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RESEARCH ARTICLE

Association between Race and Irritability, Inflammation, and Depression among Breast Cancer Patients during Chemotherapy

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ABSTRACT

Objectives: This study aimed to assess whether race modifies irritability and immunological inflammation, and their interaction to worsen depression during chemotherapy.
Methods: 25 African American and 19 White nonmetastasized breast cancer patients were assessed on irritability, inflammation biomarker (hsCRP and IL-6), and depression at baseline (T1) and after 3 months of chemotherapy (T2). Wilcoxon rank sum test was performed to compare racial groups on these study variables. Generalized estimating equations (GEE) regression models for repeated measures were computed, using the severity of depression as the dependent variable, race, an inflammation biomarker (hsCRP or IL-6), irritability, interactions of these variables, and time as independent variables, controlling for age, baseline depression severity level and its racial difference.
Results: The African American cancer patients had significantly higher levels of hsCRP ($p = .040$) and IL-6 ($p = .018$) than the White patients at T2, without a significant baseline difference. In both regression models, the African American patients experiencing greater irritability reported significantly more severe depression at T2 ($p = .0002$; .0048). In the regression model containing hsCRP, a negative interaction between irritability and hsCRP level was significantly associated with more severe depression at T2 ($p < .0001$). In the regression model containing IL-6, the African American patients ($p = .03$), most of whom had higher IL-6 ($p < .0001$), reported significantly more severe depression at T2, while White patients who had higher IL-6 levels also had more severe depression at T2 ($p = .016$).
Conclusion: Association between irritability and depression was significantly stronger for the African American patients than the White patients in this study, and the level of hsCRP influenced irritability and its association with depression. Identification of contributors to irritability, particularly for African Americans, is important for reducing irritability and depression in cancer patients undergoing chemotherapy. Moreover, the White cancer patients in the study who experienced higher IL-6 levels during chemotherapy were also at a higher risk of worsening depression and required medical attention.

Introduction

Detecting depression among African Americans is challenging because they exhibit fewer negative emotions but more somatic symptoms than Whites when feeling depressed[1]. Their depressive moods are more subdued than other depressive symptoms[2,3], while somatic symptoms such as poor appetite, sleep disturbance, weight loss, and fatigue are predominant[4-6]. The situation is further complicated by the presence of a disease. For example, detecting depression in cancer patients is increasingly difficult because depression shares an underlying inflammatory process with cancer that produces similar physical symptoms[7]. Detecting depression is particularly problematic for African American cancer patients when they underreport depressive mood.[5] Untreated depression significantly predicts cancer death[8-10], as it triples the likelihood of treatment nonadherence[11] and promotes tumor growth and cancer metastasis[12-14]. Overall, African Americans have a higher rate of cancer mortality than Whites[15], stressing the need for better diagnosing and treating depression in these patients.

Existing literature has shown that proinflammatory interlukin-6 (IL-6) is significantly associated with increasing depressive symptoms[16]. African Americans have shown a higher level of proinflammatory cytokines than Whites[17,18], and their IL-6 level remains significantly more elevated than in Whites after controlling for socioeconomic and health variables[19]. The likely reasons may include (1) genetic disposition; for example, a higher likelihood of allelic variants[20] and a pro-inflammatory interferon gene signature that promotes tumor metastasis through inflammation pathways[21-25]; and (2) environmental factors such as stress (e.g., chronic stress, early-life adversity)[26,27] and biobehaviors (e.g., smoking, alcohol use, and overweight)[28,29]. The higher incidence of diabetes, heart disease, and comorbidity in this population have been explained by the "wear and tear" effect on the neuroimmunological system[30,31]. Toxic adjuvant therapies can further inflate cytokine production in cancer patients[32,33]. A higher level of immunological inflammation in these patients is expected to result in more depression. However, whether African American cancer patients experience a higher level of depressive symptoms due to a greater inflammation impact has yet to be studied.

According to Lazarus and Folkman's theory of cognitive appraisal[34], human response to a physiological or psychological stressor involves a cognitive appraisal. Given a higher level of cytokines, presumably African Americans would exhibit some awareness of nonspecific response to immunological inflammation, which is unpleasant. A study has shown that depressed African American cancer patients experienced a higher level of irritability than others and attributed it to physical problems.[5] Similar findings associating irritability with inflammation were reported[35-38]. Previously, we published a study to show that irritability and an inflammation biomarker—high sensitivity C-reactive protein (hsCRP)—correlated significantly at baseline and these, along with IL-6, independently and significantly predicted the severity and new onset of depression after a 3-month period of chemotherapy[39]. This finding suggests that irritability predicts worsening depression, in

addition to inflammation biomarkers. Therefore, it is important to understand whether African American cancer patients would experience more irritability that results in worse depression than their White counterparts, and whether their irritability interacts with immunological inflammation to contribute to worsening depression.

There may be a variety of stressors, whether psychological or biological, that can trigger or heighten irritability. Knowing that African American cancer patients often experience more adversity in their living environment and more immunological inflammation, their experience of increasing irritability is not surprising, but its relation to depression, particularly immunological inflammation, has an important implication for the physically ill. Peripherally circulating cytokines can penetrate the blood-brain barriers through various pathways to affect central nervous system (CNS) and brain function[40,41]. Conceivably, feelings and emotions, as a part of cognitive appraisal of this underlying process, would change over time, and this temporal effect requires consideration. Therefore, we conducted a repeated measures study to find answers about these questions: Does race modify inflammation and irritability, respectively, to influence the severity level of depression? If so, could this be explained to an extent by a significant interaction between inflammation and irritability?

Methods

This is a repeated measures study of nonmetastasized breast cancer patients with two time assessments: at baseline prior to chemotherapy (T_1), and at 3 months during chemotherapy (T_2). The study was conducted at a comprehensive cancer center in Northeast Ohio in 2016 after the hospital's Institutional Review Board (IRB) had provided an approval. Patients were eligible for participation if they were newly diagnosed for stage I, II, or III breast cancers, were set to begin their first session of chemotherapy soon regardless of getting surgery, and had scored 2 or more on the 10-point National Comprehensive Cancer Network (NCCN) Distress Thermometer. They will be excluded from the study if they had a diagnosis of depressive disorders in the past, received hormonal therapy, or had a diagnosis of psychotic disorders (e.g., schizophrenia, bipolar disorder). Preexisting anxiety was not excluded.

Trained research staff used a hospital tumor registry to identify potentially eligible patients through a medical chart review. They contacted the identified patients through a letter, then made a follow-up phone call to introduce the study and obtain oral consent for screening the level of distress on the NCCN Distress Thermometer. Demographic, medical, and cancer treatment information was obtained during this contact and verified against the patient's medical chart. The research staff also collected medical information from medical charts to assess comorbidity using the Charlson Comorbidity Index. They invited eligible and consenting participants for an interview and obtained written consent at the beginning of the interview, which took place in a private hospital room. The two study assessments were conducted 3 months apart because distress and side effects of chemotherapy tend to peak after the third cycle of chemotherapy[42]. A clinical nurse drew a 12-mL

blood sample at the beginning of each interview, which was then stored in a hospital lab. The participants received $60 for completing the study.

The 17-item version of the Hamilton Depression Rating Scale (HAM-D17)[43], a commonly used depression assessment scale, was administered at T_1 and T_2. The severity level of depressive symptoms was indicated by the total score of the HAM-D17[43, 44].

The 35-item Irritability Scale-Initial Version (TISi) was used at T_1 and T_2 to measure the level of irritability based on the self-report, with a higher score indicating more irritability. The scale was originally developed for cancer patients and has satisfactory construct, structural, and content validity and reliability; Cronbach's alpha is > 0.90, test-retest reliability r = .69, ICC = .86[45].

The serum concentrations (measured in mL) of high-sensitivity C-reactive protein (hsCRP) and interleukin 6 (IL-6) were measured at T_1 and T_2. The blood samples were analyzed in a hospital lab using the Beckman AU5800 for hsCRP and Quantikine ELISA for IL-6. All samples were run in duplicates with appropriate controls.

Descriptive statistics were performed on baseline demographic and medical variables, using means and SD for continuous variables and percentages for categorical variables. Wilcoxon rank sum test was performed as appropriate to test median differences of the variables of inflammation biomarkers, irritability, and depression between racial groups. To investigate the effect of race on the severity of depressive symptoms, we applied generalized estimating equations (GEE) regression models for repeated measures data. In the multivariate models, the outcome variable was the severity of depressive symptoms (HAM-D17). Explanatory variables included race (African American vs. White), inflammation biomarker (either hsCRP or IL-6) and irritability (TISi), and a time variable (T_1 vs. T_2). The interaction between race and irritability, race and an inflammation biomarker (hsCRP or IL-6), and between an inflammation biomarker and irritability, were tested in each model. Age, baseline severity of depressive symptoms and its interaction with race were controlled in the models as covariates. Other potential covariates, marital status, education, and comorbidity, were not included in the multivariate models based on QIC (quasi-likelihood under the independence model criterion) when comparing models with and without the three potential covariates. Because this pilot study was exploratory, we did not have sufficient information to estimate the sample size prior. All statistical tests are two-sided, and a p value < 0.05 was considered statistically significant. All analyses were performed in SAS version 9.4.

Results

The study sample consisted of 44 breast cancer patients (stages I-III), including 19 White (43.2%) and 25 African American (56.8%) participants. Both the White and African American groups had similar age (mean = 55 and 56, respectively) and similar medical conditions. The majority in both groups had stage II cancer (63 to 56%), had not received surgery (58 to 60%), had 2 or 3 diseases on the average, and reported a similar level of baseline stress (mean Distress Thermometer = 5 or 4 points). The two groups

showed some differences mainly on demographic characteristics: more Whites than African Americans were married (63% vs. 32%), working either full- or part-time (74% vs. 56%), had a household income of $50,000 or more (53% vs. 36%), and had more preexisting diagnoses of anxiety disorders (21% vs. 8%). However, none of these differences reached statistical significance. The groups showed a statistically significant difference only on two variables: the African American patients had a lower percentage of college education (p = 0.01) and higher comorbidity (p = 0.02) compared to the White patients.

Table 1. Demographics and Medical Characteristics (N = 44) by Racial Group

Variable	White (n=19)	African American(n=25)	p
Age (Mean (SD))	54.47 (12.27)	55.92 (12.92)	0.71
Education (N (%))			
High school or less	4 (21.1)	6 (24.0)	0.01
Some college	4 (21.1)	15 (60.0)	
College degree or greater	11 (57.9)	4 (16.0)	
Marital status (N (%))			0.08
Married	12 (63.2)	8 (32.0)	
Not married	7 (36.8)	17 (68.0)	
Employment (N (%))			0.24
Full-time	7 (36.8)	10 (40.0)	
Part-time	7 (36.8)	4 (16.0)	
Unemployed	5 (26.3)	11 (44.0)	
Income (N (%))			0.21
>$25,000	2 (10.5)	8 (32.0)	
$25,000 - $49,999	6 (31.6)	4 (16.0)	
$50,000 - $100,000	6 (31.6)	7 (28.0)	
$100,001+	4 (21.1)	2 (8.0)	
Missing	1 (5.3)	4 (16.0)	
Cancer stage (N (%))			0.97
I	4 (21.1)	6 (24.0)	
II	12 (63.2)	14 (56.0)	
III	2 (10.5)	3 (12.0)	
Missing	1 (5.3)	2 (8.0)	
Received surgery (N (%))			0.40
No	11 (57.9)	15 (60.0)	
Yes	8 (42.1)	8 (32.0)	
Missing	0 (0.0)	2 (8.0)	
Preexisting anxiety disorders (N (%))			0.42
No	15 (79.0)	23 (92.0)	
Yes	4 (21.1)	2 (8.0)	
Charlson Comorbidity Index (Mean (SD))	0.10 (0.32)	0.60 (0.82)	0.02
Number of diseases (Mean (SD))	2.42 (2.52)	3.76 (2.98)	0.12
Baseline Distress Thermometer (Mean (SD))	5.05 (1.94)	4.15 (2.50)	0.20

Wilcoxon rank sum test shows that the African American patients had significantly higher levels of hsCRP (p = .040) and IL-6 (p = .018) than the White patients at 3 months (T_2), but not at baseline (T_2) (see Table 2). The two groups did not show a significant difference on other variables of biomarkers, irritability, and severity level of depression. As Figure 1 shows, the severity level of depression increased among African Americans and slightly decreased among Whites over time, but did not reach a statistically significant group difference at T_2. Although these study variables appear to increase more in African Americans, the paired t-test only revealed a significant increase of irritability among African Americans from baseline to 3 months (mean difference = -12.48, SD = 25.94, p = .024), but did not show a significant difference on any other variables within each racial group.

Table 2. Wilcoxon Rank Sum Test and Race Effect Sizes

Variable	Median (IQR)		Race Effect		
	African American	White	Estimated (95%CI)	Effect size**	p
IL6_T_1	2.22 (1.25–2.98)	2.10 (1.01–2.97)	0.24 (-0.67, 1.21)	0.08	0.59
IL6_T_2	4.70 (2.23–8.15)	2.12 (1.34–3.86)	1.76 (0.07, 4.47)	0.31	0.040
hsCRP_T_1	4.10 (2.70–6.70)	2.40 (0.50–5.50)	1.5 (-0.4, 3.1)	0.26	0.090
hsCRP_T_2	5.50 (2.10–10.40)	1.90 (0.80–4.75)	2.3 (0.3, 5.5)	0.36	0.018
Irritability_T_1	11.0 (5.0–45.0)	24.0 (13.0–34.5)	-6.0 (-17.0, 7.0)	0.15	0.31
Irritability_T_2	41.0 (18.0–61.0)*	27.0 (14.5–45.0)	7.0 (-8.0, 23.0)	0.13	0.38
Depression severity_T_1	8.0 (4.0–14.0)	12.0 (7.5–14.5)	-3.0 (-9.0, 1.0)	0.19	0.17
Depression severity_T_2	12.0 (8.0–17.0)	9.0 (6.5–14.5)	2.0 (-2.0, 6.0)	0.18	0.25

*:Paired t-test on the increase of irritability from T_1 to T_2 in African Americans: p = 0.024 (mean difference = 12.48, SD = 25.94). **: Effect size from Wilcoxon sum rank test.

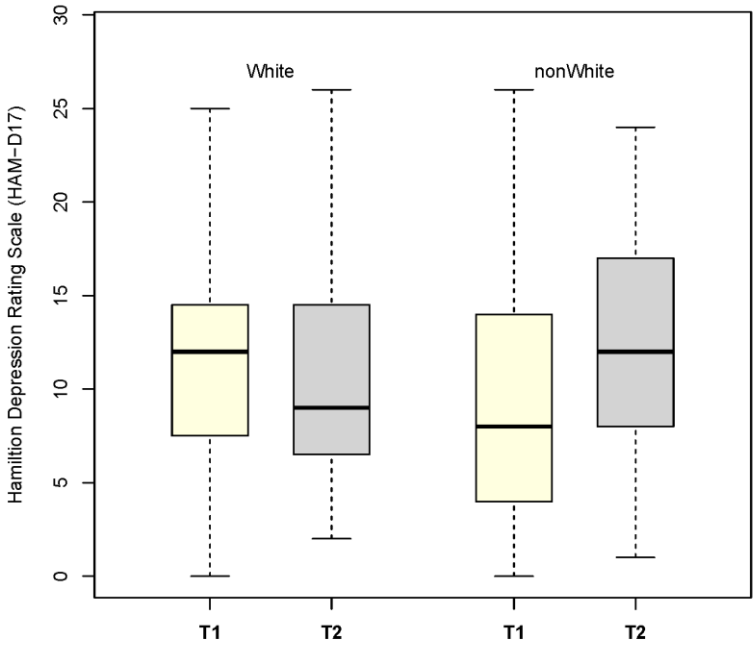

Figure 1. Three-Month Change in Depression Outcome By Race

Table 3 shows that in the model that included hsCRP as a biomarker predictor, main effects of race, irritability, and hsCRP on the severity of depressive symptoms were not significant. However, there was a significant effect of interaction between irritability and race or hsCRP. The impact of irritability on the severity of depressive symptoms was stronger for African Americans than Whites ($p = 0.0002$). The impact of irritability on the severity of depressive symptoms was stronger for those having a lower rather than a higher level of hsCRP ($p<0.0001$). The effect of interaction between race and hsCRP on the severity of depressive symptoms was not significant ($p = 0.15$). These findings were observed when age, time, and baseline severity of depressive symptoms and its interaction with race were controlled. As expected, those with more severe depressive symptoms at baseline were more likely to have more severe depressive symptoms at 3 months ($p < .0001$); in particular, Whites with more severe depressive symptoms at baseline were more likely to have more severe depressive symptoms at 3 months when compared to African Americans ($p = 0.020$).

Table 3. Race Effects on Depressive Symptom Severity: GEE Model with hsCRP

Variable	Estimate	S.E	95% CI	Z	P
Age	-0.041	0.0315	-0.1027, 0.0208	-1.3	0.1933
Race: African American vs. White	0.0216	1.6541	-3.2204, 3.2636	0.01	0.9896
Irritability total score	0.0248	0.022	-0.0183, 0.0679	1.13	0.2595
hsCRP	0.1509	0.1485	-0.1401, 0.4419	1.02	0.3095
Irritability total score × race	0.1317	0.0353	0.0625, 0.2009	3.73	0.0002
hsCRP × race	0.2208	0.1528	-0.0787, 0.5263	1.45	0.1485
Irritability total score × hsCRP	-0.0049	0.0012	-0.0073, 0.0026	4.17	<.0001
Time: T_2 vs. T_1	-0.1208	1.0133	-2.1069, 1.8652	0.12	0.9051
Depression severity (HAMD-17)	0.7761	0.1178	0.5452, 1.0069	6.59	<.0001
Depression severity × race	-0.4139	0.1784	-0.7635, 0.0643	2.32	0.0203

In the model that included IL-6 as a biomarker predictor, younger patients, African American patients, and patients having high IL-6 reported significantly more severe depressive symptoms at 3 months than patients who were older ($p = 0.026$), White (0.028), or had low IL-6 ($p < .0001$) (see Table 4). Further, the impact of irritability on the severity of depressive symptoms was stronger for the African American patients than the White patients ($p = 0.0048$), whereas the impact of IL-6 on the severity of depressive symptoms was stronger among the Whites than the African Americans ($p = 0.016$). Similar to the findings from the model of hsCRP, those with more severe depressive symptoms at baseline experienced more severe depressive symptoms at 3 months ($p < .0001$); in particular, the Whites with more severe depressive symptoms at baseline were more likely to have more severe depressive symptoms at 3 months compared to the African Americans ($p = 0.014$).

Table 4. Race Effects on Depressive Symptom Severity: GEE Model with IL-6

Variable	Estimate	S.E	95% CI	Z	P
Age	-0.074	0.0331	-0.1389, -0.0091	-2.23	0.0255
Race: African American vs. White	2.8087	1.2773	0.3053, 5.3121	2.2	0.0279
Irritability total score	0.0057	0.0217	-0.0369, 0.0483	0.26	0.7943
IL-6	0.6396	0.1617	0.3227, 0.9565	3.96	<.0001
Irritability total score × race	0.094	0.0333	0.0287, 0.1593	2.82	0.0048
IL-6 × race	-0.403	0.167	-0.7304, -0.0757	-2.41	0.0158
Irritability total score × IL-6	-0.0003	0.0022	-0.0047, 0.004	-0.15	0.8838
Time: T_2 vs T_1	0.3974	1.1197	-1.7973, 2.592	0.35	0.7227
Depression severity (HAMD-17)	0.8032	0.0902	0.6265, 0.9799	8.91	<.0001
Depression severity × race	-0.3806	0.1543	-0.683, -0.0781	-2.47	0.0136

Discussion

This study provides new evidence to show that race modifies irritability to significantly influence the severity of depressive symptoms over 3 months of chemotherapy. In the two regression models, we found that African American cancer patients experiencing more irritability were significantly more depressed at 3 months than the White or African American patients experiencing less irritability. This evidence was obtained after adjusting for baseline depression severity and its racial difference, suggesting that irritability was more strongly associated with the severity of depression among the African American patients than the White patients. Because irritability increased significantly only among the African Americans (p = .024), one may infer that more heightened irritability led to more severe depression experienced by the African American patients at 3 months. According to a well-tested Theory of Unpleasant Symptoms, a symptom such as irritability is influenced by physiological, psychological and situational factors and interactions of these factors.[46] While the effects of hsCRP and IL-6 were controlled in our models, other possible contributors to the increase of irritability, whether socioeconomic (situational), psychological or otherwise biological, were not considered. The study findings suggest that such contributors to irritability, particularly for African Americans, should be identified in order to reduce irritability and a possibility of worsening depression.

The study findings regarding whether race modifies an inflammation biomarker to influence depression severity are mixed. Wilcoxon rank sum tests show that the African American patients had higher levels of hsCRP (p = .018) and IL-6 (p = .040) than the White patients at 3 months of chemotherapy. This finding is consistent with existing literature that suggests a higher level of IL-6 among African Americans than Whites[19]. Not surprisingly, in the model that examined IL-6, the main effects of race and IL-6 were statistically significant, showing that the African Americans and those experiencing a higher level of IL-6—mostly African Americans—were significantly more depressed than others at 3 months. However, in the same model the White cancer patients with a higher level of IL-6 were also significantly more depressed at 3 months, indicating a modifying effect of race on IL-6 in relation to

depression. These findings are not necessarily inconsistent, because it is possible that only some of the White cancer patients that responded to chemotherapy with an increase of IL-6 became more depressed. The findings simply demonstrate that a subgroup of Whites were vulnerable to severe depression due to greater inflammation during chemotherapy, while African American cancer patients, overall, were more depressed over this same period of time. In the model that examined hsCRP, however, the interaction between race and hsCRP did not yield a significant effect on depression at 3 months. It is conceivable that these differential results reflect the respective roles of the two biomarkers in immune function[47]. IL-6 is a proinflammatory cytokine, and its increasing concentration signals an acute phase response to inflammatory conditions[48], which then triggers the synthesis of CRP in the liver to fortify immunological defense. To be able to observe a significant main effect of hsCRP or its interaction effect with race on the severity of depression may require a longer time or a larger sample than observing IL-6 effect in the current study.

Despite many possible contributors to increasing irritability during chemotherapy, this study focused on the influence of inflammation. The regression analysis revealed a significant effect of a negative interaction between irritability and hsCRP on the severity of depression at 3 months. This finding lends a support to the speculation that irritability and inflammation are interrelated. Literature has demonstrated a significant association between increased CRP and depression over time[49]. It is possible that the interaction between irritability and hsCRP has an inverted U-shaped effect: as hsCRP increases to a certain level, associated irritability reaches its highest impact on depression, whereas hsCRP increases excessively, depression worsens regardless of irritability[50-52]. In either scenario, keeping hsCRP low is important for reducing irritability and severity of depression, especially for African American cancer patients. This calls for adequate and effective clinical management. We did not, however, observe a significant interaction effect regarding IL-6 and irritability. Whether the observed interaction effect between irritability and hsCRP is incidental, unique to a single biomarker hsCRP, or has a broader implication, remains to be investigated in the future with a larger study sample.

The positive and significant impact of baseline depression on the severity of depression at 3 months, which was more obvious among White cancer patients in this study, is largely consistent with existing literature and not surprising. This impact has been controlled while obtaining the above-described significant study findings. Nonetheless, we must be cautious with the interpretation of study findings due to methodological limitations. The sample size of this study is small and excluded the possibility of controlling for additional demographic or medical variables. We oversampled African Americans and included females only in this study; therefore, the results may not be generalizable to male or other ethnic groups. Furthermore, because this is an exploratory pilot study and aims to generate a hypothesis rather than producing confirmative results, we did not adjust for multiple comparisons in this report. We cannot exclude a possibility of false-positive findings.

In conclusion, this study provided important information for better detecting depression among African American cancer patients. Our new evidence shows that African American cancer patients are more vulnerable than White cancer patients to irritability that is associated with worsening depression during chemotherapy. The increasing irritability may be explained in part by an increase of hsCRP in these patients. However, there is a host of biological, psychosocial, and socioeconomic factors that can promote irritability. It is important to identify such factors for African American cancer patients in order to minimize irritability for preventing worsening depression. More importantly, irritability is overtly reported and hence a good indicator of mood deregulation in these patients. Assessing irritability before and during chemotherapy may help clinicians identify depression in African American cancer patients that provide little disclosure of depressive mood, therefore enhancing the chance of early treatment of depression and better post-chemotherapy recovery, survival rate, and quality of life. Finally, consistent with existing literature, the study findings confirm the impact of proinflammatory biomarker IL-6 depression in African American and White cancer patients, but racial difference in underlying genetic, biological or psychological factors that are responsible for increasing IL-6 is beyond the scope of this study. Future investigation that utilizes more rigorous methods such as a larger study sample is warranted.

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None

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