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Association of T and non-T cell Cytokines with Anhedonia: Role of Gender Differences

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Abstract

Objective: Among individual depressive symptoms, anhedonia has been reliably associated with activation of the innate immune response. However, it is unclear whether this association extends to T cell cytokines and if gender differentially affects this association.

Method: Concentrations of T (IL-17, T-helper (Th) 1- and Th2-) and non-T cell cytokines were measured in plasma using the Bioplex Pro™ human cytokine multiplex kit in Combining Medications to Enhance Depression Outcomes (CO-MED) trial participants who provided plasma at baseline (n = 166). Anhedonia was measured with three items of the clinician-rated Inventory of Depressive Symptomatology and depression severity (minus anhedonia item) was measured with Quick Inventory of Depression Severity Self-Report version (modified-QIDS-SR). Separate generalized linear models for anhedonia and modified-QIDS-SR as dependent variables were conducted with IL-17, Th1-, Th2-, and non-T cell- cytokines as primary independent variables and gender, body mass index (BMI), and age as covariates. Exploratory analyses included gender-by-biomarker interactions.

Results: Higher levels of IL-17 (p=0.032), Th1- (p=0.002), Th2-(p=0.001) and non-T-(p=0.009) cell markers were associated with greater severity of anhedonia controlling for BMI, age, and gender. Gender also had a significant main effect on anhedonia, however, there was a significant gender by immune marker interaction only for IL-17 (p=0.050). Anhedonia severity increased with higher IL-17 in males (r=0.42, p=0.003) but not in females (r=0.09, p=0.336). Only non-T cell markers were associated with the modified-QIDS-SR, and there were no significant gender-specific associations with this variable.

Conclusions: T and non-T cell-related inflammatory markers were associated with greater severity of anhedonia, while gender moderated the association of IL-17 with anhedonia in patients with major depressive disorder.

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Keywords

Anhedonia; inflammation; interleukin 17; depression; gender

1. Introduction

Several lines of evidence implicate dysfunctional immune response in the pathophysiology of major depressive disorder (MDD) (Miller and Raison, 2016). Over one-third of patients treated with interferon alpha (an inflammatory cytokine) develop significant depressive symptoms (Raison et al., 2005). Depressive symptoms, in turn, are associated with higher levels of non-specific markers of inflammation such as c-reactive protein (CRP) (Cepeda et al., 2016). Patients with MDD have higher levels of inflammatory cytokines such as interleukin (IL)-6 in peripheral circulation and in cerebrospinal fluid as compared to controls (Kern et al., 2014; Kohler et al., 2017). Strong supportive evidence for the role of innate immune response in depressive symptoms is provided by the onset of depressive symptoms after injection of lipopolysaccharide (LPS) in animals and human volunteers (Dantzer et al., 2008; Eisenberger et al., 2010). The role of adaptive immunity in depression, however, specifically T cell-mediated immune response, remains unclear. T cell cytokines, such as interleukin 17 (IL-17), have gained recent attention for their potential role in MDD (Beurel and Lowell, 2017). Increased IL-17 has been shown to induce a depressive phenotype in male animals (Beurel et al., 2013), increase with chronic mild stress in female animals treated with vehicle versus fluoxetine (Lu et al., 2017), predict antidepressant treatment response in patients with MDD (Jha et al., 2017a), and is a target for developing novel antidepressants (Griffiths et al., 2017; Jha and Trivedi, 2018; Papp et al., 2016).

The association of T cell cytokines with overall depression severity has been inconsistent. While some studies have found altered levels of T-helper 1 (Th1) and Th2 cytokines (Kohler et al., 2017; Song et al., 2009) in patients with MDD, others have failed to find any significant association of Th1 and Th2 cytokines with depression (Dowlati et al., 2010). Similarly, IL-17 levels were not elevated in patients with MDD as compared to controls (Kohler et al., 2017) and were not significantly associated with overall depressive symptom severity (Jha et al., 2017a). A potential source of these conflicting findings could be the current definition of overall depression severity derived from the sum of nine symptoms that constitute the diagnosis of a major depressive episode. Within the heterogeneous syndromic diagnosis of MDD, anhedonia is an important symptom domain affected by immune activation (Eisenberger et al., 2010; Miller and Raison, 2016; Swardfager et al., 2016). For example, systemic inflammation, as evidenced by increased levels of CRP, is associated with reduced corticostriatal connectivity and greater severity of anhedonia symptoms in patients with MDD (Felger et al., 2016). It is unknown, however, whether IL-17 or other T cell cytokines are associated with anhedonia. Gender-specific differences in the association of inflammatory markers with depression may also account for the aforementioned conflicting findings. Gender-specific differences in immune responses are well-recognized (Klein and Flanagan, 2016). Indeed, autoimmune disorders in males typically involve a pro-inflammatory T-helper (Th1) response whereas those in females are predominantly mediated via autoantibody and Th2 immune responses (Fairweather et al., 2008). Nevertheless, the

contribution of gender-specific differences in immune responses to the pathophysiology of MDD remains unclear.

In a recent report, higher CRP was associated with greater depression severity in females but not males (Köhler-Forsberg et al., 2017). This differed from previous reports of stronger association of CRP with depressive symptoms in males as compared to females (Tayefi et al., 2017; Vetter et al., 2013). The inflammatory challenge with lipopolysaccharide injection results in a greater increase in pro-inflammatory cytokines and social disconnection in females as compared to males (Moieni et al., 2015; van Eijk et al., 2007). Similarly, higher IL-1β and TNF-α levels in depressed outpatients were associated with greater depressive symptoms in females but not males (Birur et al., 2017). Use of interferon α (IFN-α) has reportedly been associated with higher rates of depression in females in some (Koskinas et al., 2002) but not all (Bonaccorso et al., 2002; Raison et al., 2005) studies. Nevertheless, few studies have examined the association of T cell cytokines with anhedonia and other depressive symptoms, and there is a paucity of information on whether these relationships are gender-specific.

Thus, the primary aim of this report was to evaluate the association of IL-17 and other T cell and non-T cell cytokines with anhedonia and overall depressive symptom severity (minus the anhedonia item). As exploratory analyses, we also examined the role of gender-specific differences in these associations. To accomplish this aim we used plasma samples collected from a sample of convenience available through the Combining Medications to Enhance Depression Outcomes (CO-MED) trial (Rush et al., 2011).

2. Material and Methods

2.1. Study Overview

Participants of the CO-MED trial who provided plasma specimens (n=166) constitute the analytic sample of this report. As previously described in detail (Rush et al., 2011), CO-MED trial recruited treatment-seeking outpatients with MDD (ascertained by structured interview) from six primary and nine psychiatric care sites who had nonpsychotic chronic (current episode exceeded 2 years) or recurrent depression with current episode ≥2 months and a baseline 17-item Hamilton Rating Scale (HRSD17) ≥16 and not currently taking psychotropic medications. Complete list of exclusion criteria is available at https://clinicaltrials.gov/ct2/show/NCT00590863. Briefly, those with lifetime history of bipolar or psychotic disorders, current substance dependence, or had a general medical condition that is unstable or prohibited the use of study medications were excluded.

Participants (n=665) were randomly assigned after stratification for site to either SSRI monotherapy (escitalopram plus placebo), bupropion-SSRI combination (sustained-release [SR] bupropion plus escitalopram), or venlafaxine-mirtazapine combination (extended-release [XR] venlafaxine plus mirtazapine). Baseline plasma was collected as part of a separate add-on biomarker study that was optional and required an additional consent. All participants in this report provided written informed consent for participation in the main CO-MED trial, along with consent for the biomarker collection. Thus, the number of plasma samples (n=166) collected at baseline was a subset of the total number of CO-MED trial

participants (n=665). Participants who did not provide plasma (n=499) at baseline were younger (mean age=44.51 years vs. 42.11, p=0.030) and had lower use of statin medication (20.5% vs 13.6%, p=0.034) when compared to the analytic sample of this report, but did not differ on any other baseline clinical and sociodemographic features as previously reported (Jha et al., 2017b). The trial was reviewed and approved by the Institutional Review Boards at UT Southwestern Medical Center at Dallas, the University of Pittsburgh Data Coordinating Center, each participating regional center, and all relevant clinics.

2.2. Assessments

Participants provided sociodemographic information and filled out the 16-item Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR), while clinicians completed the 30-item Inventory of Depressive Symptomatology Clinician-Rated (IDS-C).

Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR): This commonly used scale has 16 items, each of which includes four choices that are scored from 0–3. A total score is calculated from nine of these 16 items (consistent with the nine criterion symptom domains of MDD) leading to a range of 0–27 (Rush et al., 2003). The QIDS-SR correlates highly (0.86–0.93) with the 17-item Hamilton Rating Scale for Depression, HRSD17 (Rush et al., 2006). In previous reports, the reported Cronbach's α of QIDS-SR has ranged from 0.86 to 0.87 (Rush et al., 2006; Rush et al., 2003; Trivedi et al., 2004). In the CO-MED trial, the QIDS-SR served as the primary depression symptom severity outcome measure (Rush et al., 2011). For this report, we created a modified QIDS-SR score by excluding the "interest" item, which reflects the severity of anhedonia, from the total QIDS-SR score resulting in a range of 0–24 for a total score of modified QIDS-SR.

Inventory of Depressive Symptomatology clinician-rated (IDS-C): Of the 30 items of IDS-C (each item has four choices that are scored from 0–3), 28 items are summed to generate a total score (range 0–84) that correlates very highly (Pearson's moment correlation equals 0.95) with the HRSD17 (Rush et al., 1996). In previous reports, the Cronbach's α of IDS-C has ranged from 0.67 to 0.94 (Rush et al., 1996; Trivedi et al., 2004). Anhedonia, as measured by a subscale of three items of IDS-C (range 0–9), was used as the primary outcome for this report. It has been shown to compare favorably to Snaith-Hamilton Pleasure Scale (Snaith et al., 1995) with correlation coefficient of 0.63 (Felger et al., 2016). The Cronbach's α of the 3-item IDS-anhedonia at baseline of CO-MED trial was 0.55.

2.3. Measurement of inflammatory biomarkers

Plasma samples extracted from CO-MED trial participants (n=166) were transported overnight to the Biologic Core of National Institute of Mental Health Repository and Genomics Resource (NIMH RGR) for storage at −80°C. All samples for this report were obtained from the NIMH RGR core. Biomarker levels were measured in all samples at the same time, blinded to treatment allocation and outcomes by the Microarray Core at UT Southwestern Medical Center using the Bioplex Pro™ human cytokine standard 27-plex kit (Bio-Rad Laboratories, Hercules, CA, USA) with a Bio-plex® 200 instrument that was equipped with Bio-Plex Manager software, version 6.0 (Bio-Rad Laboratory, Hercules, CA,

USA). The 27-plex kit measures IL-17, Th1- (interferon gamma or IFN-γ and tumor necrosis factor α or TNF-α), Th2- (IL-4, IL-5, IL-9, and IL-13), and non-Th1/Th2- (IL-1β, IL-1 receptor antagonist, IL-8, IL-6, and macrophage inflammatory protein (MIP) 1 α and β) markers. All measurements were expressed in pg/ml with correction for 4-fold dilution using the standards provided in the kit (Bio-Rad Laboratory, Hercules, CA, USA). The levels of inflammatory biomarkers were interpreted only if the intra- and inter-assay coefficients of variation were less than 10% of detection limits (or precision range) specified by the manufacturer. The upper (UD) and lower (LD) detection limits and well as median, 25th percentile (p25) and 75th percentile (p75) of these immune markers were previously reported (Jha et al., 2017a) and were as follows (all in pg/mL): IL-17 (LD =4.9, UD =12235, median = 96.0, p25 =76.5, p75=125.6), TNF-α (LD =5.8, UD =95484, median =106.2, p35 =91.9, p75 =118.3), IFN-γ (LD =92.6, UD =52719, median =255.6, p25 =180.9, 75 =338.5), IL-4 (LD =2.2, UD =3467, median =8.9, p25 =7.6, p75= 10.6), IL-5 (LD =3.1, UD =7380, median =60.9, p25 =51.4, p75 =76.9), IL-9 (LD=2.1, UD =7989, median =22.1, p25 =15.1, p75= 29.8), IL-13 (LD =3.7, UD =3137, median =13.6, p25 =8.4, p75 =25.6), IL-1β (UD =3.2, LD =3261, median =9.8, p25 =8.0, p75 =11.6, IL-1 receptor antagonist (LD =81.1, UD =70487, median =488.5, p25 =394.1, p75 =648.4), IL-8 (LD =1.9, UD =26403, median =24.0, p25 =19.3, p75 =40.0), IL-6 (LD =2.3, UD =18880, median =15.9, p25 =12.6, p75 =19.3), MIP-1α (LD =1.4, UD =836, median =8.3, p25 =7.2, p75 =10.0), and MIP-1β (LD =2.0, UD =1726, median =82.5, p25 =63.1, p75 =120.4).

2.4. Statistical Analyses

Log-transformation was used for biomarkers that were not normally distributed. As previously described (Jha et al., 2017a), immune markers were grouped into Th1- (IFN-γ factor loading =0.77, TNF-α factor loading =0.77, squared multiple correlations of the variables with each factor =0.69), Th2- (IL-4 factor loading =0.83, IL-5 factor loading =0.74, IL-9 factor loading =0.55, IL-13 factor loading =0.43, squared multiple correlations of the variables with each factor =0.77) and non-Th1/Th2- (IL-1β factor loading =0.85, IL-1 receptor antagonist factor loading =0.73, IL-8 factor loading =0.79, IL-6 factor loading =0.76, MIP-1α factor loading =0.56, MIP-1β factor loading =0.53, squared multiple correlations of the variables with each factor =0.88) factors after confirmatory factor analyses and the factor scores were used in subsequent analyses. As the primary purpose of this report was to test the association of T- and non-T cell markers with anhedonia, separate generalized linear model (GLM) analyses were used with anhedonia as the dependent variable and IL-17, Th1-, Th2- and non-Th1/Th2-factors as the primary independent variables of interest after controlling for gender and body mass index (BMI) and age. As exploratory analyses, these GLM analyses were repeated with gender-by-biomarker interactions, and stratified analyses for each gender (males and females) were conducted to quantify the effect of biomarker after controlling for age and BMI. To replicate the findings of Birur et al. (2017), separate above-specified GLM analyses were repeated with IL-1β and TNF-α in biomarker-by-gender interaction variables for anhedonia and modified QIDS-SR as dependent variables. The strength of association between depressive symptoms and inflammatory biomarkers were estimated using correlation coefficients. To visualize the gender-by-biomarker interaction, individual scores of dependent variables were plotted

against the biomarker level. All analyses were conducted with SAS version 9.3 and threshold of significance were set at $p < 0.05$.

3. Results

The mean anhedonia score (range 0–9) for the whole sample (N=166), males (n=49) and females (n=117) was 5.46 (2.04), 4.4(1.9), and 5.9 (2.0) respectively. As shown in Table 1, female participants had a significantly higher level of anhedonia when compared to males (t value=−4.41 (df=92), $p<0.001$).

There was a significant main effect of IL-17 (p=0.032) Th1- (p=0.002), Th2- (p=0.001), and non-Th1/Th2-(p=0.009) factors on severity of anhedonia after controlling for age, gender, and BMI (see Table 2). Of note, there was a main effect of gender on anhedonia in all analyses (all $p<0.01$). The Pearson's correlation coefficient between anhedonia and IL-17, Th1-, Th2-, and non-Th1/Th2-factors were 0.18 (p=0.022), 0.22 (p=0.004), 0.23 (p=0.003), and 0.19 (p=0.017) respectively. The association of inflammatory markers after controlling for age, gender, and BMI with modified depressive symptoms (minus anhedonia) was significant only for non-Th1/Th2-factor (p=0.019) but not for IL-17 (p=0.271), Th1- (p=0.580) and Th2-(p=0.422) factors, also see Table 2. The Pearson's correlation coefficient between depressive symptoms excluding anhedonia and non-Th1/Th2-factors was −0.20 (p=0.009).

Exploratory analyses revealed significant biomarker-by-gender interaction on levels of anhedonia for log IL-17 (p=0.050) but not for Th1- (p=0.219), Th2- (p=0.743) and non-Th1/Th2- (p=0.486) factor, as shown in Table 3. There was no significant biomarker-by-gender interaction for depression severity minus anhedonia item (modified-QIDS-SR; Table 3). There was no significant TNF-α-by-gender interaction for anhedonia (F=1.88, p=0.172) and modified-QIDS-SR (F=2.61, p=0.108) as well as no significant IL 1β-by-gender interaction for anhedonia (F=0.81, p=0.370) and modified-QIDS-SR (F=0.22, p=0.640)

In subsequent analyses stratified by gender, 1-unit higher value of log IL-17 was associated with 2.37 (standard error [SE]=0.76, t value=3.13, p=0.003) a higher score of anhedonia in males even after controlling for age and BMI. Conversely, 1-unit higher value of log IL-17 was not associated with any significant difference in anhedonia for females (est.=0.42, SE=0.45, t value=0.94, p=0.350). As shown in Figure 1, there was a strong correlation between log IL-17 and anhedonia in males (correlation coefficient=0.42) but not in females (correlation coefficient=0.09).

4. Discussion

In this large study of depressed outpatients, there was a significant association of IL-17 as well as Th1-, Th2-, and non-Th1/Th2-factors with the severity of anhedonia controlling for age, gender, and BMI. The severity of anhedonia was greater in participants with higher levels of these inflammatory markers. The severity of depressive symptoms excluding anhedonia was associated with non-Th1/Th2 factor only and not with IL-17 or Th1- and Th2-factors. Gender was significantly associated with severity of anhedonia in all analyses and significantly moderated the association of IL-17 and anhedonia (but not of IL-17 and

depressive symptoms excluding anhedonia or that of Th1-, Th2- and non Th1/Th2-inflammatory markers and anhedonia or depressive symptoms excluding anhedonia). In males, but not females, higher IL-17 levels were associated with greater severity of anhedonia even after controlling for age and gender. After controlling for age, gender, and BMI, there was a significant association of anhedonia with all biomarkers of inflammation assessed in this report.

The findings of this report further highlight the effect of immune dysfunction on depressive symptoms, specifically on anhedonia. While the severity of depressive symptoms excluding anhedonia was associated only with non-T cell cytokines, we found that severity of anhedonia increased with increased levels of both T- and non-T cell cytokines. Thus, the impact of the immune system appears to be prominent for anhedonia. These findings of a significant association between anhedonia and T- and non--T cell cytokines is consistent with previous reports that have reported small-to-moderate correlation between inflammatory cytokines and severity of anhedonia (Loftis et al., 2008). These are also consistent with previous findings of increased anhedonia severity with higher levels of non-specific markers of inflammation such as CRP (Felger et al., 2016). The greater severity of anhedonia in females than males may reflect different symptomatic profiles of depressive symptoms based on gender where symptoms such as irritability or agitation are seen more often in males and those of anhedonia in females (Amir A. Khan et al., 2002; Kuehner, 2003; Page et al., 2016).

This report adds to the literature regarding gender-specific differential effects of inflammation on the development of depressive symptoms. While the levels of IL-17 did not differ between males and females, the effect of IL-17 on anhedonia was significant only for males but not for females. As shown in Table 1, males and females did not differ on most clinical and sociodemographic variables except for higher rates of Hispanic ethnicity and melancholic features as well as greater severity of self-reported depressive symptoms and anhedonia in females. The lack of gender-specific association of IL-1β and TNF-α in this report differs from a previous report that found both IL-1β and TNF-α levels correlated with depressive symptoms in females but not males (Birur et al., 2017). Potential reasons for this inconsistency include the difference in measures to assess depressive symptom severity, sample size (larger number of depressed participants in the CO-MED trial), and use of single-items to measure symptom domains by Birur et al.

The biological basis for these findings is likely associated with the interaction of the immune and endocrine systems. In animal studies, testosterone has been shown to confer protection against autoimmune disorders mediated by IL-17 (Schwinge et al., 2015). Lower testosterone levels predispose rodents to develop anhedonia following chronic stress (Herrera-Perez et al., 2012) and testosterone substitution prevents the development of anhedonia and depressive symptoms in rodents with low testosterone (Carrier et al., 2015; Herrera-Perez et al., 2012). Studies that include concomitant measures of sex hormones and inflammatory markers are needed to better understand the gender-specific differences in anhedonia based on IL-17 levels. Our data suggest that relatively lower levels of testosterone may contribute to increased IL-17 and anhedonia in these patients. Future flow-cytometry studies measuring Th1, Th2, Th17, and regulatory T (Treg) cells are needed to elucidate

pathophysiological mechanisms underlying the role of inflammation and sex hormones in anhedonia. Levels of Treg cells differ in males versus females (Afshan et al., 2012); Treg cells, in turn, control the differentiation of naïve T cells to Th17 cells (Eisenstein and Williams, 2009). Additionally, while the role of IL-17 in disruption of blood-brain barrier is well recognized (Huppert et al., 2010; Kebir et al., 2007), the ratio of Th17 to Th1 cells is considered critical in the infiltration of brain parenchyma by peripheral immune cells and subsequent neuroinflammation (Stromnes et al., 2008).

There are several limitations of this report. This is a secondary analysis using a sample of convenience, thus it may have been inadequately powered to identify gender-specific differences in the association of inflammatory markers and depressive symptoms thus resulting in false negatives (or positives). The generalizability of these findings is also limited due to the higher proportion of females than males (70.5% vs. 29.5%), gender differences in severity of anhedonia, and high illness burden of CO-MED trial participants as the inclusion criteria included either chronic or recurrent MDD, and at least moderate severity of ongoing symptoms. As immune and endocrine systems are a complex interplay of multiple factors, focusing predominantly on IL-17 and using biologically based factor analysis may be insufficient. As the cytokines included in this report can be produced from multiple cell types, the levels of these cytokines may not reflect the number and function of T- and non-T cells, further supporting the need for future flow cytometry studies. Additional limitations include non-adjustment of p-values for multiple comparisons, non-availability of information regarding menstrual phase, smoking history, contraceptive use, and levels of sex steroid hormones, and lack of information regarding factors that may have introduced variability across samples such as the time of the day for plasma collection as well as average time from blood collection to plasma extraction. In light of these limitations, findings from this report are preliminary in nature and warrant future prospective studies.

5. Conclusion

The severity of anhedonia increases with increased levels of T- and non-T cell cytokines. Gender is an important biological factor that moderates the association of IL-17 with anhedonia. While males with higher levels of IL-17 experience greater severity of anhedonia, no such association is evident in females. Additionally, gender did not differentially affect the association of other depressive symptoms with IL-17 or of any depressive symptoms with Th1-, Th2-, and non-Th1/Th2-factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Elevated levels of T- and non-T-cell markers are associated with greater anhedonia severity.
- Gender differentially affects the association of anhedonia with interleukin 17 (IL-17) but not with other T- and non-T-cell markers.
- Higher IL-17 levels are associated with greater anhedonia severity in males but not in females.

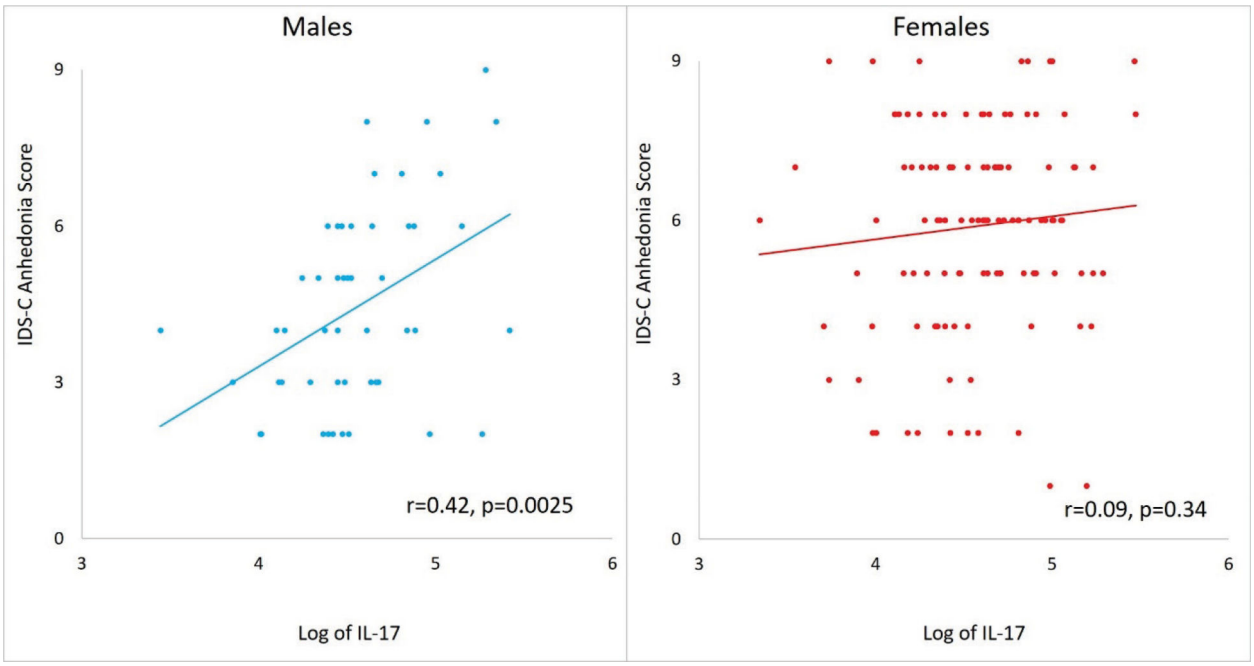

Figure 1.

Higher IL-17 levels were associated with higher IDS-C anhedonia scores in males but not female participants of CO-MED trial (n=166)

IL-17 is interleukin 17, IDS-C is 30-item Inventory of Depressive Symptomatology Clinician-Rated, CO-MED is Combining Medications to Enhance Depression Outcomes, r is Pearson's correlation coefficient.

Table 1.

Clinical and sociodemographic features based on gender in CO-MED trial participants who provided plasma at baseline (n=166)

	Total		Males		Females			p-value
Number	166		49		117			
Categorical variables	N	%	N	%	N	%	χ^2 (df)	
Race							0.78 (1)	0.677
White	107	64.5	34	69.4	73	62.4		
Black	46	27.7	12	24.5	34	29.1		
Other	13	7.8	3	6.1	10	8.5		
Hispanic ethnicity							7.58 (1)	0.006
No	139	83.7	47	95.9	92	78.6		
Yes	27	16.3	2	4.1	25	21.4		
Education							0.63 (2)	0.731
<12 years	24	14.5	7	14.3	17	14.5		
12 –15 years	98	59	27	55.1	71	60.7		
>15 years	44	26.5	15	30.6	29	24.8		
Employed at baseline	73	44.0	19	38.8	54	46.2	0.76 (1)	0.382
Anxious features present	120	72.3	31	63.3	89	76.1	2.83 (1)	0.093
Atypical features present	35	21.1	8	16.3	27	23.1	0.94 (1)	0.331
Melancholic features present	51	30.7	9	18.4	42	35.9	4.99 (1)	0.026
Suicidal ideation at baseline present	94	56.6	27	55.1	67	57.3	0.07 (1)	0.798
Onset of depression before age 18 years	67	40.4	18	36.7	49	41.9	0.38	0.538
Continuous variables	Mean	SD	Mean	SD	Mean	SD	T value (df)	
Age in years	44.5	12.0	46.5	11.2	43.7	12.2	1.42 (97)	0.160
QIDS-SR	15.6	4.1	13.9	3.6	16.2	4.2	−3.65 (103)	<0.001
Anhedonia severity from IDS-C	5.5	2.0	4.4	1.9	5.9	2.0	−4.41 (92)	<0.001
Episode duration in weeks	64.5	119.3	77.1	125.7	59.2	116.7	0.85 (84)	0.396
BMI	32.0	9.1	31.2	8.5	32.3	9.4	−0.80 (99)	0.427
Number of comorbid psychiatric conditions	1.3	1.7	1.6	2.0	1.1	1.6	1.46 (73)	0.148
Number of general medical conditions	2.1	1.6	2.3	2.0	2.0	1.5	0.82 (71)	0.417

CO-MED is Combining Medications to Enhance Depression Outcomes, QIDS-SR is Quick Inventory of Depressive Symptomatology, Self-Rated version, IDS-C is Inventory of Depressive Symptomatology Clinician-Rated Version, CAST is Concise Associated Symptom Tracking scale, BMI is body mass index.

Table 2.

Association of T- and non-T cell related inflammatory markers with anhedonia and other depressive and symptoms

	Anhedonia		Modified QIDS-SR*	
	F value	**p value**	**F value**	**p value**
Interleukin 17				
Age	0.24	0.628	1.30	0.256
BMI	1.13	0.289	0.92	0.339
Gender	18.02	<0.001	11.15	0.001
Log of IL-17	4.68	0.032	1.22	0.271
Th1-factor				
Age	0.76	0.386	1.18	0.278
BMI	1.43	0.234	1.28	0.259
Gender	18.89	<0.001	11.16	0.001
Th1-factor	9.72	0.002	0.31	0.580
Th2-factor				
Age	0.63	0.429	1.22	0.270
BMI	0.65	0.422	1.38	0.243
Gender	20.18	<0.001	11.41	<0.001
Th2-factor	10.99	0.001	0.64	0.422
Non-T cell-factor				
Age	0.27	0.603	0.66	0.419
BMI	0.73	0.393	0.48	0.490
Gender	16.64	<0.001	7.53	0.007
Non-Th1/Th2-factor	7.07	0.009	5.58	0.019

*Modified QIDS is QIDS-SR (Quick Inventory of Depressive Symptomatology Self-Rated version) minus the anhedonia item, Th1 is T-helper cell type 1, Th2 is T-helper cell type 2, Th1 cytokines include interferon gamma and tumor necrosis factor alpha (TNF-α), Th2 cytokines include interleukin (IL) 4, IL-5, IL-9, and IL-13, non-Th1/Th2 cytokines include IL-1 beta (IL-1β), IL-1 receptor antagonist, IL-8, IL-6, and macrophage inflammatory protein (MIP) 1 alpha and beta.

Table 3.

Differential association of inflammatory markers with anhedonia and other depressive symptoms based on gender

	Modified QIDS-SR*		Anhedonia	
	F value	**p value**	**F value**	**p value**
Interleukin 17				
Gender	3.76	0.054	5.51	0.020
Log of IL-17	0.09	0.768	9.13	0.003
Log of IL-17-by-gender	2.72	0.101	3.90	0.050
Th1 factor				
Gender	11.74	<0.001	20.79	<0.001
Th1 factor	0.56	0.455	11.28	0.001
Th1 factor-by-gender	1.39	0.239	1.52	0.219
Th2 factor				
Gender	12.09	<0.001	21.70	<0.001
Th2 factor	0.78	0.379	11.81	<0.001
Th2 factor-by-gender	1.39	0.240	0.11	0.743
Non-Th1/Th2 factor				
Gender	7.84	0.006	17.93	<0.001
Non-Th1/Th2 factor	5.11	0.025	8.21	0.005
Non-Th1/Th2 factor-by-gender	0.08	0.783	0.49	0.486

*Modified QIDS is QIDS-SR (Quick Inventory of Depressive Symptomatology Self-Rated version) minus the anhedonia item, Th1 is T-helper cell type 1, Th2 is T-helper cell type 2, Th1 cytokines include interferon gamma and tumor necrosis factor alpha (TNF-α), Th2 cytokines include interleukin (IL) 4, IL-5, IL-9, and IL-13, non-Th1/Th2 cytokines include IL-1 beta (IL-1β), IL-1 receptor antagonist, IL-8, IL-6, and macrophage inflammatory protein (MIP) 1 alpha and beta.