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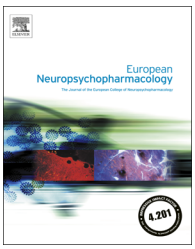

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REVIEW

Inflammation and clinical response to treatment in depression: A meta-analysis

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Abstract
The depressive state has been characterised as one of elevated inflammation, which holds promise for better understanding treatment-resistance in affective disorders as well as for future developments in treatment stratification. Aiming to investigate alterations in the inflammatory profiles of individuals with depression as putative biomarkers for clinical response, we conducted meta-analyses examining data from 35 studies that investigated inflammation before and after treatment in depressed patients together with a measure of clinical response. There were sufficient data to analyse IL-6, TNFα and CRP. Levels of IL-6 decreased with antidepressant treatment regardless of outcome, whereas persistently elevated TNFα was associated with prospectively determined treatment resistance. Treatment non-responders tended to have higher baseline inflammation, using a composite measure of inflammatory markers. Our findings suggest that elevated levels of inflammation are contributory to treatment resistance. Combining inflammatory biomarkers might prove a useful tool to improve diagnosis and detection of treatment refractoriness, and targeting persistent inflammation in treatment-resistant depression may offer a potential target for the development of novel intervention strategies.

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1. Introduction

An aberrant inflammatory profile has been widely demonstrated in depressive disorders and is believed to contribute to some of the biological mechanisms associated with disease onset and treatment response (Dowlati et al., 2010; Miller et al., 2009; Smith, 1991). Recent evidence suggests that levels of inflammation might be modifiable with pharmacological treatment (Hannestad et al., 2011; Hiles et al., 2012; Janssen et al., 2010) and preliminary evidence indicates that treatment resistance might be associated with heightened inflammation. Additionally, non-steroidal anti-inflammatory drugs might be beneficial as adjunctive treatments in unipolar (Akhondzadeh et al., 2009; Muller et al., 2006) and bipolar (Nery et al., 2008) disorders and the TNFα antagonist infliximab may particularly benefit depressed individuals with a history of treatment resistance and high inflammation (Raison et al., 2013). Treatment non-response contributes greatly to the burden of affective illnesses (Gibson et al., 2010); it is common, affecting at least a third of patients (Warden et al., 2007), and is generally associated with poorer long-term outcomes (Fekadu et al., 2009). To improve the rate and robustness of clinical response in depression there is a need for novel treatment strategies (Kupfer et al., 2012), including enhancing the personalisation of treatment provision using stratification. As such, research has been increasingly focusing on the importance of effectively screening for predictors of response across depressed populations, and using putative biomarker signatures prior to treatment provision may help to identify objective biological differences between patients who do or do not respond to treatments. Measuring 'panels' of biomarkers may assist with the discovery of biological signatures for disorders such as depression (Schmidt et al., 2011), which also may be supported using meta-analytic techniques that provide greater statistical power than individual studies. Combining these two approaches may be useful for identifying inflammatory relationships with depressed state and response to treatment, particularly as studies measuring different (but similar) data points cannot otherwise be compared in a high-powered analysis. We describe a new methodology of combining inflammatory data from different biomarkers together to enable a substantially higher statistical power.

Another important factor in this relationship is whether inflammatory profiles within a depressed state might differ between individuals with unipolar and bipolar diagnoses: although this has not been established there is some indicative evidence that inflammation is not elevated in bipolar depressed state (Munkholm et al., 2013), as opposed to mania and euthymia.

1.1. Aim of the study

With the aim of expanding on previous work, we investigated studies measuring inflammatory biomarkers in depression in relation to treatment response and hypothesised that (a) non-responsive patients would have higher levels of inflammation at baseline than responders; (b) patients would show a decrease in levels of inflammation after a course of treatment, but that; (c) treatment refractoriness would be characterised by persistently high levels of inflammation.

2. Experimental procedures

2.1. Criteria for study inclusion

A systematic search of the literature was conducted to obtain all studies that measured inflammatory responses in depression at baseline and following a course of treatment, and that also assessed treatment response. A priori inclusion criteria required eligible studies to be in English, measure in vivo at least one peripheral biomarker purporting to measure inflammation in human subjects classified as being in a depressive episode according to a clinician-rated standardised measure of depression symptomatology (e.g. HRSD, MADRS, IDS) alongside a standardised measure of clinical response to a treatment (and where relevant, a comparison of inflammation between responder and non-responder groups at one timepoint or more). To ensure we measured naturally occurring inflammation we excluded any studies which included a psychological or physiological stressor, or induced inflammation either by a targeted agent or by specific immunomodulatory drugs (e.g. non-steroidal anti-inflammatory drugs would be excluded, but not psychotropic medications). For this reason we also excluded papers reporting relevant comparisons in specifically physically ill samples (though we included studies which did not necessarily exclude individuals who had physical illnesses). Subjects were required to be of any adult age to be considered eligible.

2.2. Systematic search

We searched the databases PubMED (1960-), EMBASE (1974-), and PsycINFO (1967-), with the aim of eliciting all studies measuring peripheral markers of inflammation in patients with unipolar or bipolar depression and in relation to treatment response and/or clinical improvement, fulfilling our inclusion criteria. The full search process is depicted in Figure 1. Studies were retrieved by RS and inclusion/exclusion of studies agreed by consensus (with AC, AP). Studies were also scrutinised for potentially relevant citations. In case of incomplete information study authors were contacted to request additional data not available in the original manuscript.

2.3. Assessment of quality

Research reports were assessed using seven criteria, adapted from those developed by the Evidence-Based Medicine Working Group that had been modified for use in prognostic investigations (Fekadu et al., 2009) and the Cochrane Collaboration's Risk of Bias tool for trial designs (Higgins et al., 2011). Studies can score either positively (+1), negatively (−1) or neutrally (no score change) on each of the following domains: Cohort formation, sample size, trial/follow-up length, collection of biological data, study completion data, design of treatment provision, objective clinical assessment. This resulted in a ranking from −7 to +7 (see Table 1), which we used as a brief indicator of methodological rigour in individual studies, within the limitations of this approach.

2.4. Composite biomarker calculation

It was clear that the variation between studies of inflammatory biomarkers investigated would lead to low-powered meta-analyses of individual biomarkers. Based on the consideration that all selected biomarkers should measure the same latent construct (inflammation) and thus be correlated, we planned analyses to incorporate all possible available data. This novel method should at present be considered a preliminary test of the predictive validity of a combination of biomarkers as a measure of overall inflammatory response. The 'composite

measure' provides a preliminary and perhaps coarse representation of inflammation and its relationship with response to treatment in affective disorders, and will therefore require consideration when interpreting results. However, this method not only permits a higher powered meta-analysis, but also enables a broader perspective to be taken on the putative relationship between inflammatory profiles and clinical response to antidepressant treatments in people with depression.

To prevent bias in the composite inflammation analysis towards studies measuring multiple biomarkers, one entry per eligible study was required for each analysis. It was also important not to bias our results towards particular biomarkers. We therefore employed a method to utilise the maximum data available by averaging together all relevant biomarkers within each study prior to entering into the meta-analysis. Eligible markers were defined as pro-inflammatory cytokines (Cameron and Kelvin, 2000; Hodge-Dufour et al., 1998), as follows: tumour necrosis factor (TNFα), interferon-α or β (IFNα/IFNβ), interleukins 1 (IL-1α/IL-1β) or 6 (IL-6), c-reactive protein (CRP) which was also included as a direct marker of inflammation.

For each included study, mean data values for each eligible biomarker were first converted into pg/ml (except for CRP which was converted into mg/L), and then all relevant variables pooled to create the 'composite' measure using a pooling method embedded in the software Comprehensive Meta-analysis (version 2.2.021), for merging multiple data points within subjects (using the mean of the selected outcomes). The composite data calculated for each study, roughly representing the levels of inflammation for each comparison, provided a single-entry per study into each meta-analysis.

2.5. Statistical analysis

Meta-analyses were conducted where sufficient data were available in at least 3 studies for each primary comparison. For all possible biomarkers, the comparisons conducted were as follows:

1. Responder vs. non-responders at baseline (pre-treatment).
2. Inflammatory changes alongside treatment in responders.
3. Inflammatory changes alongside treatment in non-responders.

Additional secondary comparisons that were conducted on the above biomarkers were patients vs. controls at baseline and inflammatory change in all patients over treatment (not distinguishing between responder and non-responder groups).

Aside from the effect-size calculations for the composite analyses, statistical analysis methodology was conducted using Stata 11.0 (Stata Corp, College Station, Texas) and supplemented by 'Metan' software downloadable from the Centre for Statistics in Medicine, Oxford, UK, as reported previously (Arnone et al., 2009). Standardised mean differences were calculated using Cohen's *d* statistic and standardised effect sizes were then combined using the inverse variance method. Random effects analyses (DerSimonian and Laird, 1986) were used throughout to weight each study. The presence of heterogeneity was tested using the *Q*-test and its magnitude estimated using I^2, which can be interpreted as the proportion of effect size variance due to heterogeneity (Higgins et al., 2003). Publication bias, which describes the tendency of small studies to report large effect sizes, was examined using Egger's test (Egger et al., 1997) with the significance level set at $p<0.05$. To further investigate causes for heterogeneity, meta-regression analyses were performed in the primary analyses (outlined below). Potential confounders considered were; sex (%), age, baseline symptom severity, clinical setting (inpatient/outpatient), medication status on study-entry, standardised/naturalised treatment in study, length of treatment, study year, and study quality assessment. The STATA module "metareg" was used throughout and the REML (restricted maximum likelihood) method used to estimate the model parameters.

3. Results

The literature search yielded a total of 2053 articles, of which 35 met inclusion criteria (see Figure 1 and Table 1 for

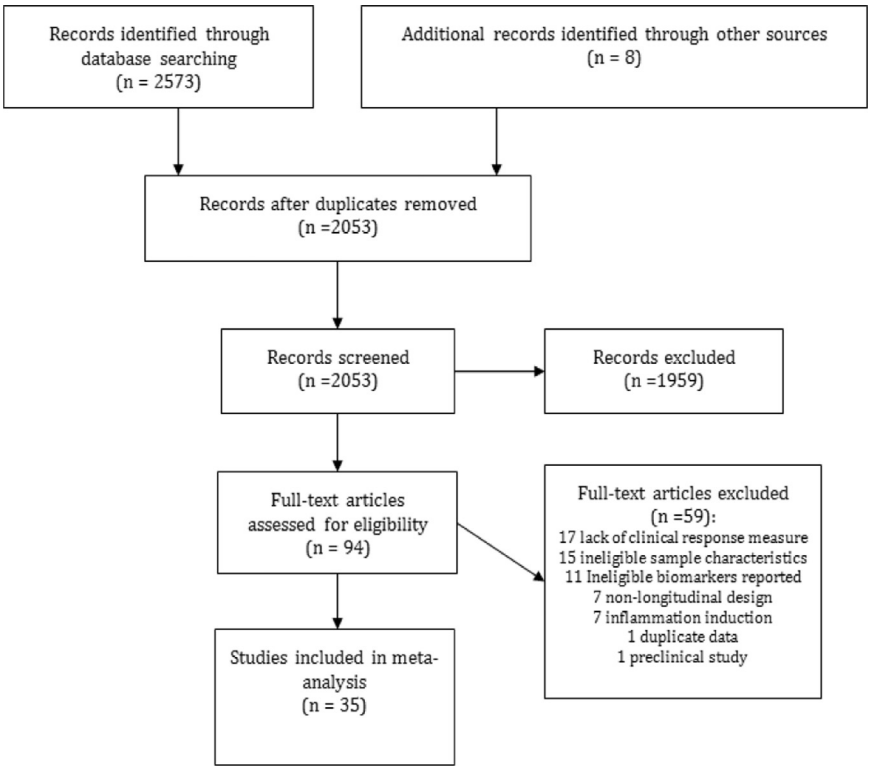


Figure 1 Flow chart of selection process for inclusion of studies.

Table 1 Characteristics of included studies.

Study	Diagnosis	Sample size	Quality rating	Response rate	Markers measured
Basterzi et al. (2005)	MD	23	*2*	74%	IL-6
Basterzi et al. (2010)	MD	69	*2*	64%	CD3, CD4, CD8, CD45, CD19
Carvalho et al. (2012)	MD	19	*1*	33%	Il-6, IL-10, IL-4
Chang et al.(2012)	MD	149	*4*	43%	CRP
Eller et al. (2008)	MD	100	*3*	74%	sIL-2R, IL-8, TNFα
Eller et al. (2009)	MD	28	*5*	64%	sIL-2R, IL-8, TNFα
Fornaro et al. (2011)	MD	16	*0*	56%	IL-6
Fornaro et al. (2013)	MD	38	*4*	40%	IL-1β, IL-2, IL-4, IL-10, IL-12, IFNy, TNFα
Frank et al. (2004)	MD	16	*3*	56%	NKCA, NKCN
Frommberger et al. (1997)	MD	12	*1*	All	IL-6
Harley et al. (2010)	MD	346	*4*	Improvement only	CRP
Hernandez et al. (2008)	MD	31	*1*	All	IL-2, IFNy, IL-4, IL-13, IL-10, IL-1β
Himmerich et al. (2006)	MD & BD	70	*1*	57%	TNFα, sTNFR p55, sTNFR p75
Himmerich et al. (2010)	MD	16	*−1*	Improvement only	Lymph.
Kook et al. (1995)	MD	24	*1*	79%	NKCA
Kubera et al. (2000)	MD	9	*−2*	Improvement only	IL-6, IL-1RA, IL10
Landmann et al. (1997)	21MD/ 1BD	22	*1*	27%	Gran., Lymph., Mono., TNFα, IFNy, CD14
Lanquillon et al. (2000)	MD	35	*4*	58%	Lymph., Mono., CRP, IL-6, TNFα
Maes et al. (1995)	53MD/ 8BD	61	*3*	All	IL-6, sIL-6 R, sIL2R
Maes et al. (1997a)	MD	25	*0*	60%	Il-6, IL-6 R, IL-1RA, sCD8
Maes et al. (1997b)	MD	36	*4*	65%	DPP-IV
Marques-Deak et al. (2007)	MD	46	*−2*	All	IL-1β, IL-6, IFNy
Mizruchin et al. (1999)	MD	15	*5*	Improvement only	NKCA
Mikova et al. (2001)	MD	28	*1*	60%	IL-8, IL-6, TNFα, IL-2 R, CC16
O'Brien et al. (2006)	MD	20	*1*	Improvement only	CRP
Pariante & Miller (1995)	MD	15	*−2*	47%	NKCA
Piletz et al. (2009)	MD	22	*3*	All	TNFα, IL-1β, MCP1, CRP, CD40
Schleifer et al. (1999)	MD	21	*1*	Improvement only	Lymph, CD4, CD8, CD29, CD45RA, CD56, NKCA
Seidel et al. (1996)	MD	33	*3*	36%	Leuk, Neut, Eos, Baso, CD4, CD8, CD19, Lymph,Mon
Song et al. (2009)	MD	95	*4*	47%	IL-1β, TNFα, IFNy, IL4, IL10
Tsai et al. (2014)	BD	32	*4*	All	CRP, sIL-2R, sIL-6R, IL-1RA
Tuglu et al. (2003)	MD	26	*1*	All	CRP, Leuk, TNFα
Uher et al. (2014)	MD	241	*3*	Improvement only	CRP
Yoshimura et al. (2009)	MD	51	*4*	61%	IL-6, TNFα
Yoshimura et al. (2013)	MD	118	*4*	49%	IL-6

Abbreviations: MD=major depression; BD=bipolar depression; IL=interleukin; CD=cluster of differentiation; CRP=c-reactive protein; sIL-2R=soluble IL-2 receptor; TNFα=tumour necrosis factor; NKCA=natural killer cell activity; NKCN=natural killer cell number; sTNFR p55 and p75=soluble TNFα receptors p55 and p75; IFNy=interferon gamma; Lymph=lymphocyte count; IL-1RA=IL-1 receptor antagonist; Gran=granulocytes, Mon=monocytes, DPP-IV=dipeptidyl-peptidase-4; MCP1; monocyte chemoattractant protein-1; Leuk=leucocytes; neut=neutrophils; Eos=eosinophils; Baso=basophils.

details and reasons for exclusion). All included studies investigated unipolar major depression except for one that only included bipolar diagnosed patients in a depressive episode (Tsai et al., 2014), and three that included both bipolar and unipolar depression (Himmerich et al., 2006; Landmann et al., 1997; Maes et al., 1995) but did not

Table 2 Results of meta-analyses.

Analysis description	Number of studies (k)	ES (95% CI's)	Significance value
R vs. NR baseline: composite	13	0.59 (−0.06, 1.36)	$p=0.073$
R vs. NR baseline: IL-6	5	0.83 (−0.41, 2.07)	$p=0.19$
R vs. NR baseline: TNFα	5	−0.08 (−0.34, 0.17)	$p=0.57$
R vs. NR baseline: CRP	4	−0.03 (−0.22, 0.16)	$p=0.76$
R baseline vs. end: composite	17	0.10 (−0.40, 0.60)	$p=0.70$
R baseline vs. end: IL-6	7	−0.19 (−0.78, 0.41)	$p=0.53$
R baseline vs. end: TNFα	8	−0.73 (−1.28, −0.19)	**$p=0.008$**
R baseline vs. end: CRP	3	0.54 (−0.31, 1.50)	$p=0.27$
NR baseline vs. end: composite	10	−0.17 (−0.86, 0.52)	$p=0.63$
NR baseline vs. end: IL-6	4	−1.11 (−2.45, 0.24)	$p=0.11$
NR baseline vs. end: TNFα	5	−0.04 (−0.58, 0.51)	$p=0.9$
NR baseline vs. end: CRP	3	0.03 (−2.00, 2.07)	$p=0.98$
All patients baseline vs. end: composite	23	−0.07 (−0.55, 0.42)	$p=0.79$
All patients baseline vs. end: IL-6	10	−0.57 (−1.09, −0.04)	**$p=0.03$**
All patients baseline vs. end: TNFα	9	−0.18 (−0.63, 0.27)	$p=0.42$
All patients baseline vs. end: CRP	5	−0.41 (−1.84, 1.01)	$p=0.57$
MD vs. HC baseline: composite	20	0.68 (0.12, 1.24)	**$p=0.017$**
MD vs. HC baseline: IL-6	10	1.02 (0.34, 1.69)	**$p=0.003$**
MD vs. HC baseline: TNFα	10	1.18 (0.18, 2.17)	**$p=0.02$**
MD vs. HC baseline: CRP	5	1.26 (0.63, 1.90)	**$p<0.0001$**

Abbreviations: R=responders; NR=non-responders; MD=depressed patients; HC=healthy controls.

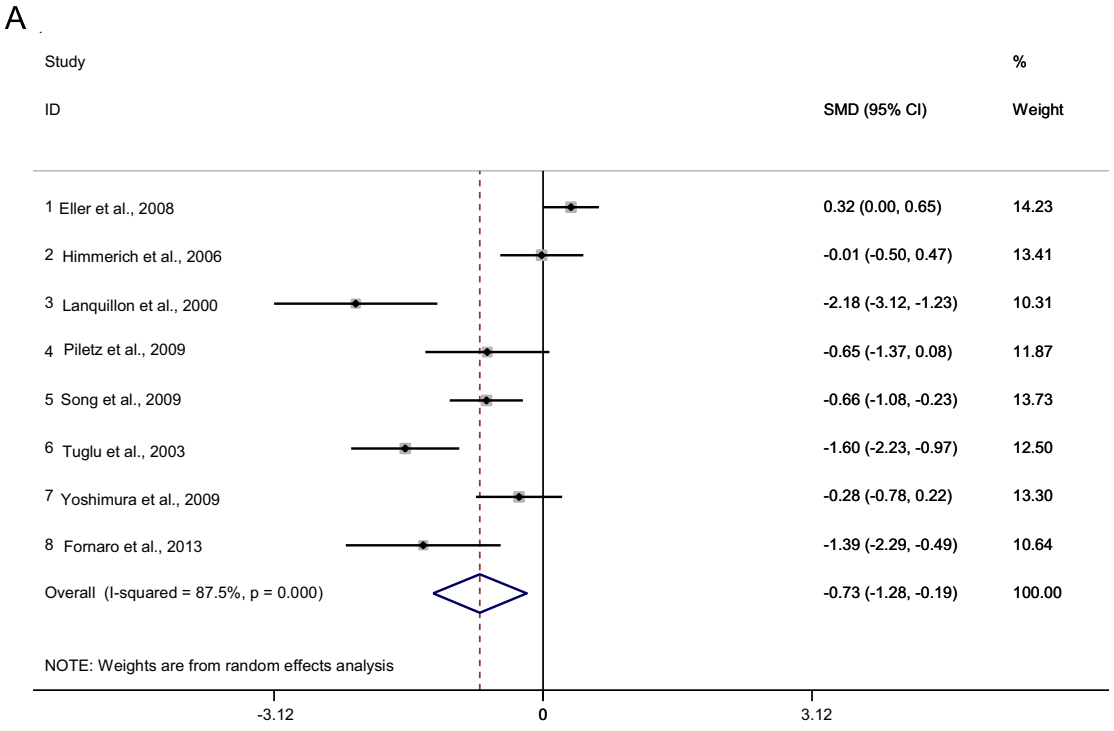
compare inflammation between the two groups. Three biomarkers were sufficiently researched to be included in primary analyses: interleukin-6 (IL-6) in 12 studies (Basterzi et al., 2005; Carvalho et al., 2012; Fornaro et al., 2011; Frommberger et al., 1997; Kubera et al., 2000; Lanquillon et al., 2000; Maes et al., 1997a; Maes et al., 1995; Marques-Deak et al., 2007; Mikova et al., 2001; Yoshimura et al., 2009; Yoshimura et al., 2013), TNFα in 11 studies (Eller et al., 2008, 2009; Fornaro et al., 2013; Himmerich et al., 2006; Landmann et al., 1997; Lanquillon et al., 2000; Mikova et al., 2001; Piletz et al., 2009; Song et al., 2009; Tuglu et al., 2003; Yoshimura et al., 2009) and CRP in 8 studies (Chang et al., 2012; Harley et al., 2010; Lanquillon et al., 2000; O'Brien et al., 2006; Piletz et al., 2009; Tsai et al., 2014; Tuglu et al., 2003; Uher et al., 2014).

3.1. Description of studies

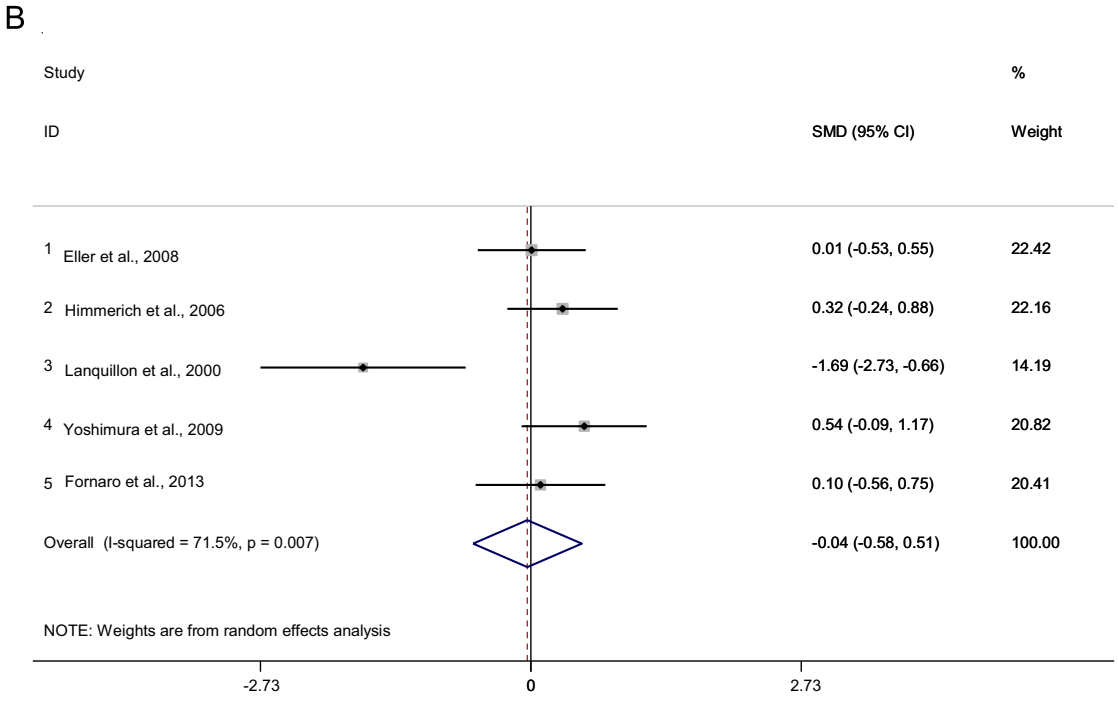
All 35 studies were longitudinal in design, measuring inflammatory markers at baseline and following up patients over the course of treatment. All but two studies (Carvalho et al., 2012; Uher et al., 2014) repeated inflammation measurements after treatment. Most articles dichotomised patients at study-end into responders and non-responders (Basterzi et al., 2005; Basterzi et al., 2010; Carvalho et al., 2012; Chang et al., 2012; Eller et al., 2008, 2009; Fornaro et al., 2011; Fornaro et al., 2013; Frank et al., 2004; Himmerich et al., 2006; Kook et al., 1995; Landmann et al., 1997; Lanquillon et al., 2000; Maes et al., 1997a; Maes et al., 1997b; Mikova et al., 2001; O'Brien et al., 2006; Pariante and Miller, 1995; Seidel et al., 1996; Song et al., 2009; Yoshimura et al., 2009; Yoshimura et al., 2013). For these studies, the criterion for response was $\geq 50\%$ reduction of score on the adopted depression severity rating scale. Seven studies reported results in responders only (Frommberger et al., 1997; Hernandez et al., 2008; Maes et al., 1995; Marques-Deak et al., 2007; Piletz et al., 2009; Tsai et al., 2014; Tuglu et al., 2003), and seven studies described clinical improvements using a continuous outcome measure (Harley et al., 2010; Himmerich et al., 2010; Kubera et al., 2000; Mizruchin et al., 1999; O'Brien et al., 2006; Schleifer et al., 1999; Uher et al., 2014). Studies were heterogeneous in terms of inflammatory biomarkers measured and patient samples, including the presence of psychiatric comorbidity, the degree of baseline treatment refractoriness and medication status at baseline. All studies investigated only pharmacological treatment, except one that compared pharmacological with psychological interventions (Harley et al., 2010); this found that high CRP was associated with good clinical response in antidepressant therapy but with poor response after psychotherapy. There were insufficient studies to compare inflammatory markers in unipolar and bipolar depression. Meta-analyses largely demonstrated significant levels of heterogeneity (I^2) and lack of publication bias (all $p>0.05$); see figures and Table 2.

3.2. Baseline inflammation and subsequent treatment-response

Elevated baseline inflammation was found in depression vs. healthy controls with all three inflammatory markers: IL-6 ($p=0.003$), TNFα ($p=0.02$) and CRP ($p<0.0001$), as well as the composite analysis ($p=0.017$). However, no significant



Egger's test for publication bias: p=0.07, I^2test for heterogeneity: p<0.001



Egger's test for publication bias: p=0.27, I^2test for heterogeneity: p<0.001

Figure 2 TNFα change in responders (Fig. 2A) vs. non-responders (Fig. 2B). Egger's test for publication bias: $p=0.07$, I^2 test for heterogeneity: $p<0.001$ and Egger's test for publication bias: $p=0.27$, I^2 test for heterogeneity: $p<0.001$.

differences in levels of baseline inflammation were identified between those subsequently responding or not responding to treatment: this was shown in TNFα ($p=0.57$), CRP ($p=0.76$), and IL-6 ($p=0.19$), though the latter was numerically higher in non-responders. The composite measure of inflammation at baseline showed higher levels were present in people subsequently not responding to treatment, which approached statistical significance ($p=0.073$). This finding remained when confining the analysis solely to unipolar patients (i.e. removing the study which contained some

bipolar depressed patients (Himmerich et al., 2006); $p=0.071$). We performed a meta-regression on the composite measure which showed that the effect of elevated inflammation on treatment non-response was more accentuated in outpatient vs. inpatient settings ($b=-0.494$, $p=0.012$), and in studies with a higher quality rating ($b=0.137$, $p=0.009$).

3.3. Effects of treatment and treatment-response on inflammation

There was no change evident in TNFα levels when simply looking at the effects of treatment i.e. when responders and non-responders were grouped together ($p=0.42$). However, there was a differential effect when treatment response was taken into account: levels of TNFα significantly decreased in treatment responders ($p=0.008$) but not in non-responders ($p=0.9$); see Figure 2. These analyses included one study where both unipolar and bipolar patients were included (Himmerich et al., 2006); exclusion of this study did not alter TNFα results (responders, $p=0.008$; non-responders, $p=0.66$). Meta-regression analyses suggested that decreased levels of TNFα in responders positively correlated with year of publication, suggesting a stronger effect in more recent studies ($b=0.205$, $p=0.026$) with a trend in non-responders ($b=0.21$, p=0.056).

In the studies measuring IL-6, there was an overall reduction following treatment irrespective of treatment response ($p=0.03$; see Figure 3). When separate analyses were conducted for responders and non-responders however, non-significant decreases were seen after treatment in both responders ($p=0.53$) and non-responders ($p=0.11$). IL-6 analyses included 8 patients diagnosed with bipolar depression (Maes et al., 1995); exclusion of the study containing these patients (as within-study bipolar/unipolar patient data was unavailable) from the analyses did not change the responders' subgroup results ($p=0.8$), and no non-responders were included in this article, but the overall analysis showed a slightly lowered significance value ($k=9$, ES $=-0.54$, CI $-1.12/0.03$, $p=0.06$).

Meta-regressions indicated a correlation in responders between age and IL-6 change over treatment; studies with a higher mean age report smaller reductions in IL-6 levels with treatment ($b=0.113$, $p=0.011$). In non-responders the degree of change in measured IL-6 levels was more significant in older studies ($b=0.236$, $p=0.024$).

There was no effect of treatment, or of treatment-response, on levels of CRP or on the composite inflammation measure. However, meta-regressions run on the composite analyses unanimously suggested that studies in which not all subjects were unmedicated at baseline showed greater variance in inflammatory changes alongside treatment: (for all depressed subjects: $b=1.23$, $p=0.017$; for responders only: $b=1.101$, $p=0.432$; for non-responders only: $b=1.215$, $p=0.053$.)

3.4. Unipolar and bipolar depression

Only Tsai et al. (2014) included solely bipolar diagnosed patients who were in a depressive episode and it was not possible to undertake a meta-analysis comparing unipolar vs. bipolar depression in the four studies identified (Himmerich et al., 2006; Landmann et al., 1997; Maes et al., 1995) due to disparate study methodologies or insufficient information being available. Tsai et al. (2014) identified a non-significant increase in levels of inflammation from acute depression to euthymia. In Maes et al. (1995), eight patients of the 61 included were bipolar patients in a depressed mood state, and the authors reported no correlations between bipolarity, IL-6 and depression severity (Maes et al., 1995). The other two articles including bipolar depressed patients did not report results separately nor any comparisons between the unipolar and bipolar diagnosed subjects. As can be seen above, removal of bipolar subjects from primary meta-analyses did not substantially affect the results.

4. Discussion

To our knowledge this is the first meta-analysis to investigate systematically the relationship between inflammation and treatment resistance in depression, both as a predictive marker and in maintenance of the illness. We found that prospectively-determined treatment resistance is associated with continued elevations in inflammation, in that there is a decrease in TNFα levels over time in treatment-responsive but not in treatment-resistant patients. We also examined a novel method for merging related inflammatory biomarker data, and its relation to treatment-resistance in affective disorders, finding a trend towards higher inflammation being associated with a poorer response to antidepressant treatment.

4.1. Inflammation and major depression

Although not the primary focus of the study, we have replicated previous findings that depression as a whole is associated with increased inflammation. Inflammatory elevations in depression have been reliably demonstrated across numerous reviews (Dowlati et al., 2010; Hannestad et al., 2011; Hiles et al., 2012; Miller et al., 2009) and there exist many plausible mechanisms by which this may occur. The causative effect of psychological and physiological stress on the inflammatory response has been well documented and this system interacts bidirectionally with other systems implicated in mood disorders, including HPA-axis activity and cortisol release (Miller et al., 1999), serotonergic pathways (Maes et al., 2011), neurogenesis and neuroinflammation (Harry and Kraft, 2012). There is additional evidence that inflammation is a causal factor in the onset of depression, supported by replicated findings that administration of inflammatory cytokines (particularly IFNα treatment for hepatitis C) can induce depressive symptoms or clinical depression in many patients (Raison et al., 2005).

An important area of uncertainty is the degree to which depression occurring as part of a bipolar disorder may differ compared to a unipolar disorder. There is a paucity of research to this end, and we were not able to identify sufficient studies to test the hypothesis that inflammatory markers may differentiate between unipolar and bipolar disorder. There is clear evidence of differential treatment strategies being appropriate in unipolar and bipolar depression (Pacchiarotti et al., 2013) and due to the unanswered

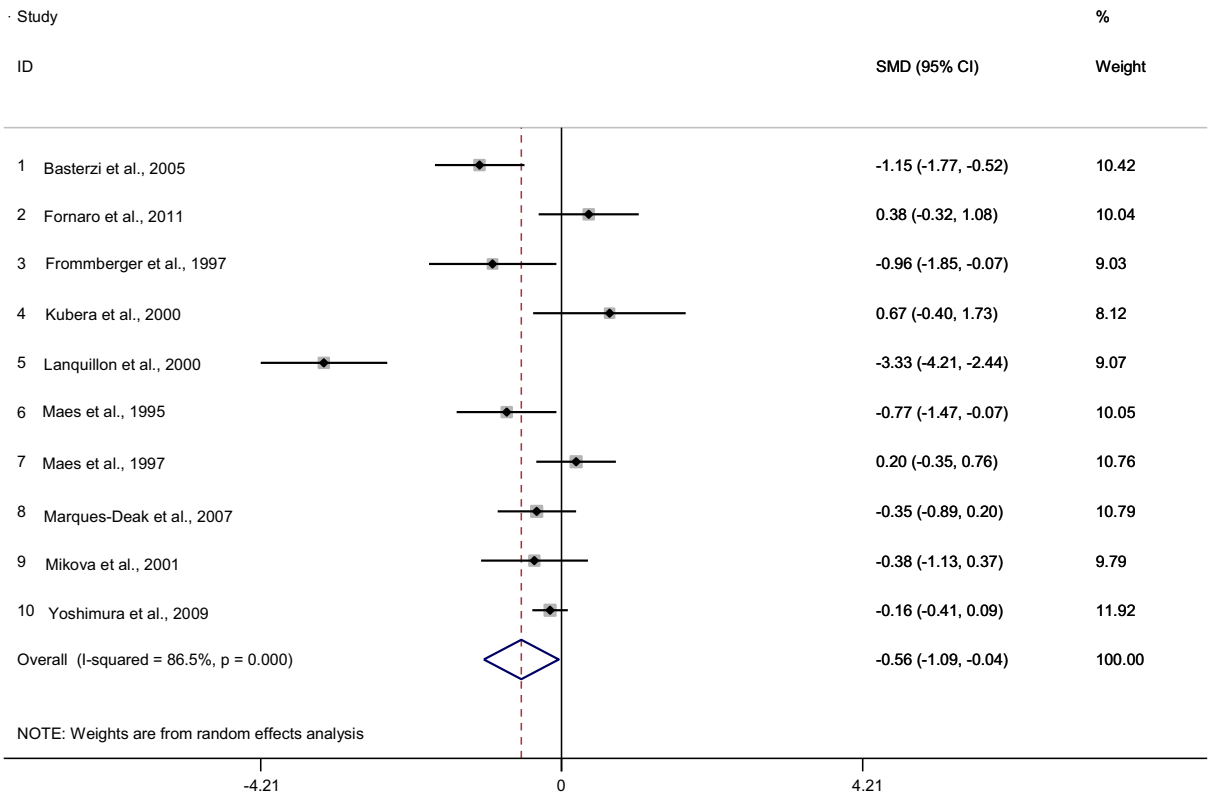


Figure 3 IL-6 alterations over treatment. Egger's test for publication bias: $p=0.47$, I^2 test for heterogeneity: $p<0.001$.

question of whether raised levels of inflammation are more specific to unipolar depression, therapeutic intervention in this domain may not be appropriate in bipolar depression. This is clearly an area which requires further investigation.

4.2. Inflammation and treatment resistance

The results of the meta-analysis demonstrate a role of inflammation in treatment-resistant depression: there were significant decreases in TNFα (towards control levels) seen only in treatment responders, whereas treatment resistance was associated with persistently elevated TNFα. This implies that maintenance of heightened levels of inflammation may at least contribute to treatment refractoriness, and thus that anti-inflammatory agents might provide a mechanism for treatment resistance in individuals with persistent high levels of TNFα. This is strengthened by recent preliminary findings that a TNFα antagonist, infliximab, can improve depression in some treatment-resistant patients (Raison et al., 2013); when stratified by pre-treatment levels of inflammation, infliximab appears to be most anti-depressant in those with higher pre-treatment inflammation. This association between TNFα modification and response may account for the lack of significant findings in a previous meta-analysis (Hannestad et al., 2011) which did not consider differential patterns of alteration in responders vs. non-responders.

We also found that, regardless of treatment response, antidepressant treatment can have anti-inflammatory effects, notably a reduction in IL-6. This may also occur in bipolar depression as indicated by the reduced significance found when removing Maes et al. (1995) whose sample was partly comprised of bipolar patients. The anti-inflammatory effects of antidepressants have been reported in preclinical (Connor et al., 1999) and in vitro (Xia et al., 1996) studies as well as clinical samples (Hannestad et al., 2011; Hiles et al., 2012). Indeed, it has been suggested that these anti-inflammatory effects may be one of the many mechanisms by which antidepressants exert their therapeutic effect (Janssen et al., 2010). It may be, therefore, that this anti-inflammatory effect of antidepressants is sufficient in many cases to reverse the overall inflammatory response seen in depression. However, in those with more severe or chronic illnesses, this effect may not in itself be sufficient to normalise the inflammation, which may then in turn act as a maintaining factor in the illness. It should also be noted that psychological interventions alone have also been reported to reduce inflammation alongside depressive symptoms (Thornton et al., 2009).

4.3. Composite biomarker measurement

While meta-regressions conducted on individual biomarkers may have been insufficiently powered to illustrate factors important in modifying the comparisons, the composite meta-regressions highlight the potential importance of medication status in the relationship between inflammation and treatment-resistance in depression. Our findings may also suggest that specific medications and their mechanisms

might explain some of the heterogeneity within results, something that we were not able to explore further. A comprehensive understanding of pharmacological effects on inflammation, and treatment-response, will require substantially larger samples of depressed individuals before, during and after treatment with a range of separate antidepressant medications.

The composite measures showed that patients with higher levels of inflammation responded less well to subsequent treatment, though this finding did not reach statistical significance. Despite the lack of significant results from the composite analyses, we suggest this approach is still worthwhile; due to the complexity of interactions between human biomarkers (as well as the heterogeneity of affective disorders), it is arguable that such methods will be more likely to detect robust and clinically useful biological indicators to predict the likelihood of treatment successes. There may be a number of methods for calculating this composite measurement, and identification of an optimal approach requires further investigation. We particularly highlight the difficulty surrounding which biomarkers should be classified as those representing inflammation, and inconsistencies within the literature on this subject. We believe that this can evolve through the use of large datasets, advanced modelling techniques, and/or new discoveries made in biochemical mechanisms.

4.4. Clinical implications

As outlined earlier, treatment resistance is a common clinical problem in affective disorders, and it is likely that there are several contributing factors in each individual patient. An important approach is to rule out alternative diagnoses that may explain the depressive symptoms, and to evaluate organic factors that may be of relevance. The results of this meta-analysis add to the suggestion that it may also be important to evaluate the presence of raised levels of inflammation. We have shown that elevated inflammatory markers predict a poorer response to antidepressants, and that those who do not respond to antidepressant treatments show persistently elevated inflammation. We suggest that there is now a clear imperative for research to investigate whether targeting this elevated inflammation will improve the outcome in treatment resistant depression, and if so, in which particular groups of patients.

Studies have rarely measured all potential inflammatory markers, and we do not yet know whether there are specific aspects of the inflammatory response that are relevant to depression or whether an approach such as that taken here of combining measures of inflammation is most likely to be of clinical relevance. We also suggest that inflammation is likely to represent just one of several potential novel treatment targets in these difficult to treat cases of depression, and that other approaches based upon other maintaining factors such as HPA axis disturbance (Juruena et al., 2009; Markopoulou et al., 2009) may also suggest differential treatment approaches on an individual level. Indeed, combining a range of inflammatory and other markers might be useful in enhancing treatment personalisation and diagnostic accuracy in the future, and complements current strategies to link clinical syndromes more closely to underlying neurobiological and other substrates (Insel, 2014). The benefits of this approach have been comprehensively outlined by Schmidt et al. (2011), which advocates the investigation of 'panels' of biomarkers (including for inflammatory, neurogenesis, endocrine and other systems) in order to improve the recognition of different patient subtypes and ultimately increase treatment response.

4.5. Limitations

There are several limitations in the interpretation of findings from this work. Our assessments using Egger's test indicate that our analyses are not likely to have been influenced by publication bias. However, due to the relatively small number of studies included in this work it is not possible to fully exclude the possibility of selective publication of positive studies. It is also notable that there were a large range of treatments, inflammatory markers and variation in patient characteristics between included studies, limiting the conclusiveness and generalisability of the present findings. In particular, the treatments studied were almost exclusively pharmacological, and therefore the results may not apply to other forms of treatment. In addition, depression is a highly diverse condition and this was evident in the significant levels of heterogeneity present in analyses, with factors including severity, depressive subtype, and degree of treatment resistance likely contributing to variation in inflammatory profiles. We explored possible sources of heterogeneity with meta-regression analyses and found some associations with effect sizes, notably those present in the composite analyses, and that IL-6 reductions with treatment were more prominent in younger samples. This may be a proxy for an earlier stage within the longitudinal course of affective illness or a representation of treatment naivety; both of these factors are associated with improved clinical response (Kornstein and Schneider, 2001). However, it is important to bear in mind that heterogeneity could only partially be explained by the confounders we considered in meta-regressions; indeed, it is likely that there is significant heterogeneity due to the very nature of depression itself. Moreover, this reinforces our message that further progress will be facilitated by defining more homogeneous groups for study, for example those with raised inflammatory markers and/or specific symptom profiles.

Utilising standardised treatment approaches, and the inclusion of psychological treatments as well as pharmacological, could improve our understanding of how different treatments can resolve inflammation. Furthermore, the relationship between inflammatory and other biological systems is clearly complex and multifaceted. Concurrent assessment of some of the parameters interacting with the inflammatory response in depression, such as the endocrine system, might prove useful in providing a fuller understanding of neurobiological dysfunction and treatment in depression.

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Contributors

R Strawbridge, Prof. Cleare & Dr. Papadopoulos conceived the design and methodology. R Strawbridge conducted the systematic review and meta-analysis, as well as primarily writing the manuscript. Dr. Arnone advised on and contributed to meta-analytic procedures. Dr. Danese and Dr. Papadopoulos provided expertise on inflammatory mechanisms, and Prof. Cleare supplied further expertise regarding data interpretation and treatment-resistant depression. All authors contributed and approved the final manuscript.

Conflict of interest

Prof. Cleare and Dr Arnone receive support from the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology & Neuroscience, King's College London. Dr Arnone's research is currently supported by the Academy of Medical Sciences (grant number AMS-SGCL8). The authors report no further potential or actual conflicts of interest. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health or the Academy of Medical Sciences.

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