

Afternoon distraction: a high-saturated-fat meal and endotoxemia impact postmeal attention in a randomized crossover trial

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ABSTRACT

Background: Saturated-fat intake and endotoxemia can impair cognition. However, their acute impact on cognitive performance is unknown.

Objective: This study assessed the impact of 2 high-fat meals and endotoxemia on attention.

Methods: In this double-blind, randomized crossover trial, 51 women ($n = 32$ breast cancer survivors, $n = 19$ noncancer controls; mean \pm SD age: 53 ± 8 y) completed the Continuous Performance Test (CPT) and had their blood drawn to assess endotoxemia markers LPS binding protein (LBP), soluble CD14 (sCD14), and the LBP to sCD14 ratio 1 h prior to eating either a high-saturated-fat meal or a high-oleic-sunflower-oil meal. Women again completed the CPT 5 h postmeal. At 1 to 4 wk later, women completed the same protocol but consumed the other meal.

Results: In adjusted models, women had more difficulty distinguishing target stimuli from distractors after consuming the high-saturated-fat meal than they did after the oleic-sunflower-oil meal ($B = 4.44$, $SE = 1.88$, $P = 0.02$). Women with higher baseline LBP had less consistent response times ($B = 0.002$, $SE = 0.0008$, $P = 0.04$). Those with higher LBP and LBP:sCD14 were less able to sustain their attention throughout the entire CPT, as reflected by their progressively slower ($B = 0.002$, $SE = 0.0006$, $P = 0.003$; and $B = 2.43$, $SE = 0.090$, $P = 0.008$, respectively) and more erratic ($B = 0.003$, $SE = 0.0008$, $P < 0.0001$; and $B = 3.29$, $SE = 1.17$, $P = 0.006$, respectively) response times. Additionally, women with higher baseline LBP or sCD14 were less able to maintain or increase response speeds at higher interstimulus intervals ($B = 0.002$, $SE = 0.0006$, $P = 0.02$; and $B = 0.006$, $SE = 0.003$, $P = 0.03$, respectively), indicating greater difficulty adapting to changing task demands. Significant meal type by LBP and LBP:sCD14 interactions emerged ($P < 0.05$), such that high LBP and LBP:sCD14 erased between-meal cognitive differences, uniformly impairing performance.

Conclusions: These results suggest that higher LBP, sCD14, and LBP:sCD14 and saturated-fat intake individually and jointly influence attention. Endotoxemia may override the relative cognitive

benefit of healthier oil choices. This trial is registered at clinicaltrials.gov as NCT04247763. *Am J Clin Nutr* 2020;111:1150–1158.

Keywords: endotoxemia, lipopolysaccharide binding protein, sCD14, attention, saturated fat

Introduction

Chronic high-fat intake—particularly SFA consumption—can impair cognition in animals (1) and humans (2, 3). A particularly compelling study assessed dietary fat's cognitive impact: healthy men had poorer attention after 5 d consuming a diet with 75% of calories from fat compared with a diet with 23% of calories from fat (4). However, this crossover trial did not examine the impact of saturated fat compared with other types of fat. Moreover, the cognitive effect of a single high-saturated-fat meal is unknown.

Saturated-fat intake may be even more insidious among those with low-grade endotoxemia. Endotoxemia markers independently predict poorer cognitive performance among people with HIV (5). In the bloodstream, bacterial endotoxin (LPS), a

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Supplemental Tables 1 and 2 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/ajcn/>.

Data described in the manuscript, code book, and analytic code will be made available upon request pending application.

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Abbreviations used: CES-D for Center for Epidemiological Studies—Depression scale; CPT, Continuous Performance Test; CRC, Clinical Research Center; LBP, LPS binding protein; sCD14, soluble CD14

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component of gram-negative bacteria, stimulates a rapid innate immune response (6). The body's rapid response, combined with LPS's short half-life, hinders accurate measurement of circulating endotoxin (7). A surrogate marker of circulating endotoxin is LPS-binding protein (LBP) (8), produced by the liver and gut epithelial cells (9, 10) in response to circulating LPS (11). Circulating LPS positively tracks with LBP (12), and LBP is considered a clinical marker of "effective endotoxemia" (8). The gastrointestinal tract houses most endotoxin (7), and most circulating endotoxin comes from the gut; for example, after 1 wk of orally administered bowel-sterilizing antibiotic therapy, gram-negative bacteria in the feces declined in concert with circulating LPS (13). Thus, bacterial endotoxin translocation through a weakened gut barrier is the primary source of circulating endotoxin among nonseptic individuals.

In the bloodstream, LBP binds LPS and presents it to both membrane-bound and soluble CD14 (sCD14). Membrane-bound CD14 stimulates proinflammatory cellular signaling via toll-like receptor 4, while sCD14 facilitates clearance of LPS via HDLs (14). Thus, the combination of high LBP and low sCD14 is particularly proinflammatory (15). Peripheral inflammation can spur neuroinflammation because cytokines cross the blood-brain barrier (16). Also, a single injection of LPS increases the number of activated brain microglia (17), which can release proinflammatory signals. Thus, the LBP-initiated inflammatory response to circulating LPS may impair cognition.

Both endotoxemia and saturated-fat intake interfere with cognition, and the combination may be particularly detrimental. Prior research has investigated the impact of longer-term dietary patterns on cognitive performance, but their acute impact after a high-fat meal remains unexplored. Accordingly, the primary aims of the current study were to investigate the following: 1) the effect of meal type on postmeal performance on the Continuous Performance Test (CPT), controlling for premeal performance; 2) the effect of endotoxemia on CPT performance; and 3) the interaction effect of meal type and endotoxemia on postmeal CPT performance, adjusting for premeal performance. We hypothesized that women's postmeal CPT performance would be poorer after consuming the high-saturated-fat meal compared with the high-oleic-sunflower-oil meal, and that higher endotoxemia would worsen CPT performance. We also predicted that the combination of endotoxemia and the saturated-fat meal would result in the worst postmeal CPT performance.

Methods

This double-blind, randomized crossover study was designed for the parent study's primary aim: assessing whether high-fat meals increased fatigue and inflammation among cancer survivors and controls (18). During 2 separate 9.5-h admissions to the Clinical Research Center (CRC) spaced 1–4 wk apart, women received 1 high-saturated-fat meal and 1 high-oleic-sunflower-oil meal in a random order. The Ohio State University Institutional Review Board approved the study, and all participants provided written consent. Data were collected between December 2010 and June 2013, and the trial ended as planned after participants had completed both visits. This trial is registered at clinicaltrials.gov as NCT04247763.

On the day before each of the 2 visits, women were given 3 standardized meals from the CRC's metabolic kitchen to reduce dietary variability. They then fasted for 12 h prior to each visit; upon admission, a catheter was inserted in their arm. To assess baseline endotoxemia, blood samples were obtained 1 h before the meal, which was served at ~09:25 h. Women also completed the CPT immediately after the baseline blood draw and before the 20-min mealtime, as well as 5 h postmeal. Prior to the postmeal CPT, participants completed tasks relevant to the parent study that were not cognitively demanding, such as resting metabolic measurements, blood pressure readings, blood draws, and mood questionnaires.

Participants

Women were recruited from a large observational study (19). For the parent study, exclusionary health problems included the following: prior history of any other cancer other than breast cancer, chronic obstructive pulmonary disease, symptomatic ischemic heart disease, immune-related conditions such as diabetes or autoimmune disease, drug or alcohol abuse, blood lipid medication usage, angiotensin type I receptor blocker usage, or usage of other medications with immune or endocrine consequences such as steroids. In the current study, 58 women participated and only 1 participant did not return for the second visit (**Figure 1**). All women had an initial abnormal mammogram; 38 were diagnosed with breast cancer and underwent treatment, while 20 were benign. Breast cancer survivors were a mean \pm SD 27 ± 17 mo since diagnosis and 20 ± 6 mo post-treatment completion, and all were in remission upon enrollment in this study.

Prestudy meals and research meals

The standardized prestudy meals and rationale are described elsewhere (18). Briefly, macronutrient targets (as % of total energy) for these meals were $55\% \pm 3\%$ carbohydrate, $28\% \pm 2\%$ fat, and $18\% \pm 1\%$ protein. The fat content was ~9% saturated fats, 9% monounsaturated fats, and 7% polyunsaturated fats. Participants could have caffeine as usual prior to the study but were instructed not to consume caffeine the day of the study.

Both research meals were 930 kcal with 60 g fat, 60 g carbohydrate, and 37 g protein, with 60% of total calories from fat. They both included eggs, turkey sausage, biscuits, and gravy. However, the saturated to unsaturated fatty acid ratios differed. The high-saturated-fat meal contained palmitic acid, while the high-unsaturated-fat meal contained oleic sunflower oil (**Table 1**).

Randomization and blinding

The data manager used a random-number generator in blocks of 6 to assign meal sequence to each participant, such that for every 6 subjects, 3 were assigned to each sequence. The data manager also assigned arbitrary names to each meal so that only the data manager and the CRC kitchen staff were unblinded. At the end of each visit, participants and experimenters guessed meal type, and Bang et al. (20) blinding indices were calculated.

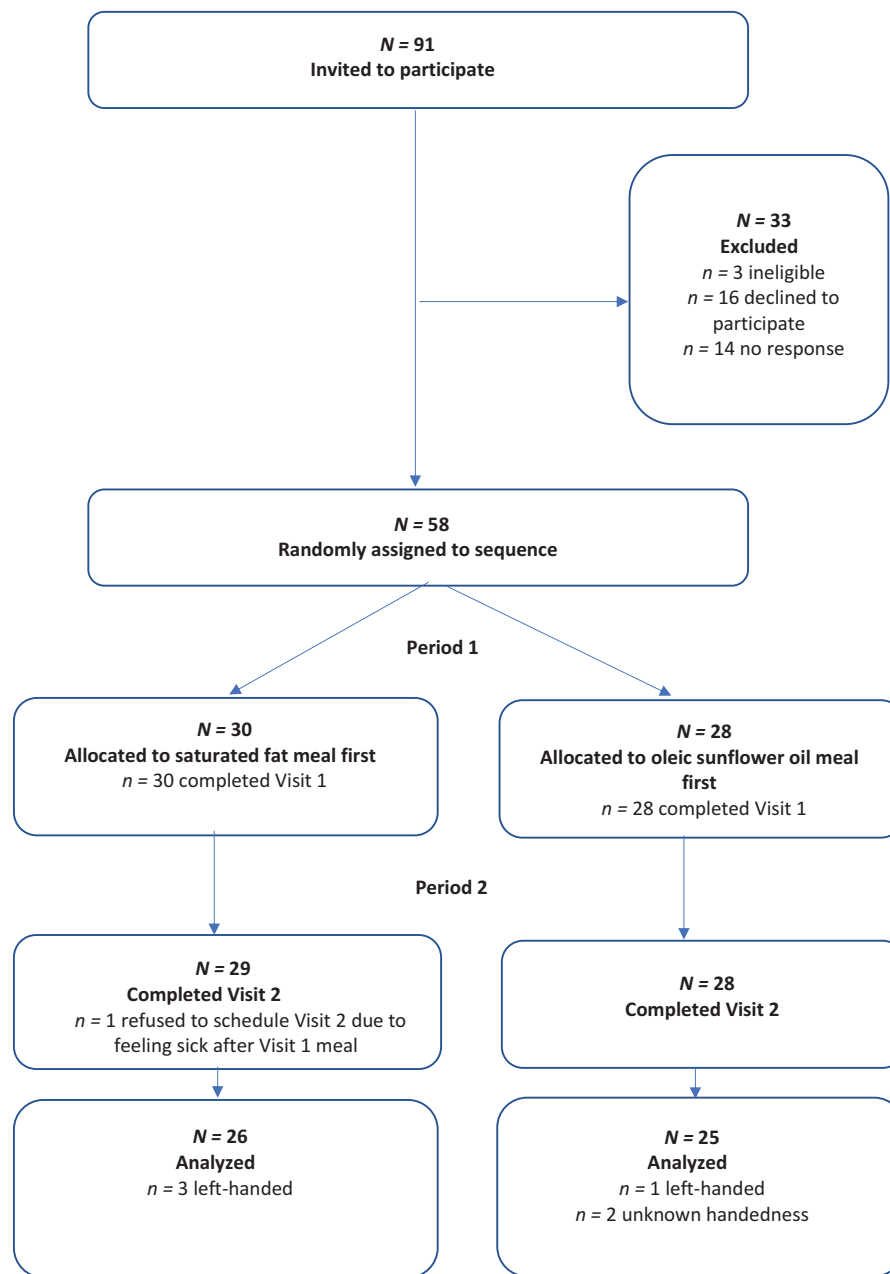


FIGURE 1 Flow of participants through the randomized crossover trial.

CPT

The CPT is a measure of sustained attention, concentration, and reaction time (21). The CPT is not subject to practice effects even with short test–retest intervals, and this permitted us to examine pre- and postmeal cognitive performance (21). Participants press a computer space bar when a target stimulus appears, which occurs at varying interstimulus intervals. The test indexes attention via reaction time, reaction time consistency, reaction time over varying interstimulus intervals, reaction time consistency over varying interstimulus intervals, errors of omission (not pressing the space bar when presented with a target), commissions (pressing the space bar in the absence of a target stimulus), and overall detectability (ability to distinguish

targets from nontargets). The CPT indexes vigilance (i.e., sustained attention) via changes in reaction time and changes in reaction time consistency from the start to end of the test. These indices are reported as t-scores ranging from 0 to 100; a score of 50 is average, with higher scores indicating poorer performance or slower and more inconsistent response times. A score of ≥ 60 can indicate clinically significant attentional impairment.

Endotoxemia

Serum LBP was multiplexed and measured using an electrochemiluminescence method with Meso Scale Diagnostics kits following the kit instructions. Plates were read using the

TABLE 1 Nutrient composition of the research meals

	High-oleic-acid-sunflower meal	Saturated-fat meal
Calories, kcal	930	930
Calories from fat, kcal	540	540
Fat, g	60	60
Saturated fats, g	15	37
Monounsaturated fats, g	35	16
Polyunsaturated fats, g	10	7
Carbohydrate, g	60	60
Protein, g	37	37

MSD Sector Imager 2400. Soluble CD14 was measured using a Quantikine CD14 ELISA kit (R&D Systems) following the kit instructions. Plates were read using a Fisher Scientific LabSystems Multiskan MCC/340 plate reader. The sensitivity for LBP and sCD14 was 0.038 ng/mL and 125 pg/mL, respectively. Inter- and intra-assay CVs for LBP and sCD14 were 2.74 and 5.47 and 8.42 and 6.30, respectively.

Covariates

Between the 2 visits and typically within 1 wk of the first visit, trained researchers conducted three 24-h dietary recalls with each participant using the gold-standard USDA Multiple-Pass Approach method (22, 23). Saturated-fat intake was calculated using an average of the 3 recalls. Using the well-validated Center for Epidemiological Studies–Depression scale (CES-D), women reported frequency of depressive symptoms during the past week, ranging from “rarely or none of the time” to “most or all of the time” (24). The continuous CES-D score was included as a covariate in all models because depressed individuals have shown attentional deficits on the CPT (25). Body composition, specifically raw trunk fat, was assessed by DXA (26). Cancer treatment type was obtained from medical records. Women reported their educational level, age, and hours of sleep the prior 2 nights.

Statistical analysis

T tests and chi-square tests were conducted, as appropriate, to test for differences between cancer survivors and controls on the variables of interest. Zero-order correlations were run between the variables of interest and Bonferroni corrected, such that only *P* values <0.00048 were considered significant (α level = 0.05/105 tests). To test the independent effects of the experimental meal and baseline endotoxemia on the cognitive performance measures (t-scores for detectability, omissions, commissions, and the reaction time and reaction time consistency measures), several linear mixed-effects models were constructed. A subject-specific random effect was used to capture within-subject correlation arising from the 2 visits per subject and 2 CPT measurement occasions per visit. All models included fixed effects for the following conceptually relevant covariates: educational level (college graduate or not), age, cancer history, chemotherapy treatment, radiation treatment, selective estrogen receptor modifier therapy, depressive symptoms, average saturated-fat intake, average hours of sleep the past 2 nights, order of meal visit, and trunk fat. Models with experimental meal type

as the predictor and postmeal cognitive performance as the outcome additionally adjusted for premeal cognitive performance. For the endotoxemia models, baseline LBP, LBP:sCD14, and sCD14 were tested as predictors of CPT performance across all 4 testing occasions. In addition to the above covariates, these models adjusted for the experimental meal and time of day the testing occurred (pre- or postmeal). Next, postmeal CPT performance was modeled with the interactions of meal type and each endotoxemia marker as the predictors of interest in separate models. These models adjusted for the above covariates as well as premeal CPT performance.

Models excluded 4 left-handed participants to eliminate the confounding of handedness that may result from differences in hemispheric lateralization (27), 2 participants with unknown handedness, and 1 woman who was taking a central nervous system depressant (also left-handed). After also excluding 1 woman who did not complete both visits and did not provide dietary saturated-fat intake, 51 women were included in the models. All analyses were performed in SAS version 9.4 (SAS Institute). Two-tailed tests were performed, and the α level for all analyses was set at 0.05. Visual inspection of residual plots to assess the normality assumption revealed 1 potentially influential observation (commissions t-score >80), which was excluded from relevant models. Additionally, cancer history was considered as a moderator in all models, but there were no significant effects, and thus reported results are averaged across groups.

Results

Preliminary analyses

At visit 1, cancer survivors did not differ from controls on any predictor or outcome of interest ($P > 0.20$) (Supplemental Table 1). Of the cancer patients, 56% received chemotherapy and 69% received radiation. Also, 34% were taking a selective estrogen receptor modulator.

Table 2 provides the sample’s demographic information. Overall, 80% of women were white and participants’ mean \pm SD age was 53 ± 8 years. Women were highly educated, and a majority (55%) had graduated from college. Additionally, average saturated-fat intake did not relate to endotoxemia markers ($P > 0.14$) or cognitive outcomes ($P > 0.56$), except that women who typically consumed more saturated fat were less likely to respond to targets (i.e., omissions) than those who consumed less saturated fat ($P = 0.044$). Women with more trunk fat or greater depressive symptoms had heightened LBP:sCD14 ($P < 0.036$). See Supplemental Table 2 for zero-order correlations.

Blinding

For participants, the Bang et al. blinding indices were 0.18 (95% CI: $-0.02, 0.37$) for the oleic sunflower oil meal and -0.28 (95% CI: $-0.48, -0.08$) for the high-saturated-fat meal. For the experimenter, these indices were 0.07 (95% CI: $-0.02, 0.16$) and 0.05 (95% CI: $-0.03, 0.14$) for the high-oleic-sunflower-oil and high-saturated-fat meals, respectively. A blinding index of zero indicates perfect blinding.

TABLE 2 Sample information at visit 1¹

Measure	<i>n</i>	Mean ± SD	<i>n</i> (%)	Range
Age, y	51	53.5 ± 8.4	—	31.0–75.0
Trunk fat (DXA), g	51	15,803 ± 5746	—	4182–27,931
Race, % white	51	—	41 (80)	—
Cancer history, % breast cancer survivors	51	—	32 (63)	—
Educational level, % college graduate	51	—	28 (55)	—
Saturated-fat intake, g/d	51	26.5 ± 9.4	—	7.9–62.3
Depression, CES-D score	50	9.7 ± 7.0	—	0.0–32.0
Average hours of sleep	51	6.7 ± 0.9	—	4.5–8.5
Baseline sCD14	51	1440 ± 353	—	783–2460
Baseline LBP	51	3999 ± 1800	—	1097–8343
Baseline LBP:sCD14	51	2.8 ± 1.3	—	0.9–7.3
Detectability, premeal CPT, t-score	49	48.4 ± 7.8	—	21.1–61.8
Omissions, premeal CPT, t-score	49	56.5 ± 16.4	—	42.8–103.8
Commissions, premeal CPT, t-score	49	47.5 ± 7.1	—	35.6–67.8
Reaction time, premeal CPT, t-score	49	52.7 ± 10.9	—	27.6–81.1
Reaction time SE, premeal CPT, ² t-score	49	56.9 ± 11.89	—	37.2–90.2

¹*n* = 51. CES-D, Center for Epidemiological Studies–Depression scale; CPT, Continuous Performance Test; LBP, LPS binding protein; sCD14, soluble CD14.

²Reaction time SE is a common measure of response speed consistency in the CPT.

Meal type and CPT performance

After consuming the saturated-fat meal, women were less able to distinguish targets from nontargets during the postmeal CPT test than they were following the high-oleic-sunflower-oil meal, adjusting for their premeal performance and other relevant covariates [$B = 4.44$, $SE = 1.88$, $F(1, 38) = 4.76$, $P = 0.02$] (Figure 2). Meal type was not associated with any other postmeal cognitive outcomes ($P > 0.08$).

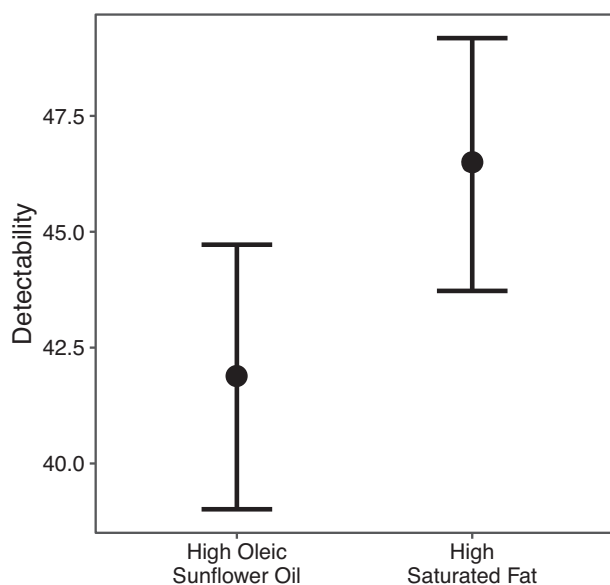


FIGURE 2 As indicated by their higher scores, women were less able to distinguish targets from nontargets during the postmeal CPT after the high-saturated-fat meal than after the high-monounsaturated-fat meal, adjusting for their premeal performance (hierarchical linear model; $P = 0.02$, $n = 51$). CPT, Continuous Performance Test.

Endotoxemia and CPT performance

Participants with higher baseline LBP had more erratic response times [$B = 0.002$, $SE = 0.0008$, $F(1, 138) = 4.33$, $P = 0.04$]. Women with higher baseline LBP and LBP:sCD14 were less able to sustain their attention throughout the entire CPT, as reflected by their progressively slower [$B = 0.002$, $SE = 0.0006$, $F(1, 140) = 9.24$, $P = 0.003$; and $B = 2.43$, $SE = 0.90$, $F(1, 140) = 7.34$, $P = 0.008$, respectively] and more erratic [$B = 0.003$, $SE = 0.0008$, $F(1, 140) = 16.32$, $P < 0.0001$; and $B = 3.29$, $SE = 1.17$, $F(1, 140) = 7.89$, $P = 0.006$, respectively] response times during a testing occasion. Additionally, women with higher baseline LBP or sCD14 were less able to sustain or increase response speeds at higher interstimulus intervals [$B = 0.002$, $SE = 0.0006$, $F(1, 138) = 5.81$, $P = 0.02$; and $B = 0.006$, $SE = 0.003$, $F(1, 138) = 4.88$, $P = 0.03$, respectively], indicating greater difficulty adapting to changing task demands. Higher baseline values of sCD14 also predicted a lower ability to distinguish targets from nontargets [detectability or d' ; $B = 0.007$, $SE = 0.003$, $F(1, 137) = 4.48$, $P = 0.02$] (Figure 3). Baseline LBP, LBP:sCD14, and sCD14 were unrelated to other postmeal measures of cognitive performance ($P > 0.16$).

Interaction of meal type and endotoxemia

LBP and LBP:sCD14 each modulated the relation between meal type and postmeal ability to distinguish targets from nontargets, controlling for premeal performance and other relevant covariates [$F(1, 36) = 8.47$, $P = 0.006$; and $F(1, 36) = 7.46$, $P = 0.01$, respectively]. Saturated fat affected cognitive performance only for those women with lower endotoxemia. That is, women at the 25th percentile for baseline LBP or LBP:sCD14 were less able to detect targets after the saturated-fat meal than they were after the high-oleic-sunflower-oil meal ($P < 0.001$). However, among women at the 75th percentile for baseline LBP or LBP:sCD14, their elevated endotoxemia tracked with worse postmeal detectability regardless of the meal

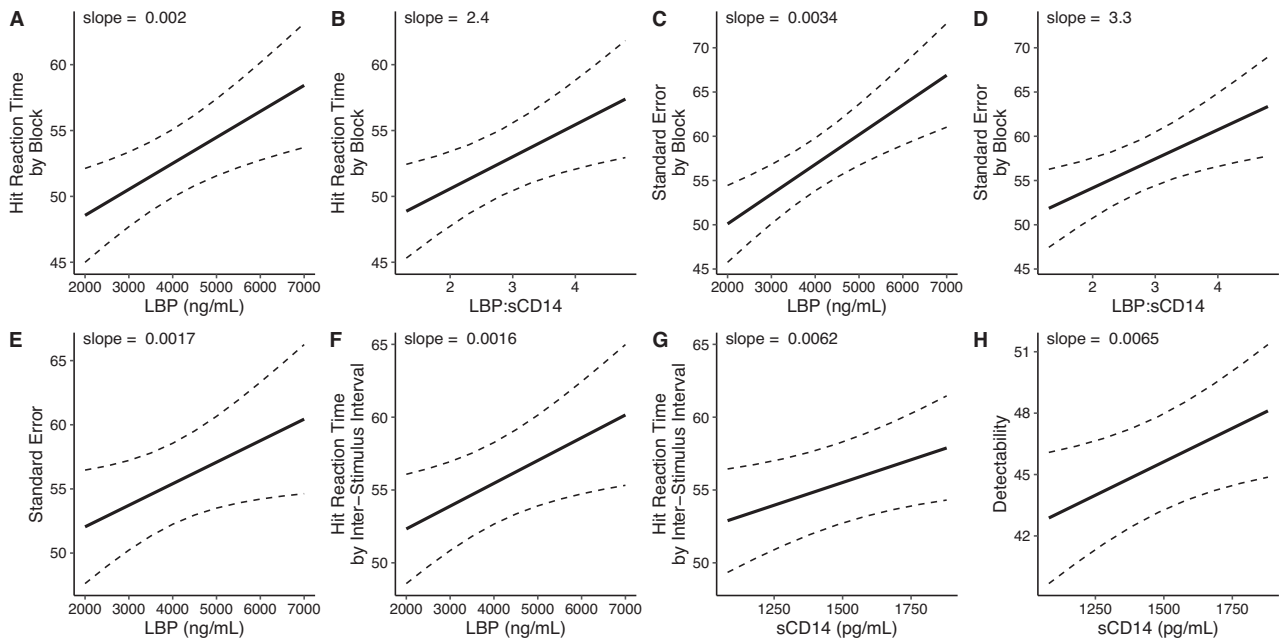


FIGURE 3 (A–H) Women with elevated endotoxemia, as indexed by LBP, sCD14, and LBP:sCD14, had poorer attention across 4 CPT testing occasions (hierarchical linear models; $P < 0.05$, $n = 51$). The outcome of panels C, D, and E is the standard error of response times, a common metric of response time variability that indexes attention. Only significant results are depicted. Slope estimates are included in figure. CPT, Continuous Performance Test; LBP, LPS binding protein; sCD14, soluble CD14.

type ($P > 0.26$) (see **Figure 4**). A similar interaction emerged for postmeal nontarget hits [i.e., commissions; $F(1, 36) = 4.15$, $P = 0.049$]; compared with the high-oleic-sunflower-oil meal, the high-saturated-fat meal worsened performance only among those at the 25th percentile for baseline LBP:sCD14 ($P = 0.01$). Among those at the 75th percentile for baseline LBP:sCD14, meal type did not influence postmeal commissions ($P = 0.48$). Meal type did not interact with endotoxemia markers to predict any other postmeal cognitive outcome ($P > 0.10$).

Discussion

This double-blind, randomized crossover trial demonstrated that a single meal high in saturated fat can impede attention—resulting in reduced detectability—compared with an identical meal high in monounsaturated fat. Importantly, each woman consumed both meals, and thus between-person biological or genetic variability did not account for the observed meal effect. Endotoxemia played a role as well, as women with elevated endotoxemia markers had poorer attention across CPT testing occasions. As the gastrointestinal tract is the primary source of endotoxin (7), these results implicate bacterial endotoxin translocation from the gut to the bloodstream (“leaky gut”) in sustained attention deficits similar to prior findings (5, 28–31).

The interaction between endotoxemia and experimental meal type was especially noteworthy: a single high-saturated-fat meal caused relatively poorer postmeal cognitive performance only in the context of low endotoxemia. That is, endotoxemia erased between-meal differences, impairing postmeal attention regardless of meal type. Notably, participants who were 1–2 SDs

above the means for endotoxemia markers approached clinically significant t-score values (>60), indicating possible cognitive impairment. Although a single meal high in saturated fat did not induce clinically significant levels of cognitive impairment, repeated exposure to high-saturated-fat intake may do so.

A saturated-fat meal and cognition

Our data suggest that a high-saturated-fat meal may transiently impede attention, compared with a high-monounsaturated-fat meal. This cognitive effect was present 5 h postmeal; although our data do not speak to the longevity of this effect, the postprandial peripheral inflammatory spike can last >3 h in those who are metabolically dysregulated (32), and the postprandial triglyceride increase is apparent even 5–8 h after a high-fat meal (33). This physiological environment may propagate poorer cognitive performance. Prior findings suggest that a longer-term high-fat diet impairs cognition (2–4), but this novel study demonstrated that even a single high-saturated-fat meal could have cognitive consequences compared with a single meal high in monounsaturated fat. In both meals, 60% of calories were from fat, and thus potentially problematic; however, the divergence in postmeal cognitive performance sets high-saturated-fat consumption apart from high intake of other fats.

There are multiple mechanisms by which saturated-fat intake could impair attention. Oleic and palmitic acid can both cross the blood–brain barrier (34), but low concentrations of oleic acid may stabilize and promote blood–brain barrier integrity (35). When fatty acids cross the blood–brain barrier, it is not always detrimental; in moderation, fatty acids may promote brain health and development (36, 37). In fact, exposure to oleic

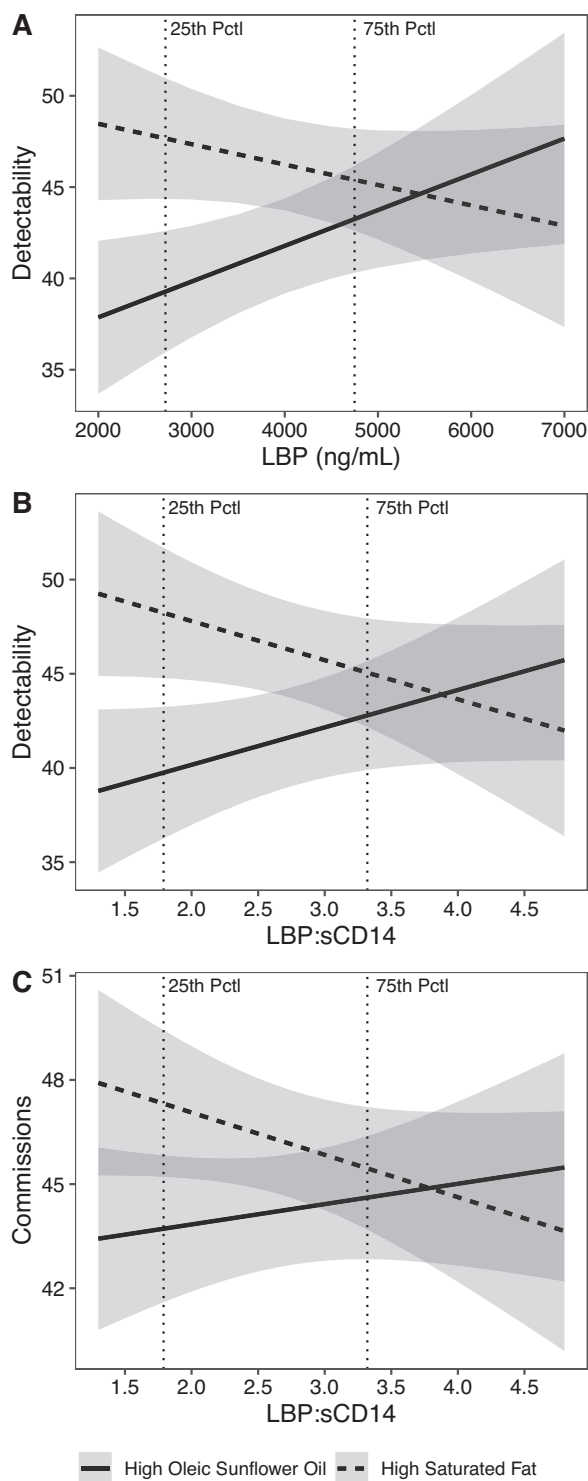


FIGURE 4 Experimental meal type interacted with endotoxemia markers to predict postmeal CPT detectability (hierarchical linear models; $P < 0.05$, $n = 51$). The saturated-fat meal only had an attentional impact in the context of minimal endotoxemia. Elevated endotoxemia erased meal-related differences, as women with higher endotoxemia performed equally poorly regardless of meal type. The shaded area represents 95% CIs. Only significant results are depicted. Slope estimates (SE) for each panel are as follows: (A) sunflower oil: 0.0020 (0.00083); saturated fat: -0.0011 (0.00082); (B) sunflower oil: 2.0 (1.1); saturated fat: -2.1 (1.1); (C) sunflower oil: 0.59 (0.70); saturated fat: -1.22 (0.74). CPT, Continuous Performance Test; LBP, LPS binding protein; Pctl, percentile; sCD14, soluble CD14.

acid reduces the brain's synthesis of oleic acid as well as other unsaturated fatty acids (38). Other evidence shows that, when excess saturated fat interacts with the hypothalamus, microglia orchestrate an inflammatory response (39). Even without crossing the blood–brain barrier, fatty acids can impact the brain via inflammation. Prior research has shown that saturated fats, which closely resemble the lipid portion of LPS, potently stimulate proinflammatory signaling via toll-like receptor-4 (40)—on par with LPS's effect (41). These proinflammatory cytokines can cross the blood–brain barrier, causing neuroinflammation (16). In sum, meals high in saturated fat cause biological changes that may interfere with cognitive function.

Endotoxemia and cognition

Our finding that endotoxemia was related to CPT attentional deficits across testing occasions (pre- and postmeal) extends prior literature, primarily among HIV-positive patients who commonly experience cognitive performance deficits. Overall, these studies have typically measured endotoxin, which is less reliable due to its short half-life in the blood (42), and/or sCD14. Across several studies, HIV-positive individuals with greater sCD14 tended to have worse cognitive functioning and steeper cognitive decline (5, 28–31). In the HIV population, higher levels of sCD14 could be a response to HIV-related infections rather than gut permeability, so only studies among those who have achieved viral suppression via antiretroviral therapy can more clearly implicate gut permeability. For instance, among HIV-positive men who achieved viral suppression, endotoxemia, as measured by LPS and sCD14, was cross-sectionally correlated with poorer processing speed (5); and among HIV-positive women who achieved viral suppression, those with greater sCD14 had worse executive functioning (28). Our results add to this literature by demonstrating that LBP and LBP:sCD14 are also cognitively relevant.

Saturated fat and endotoxemia

As described in a related study, these same high-fat meals did not trigger an acute increase in endotoxemia (43), suggesting that these markers may reflect longer-term dietary trends. Although habitual dietary saturated-fat intake and endotoxemia were unrelated in our sample, prior research suggests that consuming a high-saturated-fat diet increases the risk of low-grade endotoxemia. Fat efficiently transports LPS from the gut lumen to the bloodstream (44). Additionally, following a high-fat intake, a considerable amount of fat may reach the colon, which can cause colonic inflammation in humans (45). Given endotoxemia's association with cognitive performance, further investigation into how specific dietary components impact endotoxemia is warranted.

Strengths and limitations

Four analytical strategies make these findings particularly noteworthy: the comparison to another high-fat meal; adjustment for average saturated-fat intake, adjustment for DXA-derived trunk fat, which is superior to BMI; and adjustment for premeal cognitive performance. The saturated-fat meal's relative effect on

attention might have been even greater if the comparison meal was not also high in fat. Also, controlling for average saturated-fat intake and premeal cognitive performance ensured that the results captured a single meal's cognitive effect, rather than the effect of long-term dietary patterns or individual differences in cognitive ability, respectively. Two additional strengths of this study's design bolster these findings: the randomized crossover design and the previsit standardized meals. The randomized crossover design allowed for within- rather than between-person comparison, eliminating the potential for genetic differences to confound postprandial responses. The previsit standardized meals removed between-person dietary variability that could have masked the cognitive impact of a single meal.

Findings must be replicated in a more diverse sample to ensure generalizability as participants in the current study were all female and mostly white. Several limitations stem from the fact that these are secondary analyses, and the study was not originally designed to investigate these questions of interest. For instance, our data do not speak to the duration of the experimental meal's cognitive effect; repeated postmeal measurements of cognitive performance are an important future step. Another important limitation is that oral health status was not assessed; although intestinal permeability is the primary source of LPS in the bloodstream, poor oral health may also contribute. Therefore, further research is needed to validate LBP and LBP:sCD14 as valid markers of intestinal permeability. Last, a question for future clinical research concerns the mechanisms by which endotoxemia and a single meal high in saturated fat influence attention.

Conclusions/implications

These findings suggest that even a single meal high in saturated fat may impair attention, potentially diminishing productivity in the workplace. Higher LBP and LBP:sCD14 predicted worse attention and interacted with the experimental meal type, powerfully negating between-meal differences in cognitive performance. That is, women with elevated endotoxemia markers performed worse on the postmeal cognitive test regardless of meal type. These results suggest that low-grade endotoxemia from the gut and potentially other sources, combined with dietary choices—even a single meal—influence attentional processes, providing novel evidence of the periphery's powerful influence on the brain.

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