



Review

Tumour necrosis factor- α inhibitor therapy in chronic physical illness: A systematic review and meta-analysis of the effect on depression and anxiety



Rebecca Abbott ^{a,*}, Rebecca Whear ^a, Vasilis Nikolaou ^a, Alison Bethel ^a, Jo Thompson Coon ^a, Ken Stein ^a, Chris Dickens ^b

^a PenCLAHRC, University of Exeter Medical School, St. Luke's Campus, Exeter EX1 2LU, United Kingdom

^b Mental Health Research Group, University of Exeter Medical School, St. Luke's Campus, Exeter EX1 2LU, United Kingdom

ARTICLE INFO

Article history:

Received 23 January 2015

Received in revised form 14 April 2015

Accepted 20 April 2015

Keywords:

TNF- α inhibitor

Chronic disease

Inflammation

Depression

Systematic review

ABSTRACT

Objective: Depression is more common among individuals with chronic physical illness than in the general population. New treatments for severe and chronic inflammatory conditions which inhibit tumour necrosis factor alpha (TNF- α), a pro-inflammatory cytokine, may be able to shed some light on the role of inflammatory mediators in depression. This systematic review and meta-analysis of randomised controlled trials determined the effects of TNF- α inhibitor therapy on depression and anxiety in people with chronic physical illness.

Methods: Seven databases were searched from inception to January 2014: AMED, Central, Cochrane Database of Systematic Reviews, CINAHL, Embase, MEDLINE, and PsycINFO. Articles were screened for inclusion independently by two reviewers. Data extraction and appraisal were conducted by one reviewer and checked by a second. Random-effects meta-analyses were performed.

Results: Six randomised controlled trials (reported in seven articles) met eligibility criteria and were included in the final review. In total 2540 participants were enrolled across the trials, with participants presenting with rheumatoid arthritis ($n = 3$ trials), psoriasis ($n = 2$) or ankylosing spondylitis ($n = 1$). Meta-analyses, using standardised mean differences, showed evidence of small reductions in depression (-0.24 ; 95% CI -0.33 to -0.14 ; $p < 0.001$), and anxiety (-0.17 ; 95% CI -0.31 to -0.02 ; $p = 0.02$).

Conclusion: TNF- α inhibitor therapy reduces depression in people with chronic disease though the effects are small. Whilst this is consistent with inflammation contributing to the development of depression, further studies investigating a more detailed timeline of changes in depression, inflammatory biomarkers and disease activity status are required.

© 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Depression is two to three times more common in people with chronic physical illnesses than in the general population [1]. This is of particular concern as depression is associated with a range of adverse outcomes among people with chronic physical illnesses, including increased mortality [2–4], increased morbidity [5,6], poorer health-related quality of life [7–9], and increased healthcare use and costs [10,11]. The causes of depression in the physically ill are complex and multifactorial. General risk factors, such as being female, having a family or personal history of depression, having markers of social deprivation, a lack of social support and marked psychosocial stresses are known to be predictive of depression [12]. Factors relating to the illness and its

treatment also influence who develops depression, such as negative beliefs about illness [13], the presence of pain [12,14], disability [15,16] and unpleasant side-effects from treatment [17]. Understanding the causes of depression is of central importance in the management of individuals with chronic physical illnesses as it offers the opportunity to: i) identify those at greatest risk of additional illness burden due to depression, ii) identify those at risk of worse medical outcomes and iii) potentially reduce the risks of adverse medical outcomes, either by treating depression or increasing the intensity of medical management.

Recently there has been growing interest in the roles of inflammation in contributing to the development of depression in people with physical illness [18,19]. Depression is associated with an increase in biomarkers of inflammation, including c-reactive protein (CRP), interleukin 1 (IL-1), interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF- α), in clinical and community populations [20–22]. Epidemiological studies have demonstrated that depression is predicted by higher levels of inflammatory mediators [23,24], though such prospective

* Corresponding author at: PenCLAHRC, University of Exeter Medical School, St. Luke's Campus, Exeter, EX1 2LU, United Kingdom.

E-mail address: r.a.abbott@exeter.ac.uk (R. Abbott).

Table 1
Study characteristics and summary of main depression and anxiety outcome data.

Author	Location	Population (including prevalence of depression & anxiety)	Intervention	Depression & anxiety measure	Findings (Intervention vs Comparator)
Bae 2013 APPEAL study	Multi (Hong Kong, India, Malaysia, Philippines, Taiwan, Korea and Thailand)	300 adults with rheumatoid arthritis (who showed inadequate response to oral MTX), mean age 48 yrs Baseline depression prevalence not reported	Open-label study. ETN (25 mg 2/week) + MTX (n = 197) vs DMARD + MTX (N = 103) for 16 weeks	HADS	Depression improvement: 7.62 to 5.42 (–28.7%) for ETN vs 7.85 to 6.56 (–16.4%) for DMARD, p = 0.016 Anxiety improvement: 29.1%(ETN) vs 18.5% (DMARD) improvement, p = 0.026
Kekow 2010 COMET study	Multi (Europe, Latin America, Asia, Australia)	528 adults with early active rheumatoid arthritis, mean age 51 yrs Baseline depression: 47% Baseline anxiety: 37%	Double blind study. ETN (50 mg 1/week) + MTX (n = 265) vs MTX (n = 263) for 52 weeks	HADS	Depression no significant change: 6.82 to 4.39 (–2.43) for ETN vs 6.68 to 4.66 (–2.02) for MTX, Not Significant (NS) Anxiety no change: –2.12 (ETN) vs –1.92 (MTX) improvement, NS
Machado 2014	Multi (Argentina, Chile, Columbia, Mexico, Panama)	429 adults with rheumatoid arthritis (who showed inadequate response to MTX), mean age 48 yrs Baseline depression prevalence not reported	Open label study. ETN (50 mg 1/week) + MTX (n = 284) vs DMARD + MTX (n = 145) for 24 weeks	HADS	Depression improvement: adjusted mean change: –2.8 (0.2) for ETN vs –1.9 (0.3) for DMARD, p = 0.0077 Anxiety no change: –2.2(0.3) for ETN vs –1.7 (0.3) for DMARD, p = 0.16
Menter 2010	Multi (USA and Canada)	97 adults with psoriasis, mean age 44 yrs Baseline depression: 35%	Double blind study. ADM (40 mg 1/week) (n = 45) vs Placebo (n = 52) for 12 weeks	ZDS	Depression improvement: 42.9 (12.4) to 36.2 (11.5) for ADAL vs 45.8 (14.0) to 44.2 (14.2) for placebo Difference in change –6.0 (–9.5 to –2.5), p = 0.001 (Improvement in ZDS correlated with improvement in physical symptoms (r = 0.5, p < 0.001), but not able to assess which came first)
Packham 2012 ASCEND study ^a	Multi (centres across the UK)	Subgroup of 48 adults with ankylosing spondylitis in UK, mean age 41 yrs Baseline depression prevalence not reported	Double blind study. ETN (50 mg 1/week) (n = 29) vs SLZ (n = 19) for 16 weeks	HADS	Depression improvement: effect size (ES) greater for ETN, n = 29, (ES –0.86) compared to SSZ, n = 15 (ES –0.39), no statistics presented Anxiety no change: ES similar between 0.68 (ETN) vs 0.81 (SSZ), no statistics presented
Tyring 2006	Multi (USA and Canada)	620 adults with psoriasis, mean age 46 yrs Baseline depression: 19% mild, 15% moderate (BDI); 24% mild, 2% moderate (HAM-D)	Double blind study. ETN (25 mg 2/week) (n = 311) vs Placebo (n = 309) for 12 weeks	HAM-D and BDI	Depression: 1) HAM-D Depression improvement ETN vs Placebo, 1.5 vs 0.4, (CI 0.4–1.9, p = 0.0012), ES of 0.25 2) BDI Depression Improvement ETN vs Placebo, 1.8, (CI 0.6–2.9, p < 0.001), ES of 0.22. (Changes in depression not strongly correlated with objective clinical measures.)
Van der Heijde 2012 ASCEND study ^a	Multi (Europe, Latin America, Asia, Australia)	566 adults with ankylosing spondylitis, mean age 41 yrs Baseline depression prevalence not reported	Double blind study. ETN (50 mg 1/week) (n = 379) vs SSZ (n = 187) for 16 weeks	HADS	Depression improvement: Greater improvement in ETN vs SSZ: –0.7 (3.0), p < 0.05 Anxiety improvement: Greater improvement in ETN vs SSZ: –0.6 (3.0), p < 0.05

Drug

ADM	Adalimumab
DMARD	Disease modifying anti rheumatic drug
ETN	Etanercept
MTX	Methotrexate
SSZ	Sulphasalazine

Assessment tools

BDI	Beck Depression Inventory
HADS	Hospital Anxiety and Depression Scale
HAM-D	Hamilton's Rating Scale for Depression
ZDS	Zung's Self-rating Depression Scale

^a Same study.

associations have not been consistently observed with some finding depression predicting inflammation [22]. Controlled, experimental studies

in healthy volunteers, in which inflammation is triggered by the acute administration of an endotoxin or attenuated vaccine, have

demonstrated transient increases in the symptoms of depression associated with increases in IL-1 receptor antagonist (IL-1Ra), IL-6 and TNF- α [25,26]. Furthermore, administration of Interferon alpha, which greatly increases the level of inflammatory mediators, is associated with development of major depression in up to one third of patients [27], which is preventable in many by pre-treatment with antidepressants [28,29]. Whilst such observational studies and short-lived experimental studies provide evidence that inflammatory mechanisms contribute to the development of clinically significant depression in people with chronic physical illness, they fall short of proving the causal link.

The recent development of pharmacological agents which specifically inhibit the inflammatory mediator TNF- α , a pro-inflammatory cytokine, offer a new means of investigating the links between inflammation and depression [30]. Administration of TNF- α inhibitors have resulted in a reduction of depression-like and anxiety-like symptoms in rodent models of depression [31,32]. In clinical studies, TNF- α inhibitors have been shown to improve outcomes in a high proportion of people with severe inflammatory disorders, who have failed to respond to other treatments. Indeed, TNF- α inhibitors have also been shown to improve depressive symptoms among people with chronic inflammatory disorders [33], though this does not always appear to be the case [34]. More recently, Arisoy and colleagues [35] have shown that patients with ankylosing spondylitis who were treated with TNF- α inhibitors reported a significant decrease in depression which, importantly, was not associated with changes in markers of clinical disease activity. They, and others [36], have suggested that the improvements in depression but not markers of clinical disease activity, provides support for an inflammatory mechanism underpinning the development and maintenance of depression. Although the link between anxiety and inflammation has been much less studied, with recent findings of correlations between inflammatory markers and anxiety disorders and increased inflammatory activation in patients with anxiety disorders [37], anxiety was included as a secondary outcome of interest.

The purpose of this systematic review therefore, was to determine whether introduction of TNF- α inhibitor therapy in people with chronic physical illness reduces symptoms of depression and anxiety. As the question of this review related to the association of inflammation with depression and anxiety, we were interested in the effects across, rather than within, populations with chronic illness. Further, the review sought to explore the relationship between timing of change in depression and anxiety symptoms with change in either immunological or clinical status.

Methods

The systematic review was conducted following the general principles published by the NHS Centre for Reviews and Dissemination [38] and has been reported in accordance with the PRISMA statement [39]. The protocol was registered and published prior to the review commencing with PROSPERO (<http://www.crd.york.ac.uk/PROSPERO/>) in September 2013 (registration no. CRD 42013006068).

Types of studies

Only randomised controlled trials (RCTs) were considered eligible for the purposes of this review.

Types of participants

Individuals with any chronic physical illness that received treatment with a TNF α inhibitor as part of a randomised controlled trial. The indications for TNF- α inhibitor therapy meant that we were likely to only find populations with inflammatory related conditions such as rheumatoid arthritis, psoriasis, or ankylosing spondylitis.

Studies which involved participants being treated for mental illness alone were not eligible.

Types of interventions

The intervention of interest was treatment with TNF- α inhibitors, compared against usual care (treatment with a non TNF- α inhibitor) or control. At the time of the review, the available TNF- α inhibitors were Etanercept, Infliximab, Adalimumab, Certolizumab, and Golimumab. Studies that simply compared two doses of TNF- α inhibitors (with no control or usual care arm), or studies that assessed attenuation/escalation of TNF- α inhibitors doses, in which both intervention arms received at least one dose of TNF- α inhibitors were not considered eligible for inclusion.

Outcome measures

The primary outcome of interest in this review was depression, assessed using a validated psychological measure, such as the Hospital Anxiety Depression Scale (HADS), and the Beck Depression Inventory (BDI). A list of recognised measures of depression was agreed a priori (CD and RA). Self-reported measures of mental health related quality of life were not considered eligible. Secondary outcome measures of interest were anxiety, assessed with a recognised psychological measure, and measures of inflammatory and clinical disease status (only in relation to the timing of any changes in depression observed).

Search strategy

The search strategy was developed by an information specialist (AB) in consultation with topic and methods experts (CD, BA, BW, JTC). The strategy used a combination of MeSH terms and free text terms, including terms for TNF- α inhibitor or agonist, including the named drugs, and terms describing depression. An illustration of the exact search strategy used on MEDLINE can be seen in Fig. 1. Seven databases were searched from inception to January 2014: AMED, Central, Cochrane Database of Systematic Reviews, CINAHL, Embase, MEDLINE, and PsycINFO. No date or language restrictions were used. We also searched ClinicalTrials.gov for recently completed and ongoing studies. Forward and backward citation chasing of each included article was conducted. Two reviewers (RA, with RW or AB) independently screened titles, abstracts and full texts using the eligibility criteria. Discrepancies were discussed and resolved by a third reviewer (RW or AB) where necessary.

Risk of bias and study quality

The methodological quality of each paper was assessed using the Cochrane 'risk of bias' tool [40]. The tool includes six key criteria against which potential risk of bias is judged: adequacy of allocation sequence generation; adequacy of allocation concealment; blinding of participants, personnel or outcome assessors; completeness of outcome data; selectivity of outcome reporting, and other bias. In addition to the Cochrane risk of bias tool, four additional aspects of quality relating to reporting of eligibility criteria, similarity of baseline characteristics, compliance with intervention and data collection tool validity were assessed. Quality was assessed by one reviewer (RA, AB, or RW), with judgements checked by a second (RW, RA, or AB). Any discrepancies were discussed and resolved.

Data collection

Data on the study design, the setting, the population, the intervention, the outcomes and results, and risk of bias were collected using a standardised, piloted data extraction form. Data were extracted by one of two reviewers (RA, AB) and fully checked by another (RA or RW).

Database: Ovid MEDLINE(R) <1946 to October Week 5 2013>

Search Strategy:

```

-----
1  antiinf*.tw. (30)
2  "anti tnf*".tw. (7674)
3  tnf*.tw. (123764)
4  "Tumour necrosis factor*".tw. (18084)
5  exp Tumor Necrosis Factor-alpha/ (101615)
6  Adalimumab.tw. (3783)
7  Humira.tw. (178)
8  Etanercept.tw. (4467)
9  Enbrel.tw. (207)
10 Infliximab.tw. (7247)
11 Remicade.tw. (216)
12 Certolizumab.tw. (442)
13 Pegol.tw. (322)
14 Golimumab.tw. (242)
15 Simponi.tw. (7)
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (159371)
17 randomized controlled trial.pt. (389483)
18 controlled clinical trial.pt. (89863)
19 randomi#ed.ab. (349033)
20 placebo$.ab. (157253)
21 drug therapy.fs. (1765660)
22 randomly.ab. (199204)
23 trial.ab. (302100)
24 groups.ab. (1275059)
25 exp animals/ not humans.sh. (4058478)
26 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (3304198)
27 26 not 25 (2814515)
28 exp Depression/ (76808)
29 depress*.tw. (302892)
30 depressive disorder/ or exp depressive disorder, major/ or exp dysthymic disorder/ (78451)
31 dysthym*.tw. (2575)
32 antidepress*.tw. (45785)
33 "anti depress*".tw. (1374)
34 28 or 29 or 30 or 31 or 32 or 33 (358122)
35 16 and 27 and 34 (445)
*****

```

Fig. 1. Example of search strategy used on Medline.

Data analysis and synthesis

Since our underlying question related to the association of inflammation with depression and anxiety, rather than with specific illnesses and depression/anxiety, populations receiving TNF- α inhibitor therapy were grouped together, rather than analysed by specific conditions. Random effects meta-analyses were performed where we had sufficient data from RCTs for the effect of intervention on the outcome measures of depression and anxiety. Pooling was performed on the post intervention outcome measurement. As we used a random-effects model for the meta-analyses, the weightings for each study were determined not only by the size of each study included, but also by the estimate of between-study heterogeneity. All studies assessing depression, analysed change

in outcome between baseline and post intervention. Across the six trials there were four different scales used to assess depression, and one study [41] only reported an adjusted standardised effect size between interventions and control. Therefore, in all but one study [41], unadjusted post-intervention summary data were used to calculate standardised effect sizes (ES) between groups. In the case of the Tying et al. study [42], where two different scales were used to measure the same outcome from the same population, we computed a single effect size as the mean of the effect sizes of the two scales and a variance that takes into account the correlation between the two scales [43]. As some have queried the interpretability of standardised effect sizes [44], we also performed a random effects meta-analysis on the non standardised mean differences data for studies in which the same

depression scale only had been used. Data for this analysis is reported as the pooled mean difference with 95% confidence intervals. Anxiety was measured across the studies using the same assessment tool; however, as only the adjusted standardised effect size between groups was reported in one study [41], pooled effects are reported as standardised effects sizes with 95% confidence intervals. Heterogeneity across estimates was quantified using the I-squared statistic and tested using the Q-statistic [45]. Synthesised results are presented by outcome type. Effect sizes are expressed as small (0.2–0.5), moderate (0.5–0.8) and large (>0.8) [46]. Where pooling was not appropriate or possible, the findings have been summarised in narrative form.

Data analysis was carried out using Stata [Stata Corporation. Stata Statistical Software. Release 12.1. College Station, TX, 2011] and Review Manager (RevMan) Version 5.2 software (<http://ims.cochrane.org/revman>). Synthesised results are presented by outcome type. Effect sizes are expressed as small (0.2–0.5), moderate (0.5–0.8) and large (>0.8) [46]. Where pooling was not appropriate or possible, the findings have been summarised in narrative form.

Results

The electronic searches found a total of 1351 results, 360 of which were duplicates, leaving 991 titles and abstracts to screen. After double screening of each one, 28 full texts were retrieved for closer examination. A total of seven articles (from six trials) were included in the final review, with two identified from forward and backward citation chasing. Reasons for exclusion at the full text stage can be seen in Fig. 2. The ASCEND trial was reported in two articles: a UK group subset only [47], and the full multicentre study [41]. Data from the full study were used for all analyses where possible.

Study characteristics

All included articles reported on multi-centre randomised controlled trials conducted across more than one country (see Table 1.). Trial size ranged from 48 to 620 participants, with five of the six trials having >300 participants [34,41,42,48,49]. In total, 2540 participants were enrolled across the six trials. Participants were those presenting with rheumatoid arthritis (n = 3 trials) [34,48,49], psoriasis (n = 2) [42,50], and ankylosing spondylitis (n = 1) [41,47]. The mean age of participants recruited ranged from 41 to 51 years, and all trials were of mixed sex. All six trials were primarily safety and efficacy studies (the main clinical and safety findings being presented elsewhere) in participants with moderate to severe chronic disease, with depression being assessed as a secondary outcome measure. Only one study [42] reported excluding participants with psychiatric disease, and the same study also reported the intention to withdraw any patients who became actively

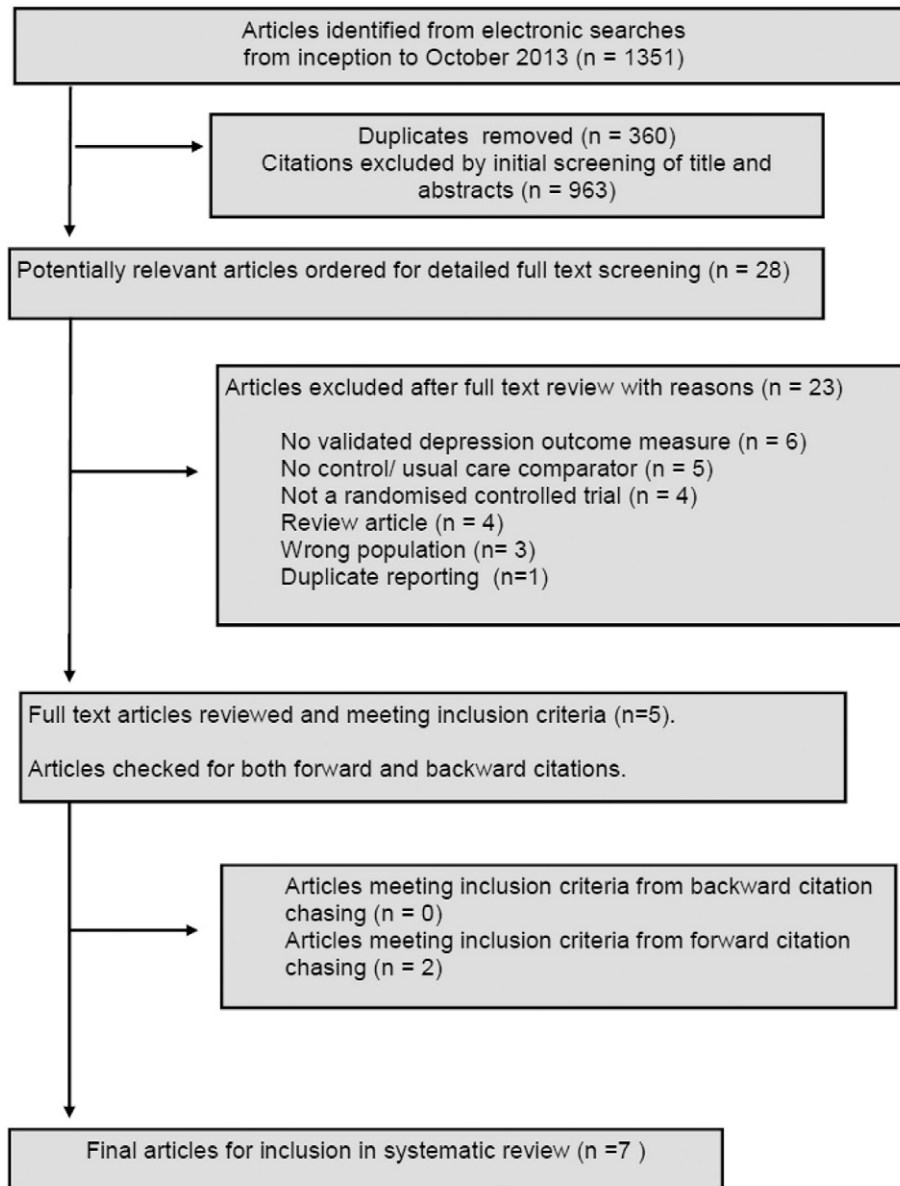


Fig. 2. PRISMA flow diagram showing identification of included studies.

suicidal during the trial. Three studies [34,42,50] reported prevalence of depression and anxiety at baseline, and the mood state in these populations were found to be representative of other studies of populations with chronic disease, ranging between 16–47% of participants showing some degree of clinical depression and/or anxiety. None of the studies proactively recruited participants with depression.

Intervention characteristics

All six trials excluded anyone that had previously received TNF- α inhibitor treatment. The three trials for participants with rheumatoid arthritis all assessed the TNF- α inhibitor etanercept. Etanercept was used in conjunction with methotrexate and compared against the standard disease modifying anti-rheumatic drug (DMARD) of choice plus methotrexate in two open-label RCTS [48,49], and against methotrexate alone in the third double-blind RCT [34]. Trial length ranged from 16 to 52 weeks. The two trials for participants with psoriasis were both placebo controlled double-blind trials and assessed the effects of adalimumab [50] and etanercept [42] respectively. Both trials were of 12 weeks duration. The trial for those with ankylosing spondylitis was a 4 month long double blind study, reported in two articles, comparing etanercept to sulphasalazine [41,47]. All six

trials found significant clinical benefit of TNF- α inhibitor treatment compared to comparator treatment [34,42,48,49,51,52].

Psychological outcome measure

Depression was assessed as a secondary outcome in all six trials. Four of the trials used the Hospital Anxiety and Depression Scale (HADS) [34,41,47–49], one used the Zung Depression Scale (ZDS) [50] and one trial used two different scales: the Hamilton Rating Scale for Depression (HAM-D) and the Beck Depression Inventory (BDI) [42]. Anxiety was also assessed as a secondary outcome in four trials, with HADS as the assessment tool [34,41,47–49].

Study quality (risk of bias)

A summary of the risk of bias is presented in Fig. 3. For a few trials, some of the information for this, where referred to and available, was taken from the 'parent' primary outcome paper [51–54] which described the trial methodology in more detail. Whilst all six included articles were RCTS, the studies were not without issues relating to possible

	Cochrane risk of bias						Other bias				
	Random sequence generation	Adequacy of allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Eligibility criteria specified	Baseline characteristics similar	Compliance with intervention	Data collection tools valid and reliable	All participants accounted for
Bae 2013	L	?	H	H	L	?	L	L	?	L	L
Kekow 2010	L	L	L	L	?	L	L	L	?	L	L
Machado 2014	L	?	H	H	L	L	L	L	?	L	L
Mentor 2012	?	?	L	L	?	?	L	L	?	L	?
Packham 2012 **	L	L	?	?	?	?	L	?	?	L	?
Tyring 2006	L	L	L	L	L	L	L	L	?	L	L
van der Heijde 2012 **	L	L	L	L	L	L	L	?	?	L	L

** Same trial




-  Unclear/ not reported
-  Low bias
-  High risk of bias

Fig. 3. Cochrane risk of bias table of included studies.

bias. For the majority of studies, the methods of randomisation and selection of eligibility criteria were well described. Four of the trials were double blind and for these studies, there was little risk of bias with regard to blinding of participants and outcome assessments. However, two open-label studies were susceptible to bias of outcome measurement, but these limitations were recognised in both papers. For most of the studies, outcome data were complete or missing data were accounted for adequately, however none of the studies reported on compliance with the intervention. Data collection tools for depression and anxiety were all valid and reliable. All articles were presenting data that was secondary to the primary aim of the trial, and all articles included authors that were either employed by a pharmaceutical company or had received monies from pharmaceutical industry, though the degree to which they were involved in data interpretation and analysis was not stated for any of the articles.

Effects on depression

Data from all six trials were included in the meta-analysis on the effects of treatment on depression. TNF- α inhibitor therapy was found to have a significant beneficial effect on depression across a variety of clinical populations in five of the six trials, showing small to medium effects. Pooling the studies together, irrespective of the depression assessment tool used, we found a small but statistically significant effect size of -0.24 in favour of the intervention group (95% CI: -0.33 to -0.14 ; $p < 0.001$). The heterogeneity between studies (38%) was not statistically significant ($p = 0.15$). The forest plot for this analysis is shown in Fig. 4. Repeating the analysis to include only studies that reported non standardised data utilising the same depression assessment tool, resulted in comparable findings: the pooled effect of TNF- α inhibitor treatment on depression in people with rheumatoid arthritis, as measured by HADS [34,48,49], resulted in an overall mean difference in HADS of -0.65 (95%CI: -1.15 to -0.16 , $p = 0.009$) in favour of the intervention group; this equates to a pooled standardised mean difference of 0.16 , in the three studies included in this sub-analysis. There was 12% heterogeneity between the three studies which was not statistically significant ($p = 0.32$).

Two studies [42,50] assessed whether there was an association between change in depression and change in clinical disease status. Menter et al. [50] found a significant correlation between the two, whilst Tyring et al. [42] found no strong correlation in the two outcomes. Neither of the studies however assessed depression frequently enough to determine whether the changes in depression appeared prior to changes in clinical disease status. None of the studies reported analysing depression in relation to inflammatory markers.

Effects on anxiety

Four studies provided data suitable for meta-analysis. Three studies were in populations with rheumatoid arthritis, and one in a population with ankylosing spondylitis and all used HADS as the assessment tool. The pooled effect of TNF- α inhibitor treatment on anxiety resulted in an overall standardised mean difference of -0.17 in

favour of the intervention group which was statistically significant at 5% level of significance, 95% CI: -0.31 to -0.02 ; $p = 0.02$ (forest plot shown in Fig. 5). There was 61.7% heterogeneity between the four studies which was borderline statistically significant ($p = 0.05$).

Discussion

This is the first systematic review and meta-analysis of the effects of TNF- α inhibitor treatment on depression and anxiety in people with chronic inflammatory disease. Data from six randomised trials (reported in seven articles), involving a total of 2540 participants with moderate to severe chronic inflammatory disease, showed a small but statistically significant effect of TNF- α inhibitor treatment on reducing depression. Although not measured in all studies, a significant beneficial effect of intervention was also observed for anxiety. The association between improvement of depression with improvement in inflammatory condition was inconsistent, however; one study reported an association between clinical improvement and improvement in depression, whereas another study observed no association between the two. None of the studies were able to determine whether the changes in depression occurred independent of, or prior to, any changes in markers of clinical disease activity.

The review followed best practice guidelines for systematic reviews [38] and did not restrict by date or language, nor by whether studies had been published or not. Authors of papers who had published abstracts only, were contacted for their data, if available. Only data from placebo (or usual care) controlled RCTs were eligible for this review, to enable us to draw inferences about the causal relationship between use of TNF- α inhibitors and improvements in depression. We pooled study findings using standardised mean differences, to enable us to combine findings using differing measures of depression and anxiety, but also presented findings for the majority of studies using the same measure using weighted mean difference, to aid interpretation. Importantly, the effect size of TNF- α inhibitor treatment on depression was comparable irrespective of the meta-analytic approach taken.

With regard to potential weaknesses, this review included RCTs for which the primary aim had to been to assess safety and efficacy of

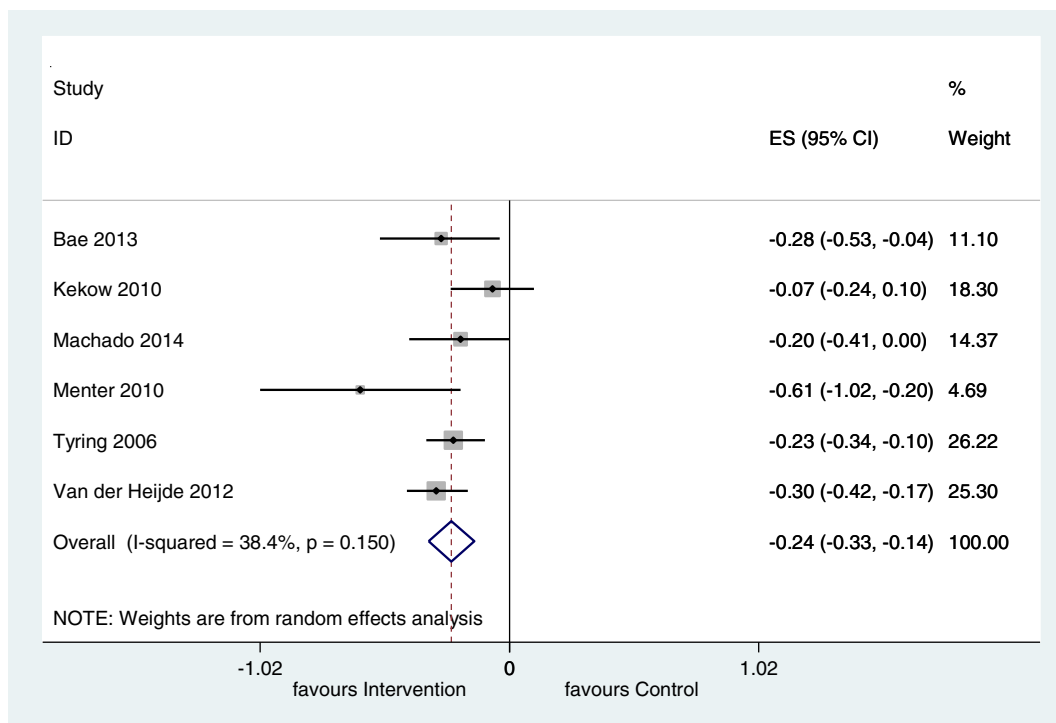


Fig. 4. Forest plot showing the results of the meta-analysis on the effects of TNF- α inhibitor treatment on depression.

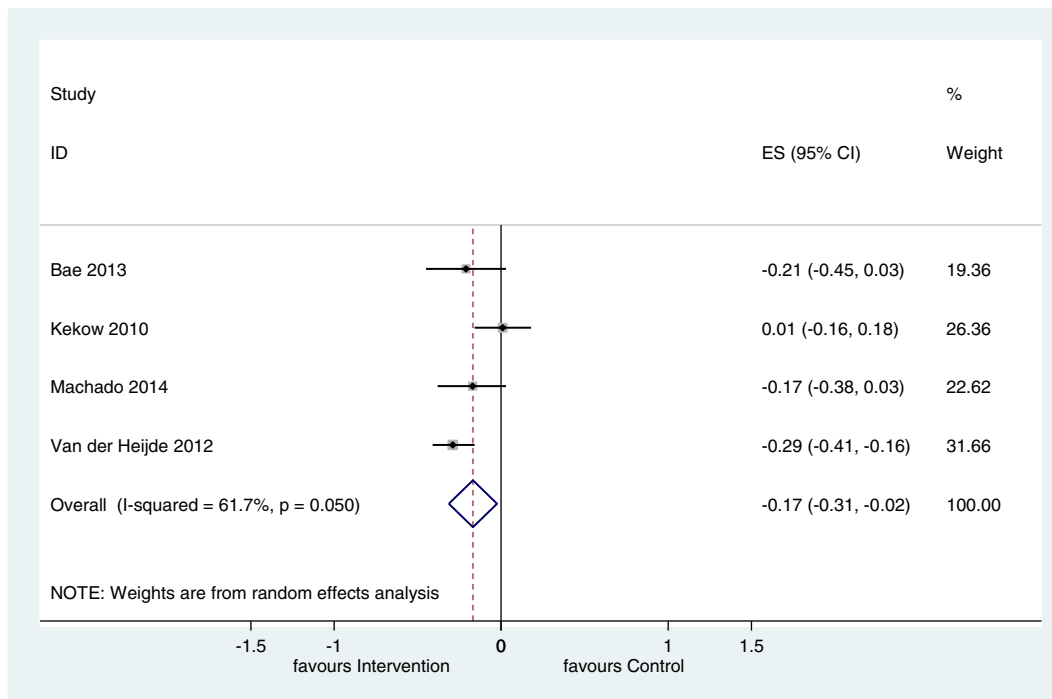


Fig. 5. Forest plot showing the results of the meta-analysis on the effects of TNF- α inhibitor treatment on anxiety.

treatment on physical health status. Whilst the designs of the included studies were robust, the primary aims of the trials were not to establish effects on psychological status, nor to relate this to clinical disease status and inflammatory biomarkers. Whilst this may be interpreted as meaning that less effort and rigour may have been invested in the assessments of depression, all the measures used were well-validated. Importantly, the self-rated assessments performed similarly to the observer rated HAM-D measure of depression in the one trial that used both forms of assessment [42], which suggests that reliance on self-rated depression measures in the majority of studies did not inflate the observed effects of TNF- α inhibitors on depression. Also by focusing on secondary outcomes of trials, it could be argued that our findings are less likely to be influenced by publication or reporting bias. Another possible limitation for this review is the small number of studies that the review located. Although the trials were of reasonable size, and data from more than 2500 participants were pooled, for example for analysis of the effects of TNF- α inhibitor therapy on depression, this does only represent six studies, and therefore the results need to be interpreted with caution. A further consideration must be given to the fact that whilst the study participants were similar on the grounds that they were receiving TNF- α inhibitor therapy for an inflammatory condition, there is likely to have been considerable variation in both the disease states, and other factors impacting on depression and anxiety of the participants within each trial, and across the trials of different chronic diseases. This variability in the nature of the underlying disease characteristics and associated factors is likely to have contributed to the heterogeneity between individual trials. Some small reassurance is given by the three studies that reported baseline mood state, which were found to be representative of other studies of populations with chronic disease.

We interpret our findings as indicating that treatment with TNF- α inhibitors in people with chronic inflammatory conditions improves depression and anxiety. The effects of TNF- α inhibitors on depression were small, however, and whilst there is no established minimum clinically important difference for the HADS depression scale, the small effect observed would be below what most would consider to be clinically significant. Such a small effect could indicate that other,

non-TNF- α mediated mechanisms were important determinants of depression among the patients studied. However, a number of methodological characteristics of the included studies could also have influenced the size of observed effect. First, these small effects could be attributable, at least in-part, to the fact that the included studies did not specifically recruit patients with depression or anxiety (one study even excluded people with significant psychopathology). The prevalence of depression and anxiety (in the three studies where these were reported) were between 16–47%, meaning that the majority of patients were not depressed, thereby limiting the potential for antidepressant effects. Secondly, in the control arm of most of the included trials, active anti-inflammatory drugs (treatment as usual) were used which may have reduced the apparent effects of TNF- α inhibitors. Effects in trials using placebo control were not systematically greater than those that had used active treatment however, suggesting this is unlikely to have influenced the findings of this review.

Other randomised studies of TNF- α inhibitor treatment in chronic disease have reported effects on depression of greater magnitudes to that found in this review. Studies which have randomised patients with psoriasis to either paused or continuous etanercept treatment, or varying doses of etanercept, found 25–30% improvement in HADS depression scores, between a 1.5–2.0 decrease (compared to our mean effect difference in our review of 0.65) [55,56]. Whilst the intervention groups in the RCTs in our present review also saw decreases in depression of similar magnitude (i.e. of between 1.0–3.0 in HADS depression score), depression scores in the control groups in our included studies were also found to improve, albeit by less, hence the lower overall mean effect difference. Loftus, in their study randomising individuals to different doses of adalimumab for Crohn's disease, found a significant reduction in depression (9 points on the ZDS), slightly higher than that reported in the study by Menter et al., included within this review [57]. Of interest, the regimes used in these dosing studies were comparable and/or higher to those used in the studies in this present review, however none of them observed greater responses with the higher doses. Whilst these trials comparing different doses of the TNF- α inhibitors were excluded by our a priori criteria, their findings are in agreement with a small but significant effect of TNF- α inhibitors on depression.

Whilst our review provides evidence that treatment with TNF- α inhibitors improves depression, it fails to indicate whether the mechanisms of improving depression are directly mediated by a reduction in TNF- α or whether the benefits to depression are secondary to reductions in pain and disability associated with improvement in chronic inflammatory condition. None of the included studies provided sufficient detail of the timing of changes in depression relative to the changes in clinical disease status to determine whether improvements in mood predate improvements in markers of clinical status. In the study by Tyring et al. [42], there was a lack of a strong correlation between the improvements in depression and in markers of clinical disease status, which led the authors to conclude that treatment affected depression directly (i.e. not secondary to improvements in clinical status).

Raison et al. [58] have recently considered the mechanism of effect of TNF- α inhibitors on depression in the first published RCT of TNF- α inhibitor therapy (infliximab) for individuals with treatment resistant depression. They found that Infliximab had no overall effect on depression in the sample as a whole. Whilst individuals with diagnosed autoimmune disorders were excluded, the authors did find reductions in depression among subjects with higher baseline levels of inflammation (hs-CRP > 5 mg/L). In addition to this, a case study of TNF- α inhibitor therapy (infliximab) for five individuals with late onset depressive disorder, found no effect on depression in four individuals, but complete disappearance of depressive symptoms in the only patient with a comorbid inflammatory condition [59]. The findings of both of these studies are consistent with the conclusion that TNF- α inhibitors improve depression directly via inflammatory pathways, though both fall short of proving this mechanism of effect.

Future research needs to advance the extant findings and start to tease out some of the unknown issues highlighted. For example, does TNF- α inhibitor therapy benefit certain subgroups of populations with depression who present with elevated inflammatory biomarkers? As such, might existing levels of TNF- α , or other inflammatory biomarker, in individuals with depression indicate who is likely to respond to therapy? Furthermore, might there be other characteristics (biological, psychological and social) that identify who are most likely to respond to TNF- α inhibitor therapy? In terms of trying to understand the mechanism, there is still uncertainty about whether TNF- α inhibitors are having a direct effect on depression or whether they are indirectly improving depression by improving the underlying physical condition. Trials that look at the timing of the depression response might shed light on this and establish whether depression improves even when physical health does not.

Conclusion

In summary, TNF- α inhibitor therapy reduces depression and anxiety in people with chronic disease. Whilst this is consistent with a proposed inflammatory mechanism of depression, further studies are required to establish the mechanism of effect, by investigating a more detailed timeline of changes in depression, clinical markers of disease activity status and inflammatory biomarkers, and the extent to which improvements in depression correlate with improvements in clinical and inflammatory status.

Funding

This systematic review was funded by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South West Peninsula at the Royal Devon and Exeter NHS Foundation Trust. The funders had no role in the design or conduct of the review, data collection, analysis or interpretation, or approval of the manuscript. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests

The authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Contribution of authors

CD conceived the concept of the study and all authors contributed to the protocol of the study. RA, RW and AB screened and data extracted the literature. VN performed the data analyses, RA drafted the manuscript, and all authors commented on subsequent drafts and contributed to the interpretation, discussion and implications.

References

- [1] National Institute for Health and Clinical Excellence. Depression in adults with a chronic physical health problem: treatment and management; 2009[London].
- [2] Katon WJ, Rutter C, Simon G, Lin EH, Ludman E, Ciechanowski P, et al. The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care* 2005;28:2668–72.
- [3] Nicholson A, Kuper H, Hemingway H. Depression as an aetiological and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J* 2006;27:2763–74.
- [4] Ellis C, Zhao Y, Egede LE. Depression and increased risk of death in adults with stroke. *J Psychosom Res* 2010;68:545–51.
- [5] van Melle JP, de Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 2004;66:814–22.
- [6] de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. *Psychosom Med* 2001;63:619–30.
- [7] Dickens CM, McGowan L, Percival C, Tomenson B, Cotter L, Heagerty A, et al. Contribution of depression and anxiety to impaired health-related quality of life following first myocardial infarction. *Br J Psychiatry* 2006;189:367–72.
- [8] Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet* 2007;370:851–8.
- [9] Keeley P, Creed F, Tomenson B, Todd C, Borglin G, Dickens C. Psychosocial predictors of health-related quality of life and health service utilisation in people with chronic low back pain. *Pain* 2008;135:142–50.
- [10] Creed F, Morgan R, Fiddler M, Marshall S, Guthrie E, House A. Depression and anxiety impair health-related quality of life and are associated with increased costs in general medical inpatients. *Psychosomatics* 2002;43:302–9.
- [11] Gilmer TP, O'Connor PJ, Rush WA, Crain AL, Whitebird RR, Hanson AM, et al. Predictors of health care costs in adults with diabetes. *Diabetes Care* 2005;28:59–64.
- [12] Dickens CM, Percival C, McGowan L, Douglas J, Tomenson B, Cotter L, et al. The risk factors for depression in first myocardial infarction patients. *Psychol Med* 2004;34:1083–92.
- [13] Dickens C, McGowan L, Percival C, Tomenson B, Cotter L, Heagerty A, et al. Negative illness perceptions are associated with new-onset depression following myocardial infarction. *Gen Hosp Psychiatry* 2008;30:414–20.
- [14] Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosom Med* 2002;64:52–60.
- [15] Prince MJ, Harwood RH, Thomas A, Mann AH. A prospective population-based cohort study of the effects of disablement and social milieu on the onset and maintenance of late-life depression. The Gospel Oak Project VII. *Psychol Med* 1998;28:337–50.
- [16] Turvey CL, Schultz SK, Beglinger L, Klein DM. A longitudinal community-based study of chronic illness, cognitive and physical function, and depression. *Am J Geriatr Psychiatry* 2009;17:632–41.
- [17] Harrison J, Maguire P. Predictors of psychiatric morbidity in cancer patients. *Br J Psychiatry* 1994;165:593–8.
- [18] Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry* 2009;65:732–41.
- [19] Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *J Affect Disord* 2013;150:736–44.
- [20] Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med* 2009;71:171–86.
- [21] Himmerich H, Fulda S, Linseisen J, Seiler H, Wolfram G, Himmerich S, et al. Depression, comorbidities and the TNF-alpha system. *Eur Psychiatry* 2008;23:421–9.
- [22] Schmidt FM, Lichtblau N, Minkwitz J, Chittka T, Thormann J, Kirkby KC, et al. Cytokine levels in depressed and non-depressed subjects, and masking effects of obesity. *J Psychiatr Res* 2014;55:29–34.
- [23] Gimeno D, Kivimaki M, Brunner EJ, Elovainio M, De Vogli R, Steptoe A, et al. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychol Med* 2009;39:413–23.

- [24] Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the directionality of the depression–inflammation relationship. *Brain Behav Immun* 2009;23:936–44.
- [25] Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry* 2001;58:445–52.
- [26] Wright CE, Strike PC, Brydon L, Steptoe A. Acute inflammation and negative mood: mediation by cytokine activation. *Brain Behav Immun* 2005;19:345–50.
- [27] Beratis S, Katrivanou A, Georgiou S, Monastirli A, Pasmatzis E, Gourzis P, et al. Major depression and risk of depressive symptomatology associated with short-term and low-dose interferon-alpha treatment. *J Psychosom Res* 2005;58:15–8.
- [28] Musselman DL, Lawson DH, Gummnick JF, Manatunga AK, Penna S, Goodkin RS, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 2001;344:961–6.
- [29] Su KP, Lai HC, Yang HT, Su WP, Peng CY, Chang JP, et al. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: results from a randomized, controlled trial. *Biol Psychiatry* 2014;76:559–66.
- [30] Liu H, Luiten PG, Eisel UL, Dejongste MJ, Schoemaker RG. Depression after myocardial infarction: TNF-alpha-induced alterations of the blood-brain barrier and its putative therapeutic implications. *Neurosci Biobehav Rev* 2013;37:561–72.
- [31] Krugel U, Fischer J, Radicke S, Sack U, Himmerich H. Antidepressant effects of TNF-alpha blockade in an animal model of depression. *J Psychiatr Res* 2013;47:611–6.
- [32] Camara ML, Corrigan F, Jaehne EJ, Jawahar MC, Anscorb H, Baune BT. Effects of centrally administered etanercept on behavior, microglia, and astrocytes in mice following a peripheral immune challenge. *Neuropsychopharmacology* 2015;40:502–12.
- [33] Lichtenstein GR, Bala M, Han C, et al. Infliximab improves quality of life in patients with Crohn's disease. *Inflamm Bowel Dis* 2002;8(4):237–43.
- [34] Kekow J, Moots RJ, Emery P, Durez P, Koenig A, Singh A, et al. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: the COMET trial. *Ann Rheum Dis* 2010;69:222–5 [Erratum appears in *Ann Rheum Dis*. 2011 Aug;70(8):1519].
- [35] Arisoy O, Bes C, Cifci C, Sercan M, Soy M. The effect of TNF-alpha blockers on psychometric measures in ankylosing spondylitis patients: a preliminary observation. *Rheumatol Int* 2013;33:1855–64.
- [36] Ertenli I, Ozer S, Kiraz S, Apras SB, Akdogan A, Karadag O, et al. Infliximab, a TNF-alpha antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level. *Rheumatol Int* 2012;32:323–30.
- [37] Vogelzangs N, Beekman AT, de Jonge P, Penninx BW. Anxiety disorders and inflammation in a large adult cohort. *Transl psychiatry* 2013;3:e249.
- [38] Centre for Reviews and Dissemination. Systematic reviews: CRDs guidance for undertaking reviews in healthcare. York: Centre for Reviews and Dissemination, University of York; 2009.
- [39] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Br Med J* 2009;339:b2535.
- [40] Higgins JPT, Altman DG, Group obotCSM, Group. atCBM. Assessing risk of bias in included studies. In: Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions: the cochrane collaboration*; 2008.
- [41] van der Heijde D, Braun J, Dougados M, Sieper J, Pedersen R, Szumski A, et al. Sensitivity and discriminatory ability of the ankylosing spondylitis disease activity score in patients treated with etanercept or sulphasalazine in the ASCEND trial. *Rheumatology (Oxford)* 2012;51:1894–905.
- [42] Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 2006;367:29–35.
- [43] Borenstein M, Hedges L, Higgins J, HR R. *Introduction to meta-analysis*. Chichester, UK: John Wiley & Sons; 2009.
- [44] Cummings P. Meta-analysis based on standardized effects is unreliable. *Arch Pediatr Adolesc Med* 2004;158:595–7.
- [45] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J* 2003;327:557–60.
- [46] Cohen J. *Statistical power analysis for the behavioural sciences (2nd ed)*. New Jersey: Lawrence Erlbaum Associates; 1988.
- [47] Packham JC, Jordan KP, Haywood KL, Garratt AM, Healey EL. Evaluation of Ankylosing Spondylitis Quality of Life questionnaire: responsiveness of a new patient-reported outcome measure. *Rheumatology (Oxford)* 2012;51:707–14.
- [48] Bae SC, Gun SC, Mok CC, Khandker R, Nab HW, Koenig AS, et al. Improved health outcomes with etanercept versus usual DMARD therapy in an Asian population with established rheumatoid arthritis. *BMC Musculoskelet Disord* 2013;14:13.
- [49] Machado DA, Guzman RM, Xavier RM, Simon JA, Mele L, Pedersen R, et al. Open-label observation of addition of etanercept versus a conventional disease-modifying antirheumatic drug in subjects with active rheumatoid arthritis despite methotrexate therapy in the Latin American region. *J Clin Rheumatol* 2014;20:25–33.
- [50] Menter A, Augustin M, Signorovitch J, Yu AP, Wu EQ, Gupta SR, et al. The effect of adalimumab on reducing depression symptoms in patients with moderate to severe psoriasis: a randomized clinical trial. *J Am Acad Dermatol* 2010;62:812–8.
- [51] Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006;55:598–606.
- [52] Braun J, van der Horst-Bruinsma IE, Huang F, Burgos-Vargas R, Vlahos B, Koenig AS, et al. Clinical efficacy and safety of etanercept versus sulfasalazine in patients with ankylosing spondylitis: a randomized, double-blind trial. *Arthritis Rheum* 2011;63:1543–51.
- [53] Kim HY, Hsu PN, Barba M, Sulaiman W, Robertson D, Vlahos B, et al. Randomized comparison of etanercept with usual therapy in an Asian population with active rheumatoid arthritis: the APPEAL trial. *Int J Rheum Dis* 2012;15:188–96.
- [54] Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008;372:375–82.
- [55] Dauden E, Griffiths CE, Ortonne JP, Kragballe K, Molta CT, Robertson D, et al. Improvements in patient-reported outcomes in moderate-to-severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. *J Eur Acad Dermatol Venereol* 2009;23:1374–82.
- [56] Gniadecki R, Robertson D, Molta CT, Freundlich B, Pedersen R, Li W, et al. Self-reported health outcomes in patients with psoriasis and psoriatic arthritis randomized to two etanercept regimens. *J Eur Acad Dermatol Venereol* 2012;26:1436–43.
- [57] Loftus EV, Feagan BG, Colombel JF, Rubin DT, Wu EQ, Yu AP, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. [Erratum appears in *Am J Gastroenterol*. 2009 Jul;104(7):1894]. *Am J Gastroenterol* 2008;103:3132–41.
- [58] Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, Drake DF, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* 2013;70:31–41.
- [59] Maas DW, Westendorp RG, Willems JM, de Craen AJ, van der Mast RC. TNF-antagonist infliximab in the treatment of depression in older adults: results of a prematurely ended, randomized, placebo-controlled trial. *J Clin Psychopharmacol* 2010;30:343–5.