NOVA

University of Newcastle Research Online

nova.newcastle.edu.au

Accessed from: http://hdl.handle.net/1959.13/1040814

Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: A meta-analysis

Sarah Hiles,

Amanda Baker

Theo de Malmanche

John Attia

Abstract

Objective: Cross sectional studies support an association between depression and inflammatory markers. However, little is known of their relationship in the context of antidepressant treatment. Our aim was to explore via meta-analysis whether antidepressant treatment is associated with a reduction in three inflammatory markers associated with depression.

Methods: A computerised search of Embase, Medline, PsycINFO and Cochrane Library databases was completed using subject headings for depression and either interleukin-6, C-reactive protein or interleukin-10, selecting studies which reported circulating levels of inflammatory markers before and after antidepressant treatment for people with depression. Outcome and moderator variables were coded for analysis, including inflammatory marker change, depression severity change, age, gender ratio, assay brand, treatment response and weight change.

Results: Pooled effect sizes showed a significant decrease in interleukin-6 ($N = 14$, $d = -0.42$, $p = .02$), marginally significant decrease in C-reactive protein ($N = 8$, $d = -0.57$, $p = .05$) and a non-significant decrease in interleukin-10 ($N = 3$, $d = -0.45$, $p = .14$) after treatment. High levels of heterogeneity were observed, which may be associated with clinical variations between the studies such as weight gain, anxiety, incomplete remission and other individual differences and comorbidities.

Conclusions: The findings of this meta-analysis indicate that there may be a normalization of overactive inflammatory processes following antidepressant treatment.

Introduction

The comorbidity of depression and inflammation-related physical illnesses, particularly cardiovascular disease, has raised the possibility of a shared, underlying inflammatory pathway involving central and systemic responses (Irwin & Miller, 2007). Proposed bi-directional mechanisms for how inflammatory processes may induce depressive mood, and vice versa, incorporate evidence that prolonged exposure to inflammatory mediators can impair the regulation of neuroendocrine stress, influence the availability of monoamine neurotransmitters, and decrease neurogenesis and neurotropic support (Maes et al., 2009; Miller, Maletic, & Raison, 2009).

Much of the evidence supporting inflammatory theories of depression is cross-sectional with many studies demonstrating that, compared to people without depressive symptoms, people with high depressive symptoms show elevated levels of inflammatory markers (including cytokines, chemokines and acute phase proteins) in peripheral serum and cerebrospinal fluid (Dowlati et al., 2010; Lindqvist et al., 2009; Zorrilla et al., 2001). These differences have been observed in both medically healthy people with depressive symptoms and those with co-occurring medical comorbidities such as cardiovascular disease, renal disease and cancer (Bossola et al., 2010; Howren, Lamkin, & Suls, 2009). Fewer studies examine the association between depression and inflammatory markers over time, although this can help develop the case for whether elevated levels of inflammatory markers may be a cause or simply a consequence of depression.

This meta-analysis is one of the first to estimate change in inflammatory markers before and after antidepressant treatment. Through narrative review and meta-analytic moderator analysis, we also explore sources of heterogeneity related to individual differences and comorbidity. The cytokine interleukin (IL)-6 and an acute phase protein, C-reactive protein (CRP), were selected as prototypical pro-inflammatory markers, robustly associated with systemic inflammatory response, and IL-10 was selected as an important anti-inflammatory marker. These are repeatedly shown to be elevated in people with depression, compared to people without depression (Dowlati, et al., 2010; Howren, et al., 2009) and assuming there is an association, we would expect these to decrease as depressive symptoms decrease in association with antidepressant treatment.

Method

Systematic search

Studies were included in the meta-analyses if they met the following criteria: (i) participants were adults either diagnosed with major depression/dysthymia or endorsing high depressive symptoms on a standardized inventory; (ii) patients were not undergoing cytokine treatment (e.g., interferon or IL-2); (iii) the study explicitly reported antidepressant treatment in the methods; (iv) mean or median resting levels of IL-6, CRP or IL-10 in circulating plasma or serum was reported before and at least once after starting antidepressant treatment; (v) either a pre-test-post-test design or a randomized controlled trial design was used; (vi)

4

publication was in English in a peer reviewed journal; and (vii) enough information to calculate an effect size was reported. Studies of people with depression and a comorbid general medical condition were included providing the methods stated that the disease and medications were stable for the duration of the study.

A computerized search of Embase, Medline, PsycINFO and Cochrane Library databases was completed in March 2011 using two different search strategies: (i) the key terms mapped to subject headings for depression (depression, depressive disorder, major depressive disorder, dysthymic disorder) and either "interleukin-6", "C-reactive protein" or "interleukin-10"; and (ii) depression subject headings and "cytokine/interleukin" or "acute phase protein" and "antidepressants". Both searches were limited to human and English language literature. The abstract of each article identified in the search was screened for relevance. If the abstracts mentioned antidepressant use and measurement of inflammatory markers, or the abstracts lacked detail, full text articles were extracted and compared against selection criteria for eligibility. The reference lists of included studies and relevant review articles were screened for additional articles.

Eligible studies were coded and blindly checked by one author (SH) for the sample size and the outcome variable of mean (with standard deviation/standard error) circulating IL-6, CRP or IL-10 before and after treatment. Means and standard errors of inflammatory markers reported only graphically were converted to numerical values using Data Thief III, version 1.5 (Tummers, van der Laan, & Huyser, 2008). Moderator and mediator variables were also coded, including: diagnosis, mean group

depressive symptom rating at baseline and follow-up, mean age, proportion of males, treatment duration, inpatient or outpatient status, proportion of treatment responders and type of antidepressant. Where not reported, these variables were coded as missing values.

Statistical methods

Statistical analyses were completed using Comprehensive Meta-Analysis II (Biostat, Inc., USA). For the antidepressant treatment arm in each study, individual study effect sizes for change in inflammatory markers and depressive symptoms were calculated as repeated-measures Cohen's *d* standardized mean difference using the pre- and post-test means, standard deviation of the difference calculated from the pre- and post-test standard deviations and an estimation of the pre- and post-test correlation (Borenstein, Hedges, Higgins, & Rothstein, 2009). If the mean was not reported, the median was used as an estimate because sample sizes were sufficiently large (Pudar Hozo, Djulbegovic, & Hozo, 2005). We used a conservative correlation of 0.5 as an estimate for the correlation between pre- and post-treatment inflammatory marker but also re-tested the meta-analysis model using other correlations ($r = 0.4$, 0.6, 0.7), with none producing a large difference in result. For one study which failed to report standard deviations/errors but otherwise met selection criteria (Dawood et al., 2007), the effect size was calculated using the difference in means, sample size and paired *p* value. For the few studies that included more than one follow-up measurement of IL-6, CRP or IL-10 (Hernandez et al., 2008; Kubera et al., 2000; Mackay et al., 2009), we calculated a study effect size for the follow-up point closest to

the mean duration of the remaining studies for that inflammatory marker, so as to reduce the variability that too large a range of treatment duration might cause. For studies reporting data for subgroups only, whole sample data points were imputed by collapsing subgroup means (Leo et al., 2006; Sluzewska et al., 1995; Yoshimura et al., 2009). A positive effect size indicates that there was an increase in the inflammatory marker over time.

Individual study effect sizes were synthesized to generate an overall effect size using a random effects model, weighted by the inverse of variance. We also completed a sensitivity analysis to identify potential outliers by removing each study one by one to examine the influence of each individual study on the overall effect size. The Egger test of funnel plot asymmetry (Egger, Davey Smith, Schneider, & Minder, 1997) and fail-safe N (Rosenthal, 1979) were calculated to assess publication bias. Heterogeneity in the meta-analysis was assessed using Cochrane's Q and I^2 which calculates a proportion of variation attributed to heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). Moderator analysis was undertaken to explore sources of heterogeneity. Subgroup analysis was completed by comparing pooled inflammatory marker effect size in subgroups of categorical moderator/mediator variables, while method of moments meta-regression was completed to explore the relationship between effect size and continuous variables.

Results

There were 22 studies relevant to these meta-analyses ($N = 14$ for IL-6, $N = 8$ for CRP and $N = 3$ for IL-10; article extraction process summarized in Figure 1, methods and relevant findings summarized in Table 1). Most study designs were of a single group of people with depression, measured before and after (or during) antidepressant treatment ($n = 15$). Seven studies were randomized control trials (RCTs) comparing an antidepressant treatment condition and either a non-antidepressant treatment or antidepressant in conjunction with non-antidepressant pharmacological treatment. Many studies included a control condition of people without depression who were measured for inflammatory markers at a single time point ($n = 17$) to infer whether levels of inflammatory markers in the depression group change to a level comparable to a non-depressed control group. Every study reporting depressive symptoms showed a significant group reduction in depressive symptoms after antidepressant treatment.
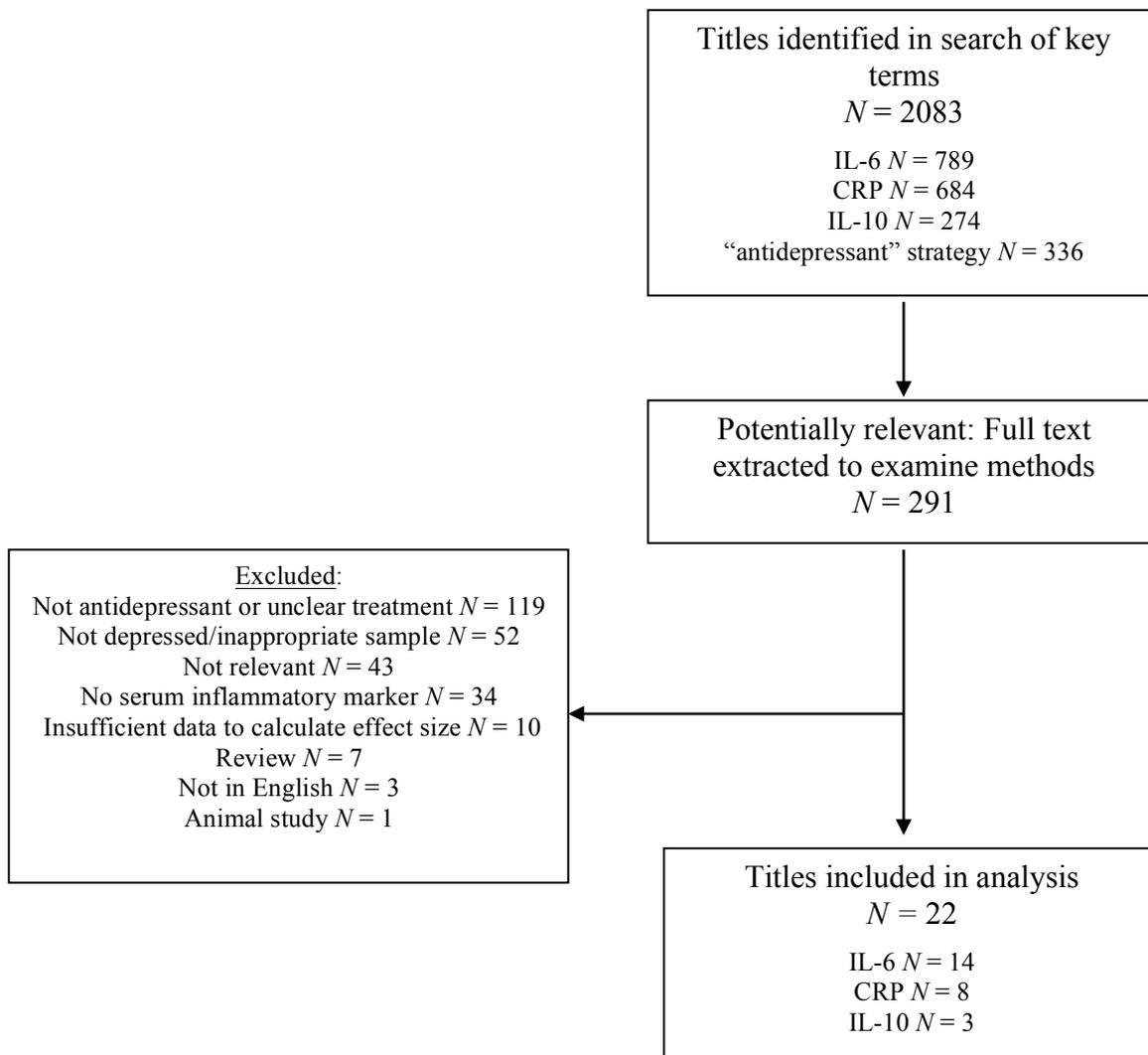
Figure 1. Summary of article extraction process after two systematic search strategies either based on search for "depression" and either the specific mediator interleukin (IL)-6, C-reactive protein (CRP) or IL-10, or "antidepressants", "cytokine/interleukin" and "acute phase protein". Reasons for exclusion are listed.

Table 1. Key characteristics of the studies included in the meta-analysis regarding changes in interleukin (IL)-6, C-reactive protein (CRP) and IL-10 following antidepressant treatment.

Study	Population				Intervention		Design/ comparator		Outcome		Change after treatment			
	Clinical description	Age M (SD)	% male	N^+	Drug (dose)	Length (weeks)	Design	Healthy control group	Depression measure	Blood measure	Dep Resp (%)	IL-6	CRP	IL-10
Maes et al 1995	Inpatients, DSM-III-R major depressive episode	39 (9.4)	53	17	Clinician decided: fluoxetine (20mg) or tricyclic antidepressants	≈ 12	Pre-test-post-test	✓ (N = 38) IL-6 higher in depression than control group	Schedule for Affective Disorders and Schizophrenia, Ham-D	Plasma, sandwich ELISA (Eurogenetics) Overnight fast, 15 min rest, collected at 0845	↓	.	→	.	.
Sluzewska et al 1995	Inpatients, DSM-III-R MDD – group with elevated IL-6 at baseline	42.5 (6.4)	13	6	Fluoxetine (20mg)	8	Pre-test-post-test Compared changes in IL-6 for groups with elevated and non-elevated IL-6	✓ (N = 11) IL-6 higher in depression than control group	Ham-D	Serum, ELISA	.	.	↓	.	.

Study	Sample	Age			Medication		Design	Finding	Measure	Assay					
	Inpatients, DSM-III-R MDD – group without elevated IL-6 at baseline	40.6 (2.5)	13	16	Fluoxetine (20mg)	8	Pre-test-post-test Compared changes in IL-6 for groups with elevated and non-elevated IL-6 at baseline	✓ (N = 11) IL-6 no different between depression and control group	Ham-D	Serum, ELISA	.		→	.	.
Maes et al 1997	Inpatients, DSM-III-R MDD	47.5 (15)	54	25	Clinician decided: trazodone (100mg), trazodone (100mg) + pindolol (7.5mg) or trazodone (100mg) + fluoxetine (20mg)	5	Pre-test-post-test	✓ (N = 15) IL-6 higher in depression than control group	Semi-structured interview for DSM-III-R, Ham-D	Serum, sandwich ELISA (Eurogenetics) Collected between 0730 and 0800	↓	60	→	.	.
Sluzewska et al 1997	Inpatients with refractory MDD (N = 19) and bipolar (N = 13)	44 (11)	19	32	Existing various antidepressants + lithium carbonate (500 – 1500 mg)	4	Pre-test-post-test	✓ (N = 20) CRP lower in depression than control group	Ham-D	Plasma, rocket immunoelect-rophoresis Overnight fast, collected at 0730	.	75	.	↓	.

Study	Sample	Age	%	N	Treatment	Weeks	Design	Finding	Measure	Assay					
Kubera et al 2000	Inpatients, DSM-IV recurrent MDD	47.3 (3)	44	9	Clinician decided: antidepressant	6 (blood also drawn at 2)	Pre-test-post-test	✓ (N = 11) IL-6 and IL-10 no different between depression and control group	Ham-D	Serum, sandwich ELISA (Eurogenetics) 10hr fast, 12hr abstain caffeine, nicotine, alcohol, collected between 0730-0830	↓	.	→	.	→
Lanquill-ion et al 2000	Inpatients, MDD	53.5 (15.2)	38	24	Amitripty-line (150 - 250mg)	6	Pre-test-post-test	✓ (N = 15) CRP higher in depression than control group	SCID, Ham-D	Routine methods Collected at 0800	↓	.	.	↓	.
Kagaya et al 2001	DSM-III-R MDD (N = 9) or dysthymia (N = 3)	31.1 (8.2) [++]	75	8	Clinician decided: antidepressant, mainly clomipramine	4	Pre-test-post-test	✓ (N = 12) IL-6 no different between depression and control group at baseline	Ham-D	Plasma, ELISA (BioSource International, Camarillo, CA) Collected between 1100-1400 in EDTA	↓	.	→	.	.

Mikova et al 2001	Inpatients, DSM-IV major depressive episode, Ham-D ≥ 18	47.3 (11.3)	18	14	Clinician decided: paroxetine or tricylic antidepressants	6	Pre-test-post-test	✓ (N = 15) IL-6 no different between depression and control group at baseline	Ham-D	Serum, ELISA, (Eurogenetics, Tessenderlo, Belgium) Collected between 0800-0900, no additive	↓	64	→	.	.
Tuglu et al 2003	Inpatients major depressive episode via SCID DSM-IIIR	39.4 (14.6)	58	30	Clinician decided: SSRI	6	Pre-test-post-test	✓ (N = 17) CRP no different between depression and control group at baseline/ follow-up	SCID DSM-IIIR, Ham-D, BDI	Serum, routine methods. Overnight fast, collected between 0700-0800, no anticoagulant	↓	92	.	↓	.

Study	Population	Age (SD)	N	N	Treatment	Weeks	Design	IL-6 finding	Depression measure	Assay					
Yao et al 2004	Inpatients, depression according to ICD-10 and CCMD-3 criteria, Ham-D > 17	37 (8)	33	40	Clinician decided: SSRI or Venlafaxine	4	Pre-test-post-test	✓ (N = 20) IL-6 higher in depression than control group at baseline, no different between depression and control group at follow-up	Ham-D	Serum, ELISA (Tianjing Jierui Biological Product Company) Collected on second morning after admission to hospital	↓	.	↓	.	.
Basterzi et al 2005	DSM-IV MDD or MDD-recurrent	33.8 (12.8)	13	23	Clinician decided: SSRI	6	Pre-test-post-test	✓ (N = 23) IL-6 no different between depression and control group at baseline	Structured clinical interview, Ham-D	Serum, Cytelisa sandwich ELISA (Cytimmune Sciences, Maryland) Collected 0830-1000, no anticoagulant	↓	74	↓	.	.
Leo et al 2006	MDD (first episode) – sertraline group	34.9 (5.9)	40	20	Setraline (100mg)	6	RCT (sertraline vs. citalopram)	✓ IL-6 higher in depression than control group	Ham-D	Quantikine High Sensitivity Immunoassay (R & D Systems, MN)	↓	.	↓	.	.

Study	Population	Age	%	N	Antidepressant	Duration	Design	Marker	Depression measure	Assay					
	MDD (first episode) – citalopram group	34.9 (5.9)	50	20	Citalopram (20mg)	6	RCT (sertraline vs. citalopram)	✓ IL-6 higher in depression than control group	Ham-D	Quantikine High Sensitivity Immunoassay (R & D Systems, MN)	↓	.	↓	.	.
O'Brien et al 2006	DSM-IV MDD with melancholic features, Ham-D > 17	37.9	0	20	Clinician decided: fluoxetine (20mg), paroxetine (20mg) or sertraline (50mg)	3	Pre-test-post-test	×	Ham-D	Serum, immunoturbimetric assay (Olympus). Collected between 0900-1100	.	90	.	↓	.
Dawood et al 2007	Outpatients recruited from the community, DSM-IV MDD, 84% recurrent	45 (11)	42	24	Clinician decided: SSRI (citalopram 40mg, sertraline 200mg, fluvoxamine 200mg, fluoxetine 40mg)	12	Pre-test-post-test	✓ (N = 15) CRP higher in depression than control group	MINI, CIDI, Ham-D	hsCRP particle-enhanced immunoturbidimetric assay (Roche Diagnostics, Mannheim, Germany) Collected in the morning after 10 mins of supine rest, 12 hours free from caffeine and tobacco	↓	88	.	↑	.

Study	Population	Age mean (SD)	n	%	Treatment	Weeks	Design	Control comparison	Measures	Assay						
Hernand-ez et al 2008	DSM-IV MDD, 52% recurrent, BMI ≤ 25	32 (9.4)	29	10	Clinician decided: SSRI	52 (blood also drawn at 5, 20 and 36)	Pre-test-post-test	✓ (N = 22) IL-10 higher in depression than control group at baseline, lower at 52 week follow-up	MINI, Ham-D, BDI	Serum, DuoSet ELISA (R & D Systems) Collected between 0800-0900	↓	100	.	.		↓
Mackay et al 2009	DSM-IV depression – fluoxetine group only	39.0 (2.4)	18	19	Fluoxetine (20mg)	18 (blood also drawn at 6, 12)	RCT (fluoxetine vs. fluoxetine + T$_3$ vs. counselling)	✗	Ham-D, CDS, BDI, MADRS, SF-36	Unclear	↓	.	.	→	.	
Pizzi et al 2009	Coronary heart disease, mild to severe depression (BDI ≥ 10)	57.4 (8.7)	47	100	Sertraline (50mg, dose increased weeks 6 - 13)	20	RCT (sertraline vs. placebo	✗	BDI	CRP: Latex/BN II (Dade Behring, Marburg, Germany) IL-6: Quantikine ELISA (R & D Systems, MN). Overnight fast, after 30min rest, collected in EDTA.	↓	55	↓	↓	.	

Study	Diagnosis				Treatment		Design	Findings	Measures	Assay					
Song et al 2009	DSM-III MDD	34 (13)	42	24	Fluoxetine (20mg)	6	RCT (fluoxetine + sham EA vs. placebo + EA vs. placebo + sham EA)	✓ (N = 30) IL-10 lower in depression than control group at baseline and follow-up.	SCID, Ham-D, Clinical Global Impression scale	Serum, ELISA (Gene May, San Diego, USA) Collected between 0700 – 0900	↓	.	.	.	→
Yoshimura et al 2009	DSM-IV MDD (first episode) – treatment responder group	40 (9)	40	31	Clinician decided: SSRI or SNRI	8	Pre-test-post-test	✓ (N = 30) IL-6 higher in depression than control group	Ham-D	Plasma, quantitative sandwich enzyme assay technique (R & D Systems, Minneapolis, MN), measured from standard curve Collected between 0800-1000 before breakfast into heparinised tubes	.	100	↓	.	.

Study	Sample	Age (SD)	N	%	Treatment	Weeks	Design	Control	Scale	Assay					
	DSM-IV MDD (first episode) – treatment non-responder group	40 (9)	42	20	Clinician decided: SSRI or SNRI	8	Pre-test-post-test	✓ (N = 30) IL-6 higher in depression than control group	Ham-D	Plasma, quantitative sandwich ELISA (R & D Systems, MN) Collected between 0800-1000 before breakfast, heparinised tubes	.	0	→	.	.
Chen et al 2010	Inpatients, DSM-IV MDD (first episode), BMI ≤ 25, 20-25 years	23.3 (2.6)	100	43	Maprotil-ine, fluoxetine, venlafax-ine, mirtazap-ine (titrated).	4	RCT (maprotiline vs. fluoxetine vs. venlafaxine vs. mirtazapine) Note: results were reported as a whole group, not these subgroups.	✗	Ham-D	CRP: Latex hs-assay (Roche Diagnostics GmbH, Mannheim, Germany) IL-6: hs-ELISA (Diaclone Research, Besancon Cedex, France) 10 hr fast, serum/plasma *	↓	.	↑	→	.

Jazayeri et al 2010	DSM-IV MDD – fluoxetine group	37 (8.5)	29	14	Fluoxetine (20mg)	8	RCT (fluoxetine vs. EPA vs.fluoxetine + EPA)	×		Ham-D	Serum, ELISA (Bender MedSystems, Austria) Fasting, collected at 0800	.	.	→	.
Fornaro et al 2011	DSM-IV MDD via SCID	51.1 (11)	25	16	Duloxetine (60mg)	6	Pre-test-post-test	✓ (N = 16) Non-depressed control group also received antidepressant treatment. IL-6 no different between depression and control group at baseline or follow-up.	SCID, Ham-D	Serum, ELISA (Bender MedSystems, Burlingame, CA) Collected between 0730 – 1000	↓	56	→	.

[+]people in the study who received antidepressants after drop outs/non-measurement.

[++]whole sample, not subset who completed treatment.

<u>Key</u>:

✓ present

× absent

↓ significant decrease after antidepressant treatment

↑ significant increase after antidepressant treatment

→ no significant change after antidepressant treatment

. measurements not reported

Abbreviations:

BDI: Beck Depression Inventory

BMI: body mass index

CCMD: Chinese Classification of Mental Disorders

CDS: Carroll Depression Scale

CIDI: Composite International Diagnostic Interview

CRP: C-reactive protein

Dep: depression

DSM: Diagnostic and Statistical Manual

EA: electroacupuncture

ELISA: enzyme-linked immunosorbent assay

EPA: eicosapentaenoic acid

Ham-D: Hamilton Rating Scale for Depression

hs: high sensitivity

ICD: International Classification of Diseases

IL: interleukin

MADRS: Montgomery–Åsberg Depression Rating Scale

MINI: Mini-International Neuropsychiatric Interview

MDD: major depressive disorder

Resp: responders (>50% reduction in depressive symptoms)

RCT: randomised controlled trial

SCID: Structured Clinical Interview for the Diagnostic and

Statistical Manual

SF-36: Short Form 36 Health Survey

SNRI: serotonin-norephinephrine reuptake inhibitor

SSRI: selective serotonin reuptake inhibitor

T3: tri-iodothyronine

Most of the included studies had similar exclusion criteria: excluding people with DSM-IV axis I disorders besides major depressive episodes or dysthymic disorder ($n = 12$; except Sluzewska et al. (1997) who additionally included people with a lifetime diagnosis bipolar disorder in a current depressive episode), people on psychotropic medication in the two weeks before blood collection ($n = 22$), people with general medical illness ($n = 15$), people with recent allergic reactions ($n = 7$) and pregnant women ($n = 7$). The study where patients had stable coronary heart disease were not acutely ill and had been stable on medication (Pizzi et al., 2009). Most studies collected blood in the morning.

Interleukin-6 and C-reactive protein

Although in two studies, administration of the serotonin reuptake inhibitor (SSRI) fluoxetine resulted in no significant change in IL-6 (Jazayeri et al., 2010) or CRP over multiple time-points (Mackay, et al., 2009), most of the remaining studies that administered SSRIs reported significant reductions in IL-6 or CRP, including other studies of fluoxetine (significant reduction only observed in people with elevated IL-6 at baseline) (Sluzewska, et al., 1995), sertraline (Leo, et al., 2006; Pizzi, et al., 2009) and citalopram (Leo, et al., 2006).

Few studies examined non-SSRI antidepressants. No significant changes in IL-6 were observed in studies administering a serotonin-norepinephrine reuptake inhibitor (duloxetine) (Fornaro, Martino, Battaglia, Colicchio, & Perugi, 2011), nor a serotonin antagonist and reuptake inhibitor (trazodone) either alone or augmented with pindodol (Maes et al., 1997). Significant reductions in CRP were observed after

administration of the tricyclic antidepressant, amitriptyline, in people with and without 50% reductions in depressive symptoms (treatment responders and non-responders, respectively) (Lanquillon, Krieg, Bening-Abu-Shach, & Vedder, 2000). People with higher levels of CRP after treatment also recorded significantly higher levels of trait anxiety than people with lower levels of CRP. Finally, Chen et al. (2010) reported a significant increase in IL-6, but no change in CRP, in young, normal weight males who were maintained on a strict diet with restricted alcohol and coffee intake while in an inpatient facility. While participants were randomized to four different SSRI and non-SSRI antidepressant conditions, the authors only reported summary statistics for the entire study sample, as the increase in IL-6 was comparable across conditions. The authors reported an increase in weight in two of the four conditions which while not statistically significant, may still be clinically meaningful in contributing to elevated IL-6.

In the remaining studies, a clinician decided case-by-case which antidepressant was administered. In the two studies where clinicians were unrestricted in their choice of antidepressant, neither demonstrated a significant change in IL-6 (Kagaya et al., 2001; Kubera, et al., 2000). No significant change in IL-6 was observed in two studies where participants were administered either a tricyclic antidepressant or a particular SSRI [fluoxetine (Maes et al., 1995) or paroxetine (Mikova, Yakimova, Bosmans, Kenis, & Maes, 2001)]. However, significant decreases were observed in IL-6 and CRP after administration of various other antidepressants from SSRI classes (Basterzi et al., 2005; O'Brien, Scott, & Dinan, 2006; Tuglu et al.,

2003). In contrast, Dawood et al. (2007) demonstrated a significant increase in CRP, with only 5 from 24 patients recording a decrease in CRP after treatment. Two studies that selected from SSRI and serotonin-norepinephrine reuptake inhibitors also reported significant reductions in IL-6, but not for treatment non-responders (Yao et al., 2004; Yoshimura, et al., 2009). Sluzewska et al. (1997) also reported a significant reduction in CRP for both treatment responders and non-responders in participants with a refractory major depressive episode receiving various antidepressants and lithium carbonate. Neither change in depressive symptoms nor change in CRP differed significantly between people with lifetime bipolar disorder or major depressive disorder admitted to the study during a depressive episode.

Interleukin-10

No significant changes in IL-10 were observed after administration of fluoxetine, although levels were initially lower than controls (Song, Halbreich, Han, Leonard, & Luo, 2009). The remaining studies reported that initially elevated levels of IL-10 reduced over treatment to a level below the controls at baseline (Hernandez, et al., 2008; Kubera, et al., 2000). Additionally, Hernandez et al. (2008) reported that while IL-10 measurements at 5, 20, 36 and 52 weeks showed decreasing trend, participants reached clinical remission for depression by 20 weeks.

Antidepressants vs. non-antidepressant treatment conditions

There were only two RCTs with placebo treatment arms. Pizzi et al. (2009) found no change in IL-6 or CRP after 20 weeks of placebo treatment. Furthermore, treatment with sertraline led to significant reductions in IL-6 and CRP compared to

placebo at follow-up (between-subjects IL-6 d = -0.74, 95% CI [-1.16, -0.32]; CRP d = -1.00, 95% CI [-1.43, -0.56]). Song et al. (2009) also showed no significant decline in IL-10 after placebo treatment; however, there was no significant difference in IL-10 between placebo and active treatment groups at follow-up, as IL-10 did not significantly decline in the active treatment groups (fluoxetine and sham electroacupuncture or anti-depression sequence of electroacupuncture and placebo capsules). The null result may possibly be due to non-specific treatment effects of sham electroacupuncture. In both studies, there was no significant decline in depressive symptoms in the placebo treatments, but significant declines in the active treatments.

Two studies randomized participants to antidepressants and other anti-depressive treatments. Neither study showed that IL-6 or CRP significantly declined within the active treatment groups over time nor significantly differed between the active treatment groups at follow-up (IL-6 after treatment with fluoxetine, eicosapentaenoic acid and fluoxetine and eicosapentaenoic acid combined for Jazayeri et al. (2010); and CRP after treatment with fluoxetine, fluoxetine with tri-iodothyronine and counselling groups for Mackay et al. (2009)). One final study treated a depressed and non-depressed control group with duloxetine, and found that IL-6 did not change in either group, although depressive symptoms declined in the depressed but not the control group (Fornaro, et al., 2011).

Meta-analysis

Firstly, we examined whether depression significantly declined over the course of antidepressant treatment. Several studies were excluded from this analysis as they did not report sufficient information (Jazayeri, et al., 2010; Mikova, et al., 2001; O'Brien, et al., 2006; Sluzewska, et al., 1995; Sluzewska, et al., 1997; Yoshimura, et al., 2009). Meta-analysis of the depression severity scores (chiefly the Hamilton Rating Scale for Depression; Hamilton, 1960) revealed a significant decrease in the studies which investigated IL-6 (N = 10, d = -1.82, 95% CI [-2.36, -1.28], I^2 = 85.4), CRP (N = 7, d = -1.93, 95% CI [-2.59, -1.27], I^2 = 90.1%) and IL-10 (N = 3, d = -4.77, 95% CI [-8.13, -1.41], I^2 = 92.0%).

Secondly, we analysed changes in inflammatory markers after antidepressant treatment. Meta-analysis revealed a significant decrease in IL-6 (N = 14, d = -0.42, 95% CI [-0.78, -0.06], Z = 2.30, p = .02, Figure 2). There was a marginally significant decrease in CRP (N = 8, d = -0.57, 95% CI [-1.140, 0.005], Z = 1.94, p = 0.052, Figure 3). In both instances, there was high heterogeneity (IL-6: I^2 = 88.2%, Q(13) = 110.23, p < .001; CRP: I^2 = 93.2%, Q(7) = 103.66, p < .001). There was no evidence of publication bias via Egger's test (IL-6: t(13) = 0.42, p = .68; CRP: t(7) = 1.53, p = .24). The fail safe N was 148 for IL-6, which means 148 extra studies would be required to bring the p value to greater than .05. Fail safe N was 82 for CRP. Based on the very few studies and a fail-safe N calculation of 5, the meta-analysis for IL-10 should be considered exploratory and considered a description of currently available data, rather than a true representation of the effect. There was a non-
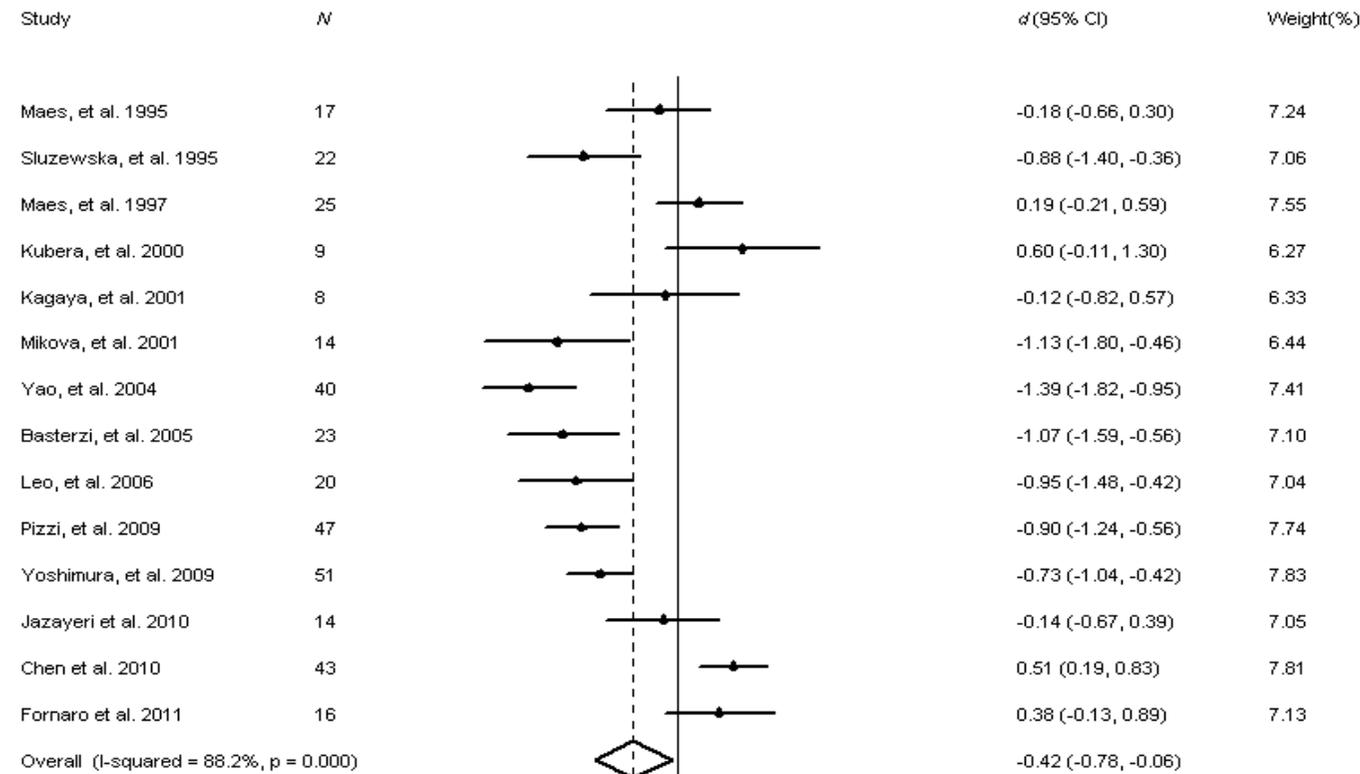
significant decrease in IL-10 following antidepressant treatment ($N = 3$, $d = $-0.45, 95% CI [-1.03, 0.14], Z = 1.49, $p = $.14, Figure 4). Significantly high heterogeneity was also observed, $I^2 = $ 77.3%, $Q(2) = $ 8.81, $p = $ .01. There was no significant publication bias according to Egger's test although this test lacks power when there are few studies, $t(2) = $ 0.76, $p = $ .59. Sensitivity analyses revealed no extreme influence of any single study in the IL-6, CRP or IL-10 analyses.

Moderator analysis

Moderator analysis was completed on the IL-6 and CRP studies (no analysis was undertaken for IL-10 as there were too few studies). Table 3.2 shows the results of random effects analysis on smaller subgroups of the included studies (whether or not a formal diagnosis was completed, whether it was a uniform or tailored antidepressant administration, whether participants were inpatients or outpatients, and IL-6 assay brand). Only the subgroup of outpatients for IL-6 resulted in a strong significant pooled effect size ($p < $ .01), recording a larger effect size than in the overall meta-analysis. There was no substantial reduction in I^2 in each subgroup, suggesting that none of these factors alone were responsible for the heterogeneity. Meta-regression compared the standardized changes in IL-6 or CRP and continuous variables of standardized change in depression severity score, weeks in treatment, age, percentage males, and percentage of responders, for studies in which these variables were reported. Meta-regression revealed significant, positive associations between standardized change in IL-6 and percentage of males ($N = $ 17, $\beta = $ -0.02, SE =

0.006, b = -1.12, p = .03). No other associations were significant (p > .05). Finally,

meta-regression of the standardized change in depressive symptoms against the

baseline levels of IL-6 and CRP showed a negative, although non-significant,

relationship (IL-6: N = 10, β = -0.14, SE = 0.15, b = -1.44, p = .39; CRP: N = 6, β = -0.26,

SE = 0.25, b = -1.58, p = .35).

| Study	N		d (95% CI)	Weight(%)
Maes, et al. 1995	17		-0.18 (-0.66, 0.30)	7.24
Sluzewska, et al. 1995	22		-0.88 (-1.40, -0.36)	7.06
Maes, et al. 1997	25		0.19 (-0.21, 0.59)	7.55
Kubera, et al. 2000	9		0.60 (-0.11, 1.30)	6.27
Kagaya, et al. 2001	8		-0.12 (-0.82, 0.57)	6.33
Mikova, et al. 2001	14		-1.13 (-1.80, -0.46)	6.44
Yao, et al. 2004	40		-1.39 (-1.82, -0.95)	7.41
Basterzi, et al. 2005	23		-1.07 (-1.59, -0.56)	7.10
Leo, et al. 2006	20		-0.95 (-1.48, -0.42)	7.04
Pizzi, et al. 2009	47		-0.90 (-1.24, -0.56)	7.74
Yoshimura, et al. 2009	51		-0.73 (-1.04, -0.42)	7.83
Jazayeri et al. 2010	14		-0.14 (-0.67, 0.39)	7.05
Chen et al. 2010	43		0.51 (0.19, 0.83)	7.81
Fornaro et al. 2011	16		0.38 (-0.13, 0.89)	7.13
Overall (I-squared = 88.2%, p = 0.000)			-0.42 (-0.78, -0.06)	

NOTE: Weights are from random effects analysis

-3 -2 -1 0 1 2 3

d (95% CI)

Figure 2. Forest plot for change in IL-6 after antidepressant treatment including study name identifier, total number of participants, the standardized paired difference in IL-6 (d, 95% CI) and the relative weight that each study contributes to the overall pooled estimate of effect. The diamond at the bottom of the effect size plot represents the overall pooled effect size for standardized change in IL-6 (d, 95% CI) and the I^2 measure of heterogeneity. Negative effect sizes represent a decrease in IL-6 following antidepressant treatment.
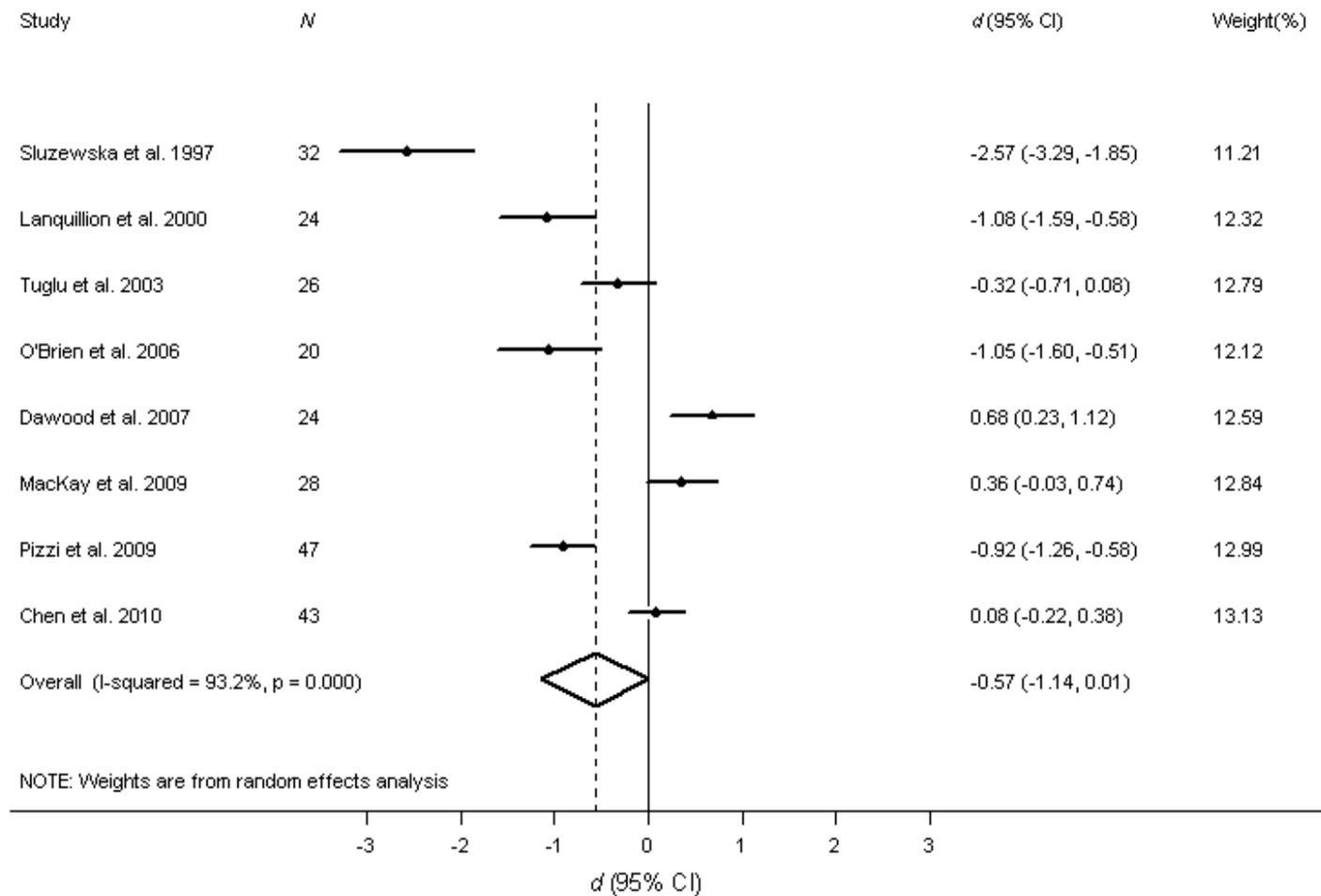
Figure 3. Forest plot for change in CRP after antidepressant treatment, details as per Figure 2.
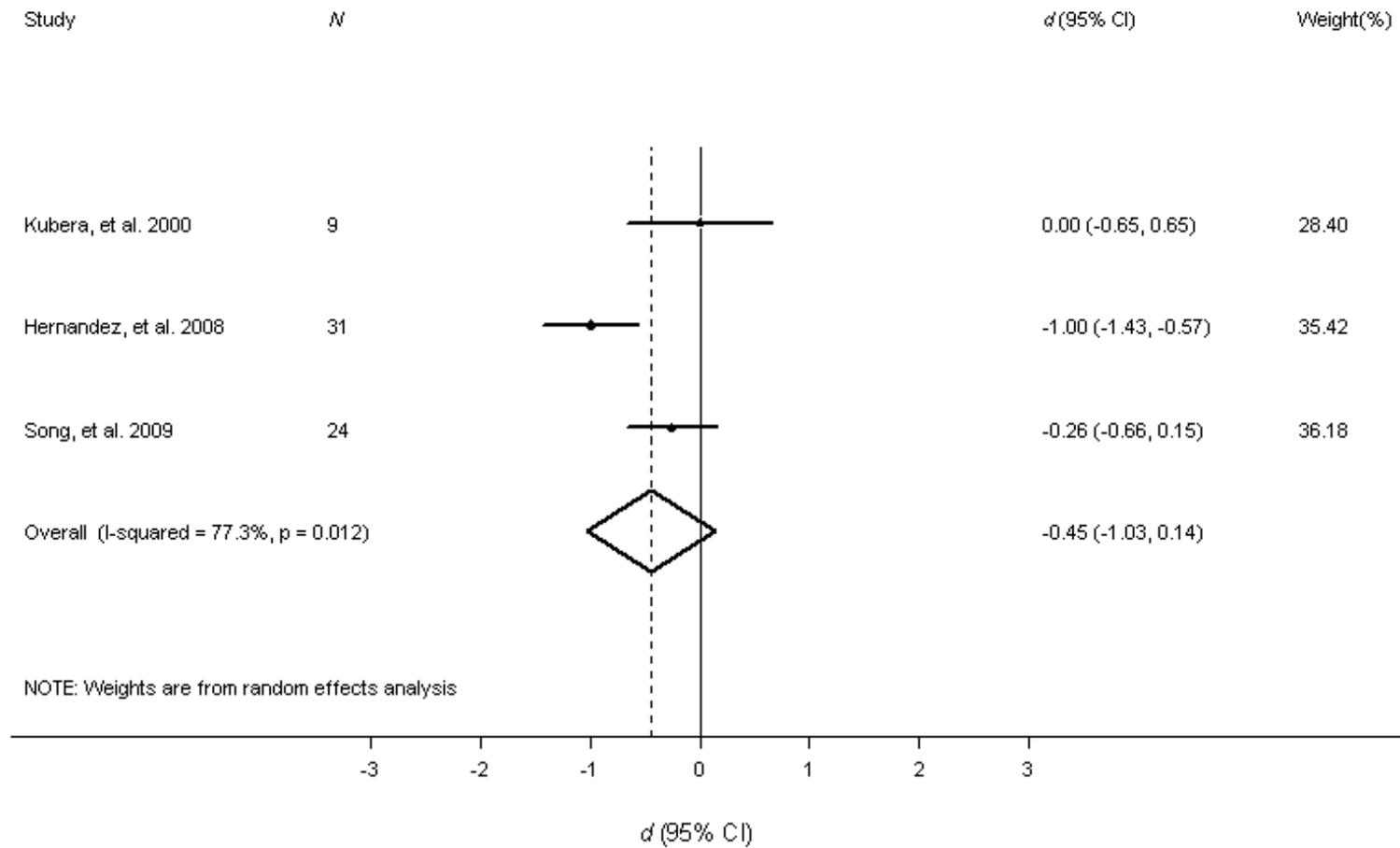
Figure 4. Forest plot for change in IL-10 after antidepressant treatment, details as per Figure 2

Table 2. Cohen's d (95% CI) pooled effect sizes under a random effects model in CRP or IL-6 following antidepressant treatment for subgroups of studies wi meta-analysis, with k number of studies and I^2 measure of heterogeneity.

	Subgroup	k	Effect size (d)	95% CI
IL-6				
	Overall	14	-0.42*	-0.78, -0.06
Formal diagnosis				
	Yes	13	-0.41*	-0.79, -0.04
	No	1	-0.90***	-1.24, -0.56
Treatment type				
	Clinical decision	8	-0.50*	-0.96, -0.04
	Uniform administration	6	-0.32	-0.91, 0.27
Patient type				
	Inpatient	7	-0.32	-0.93, 0.29
	Outpatient	7	-0.53**	-0.90, -0.16
CRP				
	Overall	8	-0.57	-1.14, 0.01
Formal diagnosis				
	Yes	7	-0.52	-1.56, 0.12
	No	1	-0.92***	-1.26, -0.58
Treatment type				
	Clinical decision	2	-0.66	-1.38, 0.06
	Uniform administration	5	-0.78	-1.58, 0.01
Patient type				
	Inpatient	4	-0.93*	-1.85, -0.003
	Outpatient	3	-0.53	-1.44, 0.38

* p < .05; ** p < .01; *** p < .001 (based on a single study)

Discussion

This study is the first to provide pooled estimates of the change in resting, circulating IL-6, CRP and IL-10 in people with depression after antidepressant treatment. Meta-analysis indicated that after various antidepressant treatment durations there was a significant pooled reduction in IL-6, marginally significant reduction in CRP, and non-significant decrease in IL-10. There was good support for the reliability of the pooled reduction in IL-6 and CRP, with no evidence of publication bias and a high fail safe N, meaning it would take many unpublished, or yet to be published, studies to negate this pooled estimate. The few studies and low fail safe N for the IL-10 meta-analysis means that this observed pooled reduction should be interpreted with caution and considered preliminary. There was high heterogeneity in all the pooled estimates that could not be explained by meta-regression and subgroup analysis. Narrative review identified several issues which may help clarify unexplained sources of heterogeneity regarding comorbidity and individual differences.

In cross sectional studies, levels of IL-6, CRP and IL-10 are elevated in people with high compared to low depressive symptoms (Dowlati, et al., 2010; Howren, et al., 2009). It is fitting that these inflammatory markers decrease as depressive symptoms decrease in association with antidepressant treatment. There may be a difference in the sensitivity of CRP and IL-6 for recording a change after treatment, with some studies demonstrating a change in IL-6 but not CRP (Chen, et al., 2010)

and the pooled decrease only marginally significant for CRP. Nevertheless, the association between antidepressant treatment and reduction in inflammatory markers was demonstrated with different antidepressants, in a depressive episode irrespective of lifetime diagnoses of major depressive disorder or bipolar disorder (Sluzewska, et al., 1997), and to a limited extent, over time (Hernandez, et al., 2008; Kubera, et al., 2000; Mackay, et al., 2009).

IL-6, CRP and IL-10 play a regulatory role in the acute phase of inflammation, with IL-6 and CRP being primarily pro-inflammatory and IL-10 being inhibitory (Gabay & Kushner, 1999; Moore, de Waal Malefyt, Coffman, & O'Garra, 2001), yet the role of each of these markers in depression is unclear. Indeed, there may be a problem in balancing pro- and anti-inflammatory agents, and the relative concentrations of the pro- and anti-inflammatory markers may be more important than the absolute levels. At a broad level, elevations in pro- and anti-inflammatory markers during depressive illness may represent a generalized over-activation of the inflammatory system during the acute emotional state, which normalizes following alleviation of depressive symptoms. This is supported in studies which showed no significant difference between levels of inflammatory markers in the depression group post-treatment and in the healthy control group (Yao, et al., 2004). However, the relationship between depression and inflammatory markers over time is not necessarily linear. For example, the longest study with multiple measurements demonstrated constant reductions in IL-10 at weeks 5, 20, 36 and 52, although depressive symptoms remained relatively consistent from week 20 (Hernandez, et al.,

2008). These results require replication due to the methodological limitations of this study, including that only 35% of participants were retained by 52 weeks.

Although no outliers were detected and there was no evidence of publication bias for the IL-6 and CRP meta-analyses, there are limitations to the interpretation of these pooled effect sizes. Firstly, it is likely that the magnitude of the decrease in these inflammatory markers is slightly inflated due to regression to the mean (Bland & Altman, 1994). This problem is characteristic of single group pre-test-post-test designs, highlighting the need for further placebo-controlled RCTs. The available placebo-capsule RCT demonstrated that sertraline use was superior to placebo at reducing inflammatory markers (Pizzi, et al., 2009). Furthermore, the high levels of heterogeneity observed in each meta-analysis make interpreting the overall pooled estimates difficult. This level of heterogeneity was expected because liberal inclusion criteria were employed to maximally canvass the literature. The liberal inclusion criteria are both a weakness and strength of this meta-analysis. While studies of low methodological quality and studies with diverse samples were included, it has also identified potential sources of heterogeneity to be considered in future research.

The main drivers of the high heterogeneity in the IL-6 and CRP data were not identified using subgroup analysis or meta-regression. This implies that there is likely a cumulative effect of patient characteristics on the degree of change in pro-inflammatory markers, and factors not reported in the primary studies that may more precisely account for unexplained heterogeneity. For instance, many studies lacked potentially useful prognostic information, such as compliance information, to consider

whether declines are associated with the biochemical effects of antidepressants compared to decline in depressive symptoms over time. In the subgroup analyses, the only highly significant effect size was for IL-6 in outpatients, which only slightly decreased the level of heterogeneity and generated a slightly larger pooled decrease in IL-6. The only significant positive linear association in the meta-regression analyses was that having fewer males in a study was associated with a larger standardized decrease in IL-6. The reason for this is unclear but may be because females tend to have higher response rates to particular antidepressant treatments (particularly SSRIs) in clinical trials (Khan, Brodhead, Schwartz, Kolts, & Brown, 2005).

Narrative review identified several other potential sources of heterogeneity in comorbidity and individual differences. Changes in weight variables were rarely reported despite the comorbidity between depression and obesity, and the relationship between antidepressant use and weight gain (Evans et al., 2005; Serretti & Mandelli, 2010). Studies which recorded an increase in IL-6 indicated that there were increases in fat distribution (Chen, et al., 2010), and adiposity is significantly associated with inflammatory changes, particularly increases in IL-6 (Park, Park, & Yu, 2005). Furthermore, people with higher levels of CRP after treatment had significantly higher levels of trait anxiety than people with lower levels of CRP (Lanquillon, et al., 2000). This finding may explain continued elevations in CRP or IL-6 in other studies which often fail to measure anxiety, despite its high comorbidity with depression (Rush et al., 2005) and independent association with inflammatory markers (O'Donovan et al., 2010).

Major depressive disorder is a clinically heterogeneous disorder and these differences may extend to differences in inflammation. Sluzewska et al. (1995) highlighted that only certain people with depression may exhibit elevated levels of IL-6, and only these people decreased their levels of IL-6. Disregarding issues of regression to the mean, this study highlights that certain people with depression may be more susceptible to elevations in pro-inflammatory markers. For instance, some research suggests that people with depression with melancholic features may exhibit a different inflammatory profile to those without melancholic features (Rothermundt et al., 2001). Depression with melancholic features is associated with a decrease in CRP in serum following treatment (O'Brien, et al., 2006) and there are indications that levels of stimulated cytokines decline in melancholic but not other depression (Rothermundt, et al., 2001), implying that perhaps the inflammatory state is more closely associated with organic rather than cognitive symptoms of depression.

Furthermore, there is a possibility that baseline levels of inflammatory markers may identify those who may respond to treatment. Meta-regression in the current review showed no significant association between baseline IL-6 or CRP and change in depressive symptoms, although the pattern across studies was that higher baseline IL-6 and CRP were related to larger decreases in depressive symptoms. In individual studies, there is evidence in support of this, with higher baseline levels of CRP in treatment responders (Sluzewska, et al., 1997), and evidence to the contrary that lower stimulated levels of IL-6 at baseline (but not baseline serum CRP) in treatment responders compared to non-responders (Lanquillon, et al., 2000).

Additionally, meta-regression showed no significant relationship between percentage of individuals who responded to treatment and inflammatory marker change, perhaps because it was infrequently reported and thus the meta-regression was restricted in range. At the individual study level, there was evidence of decreases in IL-6 for treatment responders, but not treatment non-responders (Yoshimura, et al., 2009), although two studies demonstrated a significant decrease in inflammatory markers in both responders and non-responders (people with and without a 50% reduction in depression, respectively) (Lanquillon, et al., 2000; Sluzewska, et al., 1997). It is possible that even with small decreases in depressive symptoms, substantial changes to inflammatory markers may occur. Future studies should verify whether differences exist in inflammatory marker change and baseline inflammatory markers for treatment responders and non-responders, to support whether improvement in depressive symptoms is associated with a normalization of inflammatory markers and provide evidence for whether inflammatory markers can act as a biomarker of treatment response.

On the whole, the evidence presented in this meta-analysis is consistent with the inflammation theory of depression; with a reduction in depressive symptoms, there is a co-occurring reduction in inflammatory markers. At an illustrative level, these data support the idea that the causal chain is "depression driving inflammation", because treatment for depression also has the capacity to change inflammatory markers. Yet at the same time, antidepressants may have a direct anti-inflammatory effect, thus potentially causing the reductions in depressive mood. In

vitro studies demonstrate that administration of antidepressants, particularly SSRIs, produces anti-inflammatory effects in the blood of both people with depression and healthy volunteers, decreasing pro-inflammatory markers including IL-6, IL-8 and tumor necrosis factor and increasing anti-inflammatory markers including IL-10 (Janssen, Caniato, Verster, & Baune, 2010; Kenis & Maes, 2002). The observed anti-inflammatory effects may occur through antidepressants increasing glucocorticoid receptor-mediated negative feedback of the hypothalamic-pituitary-adrenal axis or increasing intracellular cyclic adenosine monophosphate (for reviews see Carvalho, Garner, Dew, Fazakerley, & Pariante, 2010; Carvalho & Pariante, 2008; Janssen, et al., 2010; Maes, 2001). Alternatively, studies into the effect of anti-inflammatory medications on depressive symptoms would provide evidence for the "inflammation driving depression" causal chain, and if supported the idea of an underlying common cause would be persuasive. To further explore the directionality, more longitudinal and prospective measurement of depression and inflammatory markers is necessary. It would also be of benefit to investigate changes in other immunomarkers after antidepressant treatment to provide the context of the changes in the few inflammatory markers reported in this study, as cross sectional evidence suggests that depression is associated with many markers of cell-mediated immune activation (Zorrilla, et al., 2001).

References

Basterzi, A. D., Aydemir, C., Kisa, C., Aksaray, S., Tuzer, V., Yazici, K., et al. (2005). IL-6 levels decrease with SSRI treatment in patients with major depression. *Human Psychopharmacology, 20*(7), 473-476.

Bland, J. M., & Altman, D. G. (1994). Statistics notes: Some examples of regression towards the mean. *British Medical Journal, 309*(6957), 780.

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2009). *Introduction to Meta-analysis.* Chichester: John Wiley & Sons, Ltd.

Bossola, M., Ciciarelli, C., Di Stasio, E., Conte, G. L., Vulpio, C., Luciani, G., et al. (2010). Correlates of symptoms of depression and anxiety in chronic hemodialysis patients. *General Hospital Psychiatry, 32*(2), 125-131.

Carvalho, L. A., Garner, B. A., Dew, T., Fazakerley, H., & Pariante, C. M. (2010). Antidepressants, but not antipsychotics, modulate GR function in human whole blood: An insight into molecular mechanisms. *European Neuropsychopharmacology, 20*(6), 379-387.

Carvalho, L. A., & Pariante, C. M. (2008). In vitro modulation of the glucocorticoid receptor by antidepressants. *Stress: The International Journal on the Biology of Stress, 11*(6), 411-424.

Chen, Y.-C., Lin, W.-W., Chen, Y.-J., Mao, W.-C., & Hung, Y.-J. (2010). Antidepressant effects on insulin sensitivity and proinflammatory cytokines in the depressed males. *Mediators of Inflammation, epub, vol. 2010* (http://www.hindawi.com/journals/mi/2010/573594/).

Dawood, T., Lambert, E. A., Barton, D. A., Laude, D., Elghozi, J. L., Esler, M. D., et al. (2007). Specific serotonin reuptake inhibition in major depressive disorder adversely affects novel markers of cardiac risk. *Hypertension Research, 30*(4), 285-293.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., et al. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry, 67*(5), 446-457.

Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal, 315*(7109), 629-634.

Evans, D. L., Charney, D. S., Lewis, L., Golden, R. N., Gorman, J. M., Krishnan, K. R. R., et al. (2005). Mood disorders in the medically ill: Scientific review and recommendations. *Biological Psychiatry, 58*(3), 175-189.

Fornaro, M., Martino, M., Battaglia, F., Colicchio, S., & Perugi, G. (2011). Increase in IL-6 levels among major depressive disorder patients after a 6-week treatment with duloxetine 60 mg/day: A preliminary observation. *Neuropsychiatric Disease and Treatment, 7*, 51-56.

Gabay, C., & Kushner, I. (1999). Acute-phase proteins and other systemic responses to inflammation. *New England Journal of Medicine, 340*, 448-454.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry, 23*(1), 56-62.

Hernandez, M. E., Mendieta, D., Martinez-Fong, D., Loria, F., Moreno, J., Estrada, I., et al. (2008). Variations in circulating cytokine levels during 52 week course of

treatment with SSRI for major depressive disorder. *European Neuropsychopharmacology, 18*(12), 917-924.

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *British Medical Journal, 327*(7414), 557-560.

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosomatic Medicine, 71*, 171-186.

Irwin, M. R., & Miller, A. H. (2007). Depressive disorders and immunity: 20 years of progress and discovery. *Brain, Behavior, and Immunity, 21*, 374-383.

Janssen, D. G. A., Caniato, R. N., Verster, J. C., & Baune, B. T. (2010). A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. *Human Psychopharmacology, 25*(3), 201-215.

Jazayeri, S., Keshavarz, S. A., Tehrani-Doost, M., Djalali, M., Hosseini, M., Amini, H., et al. (2010). Effects of eicosapentaenoic acid and fluoxetine on plasma cortisol, serum interleukin-1beta and interleukin-6 concentrations in patients with major depressive disorder. *Psychiatry Research, 178*(1), 112-115.

Kagaya, A., Kugaya, A., Takebayashi, M., Fukue-Saeki, M., Saeki, T., Yamawaki, S., et al. (2001). Plasma concentrations of interleukin-1beta, interleukin-6, soluble interleukin-2 receptor and tumor necrosis factor alpha of depressed patients in Japan. *Neuropsychobiology, 43*(2), 59-62.

Kenis, G., & Maes, M. (2002). Effects of antidepressants on the production of cytokines. *International Journal of Neuropsychopharmacology, 5*, 401-142.

Khan, A. M. D., Brodhead, A. E. M. S., Schwartz, K. A. M. S., Kolts, R. L. P., & Brown, W. A. M. D. (2005). Sex Differences in Antidepressant Response in Recent Antidepressant Clinical Trials. *Journal of Clinical Psychopharmacology, 25*(4), 318-324.

Kubera, M., Kenis, G., Bosmans, E., Zieba, A., Dudek, D., Nowak, G., et al. (2000). Plasma levels of interleukin-6, interleukin-10, and interleukin-1 receptor antagonist in depression: Comparison between the acute state and after remission. *Polish Journal of Pharmacology, 52*(3), 237-241.

Lanquillon, S., Krieg, J. C., Bening-Abu-Shach, U., & Vedder, H. (2000). Cytokine production and treatment response in Major Depressive Disorder. *Neuropsychopharmacology, 22*, 370-379.

Leo, R., Di Lorenzo, G., Tesauro, M., Razzini, C., Forleo, G. B., Chiricolo, G., et al. (2006). Association between enhanced soluble CD40 ligand and proinflammatory and prothrombotic states in major depressive disorder: Pilot observations on the effects of selective serotonin reuptake inhibitor therapy. *Journal of Clinical Psychiatry, 67*(11), 1760-1766.

Lindqvist, D., Janelidze, S., Hagell, P., Erhardt, S., Samuelsson, M., Minthon, L., et al. (2009). Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biological Psychiatry, 66*(3), 287-292.

Mackay, G. M., Forrest, C. M., Christofides, J., Bridel, M. A., Mitchell, S., Cowlard, R., et al. (2009). Kynurenine metabolites and inflammation markers in depressed patients

treated with fluoxetine or counselling. *Clinical and Experimental Pharmacology and Physiology, 36*(4), 425-435.

Maes, M. (2001). The immunoregulatory effects of antidepressants. *Human Psychopharmacology: Clinical and Experimental, 16*(1), 95-103.

Maes, M., Bosmans, E., De Jongh, R., Kenis, G., Vandoolaeghe, E., & Neels, H. (1997). Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine, 9*, 853-858.

Maes, M., Meltzer, H. Y., Bosmans, E., Bergmans, R., Vandoolaeghe, E., Ranjan, R., et al. (1995). Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. *Journal of Affective Disorders, 34*(4), 301-309.

Maes, M., Yirmyia, R., Noraberg, J., Brene, S., Hibbeln, J., Perini, G., et al. (2009). The inflammatory and neurodegenerative hypothesis of depression: Leads for future research and new drug developments in depression. *Metabolic Brain Disease, 24*, 27-53.

Mikova, O., Yakimova, R., Bosmans, E., Kenis, G., & Maes, M. (2001). Increased serum tumor necrosis factor alpha concentrations in major depression and multiple sclerosis. *European Neuropsychopharmacology, 11*(3), 203-208.

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biological Psychiatry, 65*(6), 732-741.

Moore, K. W., de Waal Malefyt, R., Coffman, R. L., & O'Garra, A. (2001). Interleukin-10 and the interleukin-10 receptor. *Annual Review of Immunology, 19*(1), 683-765.

O'Brien, S. M., Scott, L. V., & Dinan, T. G. (2006). Antidepressant therapy and C-reactive protein levels. *British Journal of Psychiatry, 188*, 449-452.

O'Donovan, A., Hughes, B. M., Slavich, G. M., Lynch, L., Cronin, M.-T., O'Farrelly, C., et al. (2010). Clinical anxiety, cortisol and interleukin-6: Evidence for specificity in emotion-biology relationships. *Brain, Behavior, and Immunity, 24*(7), 1074-1077.

Park, H. S., Park, J. Y., & Yu, R. (2005). Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-a and IL-6. *Diabetes Research and Clinical Practice, 69*, 29-35.

Pizzi, C., Mancini, S., Angeloni, L., Fontana, F., Manzoli, L., & Costa, G. M. (2009). Effects of selective serotonin reuptake inhibitor therapy on endothelial function and inflammatory markers in patients with coronary heart disease. *Clinical Pharmacology & Therapeutics, 86*(5), 527-532.

Pudar Hozo, S., Djulbegovic, B., & Hozo, I. (2005). Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology, 5*(13).

Rosenthal, R. (1979). The file drawer problem and tolerance for null results. *Psychological Bulletin, 86*(3), 638-641.

Rothermundt, M., Arolt, V., Fenker, J., Gutbrodt, H., Peters, M., & Kirchner, H. (2001). Different immune patterns in melancholic and non-melancholic major depression. *European Archives of Psychiatry and Clinical Neuroscience, 251*(2), 90-97.

Rush, A. J., Zimmerman, M., Wisniewski, S. R., Fava, M., Hollon, S. D., Warden, D., et al. (2005). Comorbid psychiatric disorders in depressed outpatients: Demographic and clinical features. *Journal of Affective Disorders, 87*(1), 43-55.

Serretti, A., & Mandelli, L. (2010). Antidepressants and body weight: A comprehensive review and meta-analysis. *Journal of Clinical Psychiatry, 71*(10), 1259-1272.

Sluzewska, A., Rybakowski, J. K., Laciak, M., Mackiewicz, A., Sobieska, M., & Wiktorowicz, K. (1995). Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. *Annals of the New York Academy of Sciences, 762*, 474-476.

Sluzewska, A., Sobieska, M., & Rybakowski, J. K. (1997). Changes in acute-phase proteins during lithium potentiation of antidepressants in refractory depression. *Neuropsychobiology, 35*(3), 123-127.

Song, C., Halbreich, U., Han, C., Leonard, B. E., & Luo, H. (2009). Imbalance between pro- and anti-inflammatory cytokines, and between Th1 and Th2 cytokines in depressed patients: the effect of electroacupuncture or fluoxetine treatment. *Pharmacopsychiatry, 42*(5), 182-188.

Tuglu, C., Kara, S. H., Caliyurt, O., Vardar, E., Abay, E., Tuglu, C., et al. (2003). Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacology, 170*(4), 429-433.

Tummers, B., van der Laan, J., & Huyser, K. (2008). Data Thief III. 1.5. from www.datathief.org

Yao, H., Tao, L.-G., Zhang, X.-B., Sha, W.-W., Hou, G., & Zhang, Z.-J. (2004). Variety of cell-mediated immunity and the metabolic products of monoamine neural transmitter in depression patients before and after therapy. *Chinese Journal of Clinical Rehabilitation, 8*(15), 2978-2979.

Yoshimura, R., Hori, H., Ikenouchi-Sugita, A., Umene-Nakano, W., Ueda, N., & Nakamura, J. (2009). Higher plasma interleukin-6 (IL-6) level is associated with SSRI- or SNRI-refractory depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 33*(4), 722-726.

Zorrilla, E. P., Luborsky, L., McKay, J. R., Rosenthal, R., Houldin, A., Tax, A., et al. (2001). The relationship of depression and stressors to immunological assays: A meta-analytic review. *Brain, Behavior and Immunity, 15*, 199-226.