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A proinflammatory diet is associated with inflammatory gene expression among healthy, non-obese adults: Can social ties protect against the risks?

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ABSTRACT

The Western diet, characterized by high intake of saturated fat, sugar, and salt, is associated with elevated inflammation and chronic disease risk. Few studies have investigated molecular mechanisms linking diet and inflammation; however, a small number of randomized controlled trials suggest that consuming an anti-inflammatory diet (i.e., a primarily plant-based diet rich in monounsaturated fat and lean protein) decreases proinflammatory gene expression. The current study investigated the association between everyday diet and proinflammatory gene expression, as well as the extent to which central adiposity and social involvement modulate risk. Participants were healthy middle-aged and older adults (N = 105) who completed a food frequency questionnaire and reported how many close social roles they have. Anthropometric measurements and blood samples also were collected; gene expression data were analyzed from LPS-stimulated peripheral blood mononuclear cells for interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α. The inflammatory potential of each participant's diet was calculated using the Dietary Inflammatory Index (DII®). Participants with higher DII® scores, indicating a more proinflammatory diet, had greater IL-6 ($b = -0.02$, $SE = 0.008$, $p = .01$), IL-1β ($b = -0.01$, $SE = 0.006$, $p = .03$), and TNF-α ($b = -0.01$, $SE = 0.005$, $p = .04$) gene expression if they had a smaller sagittal abdominal diameter (SAD); effects were not seen among those with higher SADs. Social involvement served a protective role, such that participants with smaller SADs had greater IL-6 ($b = 0.01$, $SE = 0.004$, $p = .049$) and IL-1β ($b = 0.01$, $SE = 0.003$, $p = .045$) gene expression only if they had less social involvement; there was no effect of diet on gene expression among those who reported greater social participation. Results are the first to demonstrate a link between self-reported diet and proinflammatory gene expression. Importantly, the effect of diet on gene expression depended upon both body fat composition and social participation, both of which have previously been linked directly with proinflammatory gene expression and inflammation.

1. Introduction

Mounting evidence suggests that a calorie-dense, nutrient-sparse diet is associated with chronic, systemic inflammation and poor health (Andersen and Fernandez, 2013; Panickar and Jewell, 2015). In rodent models, changing animals' typical diet to one characterized by high saturated fat, salt, and sugar consumption (often referred to as a "Western diet") reliably increases abdominal fat, insulin resistance, atherosclerosis, and inflammation (e.g., Christ et al., 2018; Nunemaker et al., 2008; Schreyer et al., 1998; Surwit et al., 1988). In humans, consuming a Western diet has been linked to chronic, low-grade inflammation and associated diseases such as cancer, heart disease, and diabetes (Huang et al., 2013; Thorburn et al., 2014). In contrast, a Mediterranean diet, which includes high fruit and vegetable

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consumption, moderate consumption of poultry, fish, eggs, and dairy, and low consumption of red meat and processed foods, appears to protect against chronic inflammation and related diseases (Casas et al., 2014).

Consistent evidence linking dietary factors and inflammation led to the development of the Dietary Inflammatory Index (DII®) to quantify the inflammatory potential of a person's diet (Shivappa et al., 2014a). The DII® has now been associated with numerous health outcomes, including cardiovascular disease, cancer mortality, and all-cause mortality, even after controlling for factors such as physical activity level, BMI, and age (Hébert et al., 2019; Shivappa et al., 2017a, 2018b). For example, older women with higher DII® scores, indicating a more proinflammatory diet, had more severe atherosclerosis 36 months later and were at greater risk for heart disease-related death within a 15-year follow-up period compared to those who consumed a healthier diet (Bondonno et al., 2017). Evidence suggests that associations between the DII® and disease processes are driven by inflammation, as those with higher DII® scores also have higher serum inflammatory marker levels (Shivappa et al., 2017b,c, 2015; Tabung et al., 2015).

Despite clear and consistent findings of a relationship between diet and inflammation, prior studies have not investigated underlying molecular mechanisms. Although scant, prior evidence suggests that certain dietary components may induce inflammation by altering inflammatory gene expression. For example, mice that were fed a high-fat diet for 12 weeks showed alterations in 30 genes known to influence inflammatory processes (Montalvany-Antonucci et al., 2018). A few small randomized controlled trials (RCTs) in humans provide convergent data. For example, in an RCT with 56 obese adults, those who were randomized to a Nordic diet, which bears many similarities to the Mediterranean diet, had lower proinflammatory gene expression in subcutaneous adipose tissue compared to those who ate a control diet; however, the groups showed no differences in baseline weight or weight loss (Kolehmainen et al., 2015). Similarly, an RCT with 20 overweight participants showed that those randomized to a diet high in saturated fat, typical of the Western diet, had greater increases in proinflammatory gene expression compared to those who ate a diet high in monounsaturated fat, common in the Mediterranean diet (van Dijk et al., 2009). However, prior studies have not investigated the link between people's usual diets and inflammatory gene expression.

1.1. Visceral fat as a moderator

The negative effects of a poor diet may be modulated by abdominal obesity, which itself is a proinflammatory state linked with proinflammatory gene expression (Lopomo et al., 2016). Abdominal fat cells secrete proteins known to increase levels of inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α (Trayhurn and Wood, 2004). Additionally, obese individuals show alterations in activation of transcription factors involved in inflammatory gene expression (Motawi, Shaker et al., 2017; Rial et al., 2012). However, studies examining whether body composition augments the effect of diet on inflammation have provided mixed evidence. For example, a study of over 2,500 postmenopausal women found that those who consumed a more proinflammatory diet had higher plasma C-reactive protein (CRP) and TNF- α, and the effect was significantly stronger among obese participants (Tabung et al., 2015). On the other hand, data from a large, representative, national sample showed that a proinflammatory diet was more strongly associated with inflammation among non-obese individuals compared to those who were obese (Wirth et al., 2018). Thus, the interplay between diet and body fat remains unclear, warranting further exploration to identify potential factors that may increase diet-related risk. Importantly, many studies reporting an association between a proinflammatory diet and inflammatory markers control for BMI or weight (e.g., Phillips et al., 2018; Shivappa et al., 2015; Shivappa et al., 2017c) suggesting that obesity modulates, rather than drives, the association.

1.2. The protective role of social involvement

Further, lack of social integration has been reliably linked to inflammation and mortality (see Holt-Lunstad et al., 2015; Uchino et al., 2018 for *meta*-analyses). For example, in a landmark study, Cohen and colleagues (Cohen et al., 1997) demonstrated that individuals who had greater social role diversity (i.e., more types of social ties) were less likely to develop cold symptoms after being exposed to rhinoviruses, providing a clear example of social involvement's positive impact on immune function. Research suggests that a person's social environment may modulate inflammation via "social signal transduction," whereby social factors regulate human gene expression via central nervous system activation (CNS) (Cole, 2014). Providing empirical support for the notion that social factors are linked to gene expression, one study found over 200 genes were differentially expressed in lonelier individuals compared to less lonely individuals, including up-regulation of genes known to promote inflammation (Cole et al., 2007). However, prior studies have not investigated the potential link between social involvement and inflammatory gene expression.

The current study investigated the associations among diet, inflammatory gene expression, and central adiposity. Previous work suggests that central adiposity may modulate the effect of diet on inflammation (Wirth et al., 2018); however it remains unclear whether the effect of diet is stronger among those with more visceral fat or those with less. Therefore, the interaction between sagittal abdominal diameter and diet in predicting proinflammatory gene expression was explored with no *a priori* hypotheses regarding directionality. Given its consistent association with inflammation, social participation also was included as a novel psychosocial moderator to determine whether it may serve a protective function. We hypothesized that a proinflammatory diet would be most strongly associated with heightened inflammatory gene expression among individuals who were at high risk based on their body composition and low social involvement. Therefore, a three-way interaction between diet, social participation, and central adiposity also was explored.

2. Material and methods

2.1. Participants

The current sample included 105 healthy, sedentary adults ages 40–85 years who provided data as part of a parent trial investigating the effect of omega-3 supplementation on inflammation and depression (Kiecolt-Glaser et al., 2012). Analyses utilized data from the trial's baseline visit, before supplementation. Participants were excluded if they had significant medical conditions such as diabetes, heart disease, and autoimmune disease. They also were excluded if they were pregnant, vegetarian, or taking anti-inflammatory medications other than NSAIDs. Finally, participants were excluded if they engaged in > 2 h of vigorous physical activity per week or had a body mass index (BMI) below 22 or over 40 kg/m^2. The study was approved by the Ohio State University biomedical institutional review board, and every participant provided informed consent.

2.2. Procedure

Participants reported for a full-day hospital visit at the Ohio State Clinical Research Center, during which they completed questionnaires and provided blood samples. All blood samples were collected between 7:00 and 9:00am to control for diurnal variation.

2.3. Inflammatory diet and anthropometry

Participants completed the Women's Health Initiative Food Frequency Questionnaire (FFQ) to report information about foods and beverages consumed within the past 90 days (Patterson et al., 1999). A

validation study demonstrated that the Women's Health Initiative FFQ was strongly associated with repeated 24-hour dietary recalls and food diaries (Patterson et al., 1999). FFQ data were then used to calculate the Dietary Inflammatory Index (DII®) (Shivappa et al., 2014a), which provided a quantitative measure of the inflammatory potential of a participant's diet, adjusted for total energy intake. The DII® assigns weights ranging from −1 to + 1 to each food element consumed by an individual based on empirical evidence (see Shivappa et al., 2014a). Negative numbers indicate an anti-inflammatory food component, while positive numbers indicate the food component is proinflammatory. For example, polyunsaturated fat has a weight of −0.34, while saturated fat has a weight of + 0.37. The food component weight is then multiplied by a centered percentile representing an individual's exposure to the food component relative to "global mean" consumption of that food element, which is calculated based on a composite database of world dietary information described by Shivappa and colleagues (2014). The product generated is a "food parameter-specific DII® score"; scores for each food component are then summed to create an overall DII® score for each individual.

Higher DII® scores indicate a more proinflammatory diet and have been associated with inflammatory markers such as CRP and IL-6 (e.g., Shivappa et al., 2017b, 2014b). Among coronary heart disease patients, those who reported larger decreases in DII® scores after a dietary intervention had greater reductions in IL-6 and blood triglycerides (Mayr et al., 2018a).

Sagittal abdominal diameter (SAD) measurements provided data on visceral fat. Participants lay on their backs during SAD measurement. Sagittal abdominal diameter was measured as the distance from the small of one's back to the upper abdomen halfway between the top of the pelvis and the base of the ribs. SAD measurements correlate highly with other measures of abdominal visceral fat, including computed tomography (CT) and dual-energy X-ray absorptiometry (DXA) (Clasey et al., 1999).

2.4. Other self-report measures

The Social Network Index (SNI; Cohen et al., 1997) provided data on social involvement by assessing individuals' participation in various social roles and the extent to which they interact with others in these roles. Consistent with prior research identifying a link between social ties and immune function (e.g., Cohen et al., 1997), social role diversity was assessed using the High-Contact Roles subscale of the SNI. High-contact roles are defined as the number of social roles (e.g., parent, spouse, volunteer, employee, etc.) in which the participant has regular contact with at least one person, thus providing an index of social involvement.

Participants provided information regarding their sleep quality using The Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). The PSQI distinguishes between healthy and sleep-disordered individuals with 89.6% sensitivity and 86.5% specificity (Buysse et al., 1989), and *meta*-analytic evidence suggests it is highly correlated with daily sleep diaries, clinically diagnosed insomnia, and actigraphy data (Mollayeva et al., 2016). The Center for Epidemiologic Studies Depression Scale (CES-D) was used to measure participants' depressive symptoms (Radloff, 1977).

Physical activity level was assessed using the Community Healthy Activities Model Program for Seniors (CHAMPS) Questionnaire (Stewart et al., 2001). Caloric expenditure per week from all exercise, which takes into account the frequency, duration, and intensity of reported exercise, was used as an index of physical activity level. Validation studies demonstrate that the CHAMPS is associated with physical performance tests, activity monitor data, and other physical activity self-report measures (Harada et al., 2001).

2.5. Inflammatory gene expression

Gene expression data were obtained from lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMCs). After pelleting by centrifugation at 1700 rpm for 5 min and having the supernatant removed, PBMCs (3×10^6 cells/mL) were treated with 1.0 μg/mL LPS or suspended in media alone to incubate for 2 h at 37 °C, 5% CO_2 humidity. Cells were then centrifuged at 1700 rpm for 5 min, washed with phosphate-buffered saline, and centrifuged again at 1700 rpm for 5 min. After the supernatant was removed, the PBMC pellet was lysed in 1 mL of TRIzol reagent (Invitrogen, Carlsbad, CA) and stored at −80 °C for later RNA extraction. cDNA was then synthesized using Superscript III RNase H-reverse transcriptase (Invitrogen, Carlsbad, CA). TaqMan Gene Expression Assays (Thermo Fisher Scientific, Waltham, MA) were used for gene expression analyses of inflammatory cytokines IL-6, IL-1β, TNF-α, and a housekeeping gene. All samples, including each person's control cell cultures incubated in media alone, were run at the same time for each subject. Higher levels of IL-6, IL-1β, and TNF-α gene expression from PBMCs, quantified using real-time polymerase chain reaction (RT-PCR) and the comparative C_T method (Livak and Schmittgen, 2001), indicated greater expression of each gene relative to the housekeeping gene.

2.6. Analytical plan

Hypotheses were tested using generalized linear models in SAS 9.4 (Cary, NC). First, the interaction between the DII® and SAD was tested as a significant predictor of IL-6, IL-1β, and TNF-α gene expression in three separate models. The two-way interaction between the DII® and high-contact roles also was tested as a predictor of gene expression. Finally, the three-way interaction between the DII®, SAD, and high-contact roles was tested to determine whether the relationship between an inflammatory diet and inflammatory gene expression depended on both central adiposity and social participation. Significant two-way interactions were probed using the Johnson-Neyman technique (Johnson and Neyman, 1936). This technique was chosen because it identifies the range of the moderator at which the predictor is significantly associated with the outcome, thus providing a clinically useful indicator of levels at which SAD and high-contact roles may influence inflammatory gene expression. Significant three-way interactions were probed at one standard deviation below and above the means of the predictor variables.

Covariates were entered in a stepwise fashion. In the first step, the independent variable was tested as a predictor of gene expression with no covariates. In the second step, analyses co-varied for demographic variables including sex, age, education, and race. In a final step, models controlled for other health behaviors that may influence gene expression including sleep problems and physical activity. Follow-up analyses tested whether significant findings were robust to adjusting for depressive symptoms. Race and education were treated as class variables in all analyses. Gene expression variables were log-transformed to correct for skew. All predictor variables were grand-mean centered to aid in the interpretation of results.

3. Results

3.1. Demographic information and bivariate associations

On average, participants were middle-aged (mean age = 50.7, *SD* = 7.5 years), White (78.1%), and overweight according to their body mass index (BMI; $M = 31.17\ kg/m^2$, $SD = 4.48$). More than half of participants (65%) were women. For additional demographic information see Table 1.

Bivariate correlations and t-tests revealed a number of associations in the expected direction. Higher-BMI participants tended to be women ($M_{women} = 31.9$, $M_{men} = 29.9$, $t = -2.20$, $p = .03$), non-White

Table 1
Sample demographic and clinical information (N = 105).

	n	%	Mean	SD	Min	Max
Sex (male)	37	35.2				
Age (years)			50.66	7.50	40	85
BMI (kg/m^2)			31.17	4.48	22.0	43.8
Education level						
Graduate/professional degree	36	34.3				
Undergraduate degree	40	38.1				
High school degree or less	29	27.6				
Race						
White	82	78.1				
Black	18	17.1				
Asian	3	2.9				
Other	2	1.9				
Dietary Inflammatory Index Score		−0.66	2.12	−6.0	3.8	
Sagittal Abdominal Diameter (cm)		23.27	3.00	15.9	31.4	
High-contact roles*		6.80	2.03	1	11	

Note: The number of social roles (e.g., parent, spouse, volunteer, employee, etc.) in which the participant has regular contact with at least one person, thus providing an index of social involvement measured by the Social Network Index.

(M_{White} = 30.7, $M_{non\text{-}White}$ = 32.9, t = -2.15, p = .034), and those with less education at a trend level (r = -0.17, p = .082) compared to those with lower BMIs. Individuals with higher BMIs also demonstrated greater inflammatory gene expression for TNF-α (r = 0.19, p = .047); however there was no association between BMI and gene expression for IL-6 and IL-1β. Participants who consumed a more proinflammatory diet demonstrated marginally greater gene expression for TNF-α (r = 0.18, p = .087); diet was unrelated to other inflammatory gene expression markers. See Table 2 for results of all bivariate correlations between study variables.

3.2. Diet and central adiposity

There was no significant main effect of diet on proinflammatory gene expression. However, in unadjusted models, there was a significant interaction effect between inflammatory potential of diet and central adiposity when predicting gene expression of IL-6 (b = −0.02, SE = 0.008, p = .01), TNF-α (b = -0.01, SE = 0.005, p = .04), and IL-1β (b = -0.01, SE = 0.006, p = .03), such that a proinflammatory diet was associated with greater inflammatory gene expression only among those with less central adiposity. After controlling for demographic covariates in step two, the two-way interaction significantly predicted IL-6 alone (p = .04); this effect remained significant after including demographic and lifestyle covariates in step three (p = .03). In fully adjusted models, the two-way interaction effect was marginally

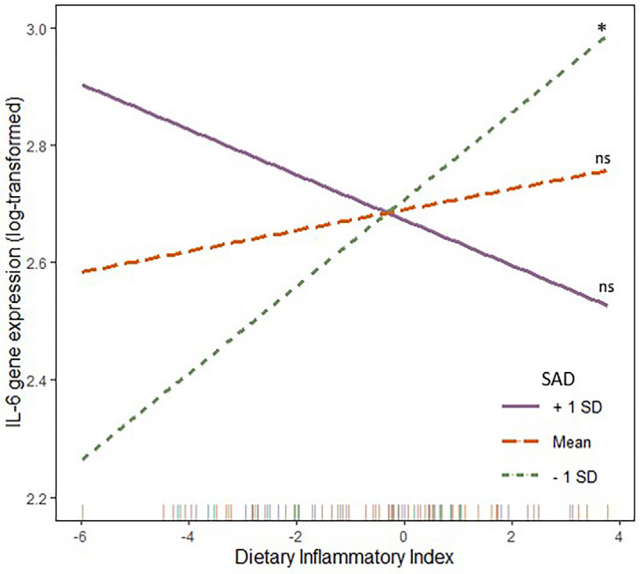

Fig. 1. Simple slopes of Dietary Inflammatory Index® predicting LPS-stimulated IL-6 gene expression at 1*SD* below the mean sagittal abdominal diameter (SAD), mean SAD, and 1*SD* above the mean SAD. The interaction effect was significant (b = −0.02, SE = 0.008, p = .034), such that a proinflammatory diet predicted greater IL-6 gene expression among those with lower SADs (b = 0.07, SE = 0.03, p = .042), but not those with average (b = 0.03, SE = 0.02, p = .310) or greater SADs (b = −0.04, SE = 0.04, p = .308). A rug plot on the horizontal axis shows the distribution of DII® scores.

significant for both TNF-α expression (p = .07) and IL-1β expression (p = .10). See Figs. 1–3 for two-way interaction graphs. Johnson-Neyman analyses used to probe interactions indicated that individuals who consumed a proinflammatory diet had greater inflammatory gene expression when central adiposity was < 20.70 cm for IL-6, 22.23 cm for TNF- α, and 21.68 cm for IL-1β.

3.3. Diet, central adiposity, and social participation

Social participation was not directly related to gene expression, and no significant two-way interactions emerged between diet and social involvement predicting inflammatory gene expression (all p-values > 0.38). In fully adjusted models, the three-way interaction among social involvement, central adiposity, and proinflammatory diet significantly predicted IL-6 (p = .049; see Fig. 4) and IL-1β gene expression (p = .045; see Fig. 5). See Table 3 for all steps in the significant three-way interaction models. The three-way interaction effect was not significant for TNF-α in any of the models (all p-*values* > 0.87).

Probing significant interactions revealed that the link between a more proinflammatory diet and greater IL-6 gene expression emerged

Table 2
Bivariate correlations between study variables.

	Age[1]	BMI[2]	SAD[3]	Physical activity[4]	PSQI[5]	DII®[6]	High-contact roles[7]	IL-6 gene expression[8]	IL-1β gene expression[9]	TNF-α gene expression[10]
1.	–									
2.	−0.23*	–								
3.	−0.13	0.82*	–							
4.	−0.06	0.15	0.19*	–						
5.	0.09	−0.16†	0.05	0.05	–					
6.	−0.01	0.11	0.16	−0.11	−0.15	–				
7.	−0.09	−0.04	−0.13	< 0.01	−0.15	−0.07	–			
8.	0.06	0.11	0.06	< 0.01	−0.12	0.09	−0.02	–		
9.	0.02	0.07	0.04	−0.06	−0.05	0.13	−0.02	0.69*	–	
10.	−0.08	0.19*	0.13	0.11	−0.18†	0.18†	< 0.01	0.76*	0.44*	–

Note: * p < .05 † p < .10.
BMI = body mass index (kg/m^2); SAD = sagittal abdominal diameter (cm); PSQI = Pittsburgh Sleep Quality Index; DII® = Dietary Inflammatory Index®.

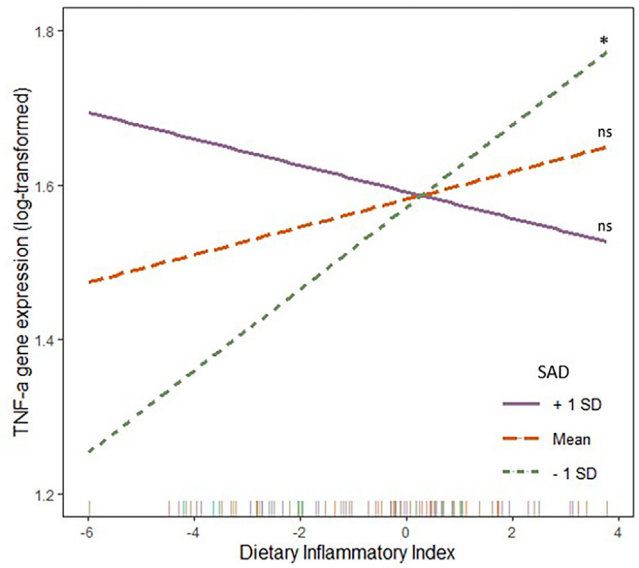

Fig. 2. Simple slopes of Dietary Inflammatory Index® predicting LPS-stimulated TNF-α gene expression at 1*SD* below the mean sagittal abdominal diameter (SAD), mean SAD, and 1*SD* above the mean SAD. The interaction effect was marginally significant ($b = -0.01$, $SE = 0.005$, $p = .069$), such that a proinflammatory diet predicted greater TNF-α gene expression among those with lower SADs ($b = 0.05$, $SE = 0.02$, $p = .021$), but not those with average ($b = 0.02$, $SE = 0.01$, $p = .093$) or greater SADs ($b = -0.01$, $SE = 0.02$, $p = .775$). A rug plot on the horizontal axis shows the distribution of DII® scores.

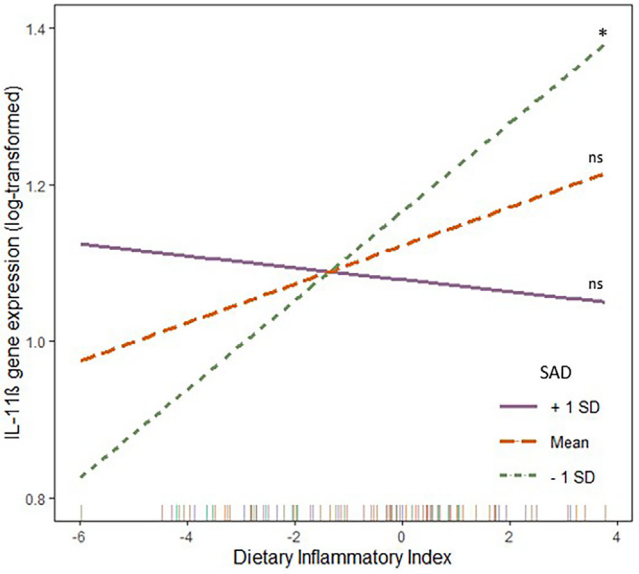

Fig. 3. Simple slopes of Dietary Inflammatory Index® predicting LPS-stimulated IL-1β gene expression at 1*SD* below the mean sagittal abdominal diameter (SAD), mean SAD, and 1*SD* above the mean SAD. The interaction effect was marginally significant ($b = -0.01$, $SE = 0.006$, $p = .095$), such that a proinflamniatory diet predicted greater IL-1β gene expression among those with lower SADs ($b = 0.06$, $SE = 0.03$, $p = .028$), but not those with average (b = *0.03*, $SE = 0.02$, $p = .141$) or greater SADs ($b = -0.01$, $SE = 0.03$, $p = .639$). A rug plot on the horizontal axis shows the distribution of DII® scores.

only among people who had less visceral fat (SAD < 20.27 cm) and lower (-1 SD high-contact roles = 4.72, $b = 0.15$, $SE = 0.05$, $p = .004$) or average social involvement (mean high-contact roles = 6.82, $b = 0.08$, $SE = 0.03$, $p = .03$). There was no effect of diet on IL-6 gene expression among those who had greater central adiposity or greater social participation. Similarly, a proinflammatory diet predicted greater IL-1β gene expression among participants who had less visceral fat (SAD < 20.53 cm) and low ($b = 0.11$, $SE = 0.04$, $p = .004$) or average social participation ($b = 0.05$, $SE = 0.03$, $p = .04$). There was no effect of diet on IL-1β gene expression among individuals who had greater central adiposity or greater social involvement, as reflected by high-contact roles. Follow-up analyses assessed whether findings were robust after adjusting for depressive symptoms – all significant findings remained after controlling for CES-D scores.

4. Discussion

4.1. Conditional effects of diet

Results suggest that individuals with less central adiposity who consumed a more proinflammatory diet—i.e., a diet characterized by high saturated fat, salt, and sugar intake—had greater proinflammatory gene expression. The effect emerged among those with a sagittal abdominal diameter smaller than ~21 cm. This threshold is close to the median SAD among U.S. adults—21.9 cm in the large, nationally representative NHANES study (Kahn et al., 2014). Thus, the association between diet and proinflammatory gene expression appears to depend on central adiposity, such that individuals with less visceral fat showed greater variability in inflammatory gene expression in association with their dietary habits compared to those with more abdominal fat. Importantly, findings were robust after adjusting for potential confounding lifestyle factors, such as sleep disturbances and physical activity level, as well as depressive symptoms.

The current study is the first to investigate the link between self-reported diet and inflammatory gene expression. These results build on and extend previous research linking the DII® to serum inflammation markers (Shivappa et al., 2015; Shivappa et al., 2014b; Shivappa et al., 2017c). Additionally, previous RCTs of overweight and obese participants found that consumption of a high-fat diet increased proinflammatory gene expression, while a low-fat, Nordic diet decreased inflammatory gene expression (Kolehmainen et al., 2015; van Dijk et al., 2009). The current study extended prior work by linking a well-validated, objective measure of dietary inflammatory potential with a novel, molecular pathway which may explain the associations among dietary factors, inflammation, and chronic disease.

Dietary components interact with one's genome to influence gene expression via numerous pathways, including alterations in DNA methylation, RNA transcription, and protein synthesis (Barnes, 2008). For example, saturated fatty acids activate nuclear factor kappa B cells (NF-κB), a transcription factor that plays an important role in proinflammatory gene expression, while omega-3 fatty acids and polyphenols common in the Mediterranean diet appear to activate PPARγ, an anti-inflammatory gene transcription factor (Sears and Ricordi, 2012).

The null association between a proinflammatory diet and inflammatory gene expression among those with greater central adiposity is consistent with prior work demonstrating links between the DII® and health outcomes in normal weight, but not overweight and obese adults. For example, Wirth and colleagues (2018), found that among individuals with BMIs < 25.0 kg/m^2, those with higher DII® scores (i.e., those who consumed more proinflammatory diets) had higher white blood cell counts compared to those who had lower scores; there was no such relationship among those with higher BMIs. Similarly, a study of 263 women found that the DII® was associated with renal cancer incidence among normal-weight women but not overweight and obese women (Shivappa et al., 2018a). Of note, the conditional nature of these prior findings and those from the current study highlight the value of testing interaction effects in biobehavioral research. Important relationships among psychological, behavioral, and physiological variables may appear only in specific subsets of the population, and these

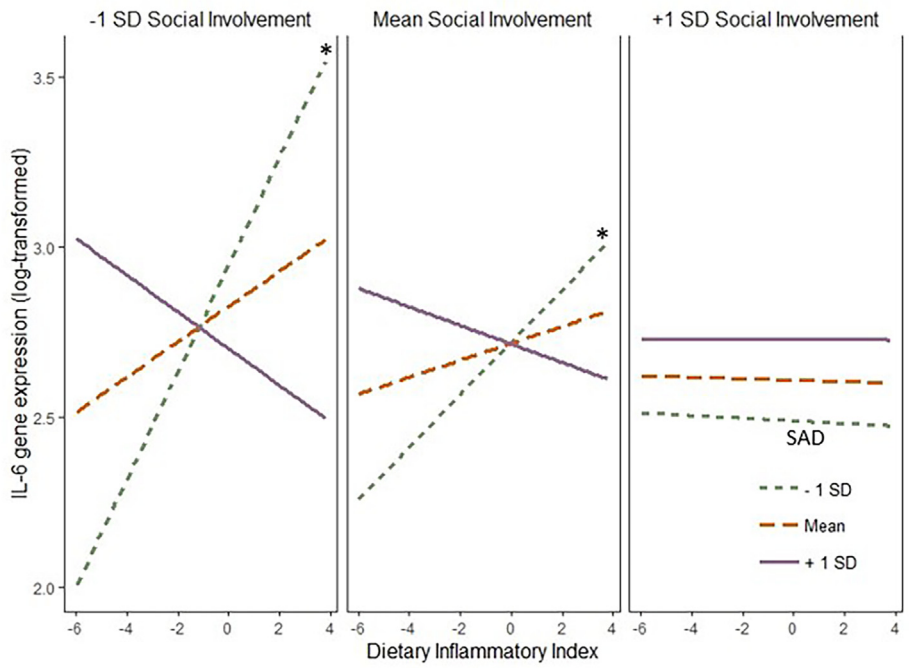

Fig. 4. Simple slopes of Dietary Inflammatory Index® predicting LPS-stimulated IL-6 gene expression at varying levels of social involvement and SAD. The three-way interaction was significant ($b = 0.01$, $SE = 0.004$, $p = .049$), such that individuals who consumed a more proinflammatory diet had increased IL-6 gene expression when they had less visceral fat (SAD < 20.27 cm) and low (-1 *SD* high-contact roles = 4.72, $b = 0.15$, $SE = 0.005$, $p = .004$) or average social involvement (mean high-contact roles = 6.82, $b = 0.08$, $SE = 0.03$,$p = .031$). There was no effect of diet on IL-6 gene expression when individuals had higher central adiposity or greater social involvement.

nuances may be overlooked when interaction effects are not investigated in addition to main effects.

The authors of these previously cited studies suggested that the effect of dietary behavior on inflammation is likely obscured among overweight and obese individuals due to the release of inflammatory cytokines by excess adipose tissue. Indeed, those with higher BMIs in the current study showed greater proinflammatory gene expression for TNF-α, but not for IL-6 or IL-1β. Another possibility is that those with greater central adiposity have less variability in diet, leaving the analyses underpowered to detect an effect of diet on gene expression in this subgroup of participants; however, visual inspection of DII® score variability in the current study did not support this hypothesis. Importantly, research has demonstrated that overweight and obese adults tend to provide less accurate self-report data regarding their dietary intake relative to their peers (Wehling and Lusher, 2017), another factor that may make detecting dietary effects on health processes difficult among those with greater central adiposity. Certainly, RCTs demonstrating that dietary interventions produce changes in proinflammatory gene expression among overweight and obese participants (e.g., Kolehmainen et al., 2015) suggest that diet *does* affect gene expression within this subgroup of the population, but the effect is more difficult to detect using self-report data. Given the current findings, RCTs which have found dietary effects among overweight and obese adults might have observed even larger effects had they included lower-

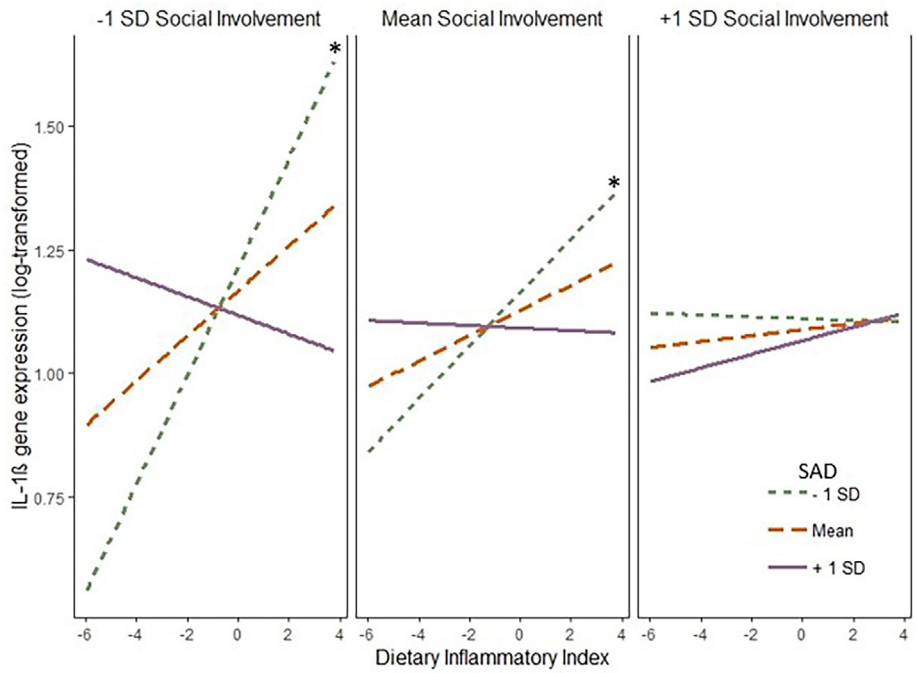

Fig. 5. Simple slopes of Dietary Inflammatory Index® predicting LPS-stimulated IL-1β gene expression at varying levels of social involvement and SAD. The three-way interaction was significant ($b = 0.01$, $SE = 0.003$, $p = .045$), such that individuals who consumed a more proinflaminator diet had increased IL-1β gene expression when they had less visceral fat (SAD < 20.53 cm) and low ($b = 0.11$, $SE = 0.04$, $p = .004$) or average social involvement ($b = 0.05$, $SE = 0.03$, $p = .038$). There was no effect of diet on IL-1β gene expression among individuals who had greater central adiposity or greater social involvement.

Table 3
Results of three-way interaction models predicting IL-6 and IL-1β gene expression.

	Step 1			Step 2			Step 3		
	b	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*
IL-6 gene expression									
Intercept	2.70	0.05	< 0.001	2.56	0.38	< 0.001	2.66	0.39	< 0.001
DII®	0.04	0.02	0.134	0.03	0.02	0.152	0.03	0.03	0.167
Central adiposity (SAD)	< 0.01	0.02	0.853	0.01	0.02	0.518	0.01	0.02	0.469
High-contact roles	−0.04	0.03	0.115	−0.05	0.03	0.086	−0.04	0.03	0.120
DII® × SAD	−0.02	0.01	0.015	−0.02	0.01	0.036	−0.02	0.01	0.034
DII® × High-contact roles	−0.02	0.01	0.176	−0.02	0.01	0.139	−0.01	0.01	0.203
SAD × High-contact roles	0.01	0.01	0.119	0.01	0.01	0.099	0.01	0.01	0.117
DII® × SAD × High-contact roles	0.01	0.004	**0.028***	0.01	0.004	**0.047***	0.01	0.004	**0.049***
Sex				−0.06	0.12	0.602	−0.05	0.12	0.704
Age				< 0.01	0.01	0.910	< 0.01	0.01	0.900
Education level									
Grad/prof degree				–	–	–	–	–	–
Undergraduate degree				0.06	0.12	0.605	0.05	0.13	0.695
High school degree or less				0.14	0.14	0.309	0.10	0.14	0.478
Race (White vs. Non-White)				0.27	0.12	0.031	0.24	0.13	0.061
Sleep disturbances							−0.01	0.02	0.747
Physical activity level							< 0.01	< 0.01	0.535
IL-1β gene expression									
Intercept	1.11	0.04	< 0.001	1.37	0.28	< 0.001	1.47	0.29	< 0.001
DII®	0.03	0.02	0.082	0.03	0.02	0.099	0.03	0.02	0.110
Central adiposity (SAD)	−0.01	0.01	0.671	−0.01	0.01	0.525	−0.01	0.01	0.632
High-contact roles	−0.01	0.02	0.468	−0.01	0.02	0.630	−0.01	0.02	0.773
DII® × SAD	−0.01	0.01	0.041	−0.01	0.01	0.114	−0.01	0.01	0.104
DII® × High-contact roles	−0.01	0.01	0.103	−0.01	0.01	0.108	−0.01	0.01	0.172
SAD × High-contact roles	< 0.01	0.01	0.948	< 0.01	0.01	0.751	< 0.01	0.01	0.696
DII® × SAD × High-contact roles	0.005	0.003	**0.081†**	0.06	0.003	**0.048***	0.01	0.003	**0.045***
Sex				−0.12	0.09	0.165	−0.12	0.09	0.193
Age				< 0.01	0.01	0.519	< 0.01	0.01	0.504
Education level									
Grad/prof degree				0.00	–	–	0.00	–	–
Undergraduate degree				0.10	0.09	0.269	0.09	0.09	0.317
High school degree or less				−0.04	0.10	0.703	−0.07	0.10	0.506
Race (White vs. Non-White)				0.09	0.09	0.315	0.07	0.09	0.453
Sleep disturbances							< 0.01	0.01	0.942
Physical activity level							< 0.01	< 0.01	0.313

Note: *p < .05 † p < .10.

weight individuals.

4.2. Protective effects of integration

Although individuals with less visceral fat who consumed a proinflammatory diet were at greater risk for heightened proinflammatory gene expression, social involvement played a protective role in the current study. The inflammatory potential of a person's diet was unrelated to gene expression among those who had a greater number of close social roles, regardless of central adiposity. Although previous research has identified a link between social integration and gene expression (Cole et al., 2011, 2007), the current study provides novel evidence that greater social participation protects against the negative effects of a proinflammatory diet on inflammatory gene expression.

Decades of research have demonstrated that human relationships impact health. More recent work has begun to highlight the molecular and genetic pathways that link social relationships and physical health. Cole (2014) describes a "social signal transduction pathway" in which social processes affect inflammatory gene expression via central nervous system functioning. In this pathway, unfavorable alterations in one's social environment induce threat perception, thus mobilizing the sympathetic and parasympathetic nervous system to alter endocrine and peripheral nervous system functioning, ultimately affecting transcription factor production (e.g., NF-κB) and therefore gene expression. In the current study, less social involvement likely had psychological repercussions which went on to produce downstream effects on inflammatory gene transcription regulation.

4.3. Limitations

The current sample was relatively healthy; even those participants in the upper SAD range were free of inflammatory diseases including diabetes and heart disease. Although this allowed us to eliminate chronic disease as a confounding factor influencing inflammatory gene expression, it also may limit study generalizability. Additionally, the racial and ethnic makeup of the sample was fairly homogeneous, and results should be replicated in a more diverse sample. Finally, as mentioned above, self-reported dietary data are vulnerable to inaccuracies, and overweight and obese individuals are more likely to under-report their dietary intake (Wehling and Lusher, 2017), which could distort exposure estimates and therefore obscure the ability to detect dietary effects on gene expression among those individuals.

4.4. Implications and future directions

The current study suggests that everyday dietary choices are associated with inflammatory gene expression, and indicates that greater social involvement may buffer the proinflammatory diet's negative effects on gene expression in vulnerable individuals. The study sample consisted of middle-aged and older adults who were free of major chronic illnesses, providing support for a relationship between diet and inflammatory gene expression even in the absence of inflammation-related diseases. However, given that 6 in 10 U.S. adults have a chronic disease, and 40% have two or more chronic diseases (Centers for Disease Control, 2019), results should be replicated in a sample more

representative of the general population.

These findings support the potential utility of dietary and social support interventions for improving immune health. Adherence to the largely plant-based Mediterranean diet has been associated with lower inflammation (Sureda et al., 2018), and anti-inflammatory dietary interventions have been shown to directly influence gene expression (Kolehmainen et al., 2015). Among those with chronic illnesses, there is a small body of evidence supporting the efficacy of dietary interventions for reducing inflammation. In a study of diabetic patients, those randomized to a Mediterranean diet demonstrated significantly larger decreases in CRP after one year compared to those randomized to a low-fat diet; greater adherence to the Mediterranean diet was associated with greater reductions in CRP (Maiorino et al., 2016). Among patients with coronary artery disease (CAD) who were randomized to a Mediterranean diet or low-fat diet, all participants demonstrated significant reductions in DII® scores and IL-6 (Mayr et al., 2018a).

Data from the current study suggest that intervening on diet alone may not be sufficient to produce changes in inflammatory gene expression; integrating social components into dietary interventions may be a useful addition. Very little information is available with respect to the effects of interventions aiming to increase social participation on inflammation or inflammatory gene expression, particularly among those with chronic illnesses. In observational studies, social support has been linked to inflammatory markers in cancer patients (e.g., Boen et al., 2018; Hughes et al., 2014) and CAD patients (Kreibig et al., 2014); however, such studies do not speak to the role of social involvement specifically. Certainly, more research, particularly intervention research, is needed in these populations.

5. Conclusions

The current study provides evidence that healthy, normal-weight individuals who consume a more proinflammatory diet are at risk for upregulation of inflammatory genes. However, participants were protected against the negative impact of their diet if they reported having greater social involvement, suggesting that fostering social relationships may serve as an important protective factor in the relationship between diet and health outcomes.

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Declaration of Competing Interest

Disclosure: Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina in order to develop computer and smart phone applications for patient counselling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2019.07.031.

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