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Inflammatory Markers of Geriatric Depression Response to Tai Chi or Health Education Adjunct Interventions

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Abstract

Background: Underlying inflammation is associated with an increased risk of depression in older adults. In this study, we examined the role of inflammatory biomarkers in antidepressant response in depressed older adults undergoing adjunct Tai Chi Chih (TCC) or Health education interventions.

Methods: Older adults aged 60 years and above with a diagnosis of major depression were randomized to 12 weeks of TCC versus Health and Wellness Education (HEW) as an adjunct therapy to their stable antidepressant treatment regimen. A panel of 19 cytokine/chemokines was measured at baseline and 12 weeks. Five factors were derived using factor analysis. General linear

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AUTHOR CONTRIBUTIONS

PS conducted the statistical analyses and drafted the manuscript. MA, AG, MC, HO, and CL helped in revising the manuscript. MM recruited participants and collected data. HL designed the study, obtained funding and participated in the writing and revision of the manuscript.

SUPPLEMENTARY MATERIALS

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models were estimated to examine the change in factor scores and the association of these changes on depression remission rates, controlling for age, sex, and body mass index.

Results: Of the 170 randomized participants (TCC: n = 85 and HEW: n = 85), 55 TCC and 58 HEW completed the 3-month assessment. The groups did not differ at baseline in any measure. At follow-up, neither the changes in cytokine/chemokines scores nor the depression remission rate differed significantly between TCC and HEW. However, remitters and non-remitters differed significantly in changes in a factor composed of growth-regulated oncogene protein-alpha (GRO-alpha), epidermal growth factor (EGF), and soluble CD40 ligand (sCD40L). GRO-alpha and EGF levels (in both groups) were significantly increased in remitters compared to non-remitters.

Conclusion: Changes in certain cytokines/chemokines may accompany improvement in depressive symptoms in older adults. Future studies will need to explore the role of these molecules in remission of late-life depression.

Keywords

Inflammation; cytokines; remission of depression; late-life depression; immune; markers

INTRODUCTION

Given the increasing prevalence of late-life depression amongst community-dwelling elderly, followed by high rates of treatment-resistant depression, relapse, and suicide, the need for understanding the causes and correlates of remission in this difficult-to-treat population is of paramount importance.[1–3] Underlying inflammation has been associated with an increased risk of depression in older adults.[4,5] Several studies have also highlighted relationships between depressive symptoms and increased markers of peripheral inflammation.[6–8] Existing antidepressants can reduce peripheral inflammation in humans and in animal models, while anti-inflammatory agents have been tried as add-on antidepressant treatment strategies with some promise.[9–12]

Tai Chi Chih (TCC) is a slow, low-impact mindfulness moving meditation well-suited to older populations. Reported adverse effects are rare and primarily musculoskeletal in origin and minor in severity.[13] Existing studies have repeatedly demonstrated numerous health promotion advantages of TCC in elderly adults, including reduced falls and physical frailty,[14] improved cardiovascular status,[15] protection of cognitive function,[16] as well as enhanced sleep quality and psychological well-being.[17,18] Beneficial effects have been found for healthy and chronically ill participants.[19] Reductions in depressive symptoms and circulating neuroinflammatory markers have been observed in healthy older adults with TCC alone.[20] However, the extent to which augmentation of antidepressant treatment with TCC in major or refractory depression changes inflammatory markers is underexplored.

We recently conducted a 3-month randomized single-blind controlled trial that assessed the efficacy and tolerability of combining TCC or Health Education and Wellness training (HEW) with a stable standard antidepressant treatment on mood symptoms in depressed older adults (NCT02460666). No differences were observed in the depression remission rate at 3 months following initiation of treatment.[21] To understand the underlying mechanisms

of the heterogeneity of treatment response and the immunological cascades that lead to the observed clinical outcome, the current study investigated whether there were inflammation-related effects and whether they impacted depression outcomes at the 3-month follow-up. Since the markers associated with remission of depressive symptoms in older adults are not well-characterized, we used a data reduction approach to examine a panel of markers without a priori restricting to a select few. Further, since many markers may have pleotropic effects and modulate several different biological processes, and in addition, more than one marker may mediate the same function,[22,23] our approach enables a comprehensive consideration of depression-related changes in inflammation.

METHODS

Participants

The study methods have been previously described and will be summarized here briefly.[21] Participants were recruited from the UCLA Neuropsychiatric Hospital inpatient and outpatient services and via community advertising between September 2016 and January 2020. In total, 606 individuals were assessed via phone screening of which 285 were eligible for an in-person assessment. Of these, 220 participants completed the in-person screen. One hundred seventy eight participants met the study's inclusion criteria and were randomized to receive either TCC (n = 89) or HEW (n = 89). The sample used in the present study included a total of 170 participants (85 randomized to TCC and 85 to HEW), who also had baseline inflammation data available (please see CONSORT diagram; Fig. 1). All participants provided written informed consent prior to enrollment and all study procedures were approved by the UCLA Institutional Review Board (NCT02460666).

Older adults aged greater than or equal to 60 years were included if they met criteria for major depressive disorder as diagnosed by the Structural Clinical Interview for DSM-IVR/DSM-5 and had a score of greater than or equal to 15 on the 24-item Hamilton Rating Scale for Depression (HAM-D). Participants were excluded if they had a 1) lifetime history of any psychiatric disorder except Major Depression Disorder (MDD) or comorbid anxiety or insomnia; 2) recent and/or current unstable medical or neurological disorders; and 3) a diagnosis of dementia, moderate or severe neurocognitive impairment. Participants were stable on antidepressant therapies for at least 4 months prior to starting the trial. Anti-depressants were not provided as part of the study. Information on anti-depressant and other medication use for participants has been previously reported.[21] All participants were TCC naïve and did not engage in any other ongoing mind-body practices. Furthermore, participants were asked not to initiate any new mind-body classes or practice for the duration of the study.

Intervention Procedures

Eligible participants were randomized in a 1:1 ratio to HEW or TCC using a computer-generated block randomization strategy throughout the trial. Participants attended classes (TCC or HEW) in-person for 60 minutes per week for a total of 12 weeks. Groups of six to eight participants were formed for each intervention.

The TCC intervention incorporated meditation and physical activity, to promote a sense of well-being and control over negative symptoms commonly associated with depression. The standard detailed protocol for TCC was adapted from “Tai-Chi-Chih! Joy Through Movement” and was previously used in several studies of our research group. Each class allowed 10 minutes of warm up (stretching and breathing) along with 5 minutes of cool down. Participants were instructed to complete at home practice for at least 20 minutes per day using handouts. The validity of the intervention was maintained through certification requirements for TCC trainers as well as weekly supervisions by study PI.

The HEW training served as an active control for non-specific treatment elements, including attention and group support that could pose as rival explanations for the effectiveness of TCC. Participants were informed that the HEW training was designed to help reduce depressive symptoms severity. The HEW protocol was implemented using a manual of educational information, learning objectives, and patient activities to promote the integration of the material. The validity of the intervention was maintained through monthly supervisions. Additionally, participants were instructed to practice at home in computer searches addressing the health topics discussed in the session for 20 minutes per day, which was discussed at the next class. Adherence to homework was monitored during each visit and each subsequent class.

The last recruited cohort attended virtual group sessions following the COVID-19 quarantine order on March 17, 2020 and received the six remaining classes virtually along with virtual assessments through November 2020.

Study Measures

Cytokine/chemokine panel—Anticoagulated blood (with anticoagulant citrate dextrose (ACD)) was transported at room temperature and processed within 18 hour of blood draw. Whole blood was centrifuged at 2000 rpm for 10 minutes and plasma was immediately stored at −80° C. We used the Human 38-plex magnetic cytokine/chemokine kits (EMD Millipore, HCYTMAG60K-PX38). The panel includes IL-1RA, IL-10, IL-1α, IL-1β, IL-6, IFN-α2, TNF/TNF-α, TNF-β/LT-α, sCD40L, IL-12p40, IFN-γ, IL-12/IL-12p70, IL-4, IL-5, IL-13, IL-9, IL-17A, GRO-alpha/CXCL1, IL-8/CXCL8, eotaxin/CCL11, MDC/CCL22, fractalkine/ CX3CL1, IP-10/CXCL10, MCP-1/CCL2, MCP-3/CCL7, MIP-1α/CCL3, MIP-1β/CCL4, IL-2, IL-7, IL-15, GM-CSF, Flt-3L/CD135, G-CSF, IL-3, EGF, FGF-2, TGF-α, and VEGF. Briefly, 5 μL undiluted samples were mixed with 5 μL magnetic $\beta$and allowed to incubate overnight at 4°C while shaking. After washing the plates twice with wash buffer in a Biotek ELx405 washer, 25 μL of biotinylated detection antibody was added and incubated for 1 hour at room temperature. 25 μL streptavidin-phycoerythrin conjugate was then added to the reaction mixture and incubated for another 30 minutes at room temperature. Following two washes, beads were resuspended in sheath fluid, and fluorescence was quantified using a Luminex 200 instrument.

We calculated analytes concentrations using Milliplex Analyst software version 4.2 (EMD Millipore). The UCLA Immune Assessment Core completed the Luminex assay and analysis. Only those analytes with no more than 25% of samples were undetectable were included in analyses. Eighteen analytes (EGF, FGF-2, eotaxin, Flt-3L, fractalkine, GRO-

alpha, IL-10, MCP-3, IL-12p40, MDC, IL-15, sCD40L, IL-1RA, IL-8, IP-10, MCP-1, MIP-1β, TNF-α) were identified in this manner. The specimens were processed in four different batches (26.5%, 24.7%, 24.4%, and 24.4% were processed separately). All longitudinal assays were processed in the same batch and there were no differences in the number of TCC and HEW samples processed in the different batches.

Depression—Depressive symptoms were assessed by HAM-D at baseline and 12 weeks. Remission was defined as a post-treatment HAM-D ≤6.

Statistical Analysis

Prior to analysis, we inspected all measures for outliers, skewness, homogeneity of variance and other assumptions to ensure their appropriateness for parametric statistical tests. All cytokine/chemokine concentration levels were log-transformed. To reduce the number of cytokine markers to be used in the analyses, we performed factor analysis using the iterated principal factor method with varimax rotation to obtain five factor scores from the log-transformed analyte concentrations at baseline. The number of factors was determined by using two criteria: (1) use of a scree plot (plot of eigenvalues on the y-axis and the number of factors on the x-axis) to determine the point where the slope of the curve leveled off to indicate the number of factors that should be kept, and (2) the total amount of variability of the original items explained by each factor solution. A factor loading of 0.5 and above was chosen as the cut-off.[24] We then imposed the same factor structure to the log-transformed cytokine concentrations at follow-up to allow for direct comparison of baseline and follow-up scores. Thus, we first estimated the factor scoring coefficients from the factor analysis at baseline. These scoring coefficients were then used to determine the factor scores for each participant at baseline and follow-up separately. The measures were first standardized, then multiplied by the matching coefficients and the resulting products were summed, and this sum yielded the factor score.

We determined whether there were significant changes in cytokine factor scores from baseline to follow-up and whether these were different between treatment groups using mixed effects general linear models, with treatment group as the between-subjects factor, visit as the within-subjects factor, and the interaction term between visit and treatment group. Significance of the interaction term was used to determine whether treatment groups differed significantly in their changes. We also examined whether the changes in cytokine factor scores were associated with remission status using similar mixed effects general linear models, and examining the significance of the interaction term remission status × visit. A three-way interaction (treatment group × remission status × visit) was also included to determine whether the associations differed by remission status in TCC versus HEW; however this was not significant for any of the models and therefore was not retained in the final model. For all analyses, age, sex, body mass index, and batch were used as covariates. We present test scores and statistics as well as effect sizes (ES, Cohen's d) for group differences where appropriate. Given that this is the first study to examine the association of cytokine markers to treatment induced remission of depression in older patients, we set the significance level at $p \leq 0.05$ for all analyses.

RESULTS

Treatment groups did not differ significantly in baseline demographic variables, including age, sex, ethnicity, body mass index, educational level, or clinical scores (Table 1). A total of 113 subjects (55 TCC and 58 HEW) completed the 3-month assessment. The depression remission rate in TCC group was 38.2% compared to 25.9% in HEW ($\chi^2(1) = 2.0$, p = 0.2) and both groups improved significantly in HAM-D. Please refer to our earlier paper for more detailed clinical results.[21] Table 1 also presents a comparison of baseline characteristics in remitters versus non-remitters. There are no significant differences, except that the remitters had a significantly lower baseline HAM-D score at baseline. Comparing remitters and non-remitters in the two treatment arms (Supplementary Table) did not yield any significant differences.

Five factor scores were chosen as the optimal number of factors to be retained, accounting for 69% of the variance. The factor loadings are presented in Table 2. Factor 1, accounting for 32% of the variance, contained IL-12p40, IL-15, fractalkine, MCP-3, IL-10, FGF-2, and Flt-3L. Factor 2 (13% of the variance) contained MIP-1β, MDC, TNF-α, and IP-10. Factor 3 (10% of the variance) contained GRO-alpha, EGF, and sCD40L. Factor 4 (8% of the variance) contained IL-1RA and IL-8. Factor 5 (6% of the variance) contained eotaxin and MCP-1.

There were no baseline differences between groups (TCC vs. HEW) or between remitters and non-remitters on the factor scores. Examination of changes in cytokine factor scores also revealed no significant between-group differences (visit × treatment group Table 3). However, remitters and non-remitters differed significantly in their changes in cytokine Factor 3 scores (visit × remission status interaction term F (1,111) = =4.05, p = 0.05; ES = 0.43) (Fig. 2; Table 3). Examining the individual cytokines belonging to Factor 3 (GRO-alpha, EGF, sCD40L), we found that changes in both GRO-alpha (F(1,111) = 6.18, p = 0.01; ES = 0.45) and EGF (F(1,111) = 4.74, p = 0.03; ES = 0.49) were significantly different between remitters and non-remitters (Fig. 2). Remitters increased significantly in both GRO-alpha (t(111) = 1.97, p = 0.05) and EGF (t(111) = 2.02, p = 0.05), while non-remitters do not change significantly (GRO-alpha: t(111) = −1.74, p = 0.08; EGF: t(111) = −0.79, p = 0.4). Changes in sCD40L were not significantly different between remitters and non-remitters (F(1,111) = 1.57, p = 0.2; ES = 0.19). Further, changes in none of the other factor scores were associated with remission (Table 3).

DISCUSSION

In this study, we found that changes in certain inflammation-associated markers were associated with anti-depressant treatment-induced remission in older adults with depression, irrespective of the adjunct treatment (TCC or HEW). While the association between depression symptoms and markers of peripheral inflammation has previously been discussed in the literature,[6,8] this is the first investigation to indicate that changes in regulatory markers accompany remission in older depressed participants. Notably, we did not find that changes in the inflammatory markers differed significantly between treatment groups and further, the changes associated to overall depressive remission, and not treatment-specific

remission. The parent clinical trial showed similar improvement in depression symptoms within both intervention arms, TCC and HEW, combined with a standard antidepressant treatment. Consistent with this result, we found that changes in the inflammatory markers were only associated with remission of depression, and not differentially associated with either intervention. We also note that, of the five cytokine factors examined, change in only one factor demonstrated an association with improvement in depressive symptoms.

Caution is always advised when interpreting cytokines/chemokines as these agents possess pleotropic properties and induce different effects depending on tissue, timing, signaling pathway, and other environmental contexts.[22,25] Many cytokines/chemokines mediate functions in the central nervous system outside of inflammation, including synaptic transmission as well as neuronal survival and regeneration. Furthermore, peripheral expression of a protein may not necessarily correspond to similar expression changes in the brain. Molecular signatures of MDD and antidepressant response also tend to be highly heterogeneous, reflective of the multiplicity of pathways that participate in these complex processes.

From the current analysis, two agents were identified as significantly increased in depression remitters compared to non-remitters: growth-regulated protein alpha GRO-alpha (encoded by the *CXCL1* gene), and epidermal growth factor EGF (encoded by the *EGF* gene). The role of these two molecules in depression susceptibility and/or antidepressant response has been previously examined. Reduced levels of GRO-alpha have been associated with depression in the elderly.[26] Gene expression data has demonstrated reduced levels of *CXCL1* in individuals with depression compared to healthy controls.[27] In post-mortem samples of prefrontal cortex, *CXCL1* is decreased in depressed suicidal patients compared to controls.[28] By contrast, in post-partum depression, circulating GRO-alpha is elevated.[29] Likewise, in mouse models, increased *CXCL1* expression is associated with increased depression-associated behaviors at least partly reversed by fluoxetine.[30,31] In cultured astrocytes, imipramine attenuates *CXCL1* expression.[32] With respect to EGF, a neurotrophic factor, altered trophic support has been implicated in the pathogenesis of MDD and antidepressant treatment is hypothesized to stimulate trophic factors to increase progenitor cell proliferation and promote hippocampal neurogenesis in adults.[33,34] In late-life depression, reduced neurotrophic support has been implicated as underlying depression and cognitive impairment.[35,36] Reductions in EGF have been in shown in MDD compared to controls in several studies,[37,38] however, some investigations have demonstrated increased or unaltered EGF between these groups.[39] One prior study found no differences between late-life depression and controls in circulating EGF.[40] Peripheral EGF increases have been reported with the trajectory of antidepressant treatment response.[41] Results from the present study add to this literature, suggesting that the association between these molecules and depression pathogenesis and response to treatment vary by age and treatment type, respectively.

The current study has several strengths. Few studies have undertaken an examination of circulating inflammatory markers in late-life depression. Earlier studies have examined the role of specific inflammatory markers, most commonly C-reactive Protein, Il-6, TNF-α [11,42,43] and their relationship to depression, primarily in younger patients. In contrast, we

used a combination of markers from a panel of cytokines/chemokines and associated factors. This approach is not only more powerful, but also allows us to study the effect of these agents as an aggregate, rather than individually. Elevated inflammation and its effect on depression is likely due to several inflammatory markers rather than only an isolated few.

The limitations of our study include the relatively high dropout rate across both arms of the intervention, resulting in a smaller number of subjects who completed the follow-up assessments. While the dropout rate was higher than desired for randomized single-blind controlled trials, it is to be expected in an older depressed outpatient sample. In addition, our sample was relatively homogenous, with most of the participants being Caucasian and well-educated. Thus, the findings need to be replicated in a larger, more diverse sample. Further, this study was a secondary analysis of a clinical trial that was designed to evaluate the effects of a mind-body intervention as an adjunct to anti-depressant treatment in older adults. The parent clinical trial was therefore not powered to detect changes in inflammatory markers. It is also important to note that of the five cytokine factors studied, change in only one was significantly associated with remission; thus the replication of these findings in a future study is crucial. We also did not exclude participants with autoimmune or inflammatory illnesses from the study and did not collect information on whether participants were currently on anti-inflammatory or immune-modulating treatments. Additionally, participants were not required to fast before blood collection took place, introducing the possibility of uncontrolled biologic variability. While blood-based markers of inflammation are widely used as a proxy to study neuroinflammation, their levels may be very low in the circulation. To increase the resolution for quantification of low concentration chemokines and cytokines included in the Luminex array, it may have been preferable to use ultra-sensitive methods for cytokine detection (e.g., Simoa assay) that reaches sensitivity down to fg/mL and improves the discrimination of cytokine concentrations that are biologically relevant for the study. We also acknowledge that the inflammatory markers have multiple, possibly overlapping, functions and definitive determination as to the role of these molecules in remission of depression needs further study.

In summary, the present study reveals that changes in inflammation accompany changes in depressive symptoms in older adults who were on a stable anti-depressant regimen treated with adjunctive TCC or HEW. Future studies should explore the role of these inflammatory markers in late-life depression and further evaluate the therapeutic potential of targeting immune markers to treat depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DISCLOSURE

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The authors report no conflicts with any product or concept discussed.

DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings.

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Highlights

- What is the primary question addressed by this study?
- Since the role of inflammatory biomarkers to treatment response in late-life depression remains unclear, we examined changes in inflammatory markers in depressed older adults undergoing adjunct Tai Chi Chih or Health education interventions combined with a stable standard antidepressant treatment.
- What is the main finding of this study?
- We found that changes in cytokines/chemokines scores did not differ significantly between the two interventions. However, changes in inflammation accompany remission of depressive symptoms across both groups.
- What is the meaning of the finding?
- These findings may point to the therapeutic potential of targeting immune markers to treat geriatric depression.

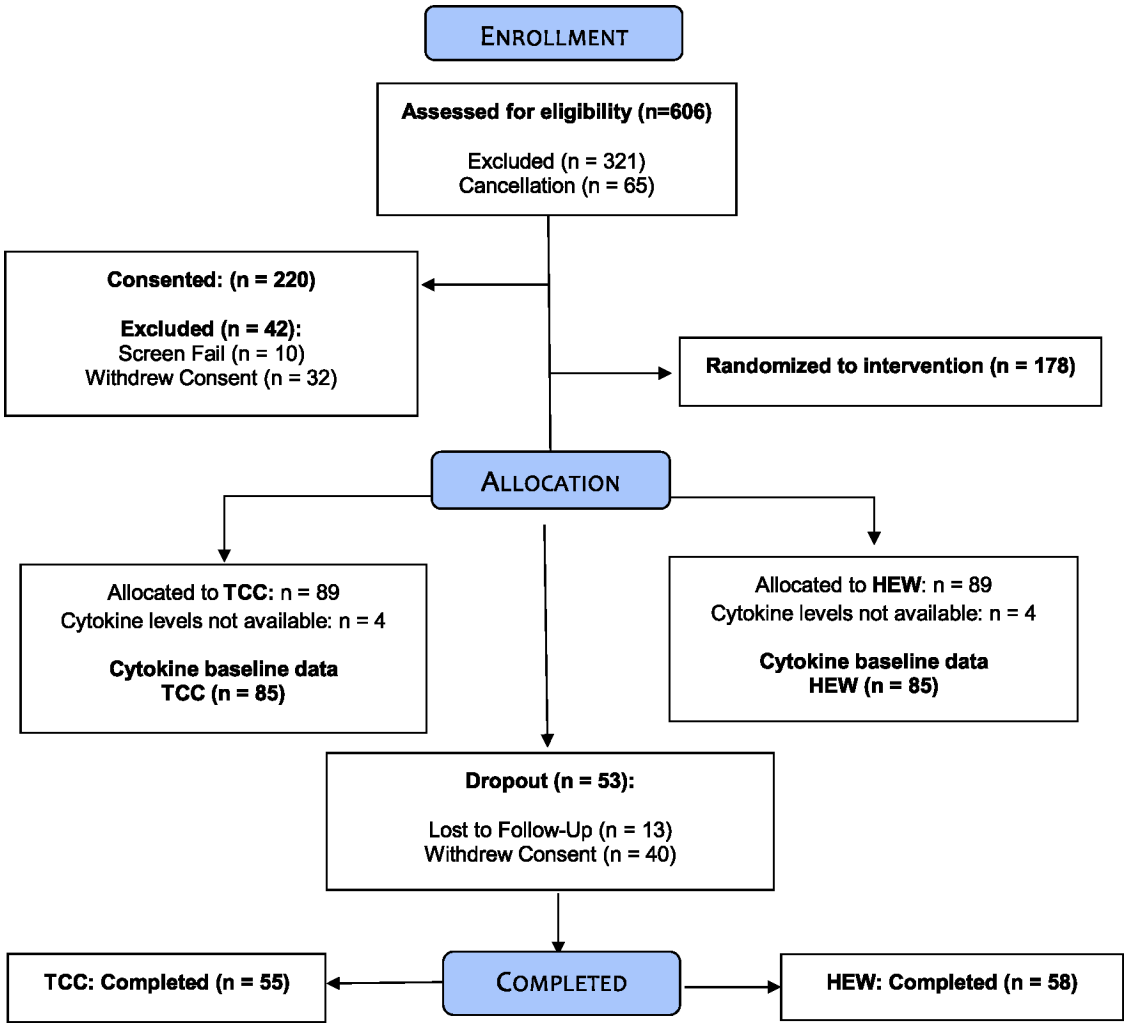

FIGURE 1.
CONSORT diagram.

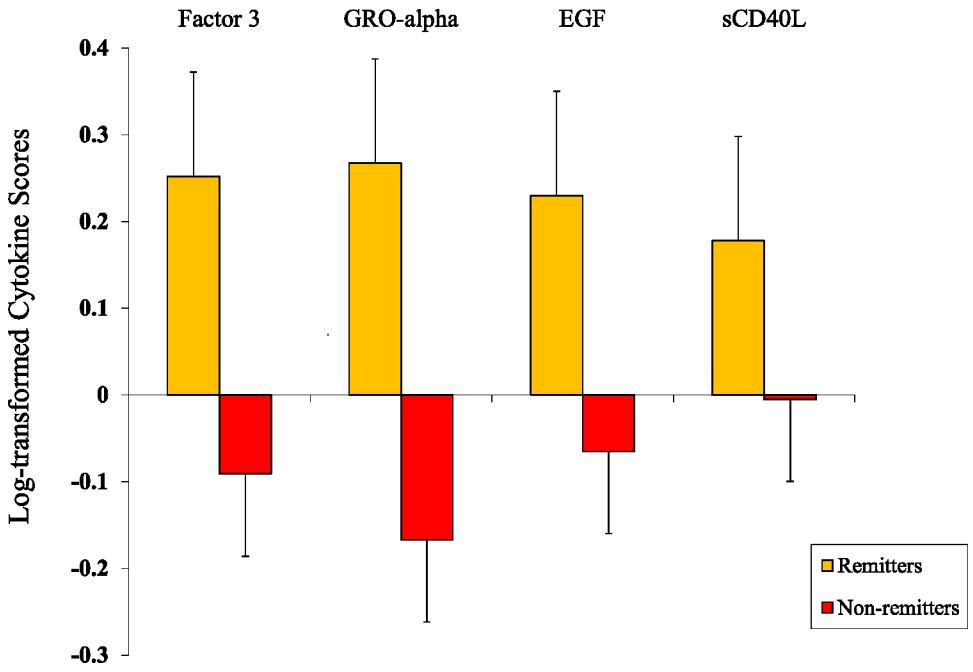

FIGURE 2.

Mean changes in cytokine scores in remitters and non-remitters (error bars represent standard errors).

TABLE 1.

Comparison of Baseline Demographic and Clinical Characteristics

Variable	Treatment Group			Remission Status[b]		
	TCC[a]	HEW[a]	Statistic	Remitters	Non-Remitters	Statistic
	(n = 85)	(n = 85)		(n = 36)	(n = 77)	
Age	69.0 (6.7)	69.5 (6.3)	t(168) = −0.5, p = 0.6	69.6 (7.1)	68.5 (6.1)	t(111) = 0.8, p = 0.4
Women	59 (69.4%)	64 (75.3%)	$\chi^2(1) = 0.7$, p = 0.4	23 (63.9%)	57 (74.0%)	$\chi^2(1) = 1.2$, p = 0.3
Education	16.0 (2.0)	15.5 (2.1)	t(168) = 1.6, p = 0.1	15.9 (1.9)	15.6 (2.1)	t(111) = 0.7, p = 0.5
Race			Fisher's exact p = 0.8			Fisher's exact p = 0.2
Caucasian	70 (82.4%)	71 (83.5%)		27 (75.0%)	69 (89.6%)	
African American	5 (5.9%)	8 (9.4%)		3 (8.3%)	2 (2.6%)	
Asian	5 (5.9%)	3 (3.5%)		3 (8.3%)	3 (3.9%)	
Hispanic	3 (3.5%)	2 (2.4%)		1 (2.8%)	2 (2.6%)	
Other	2 (2.4%)	1 (1.2%)		2 (5.6%)	1 (1.3%)	
Chronic Depression (> 24 mos.)	54 (64.3%)	65 (76.5 %)	$\chi^2(1) = 3.0$, p = 0.1	23 (63.9%)	59 (76.6 %)	$\chi^2(1) = 2.0$, p = 0.2
Age of Onset	38.6 (20.9)	37.2 (20.7)	t(168) = 0.4, p = 0.7	42.7 (21.4)	37.5 (19.5)	t(111) = 1.3, p = 0.2
MMSE	28.7 (1.3)	28.8 (1.1)	t(168) = −0.9, p = 0.4	28.6 (1.5)	28.8 (1.2)	t(111) = −0.7, p = 0.5
BMI	27.3 (5.3)	27.7 (6.3)	t(168) = −0.5, p = 0.6	26.5 (5.3)	26.5 (6.0)	t(111) = 0.0, p = 1.0
HAM-D (baseline)	18.9 (3.9)	19.1 (3.6)	t(168) = −0.4, p = 0.7	17.0 (2.1)	19.3 (3.4)	t(111) = −3.8, p = 0.001
HAM-D (3-mo follow-up)[c]	9.0 (5.3)	9.7 (5.3)	t(111) = 0.8, p = 0.5	3.2 (2.0)	12.3 (3.6)	$d_{t(110)} = -12.8$, p<0.0001
Remitters[c]	21 (38.2%)	15 (25.9%)	$\chi^2(1) = 2.0$, p = 0.2			
TCC arm				21 (58.3%)	34 (44.2%)	$\chi^2(1) = 2.0$, p = 0.2

[a] TCC: Tai Chi Chih; HEW: health education and wellness.

[b] Remission defined as HAM-D score of less than or equal to 6 at the time of 3-month follow-up; results presented for the 113 participants who completed 3-month follow-up.

[c] n = 55 for TCC and n = 58 for HEW at the 3-month follow-up.

[d] Statistics comparing follow-up HAM-D score, controlling for baseline score.

TABLE 2.

Cytokine Factor Loadings

	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
IL_12p40	0.85	0.27	0.04	0.01	0.14
IL_15	0.84	0.22	−0.02	0.00	0.01
Fractalkine	0.84	0.05	0.04	0.14	0.06
MCP-3	0.83	−0.12	−0.07	0.16	0.05
IL-10	0.81	0.19	0.00	−0.02	0.18
FGF-2	0.63	0.11	0.12	0.35	−0.02
Flt-3L	0.54	0.12	0.38	−0.29	−0.02
MIP-1β	0.11	0.70	0.01	0.26	−0.17
MDC	0.00	0.70	0.10	−0.11	0.16
TNF-α	0.24	0.65	0.23	0.27	0.17
IP-10	0.22	0.50	0.02	−0.07	0.27
GRO	−0.13	0.16	0.76	−0.04	−0.20
EGF	0.37	−0.01	0.76	0.16	0.08
sCD40L	−0.07	0.12	0.72	0.44	0.13
IL-1RA	0.06	0.10	0.15	0.89	0.12
IL-8	0.45	0.06	0.13	0.64	0.04
Eotaxin	0.03	0.01	0.04	0.15	0.84
MCP-1	0.15	0.29	−0.10	0.00	0.69

TABLE 3.

Changes in Factor Scores by Treatment and by Remission Status[a]

Variable	TCC[b] (n = 55)	HEW[b] (n = 58)	Statistic[c]	Remitters (n = 36)	Non-Remitters (n = 77)	Statistic[c]
Factor 1 change[d]	0.03 (−0.08, 0.13)	−0.07 (−0.18, 0.05)	F(1,111) = 1.59, p = 0.2	−0.03 (−0.16, 0.09)	−0.01 (−0.11, 0.08)	F(1,111) = 0.23, p = 0.6
Factor 2 change[d]	−0.06 (−0.32, 0.20)	0.05 (−0.22, 0.31)	F(1,111) = 1.76, p = 0.2	0.11 (−0.22, 0.44)	−0.06 (−0.29, 0.16)	F(1,111) = 0.03, p = 0.9
Factor 3 change[d]	0.04 (−0.18, 0.26)	0.00 (−0.21, 0.22)	F(1,111) = 0.0, p = 1.0	0.27 (0.02, 0.51)	−0.09 (−0.28, 0.10)	F(1,111) = 4.05, p = 0.05
Factor 4 change[d]	0.06 (−0.03, 0.16)	−0.08 (−0.20, 0.04)	F(1,111) = 0.17, p = 0.7	−0.03 (−0.18, 0.11)	0.01 (−0.09, 0.09)	F(1,111) = 0.34, p = 0.6
Factor 5 change[d]	0.00 (−0.10, 0.10)	−0.06 (−0.17, 0.04)	F(1,111) = 1.51, p = 0.2	−0.03 (−0.17, 0.10)	−0.03 (−0.12, 0.06)	F(1,111) = 0.35, p = 0.6

[a]Remission defined as HAM-D score of less than or equal to 6 at the time of 3-month follow-up.

[b]TCC: Tai Chi Chih; HEW: health education and wellness.

[c]Statistics reported are the F-statistics of the interaction term (treatment group/remission status × visit) from mixed effects general linear models, controlling for age, sex, body mass index (BMI), and batch.

[d]Mean unadjusted changes (and their 95% confidence intervals in parentheses) are reported.