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# **Full search string used in PubMed**

Non-MeSH search terms:

((((((((((((((((renal dialysis) OR ((hemodialysis) OR haemodialysis)) OR ((end stage kidney disease) OR ESKD)) OR ((end stage kidney failure) OR ESKF)) OR ((end stage renal failure) OR ESRF)) OR ((hemodiafiltration) OR haemodiafiltration)) OR ((end stage renal disease) OR ESRD)) OR dialysis) OR ((chronic kidney disease) OR CKD)) OR ((chronic kidney failure) OR CKF)) OR kidney disease\*) OR ((pre dialysis) OR pre-dialysis)) OR renal replacement therapy) OR chronic renal disease)) AND (((((low mood) OR ((probable major depression) OR PMD)) OR dysthym\*) OR antidepressant\*) OR depress\*)) AND (((((((((((tumor necrosis factor) OR TNF)) OR (((C reactive protein) OR CRP) OR C-reactive protein)) OR ((interleukin) OR IL)) OR inflamm\*) OR cytokine) OR ((pro-inflammatory) OR pro inflammatory)) OR ((white blood cell\*) OR white cell count)) OR ((fibrinogen) OR factor I)) OR ((e-selectin) OR CD62))

MeSH search terms:

((((((("Depression"[Mesh]) OR "Depressive Disorder"[Mesh]) OR "Depressive Disorder, Major"[Mesh]) OR "Dysthymic Disorder"[Mesh]) OR "Antidepressive Agents"[Mesh])) AND (((((((("E-Selectin"[Mesh]) OR "Fibrinogen"[Mesh]) OR (("Leukocytes"[Mesh]) OR "Leukocyte Count"[Mesh])) OR (("Cytokines"[Mesh]) OR "Chemokines"[Mesh])) OR "Inflammation"[Mesh]) OR "Interleukins"[Mesh]) OR (("C-Reactive Protein"[Mesh]) OR "C-reactive protein receptor, human" [Supplementary Concept])) OR "Tumor Necrosis Factor-alpha"[Mesh])) AND (((((((("Kidney Failure, Chronic"[Mesh]) OR ((("Renal Dialysis"[Mesh]) OR "Dialysis"[Mesh]) OR "Kidneys, Artificial"[Mesh])) OR "Hemodialysis Units, Hospital"[Mesh]) OR "Kidney Diseases"[Mesh]) OR "Renal Insufficiency"[Mesh]) OR "Renal Insufficiency, Chronic"[Mesh]) OR "Hemodiafiltration"[Mesh]) OR "Renal Replacement Therapy"[Mesh])

# **Fields used for data extraction**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Details of article** | **Study characteristics**  | **Sample population characteristics** | **Depression data** | **Inflammation data** | **Results and statistics**  |
| Study ID  | Country of origin  | Eligible patients (inclusion) | Depression measure  | Inflammatory marker(s) used (measurement) | Main results |
| Date of extraction | Type of publication  | Exclusions | When was the depression measure administered | Is the inflammation binary, categorical or numerical? | Statistical test  |
| Data extractor (initials)  | Does the study meet inclusion criteria?  | Population  | Cut off scores for depression/severity of depression  | Cut off scores to diagnose high level of inflammation (measurement) | Test statistic |
| Authors  | Does the study meet exclusion criteria?  | Mininum HD duration  | Depression sample size n (%) (sample of population who are depressed) | Mean inflammation score (SD) for sample population of interest  | P-value  |
| Title  | Aims/objectives of study  | Sample size (n) | Range for depression score  | Range or IQR inflammation score for sample population of interest  | Cut off used for statistical significance? |
| Journal  | Data source  | Co-morbidities (n, %) | Mean depression score (SD) for population of interest  | Mean inflammation score for depressed group (SD) | Control for other relevant variables |
| Year  | Study design  | Age range (population of interest) | Is the depression outcome binary (depressed vs. non depressed), categorical or numerical (scores)? | Range/IQR inflammation score for depressed group  |  |
|  | Study period  | Mean age (SD) (population of intertest) | No depression group n (%)  | Mean inflammation score for not depressed group (SD) |  |
|  |  | Age range (healthy control group) | Control/comparison group  | Range/IQR inflammation score for not depressed group  |  |
|  |  | Mean age (SD) (Healthy control) | Control sample size  | When were blood samples taken?  |  |
|  |  | Age SD (Healthy control group) |  | How was inflammation measured? |  |
|  |  | Female n (%) In population of interest  |  |  |  |
|  |  | Ethnicity  |  |  |  |

# **Assessment tools used to assess study quality and risk of bias**

Risk of Bias 2 (RoB 2): RCT’s were assessed using RoB 2. RoB 2 assesses risk of bias for a single outcome across five domains (randomisation, deviations from intended interventions, missing outcome data, measurement of outcome, and selection of reported result). It also provides an overall judgement about risk of bias for each domain as well as overall risk of bias judgement.

Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I): ROBINS-I was used to assess Non randomised interventional studies. ROBINS-I contains seven domains through which risk may be introduced into a study these include confounding and selection of participants into a study, classification of intervention, deviations from intended intervention, missing data, measurement of outcomes and selection of reported result. Responses to each of these items provide domain-level judgements about risk of bias, using which we made an overall judgement of bias for a particular outcome (low risk, moderate risk, serious risk and critical risk of bias).

The Newcastle-Ottawa Scale (NOS): NOS was used to was used to assess the quality of cohort studies (CS). This assigns up to nine stars across three domains: 1) selection of study groups (4 stars); 2) comparability of groups (2 stars), and 3) ascertainment of exposure and outcomes (3 stars). Visually, more stars reflect less bias and study quality is rated as good, fair, or poor. In addition, studies were awarded one point for ascertainment of exposure if information was provided on how inflammatory biomarkers were measured (i.e., blood samples or medical records). For assessment of outcome, studies were awarded one star if depression was diagnosed through a structured clinical interview or if data was obtained from medical records; no stars were allocated for self-report measures or no description.

AXIS: Cross-sectional studies (CSSs) were assessed using the AXIS tool designed specifically for CSSs. The tool includes twenty questions relating to study design, sample size justification, target population, sampling frame, sample selection, measurement validity and reliability, and overall methods as opposed to the interpretation (e.g., discussion and conclusion) of the study. The tool does not provide a numerical score but allows the reviewer to assess each individual aspect of study design based on to give an overall judgment of study quality.

# **Supplementary Table 1: characteristics of 60 studies included in the review**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Study data type**1 | **Study location**  | **Sample**  | **Depression definition**  | **Patients with depression n(%)** | **Inflammatory biomarker(s)** | **Fit for purpose studies** | **Included in meta-analysis** |
| Alshogran2018 | Cross sectional | Jordan  | 274 HD | HADS-D ≥ 11 | 141 (51.5%) | IL-6 | yes | yes |
| Armaly2012 | Cross sectional | Israel  | 96 HD and controls  | BDI>11, DSM-IV criteria  | 31 (43.7%) | CRP | no | yes |
| Atalay2010 | Cross sectional  | Turkey  | 124 PD | BDI≥ 17, DSM-IV criteria  | 32 (25.8%) | CRP | no | yes |
| Barros 2016 | Cross sectional/ longitudinal cohort  | Brazil | 104 HD | BDI≥ 15 | 32 (30.8%)  | CRP | no | yes |
| Bornivell 2012 | Cross sectional  | Greece | 45 HD | HAM-D>7 | 16 (35%)  | CRP | no | yes |
| Bossola 2010 | Cross sectional  | Italy | 80 HD | BDI >14 | 42 (52.5%) | CRP; IL-6; Fibrinogen | no | yes |
| Bossola 2012 | Longitudinal cohort  | Italy  | 38 HD | BDI ≤14 | 19 (50%) | CRP; IL-6; Fibrinogen | no | no |
| Bossola 2015 | Cross sectional  | Italy | 100 HD | BDI≥ 10 | 74 (74%) | CRP; IL-6; Fibrinogen | yes | yes |
| Boulware2006 | Cross sectional  | US | 688 HD229 PD | MHI-5≥52 | 221 (24.1%) | CRP; IL-6; WBC count | yes | yes |
| Brys2020 | Cross sectional  | Italy | 59 HD | GDS ≥ 11 | NR | CRP; IL-6 | yes | yes |
| Chilcot 2017 | Cross sectional  | UK | 396 HD | BDI-II score ≥ 16PHQ9 score ≥ 10 | BDI-II: 121 (31.1%)PHQ 9: 108 (27.8%) | CRP | yes | yes |
| Chilcot2009 | Cross sectional | UK | 106 HD | BDI-II score ≥ 16 | 33 (31.1%) | CRP | no | no |
| Chilcot2011 | Cross sectional  | UK | 160 HD | BDI ≥ 16 | 41 (25.6%) | CRP | no | no |
| Choi2013 | Cross sectional  | Korea | 81 HD | BDI>18DSM-IV | 41 (50.6%) | Hs-CRP | no | yes |
| Cilan2012 | Cross sectional | Turkey | 60 HD 20 controls  | BDI (cut off not reported)HAM-D (cut off not reported)SCID | 9 (22.5%) | IL-6; TNF-a; IL-1 | yes | yes |
| Cilan2013 | Cross sectional | Turkey  | 40 PD20 controls  | BDI (cut off not reported)HAM-D (cut off not reported)SCID | 10 (25%) | HS-CRP; IL-6; TNF-a; IL-1 | yes | yes |
| Contreras2020 | Cross sectional | Mexico | 36 HD and PD | BDI (cut of score not stated) | 21 (58.3%) | Hs-CRP, Fibrinogen | yes | yes |
| Damayanti2018  | Cross sectional  | Indonesia | 47 HD | BDI>13 | 22 (100%) | IL-6 | yes | yes |
| Dervisoglu2008  | Cross sectional  | Turkey  | 93 HD and PD | BDI-II score ≥ 17 | 37 (40%) | Hs-CRP; IL-6; TNF-a | yes | yes |
| Dogan2005 | Cross sectional  | Turkey  | 43 HD | HAM-D >7 | 21 (48.8%) | CRP | no | yes |
| Dong2016 | Cross sectional  | China | 458 PD  | Zung self-rating depression scale > 0.5 | Mild:134 (29.3%)Moderate/severe: 104 (22.7%) | Hs-CRP  | no | yes |
| Fan2014 | Cross sectional  | US | 323 HD  | CES-D ≥ 17 | 83 (26%)  | CRP; WBC count | no | yes |
| Guenzani2019 | Cross sectional  | Italy | 132 CKD | GDS >5 | 81 (61.4%) | CRP; IL-6; TNF-a; IL-10; IL-12p70; IL-17  | yes | yes |
| Guney2009 | Cross sectional  | Turkey  | 124 PD | BDI ≥ 17 | n=32 (25.8%) | CRP | no | yes |
| Gyamlani2011 | Cross sectional  | US | 71 CKD  | PHQ2: 'yes' to either item 1 and/or2CES-D: ≥16 | PHQ2: 21 (30%)CES-D: 18 (25%) | CRP | yes | yes |
| Hao2021 | Cross sectional | China | 321 HD and PD | Zung self-rating depression scale≥ 50 | Mild: 69 (66.99%)Moderate: 32 (31.07%)Severe: 2 (1.94%) | Hs-CRP | yes | yes |
| Haverkamp2018 | Cross sectional  | Netherlands | 490 HD and PD  | BDI >13 | n=211 (43%) | Hs-CRP; IL-6; TNF-a; IL-10; IL-1B | yes | yes |
| Haverkamp2019 | Cross sectional/longitudinal cohort | Netherlands | Full sample: 513 HD and PD(complete sample: data at all three time points n=197)  | BDI-II >13 | Full sample: 226 (44%)Complete sample: 89 (45%) | Hs-CRP; IL-6; IL-10; TNF-a; IL-1B;  | yes | yes |
| Hsu2009 | Cross sectional  | Taiwan | 80 HD | HADS-D ≥8 | 30 (37.5%) | CRP | no | yes |
| HsuChen2009 | Cross sectional  | Taiwan | 51 HD | HADS-D ≥9 | 18 (35.3%) | CRP | no | yes |
| Hung2010 | Cross sectional  | Taiwan | 146 HD | BDI ≥14 | 68 (46.6%) | Hs-CRP; IL-6 | no | yes |
| Jong2017 | Cross sectional  | Taiwan | 130 HD  | BDI ≥15 | 43 (33.3%) | Hs-CRP; IL-6; TNF-a | no | yes |
| Kalendar2006 | Cross sectional  | Turkey  | 141 ESRD and CKD  | SCID | 34 (24.1%) | CRP | yes | yes |
| Kalendar2007 | Cross sectional  | Turkey  | 42 PD | SCID | 11 (26.2%) | Hs-CRP; IL-6; TNF-a; IL-1 | yes | yes |
| Kim2012 | Cross sectional  | Korea | 78 HD | BDI-II ≥ 20 | 35 (44.9%) | Hs-CRP | no | yes |
| Knuth2014 | Cross sectional  | Brazil | 75 HD | BDI ≥ 14 | 36 (48.0%) | IL-6 | yes | yes |
| Ko2010 | Cross sectional  | Korea | 81 PD  | BDI>15 | 43 (53.8%) | Hs-CRP; IL-10; TNF-a; Fibrinogen  | yes | yes |
| Kusztal2018 | Cross sectional  | Poland | 205 HD | HADS-D ≥ 8 | 62 (30.2%) | CRP | no | yes |
| Li2011 | Cross sectional  | China | 142 PD  | HAM-D≥10 | 37 (26.1%) | CRP | yes | yes |
| Lin2013 | Cross sectional  | China | 191 PD | BDI-II≥14 | 65 (34.0%)  | CRP | no | no |
| Malhotra2017 | Cross sectional  | US | 92 HD  | PHQ9 >10 | NR  | CRP | no | yes |
| Micozkadioglu2006 | Cross sectional  | Turkey  | 110 HD | CID>10 | 71 (64.5%) | CRP | no | yes |
| Mok2018 | Cross sectional  | Hong Kong | 182 PD  | HADS-D >11 | 110 (60.4%) | CRP | no | yes |
| Montinaro2010 | Cross sectional  | Italy | 150 CKD & HD | HADS-D≥8 | HD: 15 (50%)CKD: 4 (20%) | IL-6; TNF-a; IL-1; IL-10 | yes | no |
| Nie2019 | Cross sectional  | China | 458 PD | SDS >0.5 | mild depression: 134 (29.3%)moderate/severe depression:104 (22.7% | Hs-CRP | no | yes |
| Nowak2013 | Cross sectional  | Poland | 694 HD  | BDI>16 | 268 (38.6%) | CRP | yes | yes |
| Ogrizovic2008 | Cross sectional | Serbia  | 128 HD and PD | BDI-II>13 | 58 (45.3%) | Hs-CRP; IL-6; IL-10 | no | yes |
| Oguz2016 | Cross sectional  | Turkey  | 40 PD  | BDI ≥10 | 16 (40.0%) | Hs-CRP | no | yes |
| Park2010 | Cross sectional  | Korea | 160 HD  | BDI≥18 | 51 (31.9%) | CRP | no | yes |
| Park2012 | Cross sectional  | Korea | 105 PD | BDI>19 | 26 (24.8%) | CRP | no | yes |
| Schricker2019 | Cross sectional  | Germany  | 54 HD; PD; controls  | ADS-L >23 | NR | CRP; IL-6 | yes | yes |
| Sonikian2010 | Cross sectional  | Greece | 64 HD;PD; controls | SDS≥ 50 | NR | IL-6 | yes | yes |
| Su2012 | Cross sectional  | Taiwan | 320 HD  | BDI >14 | (data provided for sub-groups only)SHD: 118 (43.1%)HDF: 11 (23.9%)  | Hs-CRP | no | yes |
| Taraz2012 | Cross sectional  | Iran | 83 HD  | BDI≥16 | 51 (61.4%)  | Hs-CRP; IL-6; TNF-a; IL-1B; IL-10 | yes | yes |
| Tufan2014 | Cross sectional  | Turkey  | 80 HD | BDI≥17 | 19 (23.8%) | CRP | yes | yes |
| Uglesic2015 | Cross sectional  | Croatia | 88 HD and PD  | BDI≥16 | 25 (28.4%)HD: 18 (35%)PD: 7 (18.1%) | CRP; IL-6 | no | yes |
| Wang2016 | Cross sectional  | Taiwan | 195 HD  | DSM-IV | 47 (24.1%) | CRP; IL-6; TNF-a; IL-1 | yes | yes |
| Yavuz2015 | Cross sectional  | Turkey  | 137 HD  | BDI≥17 | 55 (40.2%) | CRP | yes | yes |
| Zhang2014 | Cross sectional/Interventional non RCT | China | 484 HD and PD  | BDI>16 | 213 (44.0%) | Hs-CRP | yes | yes |
| Zhao2017 | Cross sectional/ RCT  | China | 189 HD (MG -medicine group; MAG - medicine and aerobics group; AG -aerobics group) | BDI-IINo symptoms (0–13)mild (14–19)moderate (20–28)severe (29–63) | Depression severity (%)MG groupNo symptoms: 8Mild: 5Moderate: 7Severe: 42MAG group: No symptoms: 11Mild: 5Moderate: 4Severe: 43AG group:No symptoms: 13Mild: 9Moderate: 8Severe: 33 | IL-6, IL-18 | yes | yes |

RCT: Randomised Control Trial; US: United States; UK: United Kingdom; HD: Hemodialysis; SHD: Standard Hemodialysis; HDF: Hemodiafiltration; PD: Peritoneal Dialysis; CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease; NR: Not Reported; IL-6: Interleukin 6; CRP: C-Reactive Protein; Hs-CRP: Higher sensitivity C-Reactive Protein; WBC: White Blood Cell; IL-1: Interleukin 1; TNF-a: Tumour Necrosis Factor Alpha; IL-10: Interleukin 10; IL-1b: Interleukin 1 beta; IL-17: Interleukin 17; IL-18: Interleukin 18; IL-12p70: Interleukin 12.

# **Supplementary table 2: Study quality or risk of bias for all studies included in the review**

|  |  |  |  |
| --- | --- | --- | --- |
| **Study ID** | **Study data type** | **Quality assessment tool**  | **Quality rating** |
| Alshogran2018 | Cross sectional | AXIS | Good |
| Armaly2012 | Cross sectional | AXIS | Fair |
| Atalay2010 | Cross sectional  | AXIS | Good |
| Barros 2016 | Cross sectional/ longitudinal cohort  | AXISNOS | AXIS - GoodNOS - Fair |
| Bornivell 2012 | Cross sectional  | AXIS | Poor |
| Bossola 2010 | Cross sectional  | AXIS | Good |
| Bossola 2012 | Longitudinal cohort  | NOS | Fair |
| Bossola 2015 | Cross sectional  | AXIS | Good |
| Boulware2006 | Cross sectional  | AXIS | Fair |
| Brys2020 | Cross sectional  | AXIS | Good |
| Chilcot 2017 | Cross sectional  | AXIS | Good |
| Chilcot2009 | Cross sectional | AXIS | Good |
| Chilcot2011 | Cross sectional  | AXIS | Good |
| Choi2013 | Cross sectional  | AXIS | Fair |
| Cilan2012 | Cross sectional | AXIS | Good |
| Cilan2013 | Cross sectional | AXIS | Good |
| Contreras2020 | Cross sectional  | AXIS | Poor |
| Damayanti2018  | Cross sectional  | AXIS | Good |
| Dervisoglu2008  | Cross sectional  | AXIS | Good |
| Dogan2005 | Cross sectional  | AXIS | Fair |
| Dong2016 | Cross sectional  | AXIS | Good |
| Fan2014 | Cross sectional  | AXIS | Good |
| Guenzani2019 | Cross sectional  | AXIS | Good |
| Guney2009 | Cross sectional  | AXIS | Fair |
| Gyamlani2011 | Cross sectional  | AXIS | Good |
| Hao2021 | Cross sectional  | AXIS | Good |
| Haverkamp2018 | Cross sectional  | AXIS | Good |
| Haverkamp2019 | Cross sectional/longitudinal cohort | AXISNOS | AXIS - GoodNOS - Good |
| Hsu2009 | Cross sectional  | AXIS | Good |
| HsuChen2009 | Cross sectional  | AXIS | Good |
| Hung2010 | Cross sectional  | AXIS | Good |
| Jong2017 | Cross sectional  | AXIS | Good |
| Kalendar2006 | Cross sectional  | AXIS | Good |
| Kalendar2007 | Cross sectional  | AXIS | Fair |
| Kim2012 | Cross sectional  | AXIS | Good |
| Knuth2014 | Cross sectional  | AXIS | Good |
| Ko2010 | Cross sectional  | AXIS | Good |
| Kusztal2018 | Cross sectional  | AXIS | Good |
| Li2011 | Cross sectional  | AXIS | Fair |
| Lin2013 | Cross sectional  | AXIS | Good |
| Malhotra2017 | Cross sectional  | AXIS | Good |
| Micozkadioglu2006 | Cross sectional  | AXIS | Fair |
| Mok2018 | Cross sectional  | AXIS | Good |
| Montinaro2010 | Cross sectional  | AXIS | Fair |
| Nie2019 | Cross sectional  | AXIS | Good |
| Nowak2013 | Cross sectional  | AXIS | Good |
| Ogrizovic2008 | Cross sectional | AXIS | Fair |
| Oguz2016 | Cross sectional  | AXIS | Good |
| Park2010 | Cross sectional  | AXIS | Good |
| Park2012 | Cross sectional  | AXIS | Good |
| Schricker2019 | Cross sectional  | AXIS | Fair |
| Sonikian2010 | Cross sectional  | AXIS | Fair |
| Su2012 | Cross sectional  | AXIS | Fair |
| Taraz2012 | Cross sectional  | AXIS | Good |
| Tufan2014 | Cross sectional  | AXIS | Good |
| Uglesic2015 | Cross sectional  | AXIS | Good |
| Wang2016 | Cross sectional  | AXIS | Good |
| Yavuz2015 | Cross sectional  | AXIS | Good |
| Zhang2014 | Cross sectional  | AXIS | Fair |
| Zhao2017 | RCT  | RoB-2 | RoB-2 -Low risk |

# **Overview of narrative synthesis**

A narrative synthesis was carried out according to published guidance[[1]](#footnote-1). Initially the preliminary synthesis was developed by tabulation of study design, aims, study location, total sample, mean age ± SD, n and % women, depression definition, sample size and percentage of patients with depression, specific inflammatory biomarkers, summary of main findings, as well as information about interventions and follow up time points (if relevant). The main overarching themes were identified across the studies and subcategorized according to specific inflammatory biomarkers. Inflammatory markers reported within the theme and whether the study reported a significant or non-significant result for the specified outcome. Studies reporting data on IL-1 inflammatory marker were not included as none specified the type of IL-1 marker.

Following familiarisation and comparison for similarities and contrasts, preliminary synthesis was performed to capture relationships between individual characteristics of studies and the findings. This was done by looking at heterogeneity in the included studies, which involved detailed inspection of sample sizes, sample characteristics, study location, depression definition as well as patient inclusion and exclusion criteria. Finally, the strength of evidence provided by the studies was assessed by consistency of findings for similar designs and outcomes, accounting for quality and risk of bias.

# **Supplementary Figure 1: Random effects meta-analysis forest plot of all studies with baseline IL-1B levels in depressed and non-depressed patients**



Heterogeneity: Tau2= 0.00, Q-value = 0.98, df (Q)=2, I2=0%, p=0.61

Overall

# **Supplementary Figure 2: Random effects meta-analysis forest plot of all studies with baseline fibrinogen levels in depressed and non-depressed patients**



Heterogeneity: Tau2= 0.04, Q-value = 4.67, df (Q)=2, I2=35.79%, p=0.2

Overall

|  |  |
| --- | --- |
|  | **Heterogeneity** |
| **Inflammatory marker** | **Depression definition** | **No. of studies**  | **Pooled standardized mean difference** | **p-value** | **95% CI - lower limit** | **95% CI- upper limit** | **Q-value** | **df (Q)** | **p-value** | **I-squared (%)** | **Tau**² |
| CRP | Validated self-report depression tool | 44 | 0.488 | **<0.0001\*** | 0.245 | 0.731 | 1032.712 | 43 | **<0.0001\***  | 95.836 | 0.791 |
| Structured clinical interview  | 7 | 0.56 | 0.08 | -0.043 | 1.160 | 13.435 | 6 | **0.037\*** | 55.339 | 0.069 |
| IL-6 | Validated self-report depression tool | 25 | 0.736 | **<0.001\*** | 0.389 | 1.084 | 692.916 | 24 | **<0.001\*** | 96.536 | 0.754 |
| Structured clinical interview | 4 | 0.228 | 0.62 | -0.664 | 1.121 | 1.101 | 3 | 0.777 | 0.000 | 0.000 |
| TNF-a | Validated self-report depression tool | 7 | 0.592 | **0.027** | 0.069 | 1.115 | 136.584 | 6 | **<0.0001** | 95.607 | 0.505 |
| Structured clinical interview  | 4 | 0.005 | 0.988 | -0.720 | 0.731 | 2.221 | 3 | 0.528 | 0.000 | 0.000 |
| IL-10 | Validated self-report depression tool | 6 | -0.574 | **<0.0001\***  | -1.090 | -0.059 | 95.024 | 5 | **<0.0001\***  | 94.738 | 0.376 |
| IL-1B | Validated self-report depression tool | 3 | -0.007 | 0.093 | -0.127 | 0.112 | 0.978 | 2 | 0.613 | 0.000 | 0.000 |
| Fibrinogen  | Validated self-report depression tool | 4 | 0.636 | **<0.0001\***  | 0.325 | 0.946 | 4.672 | 3 | 0.197 | 35.791 | 0.036 |

# **Supplementary Table 3: meta-analysis for baseline inflammatory markers and depression groups defined by self-report or clinical interview.**

 \*p<0.05 NB:All baseline studies reporting IL-10, IL-1B and fibrinogen data used a validated self-report depression tool to define depression

# **Supplementary Table 4: Sensitivity analysis on study quality for baseline study data on inflammation and depression**

|  |  |
| --- | --- |
|   | **Heterogeneity** |
| **Inflammatory marker** | **Analysis** | **No. of studies**  | **Subgroup**  | **Pooled standardized mean difference** | **p-value** | **95% CI - lower limit** | **95% CI- upper limit** | **Q-value** | **df (Q)** | **p-value** | **I-squared (%)** | **Tau**² |
| CRP | Study quality of all observational studies  | 2 | Poor | 0.843 | 0.161 | -0.336 | 2.002 | 0.019 | 1 | 0.891 | 0.000 | 0.000 |
| 13 | Fair | 0.577 | **0.017\*** | 0.105 | 1.048 | 120.429 | 11 | **<0.001\*** | 90.866 | 0.814 |
| 36 | Good | 0.41 | **0.003\*** | 0.143 | 0.672 | 705.714 | 35 | **<0.001\*** | 95.040 | 0.548 |
| Study quality: (total between group heterogeneity | n/a | n/a  | n/a | n/a | n/a | n/a | 1.580 | 2 | 0.454 | n/a | n/a |
| IL-6 | Study quality of all observational studies  | 5 | Fair | 0.524 | 0.190 | -0.259 | 1.306 | 19.555 | 4 | **0.001** | 79.545 | 0.171 |
| 21 | Good | 0.503 | **0.009** | 0.126 | 0.879 | 586.095 | 20 | **<0.001** | 96.588 | 0.789 |
| Study quality: observational good vs fair quality studies (total between group heterogeneity | n/a | n/a | n/a | n/a | n/a | n/a | 0.002 | 1 | 0.962 | n/a | n/a |
| TNF-a | Study quality of all observational studies | 1 | Fair  | 0.176 | 0.81 | -1.255 | 1.608 | 0.00 | 0 | 1.000 | 0.000 | 0.000 |
| 10 | Good | 0.401 | 0.066 | -0.026 | 0.829 | 138.879 | 9 | **<0.0001** | 93.520 | 0.410 |
| Study quality: observational good vs fair quality studies (total between group heterogeneity | n/a | n/a | n/a | n/a | n/a | n/a | 0.087 | 1 | 0.768 | n/a | n/a |
| IL-10 | Study quality of all observational studies | 1 | Fair | 0.119 | 0.861 | -1.217 | 1.454 | 0.000 | 1 | 1.000 | 0.000 | 0.000 |
| 5 | Good | -0.729 | **0.018** | -1.332 | -0.125 | 91.051 | 4 | **<0.0001\***  | 95.607 | 0.433 |
| Study quality: observational good vs fair quality studies (total between group heterogeneity | n/a | n/a  | n/a | n/a | n/a | n/a | 1.285 | 1 | 0.257 | n/a | n/a |
| Fibrinogen | Study quality of all observational studies | 3 | Good | 0.522 | **<0.0001\*** | 0.263 | 0.780 | 0.692 | 2 | 0.707 | 0.000 | 0.000 |
| 1 | Poor | 1.308 | **<0.0001\*** | 0.580 | 2.037 | 0.000 | 0 | 1.000 | 0.000 | 0.000 |
| Study quality: observational good quality studies vs poor quality studies (total between group heterogeneity | n/a | n/a  | n/a | n/a | n/a | n/a | 3.980 | 1 | 0.046 | n/a | n/a |

\* p<0.05 NB: RCT’s were not included in sensitivity analyses as they were all of good quality with low risk of bias. Study quality sensitivity analyses was not carried out for IL-1B and fibrinogen as all studies were of good quality

# **Supplementary Table 5: Sensitivity analysis on effect size calculation format for baseline study data on inflammation and depression**

|  |  |
| --- | --- |
|   | **Heterogeneity** |
| **Data timepoint**  | **Analysis**  | **No. of studies**  | **Subgroup**  | **Pooled standardized mean difference** | **p-value** | **95% CI - lower limit** | **95% CI- upper limit** | **Q-value** | **df (Q)** | **p-value** | **I-squared (%)** | **Tau**² |
| CRP | Effect size calculation formats  | 39 | Means and SD | 0.53 | **<0.0001\*** | 0.472 | 0.580 | 997.857 | 38 | **<0.0001\***  | 96.19 | 0.761 |
| 7 | Correlation analysis  | 0.38 | **<0.0001\*** | 0.228 | 0.527 | 11.504 | 6 | 0.07 | 47.844 | 0.044 |
| 2 | Regression analysis  | 0.498 | 0.10 | 0.339 | 1.934 | 20.273 | 1 | **<0.0001\***  | 95.067 | 0.439 |
| 3 | Frequency distribution | 0.178 | **0.042\*** | 0.007 | 0.657 | 0.266 | 2 | 0.88 | 0.000 | 0.000 |
| Effect size calculation format: Means and SD vs correlation analysis (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 0.031 | 1 | 0.86 | n/a | n/a |
| Effect size calculation format: Means and SD vs regression analysis (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 0.199 | 1 | 0.66 | n/a | n/a |
| Effect size calculation format: Means and SD vs frequency distribution (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 0.463 | 1 | 0.5 | n/a | n/a |
| IL-6 | Effect size calculation format | 10 | Mean and SD | 0.532 | **0.018** | 0.091 | 0.973 | 576.272 | 16 | **<0.001** | 97.224 | 0.815 |
| 17 | Correlation | 1.104 | **<0.001** | 0.561 | 1.648 | 65.463 | 9 | **<0.001** | 86.252 | 0.653 |
| Effect size calculation format: Means and SD vs correlation analysis (total between group heterogeneity) | n/a | n/a | n/a | n/a | n/a | n/a | 2.566 | 1 | 0.11 | n/a | n/a |
| TNF-a | Effect size calculation format | 8 | Means and SD | 0.656 | 0.054 | -0.013 | 1.325 | 137.37 | 7 | **<0.0001** | 94.904 | 0.838 |
| 1 | Correlation analysis  | -0.110 | 0.602 | -0.524 | 0.304 | 0.00 | 0 | 1.000 | 0.000 | 0.000 |
| 2 | Regression analysis | -0.006 | 0.939 | -0.162 | 0.150 | 0.374 | 1 | 0.541 | 0.000 | 0.000 |
|  |  |  |  |  |  |  |  |  |  |  |  |
| Effect size calculation format: Means and SD vs correlation analysis (total between group heterogeneity) | n/a | n/a | n/a | n/a | n/a | n/a | 3.638 | 1 | 0.056 | n/a | n/a |
| Effect size calculation format: Means and SD vs regression analysis (total between group heterogeneity) | n/a | n/a | n/a | n/a | n/a | n/a | 3.563 | 1 | 0.059 | n/a | n/a |
| IL-10 | Effect size calculation format | 4 | Means and SD | -0.934 | 0.062 | -1.913 | 0.046 | 88.468 | 3 | **<0.0001\***  | 96.609 | 0.946 |
| 2 | Regression analysis  | -0.075 | 0.347 | -0.230 | 0.081 | 0.362 | 1 | 0.547 | 0.000 | 0.000 |
| Effect size calculation format: Means and SD vs regression analysis (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 2.881 | 1 | 0.090 | n/a | n/a |
| IL-1B | Effect size calculation format | 2 | Means and SD | 0.027 | 0.749 | -0.139 | 0.193 | 0.629 | 1 | 0.428 | 0.000 | 0.000 |
|  | 1 | Regression analysis  | -0.045 | 0.609 | -0.219 | 0.128 | 0.000 | 0 | 1.000 | 0.000 | 0.000 |
|  | Effect size calculation format: Means and SD vs regression (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 0.349 | 1 | 0.555 | n/a | n/a |

\* p<0.05 NB: Effect size calculation for fibrinogen levels were based on means and standard deviations.

# **Supplementary Table 6: additional sensitivity analysis for study design for IL-6 and depression**

|  |  |
| --- | --- |
|  | Heterogeneity |
| Inflammatory marker  | Analysis | No. of studies  | Subgroup  | Pooled standardized mean difference | p-value | 95% CI - lower limit | 95% CI- upper limit | Q-value | df (Q) | p-value | I-squared (%) | Tau² |
| IL-6 | Study design | 26 | Cross sectional  | 0.506 | **0.002** | 0.183 | 0.829 | 633.987 | 25 | **<0.001** | 96.057 | 0.657 |
| 3 | RCT | 2.249 | **<0.001** | 1.238 | 3.259 | 0.733 | 2 | 0.693 | 0.000 | 0.000 |
| Study design: Cross sectional vs RCT (total between group heterogeneity) | n/a | n/a | n/a | n/a | n/a | n/a | 10.358 | 1 | **0.001** | n/a | n/a |

 \*p<0.05 NB: data for IL-6 inflammatory markers were from mixed study designs. Data for all other inflammatory markers were from cross sectional studies.

# **Supplementary Table 7: additional subgroup analysis for studies excluding patients with infections/inflammatory diseases**

|  |  |
| --- | --- |
|   | **Heterogeneity** |
| **Data timepoint**  | **Analysis**  | **No. of studies**  | **Subgroup**  | **Pooled standardized mean difference** | **p-value** | **95% CI - lower limit** | **95% CI- upper limit** | **Q-value** | **df (Q)** | **p-value** | **I-squared (%)** | **Tau**² |
| CRP | Infections/inflammatory diseases |  | Excluded | 0.447 | **0.02\*** | 0.82 | 0.8 | 155.59 | 17 | **<0.001\*** | 89.07 | 0.34 |
|  | Not stated | 0.523 | **<0.001\*** | 0.25 | 0.8 | 873.60 | 32 | **<0.001\*** | 96.34 | 0.67 |
| Infections/inflammatory diseases: excluded vs not stated (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 0.11 | 1 | 0.75 | n/a | n/a |
| IL-6 | Infections/inflammatory diseases | 17 | Excluded | 0.741 | **<0.001\*** | 0.31 | 1.18 | 113.68 | 16 | **<0.001\*** | 85.93 | 0.35 |
| 12 | Not stated | 0.576 | **0.02\*** | 0.08 | 1.08 | 581.8 | 11 | **<0.001\*** | 98.11 | 0.94 |
| Infections/inflammatory diseases: excluded vs not stated (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 0.24 | 1 | 0.63 | n/a | n/a |
| TNF-a | Infections/inflammatory diseases | 5 | Excluded | 0.9 | **<0.001\*** | 0.26 | 1.54 | 128.14 | 4 | **<0.001\*** | 96.88 | 2.88 |
| 6 | Not stated | 0.02 | 0.94 | -0.51 | 0.56 | 3.31 | 5 | 0.65 | 0.00 | 0.00 |
| Infections/inflammatory diseases: excluded vs not stated (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 4.26 | 1 | **0.04\*** | n/a | n/a |
| IL-10 | Infections/inflammatory diseases format | 3 | Excluded | -1.14 | **0.00\*** | -1.92 | -0.35 | 82.96 | 2 | **0.00\*** | 97.59 | 2.34 |
|  | 3 | Not stated | -0.89 | 0.82 | -0.833 | 0.66 | 4.44 | 2 | 0.11 | 54.94 | 0.02 |
| Infections/inflammatory diseases: excluded vs not stated (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 3.58 | 1 | 0.06 | n/a | n/a |
| IL-1B | Infections/inflammatory diseases format |  1 | Excluded | 0.19 | 0.39 | -0.25 | 0.64 | 0.00 | 0 | 1.00 | 0.00 | 0.00 |
| 2 | Not stated | -0.02 | 0.71 | -0.15 | 0.10 | 0.13 | 1 | 0.72 | 0.00 | 0.00 |
| Infections/inflammatory diseases: excluded vs not stated (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 0.85 | 1 | 0.36 | n/a | n/a |
| Fibrinogen  | Infections/inflammatory diseases format | 2 | Excluded  | 0.45 | **0.007\*** | 0.12 | 0.77 | 0.00 | 1 | 0.95 | 0.00 | 0.00 |
| 2 | Not stated | 0.86 | **<0.001\*** | 0.47 | 1.25 | 2.08 | 1 | 0.15 | 51.89 | 0.13 |
|  | Infections/inflammatory diseases: excluded vs not stated (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 2.52 | 1 | 0.11 | n/a | n/a |

\* p<0.05

# **Supplementary Table 8: additional subgroup analysis for studies excluding patients on NSAIDs**

|  |  |
| --- | --- |
|   | **Heterogeneity** |
| **Data timepoint**  | **Analysis**  | **No. of studies**  | **Subgroup**  | **Pooled standardized mean difference** | **p-value** | **95% CI - lower limit** | **95% CI- upper limit** | **Q-value** | **df (Q)** | **p-value** | **I-squared (%)** | **Tau**² |
| CRP | NSAIDs | 5 | Excluded | 0.35 | 0.33 | -0.39 | 1.06 | 2.76 | 4 | 0.6 | 0.00 | 0.00 |
| 46 | Not stated | 0.51 | **<0.001\*** | 0.28 | 0.74 | 1040.66 | 45 | **<0.001\*** | 95.68 | 0.78 |
| NSAIDs: excluded vs not stated (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 0.18 | 1 | 0.67 | n/a | n/a |
| IL-6 | NSAIDs | 4 | Excluded | 0.45 | 0.33 | -0.44 | 1.34 | 5.34 | 3 | 0.15 | 43.8 | 0.28 |
| 25 | Not stated | 0.7 | **<0.001\*** | 0.36 | 1.05 | 691.29 | 24 | **<0.001\*** | 96.53 | 0.86 |
| NSAIDs: excluded vs not stated (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 0.28 | 1 | 0.6 | n/a | n/a |
| TNF-a | NSAIDs | 2 | Excluded | -0.19 | 0.46 | -0.71 | 0.32 | 0.59 | 1 | 0.44 | 0.00 | 0.00 |
| 2 | Not stated | 0.19 | 0.2 | -0.1 | 0.49 | 0.00 | 1 | 0.95 | 0.00 | 0.0 |
| NSAIDs: excluded vs not stated (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 1.62 | 1 | 0.2 | n/a | n/a |
| IL-10 | NSAIDs | 1 | Excluded | -0.26 | 0.71 | -1.61 | 1.09 | 0.00 | 0 | 1.00 | 0.00 | 0.00 |
| 5 | Not stated | -0.65 | 0.03 | -1.24 | -0.5 | 94.99 | 4 | **<0.001\*** | 95.79 | 0.65 |
| NSAIDs: excluded vs not stated (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 0.26 | 1 | 0.61 | n/a | n/a |
| IL-1B | NSAIDs | 1 | Excluded | 0.19 | 0.39 | -0.25 | 0.64 | 0.00 | 0 | 1.00 | 0.00 | 0.00 |
| 2 | Not stated | -0.02 | 0.71 | -0.15 | 0.1 | 0.13 | 1 | 0.72 | 0.00 | 0.00 |
| NSAIDs: excluded vs not stated (total between group heterogeneity) | n/a | n/a  | n/a | n/a | n/a | n/a | 0.85 | 1 | 0.36 | n/a | n/a |

\* p<0.05 NB: all studies for fibrinogen did not state whether patients on NSAIDs were excluded.

# **PRISMA checklist 2020**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section and Topic**  | **Item #** | **Checklist item**  | **Location where item is reported** |
| **TITLE**  |  |
| Title  | 1 | Identify the report as a systematic review. | 1 |
| **ABSTRACT**  |  |
| Abstract  | 2 | See the PRISMA 2020 for Abstracts checklist. | 1-2 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of existing knowledge. | 3-4 |
| Objectives  | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 4 |
| **METHODS**  |  |
| Eligibility criteria  | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 4 |
| Information sources  | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 5 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | 5 (supplementary materials page 2)  |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 5 |
| Data collection process  | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 6 |
| Data items  | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | 6 |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | 6 (supplementary materials page 3) |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 6-7 (supplementary materials page 5) |
| Effect measures  | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | 7-8 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | 7 |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | 7 |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | Supplementary materials page 11 |
| 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | 8 |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | 8-9 |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | 8-9 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 9 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | 9 |
| **RESULTS**  |  |
| Study selection  | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | 9, figure 1 |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | Figure 1, page 16 |
| Study characteristics  | 17 | Cite each included study and present its characteristics. | Supplementary table 1 |
| Risk of bias in studies  | 18 | Present assessments of risk of bias for each included study. | Supplementary table 2 |
| Results of individual studies  | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | Figure 2-5  |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | 9 |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 10-16, Figure 2-5, table 3 |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | 10-16, supplementary table 4-6 |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Table 4-6 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | n/a |
| Certainty of evidence  | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | 10-16, Figure 2-5, table 3 |
| **DISCUSSION**  |  |
| Discussion  | 23a | Provide a general interpretation of the results in the context of other evidence. | 16-19 |
| 23b | Discuss any limitations of the evidence included in the review. | 19 |
| 23c | Discuss any limitations of the review processes used. | 19 |
| 23d | Discuss implications of the results for practice, policy, and future research. | 18-19 |
| **OTHER INFORMATION** |  |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | 4 |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | 4 |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | n/a |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | 21 |
| Competing interests | 26 | Declare any competing interests of review authors. | 21 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | n/a |

1. Popay, J, Roberts, H, Sowden, A, Petticrew, M, Arai, L, Rodgers, M, Britten, N, Roen, K, Duffy, S (2006). Guidance on the Conduct of Narrative Synthesis in Systematic Reviews. ESRC Methods Programme: University of Lancaster, UK [↑](#footnote-ref-1)