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## Pro-Inflammatory Cytokines as Predictors of Antidepressant Effects of Exercise in Major Depressive Disorder

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### Abstract

Exercise is an efficacious treatment for Major Depressive Disorder (MDD) and has independently been shown to have anti-inflammatory effects in non depressed subjects. Patients with MDD have elevated inflammatory cytokines but it is not known if exercise affects inflammation in MDD patients and whether these changes are clinically relevant. In the Treatment with Exercise Augmentation for Depression (TREAD) study, participants who were partial responders to a Selective Serotonin Reuptake Inhibitor (SSRI) were randomized to receive one of two doses of exercise: 16 kilocalories per kilogram of body weight (KKW), or 4 KKW for 12 weeks.

Blood samples were collected before initiation and again at the end of the 12-week exercise intervention. Serum was analyzed using a multiplexed ELISA for Interferon- $\gamma$  (IFN- $\gamma$ ), Interleukin 1- $\beta$  (IL-1 $\beta$ ), Interleukin-6 (IL-6), and Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ).

Higher baseline levels of TNF- $\alpha$  were associated with greater decrease in depression symptoms over the 12 week exercise period ( $p = 0.0023$ ). In addition, a significant positive correlation between change in IL-1 $\beta$  and change in depression symptom scores was observed ( $p=0.0441$ ). There were no significant changes in mean level of any cytokine following the 12-week

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intervention, and no significant relationship between exercise dose and change in mean cytokine level.

Results suggest that high TNF- $\alpha$  may differentially predict better outcomes with exercise treatment as opposed to antidepressant medications for which high TNF- $\alpha$  is linked to poor response. Our results also confirm findings from studies of antidepressant medications that tie decreasing IL-1 $\beta$  to positive depression treatment outcomes.

## Keywords

exercise; physical activity; depression; inflammation; cytokines

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## Introduction

The prevalence of depressive disorders and their associated socioeconomic burden are of growing concern. Evidence suggests that of those receiving adequate medication trials, most will not achieve remission following initial treatment<sup>1</sup> and nearly one-third will not achieve remission even following several treatment steps<sup>2, 3</sup>. The identification of moderators of treatment response is a critical step in the pursuit of developing methods to better match patients with treatments. These moderators could be used to develop new diagnostic methods that subtype patients into groups with differences in underlying pathophysiology as well as for personalizing treatment.

Exercise has been shown to be efficacious as a stand-alone<sup>4, 5</sup> and as an augmentation treatment<sup>6-8</sup> for MDD. Our recent work identified gender and family history as significant moderators of treatment response for exercise augmentation<sup>8</sup>. In addition, we examined changes in Brain-Derived Neurotrophic Factor (BDNF) associated with exercise augmentation and found higher levels of BDNF at baseline predicted a significantly greater decrease in depressive symptoms following exercise treatment<sup>9</sup>. These findings, along with previous research showing that treatment outcome may be based in part on underlying genetic variation<sup>10</sup>, suggest there may be underlying biological moderators associated with antidepressant response to exercise and support the further identification of biomarkers related to the treatment effect of exercise.

Inflammatory cytokines have potential for biomarker development in MDD. Recent studies have revealed that these markers are elevated in depressed patients when compared to healthy controls. Elevations of Interleukin-6 (IL-6) and Tumor Necrosis Factor  $\alpha$  (TNF- $\alpha$ ) have been confirmed in a meta-analysis<sup>11</sup>. In addition, antidepressant treatment, particularly with SSRIs, has been shown to decrease some MDD associated cytokine elevations. In a recent meta-analysis<sup>17</sup> findings confirmed that levels of inflammatory cytokines Interleukin 1- $\beta$  (IL-1 $\beta$ )<sup>12, 13</sup>, IL-6<sup>14, 15</sup>, and TNF- $\alpha$ <sup>15, 16</sup> are reduced following treatment with SSRIs. Studies have also shown that elevated baseline TNF- $\alpha$  and IL-6 correlate with treatment failure of SSRIs<sup>17, 18</sup>. In studies of healthy controls and subjects with medical illness, exercise interventions reduced levels of IL-6, TNF- $\alpha$ , and Interferon  $\gamma$  (IFN- $\gamma$ )<sup>19-21</sup>. To our knowledge, no study has evaluated the relationship between exercise and inflammatory markers in a depressed sample.

In the **T**reatment with **E**xercise **A**ugmentation for **D**epression (TREAD) study, adults with MDD who failed to remit with an adequate trial of a single SSRI were treated with an exercise augmentation regimen. Subjects provided blood samples for analysis of inflammatory markers at baseline and at the end of treatment.

This report examines the extent to which inflammatory markers (IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IFN- $\gamma$ ) can be used to predict response to exercise treatment after an incomplete response to an SSRI. It also examines how the inflammatory markers change with exercise and if those changes are associated with dose of exercise or changes in symptom severity.

## Materials and Methods

Details of the design and outcomes of the TREAD study have been published previously<sup>8, 22, 23</sup>.

### Participants

TREAD recruited adults, age 18-70, with MDD, who were currently taking an adequate dose of a single SSRI but were non-responders as defined by a score of  $\geq 14$  on the 17-item Hamilton Rating Scale of Depression (HRSD<sub>17</sub>), following  $>6$  weeks and  $<6$  months of treatment. Participants were excluded for presence of psychosis or if they regularly engaged in physical activity.

**Intervention**—Participants were randomly assigned to one of two exercise dose groups: the low dose group had a target energy expenditure of 4 kilocalories per kilogram of body weight per week (KKW) and the high dose group 16 KKW over 12 weeks. The high dose was designed to meet or exceed current physical activity guidelines for public health from federal agencies and professional associations<sup>24, 25</sup>. Participants engaged in aerobic exercise (treadmill, cycle ergometers or a combination) at self-selected exercise intensity. The exercise dose was completed in a combination of supervised and home-based sessions, and participants logged actual activity using a web based system.

### Assessments

Self-report and clinician-rated measures were collected prior to the first exercise session of each week. Trained personnel blinded to group assignment completed clinician-rated assessments. The primary outcome assessment was the 30-item clinician-rated Inventory of Depressive Symptomatology (IDS-C<sub>30</sub>)<sup>26-28</sup>; additional assessments of depressive symptoms included the 30-item self-rated Inventory of Depressive Symptomatology (IDS-SR<sub>30</sub>)<sup>26-28</sup> and the (HRSD<sub>17</sub>)<sup>29</sup>.

**Sample Collection and Analysis**—Of the 126 randomized TREAD participants, 108 signed additional consent for blood analysis at baseline (105 samples were available); 73 of these completed the study and provided week 12 samples. Resting blood samples were collected at baseline and following the 12-week intervention. All samples were drawn in the morning; participants fasted a minimum of 3 hours prior to blood draw, and were at least 24 hours from the last exercise session. Ten ml of peripheral venous blood was drawn and centrifuged at 900rpm for ten minutes at room temperature to separate the blood

components. Serum was subsequently frozen at  $-80^{\circ}\text{C}$  until the time of analysis. We analyzed samples in duplicate using a multiplexed chemo-luminescence ELISA method (MesoScale Discovery, Gaithersburg, MD) for IFN- $\gamma$ , IL-1 $\beta$ , IL-6, and TNF- $\alpha$ . The plates were read using the MSD Discovery Workbench analyzer and software package (MesoScale Discovery). All data were calibrated using standard curves generated for each cytokine.

### Statistical Analysis

Demographic and clinical characteristics for the evaluable sample and for both dose groups were described using the sample mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. We compared variables across dose groups using independent sample *t*-tests (for continuous variables) correcting for unequal variances with the Satterthwaite method as needed, or Chi-square tests (for categorical variables).

We used a linear mixed model repeated measures analysis to examine the relationship between each baseline cytokine level and treatment outcome on the IDS-C over the 12-week study period. Each model contained fixed effects terms for baseline cytokine level (pg/mL), time, and cytokine level by time interaction. The intercept was included as a random effect. Time was log transformed to provide a more linear relationship with outcome. Restricted maximum likelihood estimation and Type 3 tests of fixed effects were used, with the Kenward-Roger correction<sup>30</sup> applied to the spatial power covariance structure. The parameter estimate was interpreted from the solution for fixed effects in the mixed model analysis. The following covariates were included in the mixed model: Baseline IDS-C, Family History of MDD, Recurrent MDD, Gender, Age, Race, BMI, SF36 Mental, and SF36 Physical. Covariates and baseline cytokine level were centered.

We conducted a non-parametric analysis to determine the relationship between change in each cytokine and change in symptom severity. Specifically, Spearman's rank-order correlation coefficient ( $r_s$ ) was used to examine the relationship between change in each inflammatory cytokine and change in depression severity on the HRSD<sub>17</sub>, IDS-C<sub>30</sub>, and IDS-SR<sub>30</sub>, for all participants who completed the study (N=73) and separately within each dose group.

We computed the mean level of each cytokine at baseline and week 12, and compared the mean change using the Wilcoxon Signed-Rank test for all participants who had a week 12 sample, and separately within the 16 KKW and 4 KKW dose-exercise groups. In order to determine the effect of exercise dose on change in cytokine level over the study period, we performed an Analysis of Covariance (ANCOVA) on each cytokine level at week 12, while controlling for baseline cytokine level, BMI, and the physical subscale of the SF-36.

The current study examines four inflammatory markers as potential mediators and moderators of treatment response. Since we are examining a limited number of markers that have been potentially shown to be associated with antidepressant treatment response, all tests were conducted as two-tailed at the  $p < 0.05$  and not corrected for multiple comparisons, as emphasized by Lazzeroni & Ray<sup>31</sup>, Bender & Lange<sup>32</sup>, and Rothman<sup>33</sup>. All

analyses were carried out using SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina, USA).

## Results

### Participant Characteristics

A total of 105 baseline samples were available and analysed by cytokine assay. One baseline value for TNF- $\alpha$  and two baseline values for IFN- $\gamma$  were greater than five standard deviations above the sample mean and thus excluded from further analysis. Two participants had missing baseline values for IL-1 $\beta$  and were also excluded. An additional participant sample had no value for 12 week IL-1 $\beta$  – this participant was included in the mixed model but excluded from the correlation analysis. Tables 1 and 2 show the number of participants who were included in each analysis.

Participants' baseline demographic and clinical characteristics as well as mean baseline cytokine levels for all participants and for each exercise dose group are reported in Table 1. The sub-sample of those who completed the study did not differ in any demographic or clinical variable from the entire sample.

### Effect of Baseline Cytokine Level on Depression Symptom Improvement

The linear mixed model repeated measures analyses revealed a significant two-way TNF- $\alpha$   $\times$  time interaction (parameter estimate =  $-0.6155$ ,  $p=0.0023$ ) on the primary outcome of IDS-C total, indicating that higher levels of baseline TNF- $\alpha$  were related to a greater decrease in IDS-C total scores over the course of the 12-week study. The pattern of this relationship is graphically depicted in Figure 1, which presents adjusted Least Squares Means for IDS-C Total by Week for those above ( $>$ ) and below ( $<$ ) the median baseline TNF- $\alpha$  value of 5.493 pg/mL. Separate linear mixed model repeated measures analyses showed no significant 3-way (cytokine  $\times$  group  $\times$  time) interactions, indicating dose of exercise did not affect this relationship (results not shown). No other baseline cytokine affected treatment outcome in our analysis.

### Correlation between Change in Cytokine Level and Depression Symptoms

Spearman correlation coefficients between the change in each inflammatory cytokine level and change in depression severity for all completers and within each dose group are shown in Table 2. The Spearman correlations for all completers revealed a significant positive relationship between change in IL-1 $\beta$  and change in IDS-C<sub>30</sub> ( $r_s = 0.24$ ,  $p<0.05$ ), change in HRSD<sub>17</sub> ( $r_s = 0.2415$ ,  $p<0.05$ ), and change in IDS-SR<sub>30</sub> ( $r_s = 0.2417$ ,  $p=0.0470$ ). Significant associations were also observed in the high dose exercise group, with significant positive relationships between change in IL-1 $\beta$  and change in HRSD<sub>17</sub> ( $r_s = 0.38$ ,  $p<0.04$ ) as well as change in IDS-SR ( $r_s = 0.36$ ,  $p<0.05$ ), respectively. Correlations between change in depression severity and change in other cytokines were not significant (Table 2).

### Change in Cytokine Level

Mean inflammatory cytokine levels at baseline and week 12, as well as change in the means for all completers and by dose group, are reported in Table 3. There was no significant

change in any of the mean cytokine levels over the study period in the entire sample or within either exercise-dose group.

### Exercise Group Effect on Cytokine Level

The ANCOVA of each inflammatory cytokine outcome, controlling for baseline cytokine level, BMI, and SF-36 physical health, revealed no significant exercise group differences in any of the individual cytokine mean values at week 12 ( $p$ 's > 0.37) (Table 4). We carried out similar ANCOVA models with baseline IDS-C, age, gender, years of illness, and length of current MDD episode (years) included as covariates in the model, but the basic results did not differ from those mentioned above (results not reported).

## Discussion

Our analysis provides evidence that inflammatory cytokines may be useful biomarkers of the antidepressant action of exercise. We found that TNF- $\alpha$  level at baseline functioned as a predictor of treatment outcome, with higher TNF- $\alpha$  associated with more rapid improvement on the IDS-C. Additionally, we found a significant positive correlation between changes in IL-1 $\beta$  and depressive symptoms on all three symptom measures used in TREAD, such that participants who experienced larger drops in IL-1 $\beta$  level also had larger decreases in symptom scores. This relationship maintained significance in the higher dose 16 KKW subgroup, but not in the lower dose 4 KKW subgroup, indicating a dose response relationship. Contrary to our initial assumption, we did not find that exercise augmentation treatment lowered mean cytokine levels or that a higher dose of exercise had a stronger effect on mean cytokine levels.

Interestingly, our finding associating higher baseline TNF- $\alpha$  with a more rapid drop in depressive symptom severity over the course of the 12-week study is in contrast to several studies examining medication treatment. Eller et al.<sup>17</sup> found higher baseline levels of TNF- $\alpha$  were associated with non-response to an SSRI, while Lanquillon et al.<sup>18</sup> found no moderating effect of baseline levels of TNF- $\alpha$  on antidepressant response. The Hannestad et al. meta-analysis<sup>34</sup> also supports the association between higher baseline TNF- $\alpha$  and treatment resistance with medication. These findings suggest that TNF- $\alpha$  may be a differential moderator between SSRI and exercise treatment. Although further work clarifying this effect is needed, we hypothesize that since the TREAD sample was comprised of MDD patients who had an inadequate response to an SSRI, it likely contained a subset of patients with high TNF- $\alpha$  who presumably failed SSRIs directly or indirectly because of this elevation. We can postulate that exercise successfully treated this subset, whereas the rest of our sample may have failed initial SSRI treatment due to other, unknown, reasons, which may or may not have responded to exercise. Taken together with our previous findings of a moderating effect of BDNF on treatment outcome with exercise, these results provide an attractive model to test in future prospective randomized comparisons of exercise and SSRI in order to develop a personalized treatment approach. If the finding that exercise treatment is superior to antidepressant medication for those with high TNF- $\alpha$  is confirmed, it would be significant since TNF- $\alpha$  level could be used to recommend exercise rather than medication as part of a personalized treatment algorithm.

Our finding that a change in IL-1 $\beta$  correlates with change in symptom severity, on the other hand, is consistent with a growing body of research on cytokines and SSRI treatment. For example, Song et al.<sup>35</sup> found that responders to SSRI treatment had lower end treatment IL-1 $\beta$  than non-responders. The recent meta-analysis by Hannestad et al.<sup>34</sup> also found reductions in IL-1 $\beta$  correlate with better outcome with SSRIs. Our finding is significant, however, in that it is the first replication of this relationship in a sample treated with exercise. We also found significant correlations between change in IL-1 $\beta$  and change in depressive symptom severity in the 16 KKW group but not in the 4 KKW group. This suggests a dose-response effect on IL-1 $\beta$  might have been found in a larger or better characterized (i.e. for inflammatory abnormalities) sample. Since animal studies have shown that IL-1 $\beta$  down regulates hippocampal neurogenesis<sup>36</sup> there is theory to support the importance of IL-1 $\beta$  in the pathophysiology of at least some cases of depression. All of these results suggest that IL-1 $\beta$  should be a focus of future clinical trials aimed at identifying and treating depression associated with inflammation.

We did not find that exercise augmentation treatment lowered mean cytokine levels or that a higher dose of exercise had a stronger effect on mean cytokine levels. This finding is in disagreement with both studies of exercise in healthy and medically ill samples, and with studies of SSRI treatment in depressed samples. Similarly, we failed to find a dose effect on cytokine change. It is probable that pretreatment with SSRIs in this sample obscured our ability to detect change in cytokine levels, since SSRIs are known to lower cytokines. Similarly, SSRI pretreatment likely reduced baseline depressive symptoms in our sample. Future research examining the effect of exercise on inflammatory cytokines in treatment-naïve patients would provide the information necessary for comparison to previous SSRI trials. The severity of depression at baseline in this study's population appears to be intermediate between that of effectiveness augmentation trials such as STAR\*D<sup>37</sup> and that of efficacy augmentation trials such as ADAPT-A<sup>38</sup> and this may have had an impact on the levels of cytokines reported. In addition, there are other factors that may have confounded our results, including the age distribution of participants – although we attempted to address these by adjusting our model, future studies prospectively accounting for sample characteristics are desirable.

While it is clear that there is a substantial relationship between inflammation and depression, several mechanisms appear to be involved and may play different roles across patients<sup>39</sup>. These include inflammatory disruption of synthesis, reuptake and metabolism of neurotransmitters<sup>40</sup>, alteration of hypothalamic-pituitary-adrenal (HPA) axis function<sup>41</sup>, and decrease in hippocampal neurogenesis<sup>36</sup>. Not only has exercise been shown to be broadly anti-inflammatory, but it has been specifically demonstrated to act on each of these pathways to reverse the effects of inflammation<sup>42</sup>. Any or all of these mechanisms could be involved in the efficacy of exercise as a treatment of MDD, and future studies better characterizing baseline inflammation and its change over the course of exercise treatment may elucidate which mechanisms are most important in clinical recovery.

Broadly, our results suggest that exercise may be an effective treatment strategy within specific subpopulations of those with MDD. For example, chronic elevation of inflammatory markers is associated with metabolic syndrome and insulin resistance<sup>43</sup>, syndromes which,

in turn, may be associated with treatment-resistant depression<sup>44</sup>. Given that exercise typically reduces inflammation<sup>45</sup>, normalizes insulin resistance<sup>46, 47</sup>, and improves several characteristics of metabolic syndrome<sup>48-50</sup>, it is plausible that exercise may be especially effective as a stand alone or augmentative treatment for MDD in patients with comorbid metabolic syndrome, diabetes, and other inflammatory conditions.

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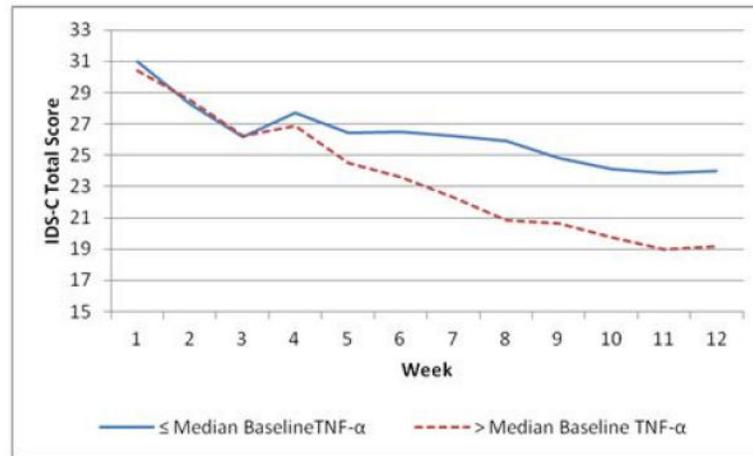
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**Figure 1.** Plot of adjusted Least Squares Means\* for IDS-C Total by Week for those above (>) and below ( ) the median baseline TNF- $\alpha$  value of 5.493 pg/mL.

\*Least Squares Means were adjusted for Baseline IDS-C, Family History of MDD, Recurrent MDD, Gender, Race, BMI, SF36 Mental, and SF36 Physical and Age.

**Table 1**

**Baseline Demographic and Clinical Characteristics for Total Sample**

Variable	AI	N	M(SD)	16 KK W n	M(SD)	4 KKW n	M(SD)	t-test or $\chi^2$	p-value <sup>d</sup>
Age (years)	105		47.51 (9.44)	53	45.83 (9.54)	52	49.23 (9.11)	1.87	0.06
Female (%)	105		80	53	84.91	52	75	1.61	0.20
IDS-C	105		34.14 (7.25)	53	33.15 (6.49)	52	35.15 (7.88)	1.42	0.16
IDS-SR	101		32.66 (9.38)	50	31.68 (7.84)	51	33.62 (10.67)	1.05	0.30
HRSD	105		18.10 (3.86)	53	17.79 (3.80)	52	18.42 (3.94)	0.83	0.41
IFN- $\gamma$	103		1.33 (1.11)	52	1.21 (0.71)	51	1.45 (1.39)	1.09	0.28
IL-1 $\beta$	103		0.10 (0.06)	52	0.09 (0.07)	51	0.10 (0.06)	0.69	0.49
IL-6	105		0.88 (0.68)	53	0.89 (0.67)	52	0.88 (0.69)	0.04	0.97
TNF- $\alpha$	104		5.75 (1.67)	53	5.31 (1.58)	51	6.20 (1.70)	2.76	0.01
BMI	105		30.89 (6.31)	53	30.36 (6.99)	52	31.44 (5.55)	0.87	0.39
SF-36 Physical Health	101		80.18 (20.79)	50	80.60 (19.83)	51	79.77 (21.88)	0.2	0.84
Recurrent MDD (%)	105		67.62	53	67.92	52	71.15	0.13	0.72
Family History of MDD (%)	105		67.62	53	67.92	52	67.31	0.004	0.95
Length of Illness (years)	104		20.19 (12.12)	52	18.31 (11.17)	52	22.07 (12.82)	1.6	0.11
Length of Current MDD Episode (years)	105		7.09 (8.28)	53	6.21 (7.81)	52	7.99 (8.73)	1.1	0.28

<sup>d</sup>Tested for differences between 16 KKW and 4 KKW exercise groups on each demographic/clinical characteristic in a separate model.

The two-independent sample t-test (for continuous outcomes), with Satterthwaite method for unequal variances was used when appropriate.

Note. Mean=sample mean; SD=standard deviation; N=total sample size of all completers; n=sample size per group; each cytokine was measured in pg/mL; KKW=Kilocalories per Kilogram per Week; IDS-C=Inventory of Depressive Symptoms - Clinician Rated; Inventory of Depressive Symptoms - Self-Rated; HRSD=Hamilton Rating Scale for Depression; MDD=Major Depressive Disorder

**Table 2**

Spearman correlation coefficients ( $r_s$ ) between the change in each inflammatory cytokine level and change in depression severity for all completers and within each dose-exercise group

Change in Depression Severity	Group	INF- $\gamma$			IL1- $\beta$			IL-6			TNF- $\alpha$		
		n	$r_s$	p-value	n	$r_s$	p-value	n	$r_s$	p-value	n	$r_s$	p-value
HRSD	ALL	71	0.02	0.89	69	0.24	<b>0.05</b>	72	0.22	0.07	71	-0.01	0.95
	4 KKW	39	-0.12	0.45	38	0.13	0.42	39	0.23	0.15	38	-0.18	0.29
	16 KKW	32	0.21	0.24	31	0.38	<b>0.04</b>	33	0.17	0.35	33	0.19	0.29
IDS-C	ALL	70	-0.04	0.75	68	0.24	<b>0.04</b>	71	0.20	0.09	70	0.05	0.69
	4 KKW	39	-0.19	0.25	38	0.20	0.23	39	0.23	0.16	38	-0.04	0.83
	16 KKW	31	0.12	0.52	30	0.29	0.12	32	0.15	0.41	32	0.09	0.62
IDS-SR	ALL	69	-0.10	0.42	68	0.24	<b>0.05</b>	70	0.02	0.90	69	-0.11	0.38
	4 KKW	38	-0.25	0.13	37	0.16	0.35	38	0.13	0.44	37	-0.15	0.37
	16 KKW	31	0.07	0.70	31	0.36	<b>0.05</b>	32	-0.03	0.25	32	-0.10	0.60

Note: Change was operationally defined as week 12 cytokine level minus baseline cytokine level.

Note. KKW=Kilocalories per Kilogram per Week; IDS-C=Inventory of Depressive Symptoms - Clinician Rated; Inventory of Depressive Symptoms - Self-Rated; HRSD=Hamilton Rating Scale for Depression

Change in mean and median inflammatory cytokine levels for all completers and within each dose-exercise group from baseline to week 12

**Table 3**

Group	Baseline		Week 12		M	p-value <sup>a</sup>
	n	M(SD)	M(SD)	M(SD)		
<b>IFN-<math>\gamma</math></b>						
All Completers	72	1.36(1.21)	1.45 (1.16)	0.09 (0.93)		0.32
4 KKW	40	1.54(1.55)	1.60 (1.49)	0.06 (1.15)		0.96
16 KKW	32	1.13 (0.43)	1.25 (0.45)	0.12 (0.56)		0.13
<b>IL-1<math>\beta</math></b>						
All Completers	70	0.10 (0.07)	0.13 (0.27)	0.03 (0.28)		0.38
4 KKW	39	0.10 (0.06)	0.11 (0.06)	0.01 (0.07)		0.77
16 KKW	31	0.09 (0.08)	0.16 (0.41)	0.07 (0.42)		0.2
<b>IL-6</b>						
All Completers	73	0.89 (0.77)	0.77 (0.52)	-0.12 (0.79)		0.57
4 KKW	40	0.87 (0.75)	0.79 (0.56)	-0.08 (0.79)		0.88
16 KKW	33	0.91 (0.79)	0.74 (0.46)	-0.17 (0.81)		0.52
<b>IL-6</b>						
All Completers	72	5.77 (1.74)	5.60 (1.67)	-0.17 (0.97)		0.19
4 KKW	39	6.18 (1.75)	5.86 (1.67)	-0.32 (1.06)		0.14
16 KKW	33	5.28 (1.62)	5.29 (1.64)	0.01 (0.83)		0.91

Note. *M* =Sample Mean; *SD* =Standard Deviation; *M* = Mean change in cytokine level; KKW = Kilocalories per Kilogram per Week

Note. Each cytokine was measured in pg/mL.

Note. p value = Wilcoxon signed ranked test was used to test for differences in sample

<sup>a</sup> p-value from Wilcoxon signed rank test (two-tailed) for test of Mean change.

**Table 4**  
ANCOVA results for exercise group effect on each inflammatory cytokine at week 12

<b>IFN-<math>\gamma</math></b>						
<b>Exercise Group</b>	<b>n</b>	<b>M</b>	<b>SE</b>	<b>95% CI for M</b>	<b>F</b>	<b>p-value</b>
Week 12					0.39	0.54
4 KKW	40	1.51	0.14	1.24 to 1.78		
16 KKW	32	1.38	0.15	1.07 to 1.68		
<b>IL-1<math>\beta</math></b>						
<b>Exercise Group</b>	<b>n</b>	<b>M</b>	<b>SE</b>	<b>95% CI for M</b>	<b>F</b>	<b>p-value</b>
Week 12					0.79	0.38
4 KKW	39	0.11	0.05	0.02 to 0.2		
16 KKW	31	0.17	0.05	0.07 to 0.27		
<b>IL-6</b>						
<b>Exercise Group</b>	<b>n</b>	<b>M</b>	<b>SE</b>	<b>95% CI for M</b>	<b>F</b>	<b>p-value</b>
Week 12					0.20	0.66
4 KKW	40	0.75	0.07	0.62 to 0.88		
16 KKW	33	0.79	0.07	0.65 to 0.94		
<b>TNF-<math>\alpha</math></b>						
<b>Exercise Group</b>	<b>n</b>	<b>M</b>	<b>SE</b>	<b>95% CI for M</b>	<b>F</b>	<b>p-value</b>
Week 12					0.74	0.39
4 KKW	39	5.51	0.15	5.21 to 5.81		
16 KKW	33	5.71	0.17	5.38 to 6.04		

Note. M = Least Squares Mean; SE = Standard Error; 95% CI = 95% Confidence Interval for the expected mean value; n = sample size per group; KKW = Kilocalories per Kilogram per Week. Each cytokine was measured in pg/mL. F statistic was used to test for mean cytokine level difference between the two Dose-Exercise Groups at week 12 while controlling for baseline cytokine level, BMI, SF-36 Physical Health. Least squares means at week 12 were adjusted for respective baseline cytokine level, BMI, and SF-36 Physical Health.