.001), CRP (r=0.482, p < 0.001), TNF-α (r=0.145, p=0.012), and inflammatory burden (r=0.309, p<0.001). Soluble CD14 was not associated with any inflammatory marker (*p*s>0.19). Also, women with more depressive symptoms had greater CRP (r=0.168, p=0.003), higher inflammation, (r=0.135, p=0.011), and marginally elevated LBP (r=0.111, p=0.056). In terms of health behaviors, women who ate a healthier diet as indexed by the aHEI had lower CRP (r= -0.160, p=0.034), while smokers (r=0.143, p=0.011) and less active women (r= -0.252, p < 0.001) had higher CRP, and less active women also had greater LBP (r= -0.211, p=0.001) and LBP/sCD14 (r= -0.207, p=0.004). See Table 2 for zero-order correlations.

3.1. Trajectories of primary variables

On average, inflammatory burden increased throughout the study

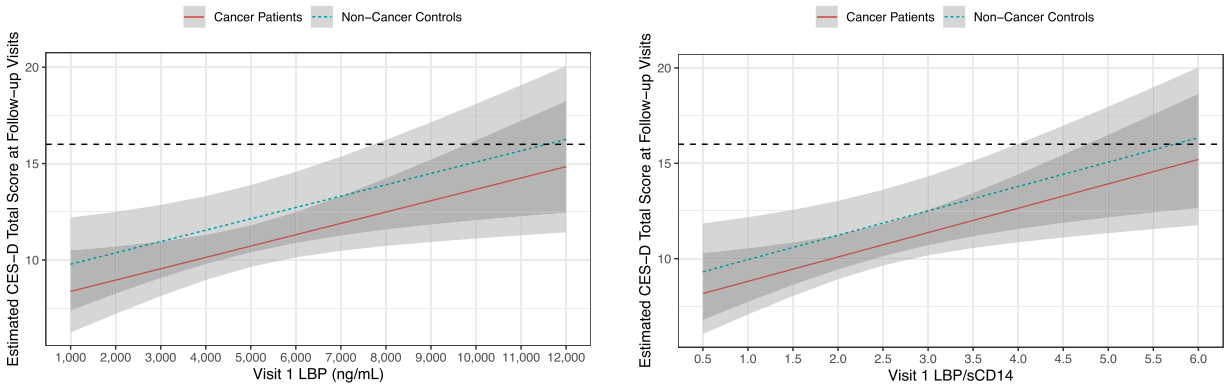

Fig. 1. Full models depicting visit 1 endotoxemia markers predicting follow-up CES-D total scores for breast cancer survivors and non-cancer patient controls. Shaded area represents 95 % confidence interval. Horizontal dashes represent CES-D cut score for clinically significant depressive symptoms. There was no between-group difference in follow-up CES-D scores (*ps*>0.21).

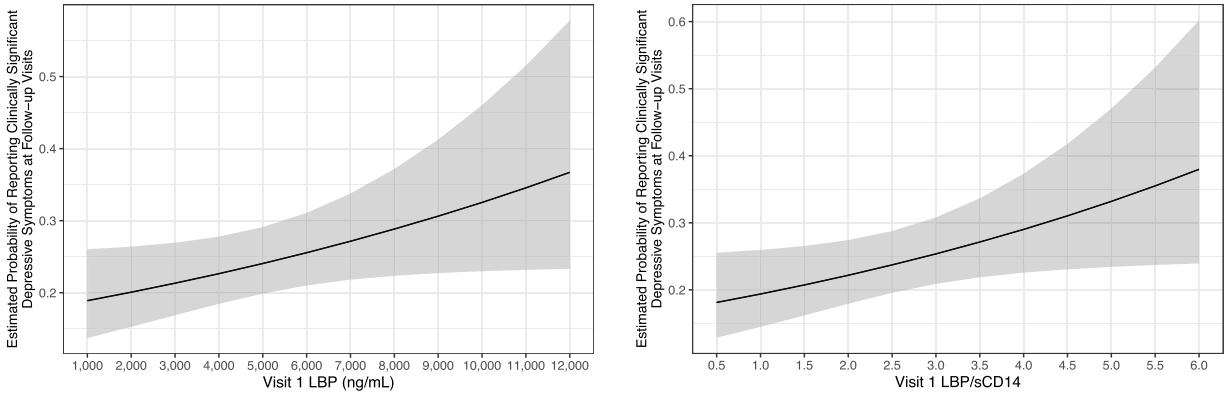

Fig. 2. Visit 1 endotoxemia markers predicting probability of reporting clinically significant depressive symptoms (CES-D ≥ 16) at follow-up for participants with and without clinically significant depressive symptoms at visit 1. Shaded area represents 95 % confidence interval.

($p < 0.001$). For both groups, mean LBP/sCD14 declined from visit 1 to visit 2 ($p < 0.001$) but remained stable from visit 2 to visit 3 (p=0.07). These trajectories were not different for cancer survivors compared to controls (*ps*>0.36). LBP did not change across visits (p=0.34). Breast cancer survivors and non-cancer patient controls had different trajectories of sCD14 ($p = 0.014$) and marginally different trajectories of CES-D scores across visits (p=0.054). Compared to cancer survivors, controls had lower sCD14 at visit 1 (p=0.015), and then a greater increase between visit 1 and visit 2 (p=0.013), thereby eliminating between-group differences at visits 2 and 3 (*ps*>0.55). Compared to controls, cancer survivors had higher depressive symptoms at visit 1 (p=0.039), but then had a steeper reduction in depressive symptoms between visit 1 and visit 2 (p=0.018) so that between-group differences disappeared at visits 2 and 3 (*ps*>0.85). Among the cancer survivors, there were no cancer treatment-related differences in trajectories of sCD14 (p=0.35), LBP/sCD14 (p=0.35), and CES-D (p=0.98), but there was a marginally nonsignificant trend for LBP (p=0.055), such that those who received both chemotherapy and radiation had greater increases in LBP from visit 1 to visit 2, but returned to levels comparable to the other treatment groups at visit 3.

3.2. Endotoxemia predicting later depressive symptoms

In step one models, visit 1 LBP/sCD14 ($p = 0.009$) and LBP ($p = 0.018$) but not sCD14 ($p = 0.46$) predicted visits 2 and 3 CES-D scores, such that women with greater endotoxemia at visit 1 reported higher depressive symptomology at follow-up. These results were largely robust to covariate inclusion. In full models, greater visit 1 LBP/sCD14 (p=0.007) and LBP (p=0.013) predicted higher depressive symptoms, respectively, at follow-up, while visit 1 sCD14 remained unrelated to future depression (p=0.85). See Table 3 and Fig. 1.

Women who had higher LBP/sCD14 (p=0.040) and LBP (p=0.052) at visit 1 had a greater and marginally greater risk, respectively, of reporting clinically meaningful depressive symptoms on the CES-D at follow-up, compared to those with less endotoxemia (Fig. 2). In our sample, 41 % of women at or above the 75th percentile for LBP (5950 ng/mL) and 40 % of women at or above the 75th percentile for LBP/sCD14 (2.99) at visit 1 had clinically significant depressive symptoms at visit 2, compared to 29 % of women at or below the 25th percentile for LBP (3,427 ng/mL) and 31 % of women at or below the 25th percentile for LBP/sCD14 (1.78). In models that adjusted for CES-D cut score status at visit 1, a woman at the 75th percentile for LBP/sCD14 at visit 1 was 18 % more likely than someone at the 25th percentile to report clinically significant depressive symptoms at follow-up (LBP/sCD14 RR: 1.18, 95 % CI: 1.008–1.37).

3.3. Depressive symptoms predicting later endotoxemia

In step one models, continuous CES-D scores did not predict sCD14 ($p = 0.48$) but were positively related to follow-up LBP ($p = 0.050$) and marginally predicted LBP/sCD14 ratio ($p = 0.064$) at follow-up. In steps two through four models, CES-D was not associated with follow-up endotoxemia markers (*ps*>0.13), with the exception of a marginal positive relationship with LBP/sCD14 in the step 4 model (p=0.088) (Table 4).

Table 4
Estimated effects of baseline CES-D total score on endotoxemia measures at follow-up.

Outcome	Model	Slope	(SE)	95 % CI	F statistic	P-value
sCD14	Step 1	1.85	(2.6)	−3.3–7.0	F(1, 222) = 0.5	0.48
	Step 2	1.31	(2.8)	−4.3–6.9	F(1, 212) = 0.22	0.64
	Step 3	−0.31	(3.3)	−6.9 to 6.3	F(1, 194) = 0.01	0.93
	Step 4	−0.56	(3.4)	−7.2–6.1	F(1, 189) = 0.03	0.87
LBP	Step 1	19.1	(9.7)	0.04–38.2	F(1, 229) = 3.9	**0.05**
	Step 2	13.7	(10.0)	−6.0–33.4	F(1, 223) = 1.87	0.17
	Step 3	8.7	(11.3)	−13.6–31.0	F(1, 197) = 0.59	0.44
	Step 4	9.8	(11.4)	−12.6–32.2	F(1, 191) = 0.75	0.39
LBP/sCD14	Step 1	0.0069	(0.0037)	−0.00042 to 0.014	F(1, 233) = 3.45	0.06
	Step 2	0.0050	(0.0040)	−0.0029 to 0.013	F(1, 229) = 1.54	0.22
	Step 3	0.0067	(0.0044)	−0.0020 to 0.015	F(1, 205) = 2.28	0.13
	Step 4	0.0076	(0.0044)	−0.0011 to 0.016	F(1, 200) = 2.95	0.09

Step 1: Controlling for group (cancer vs. control), visit, and baseline endotoxemia measure.
Step 2: Additionally controlling for age, comorbidities, BMI, and antidepressant use.
Step 3: Additionally controlling for diet quality, sleep quality, self-reported physical activity level, alcoholic beverages consumed per week, and current smoking status.
Step 4: Additionally controlling for cancer treatment type.

3.4. Inflammatory burden as an amplifier

In the fully adjusted model, visit 1 inflammation amplified the relationship between visit 1 LBP/sCD14 and follow-up depressive symptoms (p=0.040). That is, among women who were at the 25th percentile for inflammatory burden at visit 1 (z-score = -0.497), LBP/sCD14 was unrelated to follow-up depressive symptoms (p=0.29). However, among women at the 75th percentile for visit 1 inflammation (z-score = 0.139), those with greater LBP/sCD14 reported more depressive symptoms at follow-up (p=0.001) (Fig. 3). Inflammation did not heighten the relationships between visit 1 LBP (p=0.17) or sCD14 (p=0.67) and later depressive symptoms.

4. Discussion

4.1. Primary findings

This two-year observational study examined longitudinal associations between depressive symptoms and markers of endotoxemia, as well as the role of inflammation in this relationship. We found evidence for a periphery-to-brain pathway, such that the combination of endotoxemia and heightened inflammation predicted depressive symptoms one and two years later. These findings extend recent cross-sectional evidence of gut barrier dysfunction among depressed individuals (Stevens et al., 2018). Importantly, this longitudinal relationship remained even after adjusting for visit 1 depressive symptoms, concurrent health behaviors, demographic variables, and cancer status and treatment, suggesting that endotoxemia and related inflammation uniquely set the stage for later depressive symptoms.

Prior findings support the notion that endotoxemia and inflammation predispose to depression. Stress-induced gut leakiness and inflammation lead to depressive-like behavior in rodents (Cheng et al., 2016; Gárate et al., 2013, 2011). In humans, endotoxin injections produce transient spikes in IL-6 and TNF-α and simultaneously promote depressive symptoms (Reichenberg et al., 2001). Moreover, in line with this enhancement of depressive symptoms, interferon gamma administration to treat Hepatitis C and cancer elicits MDD episodes in up to 50 % of patients (Raison et al., 2006), which may initially remit after treatment cessation, but often recur (Chiu et al., 2017). Conversely, proinflammatory cytokine antagonists may lessen depressive symptoms (Tyring et al., 2006). In accord with this physiological pathway to depression, our data suggest that the body's response to circulating endotoxin precedes and predicts depressive symptoms. Endotoxemia only exacerbated depression when elevated systemic inflammation was also present, providing a backdrop to the established interplay between inflammation and depression.

4.2. Additional considerations

Our use of endotoxemia markers from the blood rather than GI symptomology rules out the possibility that poor gut health paves the way for mood disorders solely via psychosocial phenomena, such as

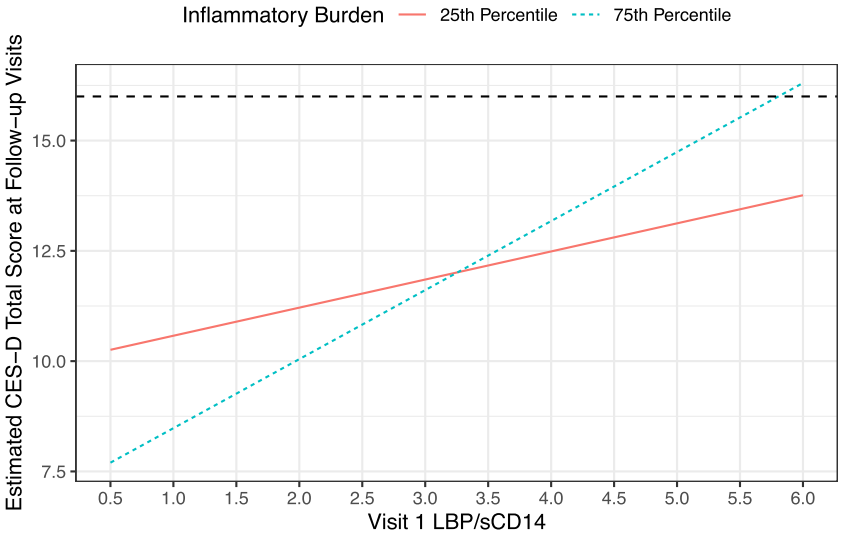

Fig. 3. Visit 1 inflammatory burden moderating the relationship between visit 1 LBP/sCD14 and follow-up depressive symptoms, adjusting for age, comorbidities, BMI, antidepressant usage, diet quality, alcohol consumption, sleep quality, physical activity level, smoking behavior, visit 1 depressive symptoms, and cancer status and treatment type. Among women at the 75th percentile for inflammatory burden at visit 1, greater LBP/sCD14 predicted more depressive symptoms at follow-up (p=0.001); however, this relationship did not hold among women at the 25th percentile for inflammatory burden (p=0.29).

symptom burden. Rather, our data suggest that gut-related systemic immune activation may increase risk for depression. Because the gastrointestinal tract is the primary site of LPS in the body (Kell and Pretorius, 2015), these results suggest that bacterial endotoxin translocation may play a role in the etiology of depression.

The primary findings did not differ by cancer status or treatment type, suggesting that endotoxemia coupled with inflammation may represent a more general risk factor for heightened depressive symptoms. From a clinical perspective, it is notable that heightened endotoxemia and inflammation prior to cancer treatment predicted post-treatment depressive symptoms, even after adjusting for treatment type. These findings are striking given that cancer treatment can also provoke depression, and yet these pre-treatment physiological markers related to post-treatment mood above and beyond cancer treatment type. Identifying such pre-treatment factors that increase risk for poorer quality of life after treatment provides targets for preventative interventions.

4.3. Future directions

A healthy gut microbiota facilitates gut barrier function. Among overweight individuals, a decrease in plasma LBP correlated with a greater prevalence of gut bacteria that fortify the intestinal barrier (*Faecalibaceterium* and *Odoribacter*) and reduced prevalence of proinflammatory gut bacteria (*Parvimonas*) (González-Sarrías et al., 2018). Moreover, colonizing germ-free adult mice with microbiota from a healthy human donor caused colonic barrier maturation within one week after colonization (Hayes, 2017). With a thicker mucosal lining and tighter junctions, this barrier reduced systemic microbial exposure and was much more resilient to injury (Hayes, 2017). Even oral administration of a probiotic with certain *Lactobacillus* and *Bifidobacterium* species restored gut barrier integrity and prevented stress-related changes to the HPA axis and autonomic nervous system in rodents (Ait-Belgnaoui et al., 2014). In contrast, gut dysbiosis can increase intestinal permeability (Thevaranjan et al., 2017).

Several studies have found microbiota differences when comparing depressed patients with nondepressed controls (Jiang et al., 2015; Naseribafrouei et al., 2014). In fact, transferring depressed humans' gut microbiota to germ-free rats triggered depressive-like behaviors (Kelly et al., 2016), warranting further exploration of poor gut barrier function resulting in systemic immune activation as a possible mechanism.

Endotoxemia may partially account for the established relationship between diet and depressive symptoms. In a recent meta-analysis of 16 randomized, controlled trials, depressive symptoms decreased among those who received plant-based, fiber-rich dietary interventions, and this effect was amplified in women (Firth et al., 2019). Also, fermented foods that contain live bacteria may boost barrier function and mood. For instance, nine weeks of yogurt consumption reduced the LBP/sCD14 ratio but not sCD14 among healthy premenopausal women (Pei et al., 2017), and high-fat yogurt intake lowered depression risk (Perez-Cornago et al., 2016). In our sample, a higher quality diet corresponded with lower inflammation and fewer depressive symptoms but was unrelated to endotoxemia markers. However, among a predominately male sample undergoing colonoscopies, those with higher quality diets (e.g., greater fruit consumption; fewer calories from solid fats, alcohol, and added sugar) had greater microbiota diversity and abundance of beneficial bacteria in the colonic mucosa (Liu et al., 2019). A question for further investigation is whether the microbiota that correspond with a healthy diet reduce endotoxemia [see Fuke et al., 2019 for a review of this nascent translational literature] – and thereby lessen depression risk.

4.4. Strengths and limitations

This study featured three visits over two years in a large sample. Additionally, the data analytic strategy accounted for a wide range of potential confounding variables. However, gastrointestinal symptoms were not assessed throughout the study, a limitation. Additionally, our study is limited by its observational nature, as well as a relatively homogeneous sample of middle-aged, primarily white females. Moreover, stool samples were not collected in this study; thus, we did not have gut microbiota data – an important area for future work. Our findings are also specific to our measures, and future studies should examine whether these results generalize to clinical depression, as assessed by a clinical interview, as well as other markers of gut barrier permeability (e.g., zonulin and intestinal fatty acid binding protein). Lastly, the present results do not rule out the possibility that depression and related physiological changes promote endotoxemia; further research is needed to explore these relationships over varying timescales.

5. Conclusion

Our results showed that endotoxemia combined with heightened inflammation predicted later depressive symptoms. As bacterial endotoxin from the gut is likely a major source of circulating LPS among individuals without active bacterial infections, these findings suggest that gut-related systemic immune activation may be particularly depressogenic. Importantly, models adjusted for relevant demographic variables, antidepressant usage, health behaviors, and cancer status and treatment, suggesting that endotoxemia and inflammation are risk factors for elevated depressive symptoms in and of themselves. Therefore, gut health may be relevant to depression etiology and treatment even in the absence of gastrointestinal disease. Replication and extension of these findings could provide rationale for exploring new preventative strategies for depression.

Declaration of Competing Interest

All authors declare no conflicts of interest.

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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.2020.104864.

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