A Systematic Review and meta-analysis of the Evidence on Inflammation in Depressive Illness and Symptoms in Chronic and End Stage Kidney Disease

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Abstract

Background

Depression affects approximately 27% of adults with chronic kidney disease (CKD) and End Stage Kidney Failure (ESKF). Depression in this population is associated with impaired quality of life and increased mortality. The extent of inflammation and the impact on depression in CKD/ESKF is yet to be established. Through a systematic literature review and meta-analysis, we aim to understand the relationship between depression and inflammation in CKD/ESKF patients.

Methods

We searched nine electronic databases for published studies up to January 2022. Titles and abstracts were screened against an inclusion and exclusion criteria. Data extraction and study quality assessment was carried out independently by two reviewers. A meta-analysis was carried out where appropriate, otherwise a narrative review of studies was completed.

Results

Sixty studies met our inclusion criteria and entered the review (9481 patients included in meta-analysis). Meta-analysis of cross-sectional associations revealed significantly higher levels of pro-inflammatory biomarkers; C-reactive protein (CRP); Interleukin 6 (IL-6) and Tumor necrosis factor alpha (TNF-a) in patients with depressive symptoms (DS) compared to patients without DS. Significantly lower levels of anti-inflammatory cytokine Interleukin 10 (IL-10) were found in patients with DS compared to patients without DS. Considerable heterogeneity was detected in the analysis for most inflammatory markers.

Conclusion

We found evidence for an association of higher levels of pro-inflammatory and lower anti-inflammatory cytokines and DS in patients with CKD/KF. Clinical trials are needed to investigate whether anti-inflammatory therapies will be effective in the prevention and treatment of DS in these patients with multiple comorbidities.

Introduction

Chronic Kidney Disease (CKD) is a persistent decline of the kidney function and or urinary abnormalities such as haematuria and proteinuria for over three months and affects 10% to 15% of the world population (Levey et al., 2020). The most severe stage is called End Stage Kidney Failure (ESKF), when patients will require haemodialysis, peritoneal dialysis or kidney transplant (Bikbov et al., 2020; Harris et al., 2019). The prevalence of CKD and ESKF has been rising over the last 18 years and is anticipated to double by 2030-2040 (Foreman et al., 2018; Liyanage et al., 2015). The aetiology of CKD and ESKF most commonly involves diabetes (type 1 and 2) and hypertension (Bikbov et al., 2020) and, to a lesser extent auto-immune and infectious diseases, environmental pollution (Ekrikpo et al., 2018) and genetic conditions(Lunyera et al., 2016).

Around 27% of CKD/ESKF patients have depression (Mosleh et al., 2020). Depression among CKD/ESKF patients seems to be associated with early initiation of dialysis and an increased mortality compared to those without depression (Farrokhi, Abedi, Beyene, Kurdyak, & Jassal, 2014; Palmer et al., 2013). Preventing, diagnosing, and treating depression in this population is challenging. Research guidance is inconclusive due to small sample sizes, the inclusion of individuals with different aetiologies of disease or types of dialysis, and a lack of appropriate control groups. Evidence for the efficacy of antidepressant medication in patients with CKD/ESKF and depression is poor as these patients are generally excluded from trials due to concerns about safety and adverse events. There are also reports that Selective Serotonin Reuptake Inhibitors (SSRIs) may not be effective in this population (Hedayati et al., 2017) and there is sub-optimal management of antidepressant medication in the dialysis population in the UK (Guirguis et al., 2020).

Inflammation is present in up to 50% of individuals with CKD/ESKD and may increase with the progression of the illness (Rapa, Di Iorio, Campiglia, Heidland, & Marzocco, 2019). There is growing evidence that inflammation may lead to DS and depressive disorders. While comorbidity of CKD and ESKF with depression is evident, it is unclear whether inflammation is more prevalent in individuals with depression and CKD/ESKF individuals compared to individuals with CKD/ESKF, who do not have depression. If proven, such findings would highlight potential benefit of prevention and treatment strategies for depression that targets inflammation. Clinicians need better guidance on treating

depression in ESKF patients, taking account of comorbidities and associated inflammation as a contributing factor.

We conducted a systematic review and meta-analysis on inflammation and depression in patients with CKD/ESKF to clarify the evidence base on the relationship between depression and CKD/ESKF and to identify inflammatory biomarkers associated with depression in CKD/ESKF patients.

Methods

The review was conducted in accord with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021), and registered on PROSPERO on 28th August 2019 (CRD42019141305) (Jayakumar et al., 2019).

Search strategy

A sample search is shown in supplement document. The search was initially run in May 2019 and re-run in September 2020 and January 2022, where 2 eligible studies were identified for inclusion. We searched electronic databases (PubMed, Embase, MEDLINE, PsychINFO/PsychArticles, Scopus, Web of Science, CINAHL and Cochrane CENTRAL) for published studies from inception of database up to 19 January 2022, using a search strategy developed with an information scientist. To optimise the capture of relevant research, the first 200 relevant publications from Google Scholar were also considered (Bramer, Rethlefsen, Kleijnen, & Franco, 2017). Controlled (MESH terms) and text entries were used across all electronic databases (see supplement document for MESH terms used). Databases such as DARE, ETHOS, OATD, NICE and PROSPERO were checked for existing or ongoing reviews prior to database searches. Forward and backward citation tracking was undertaken for studies that entered the review and progressed to data extraction.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were set out using the Population, Exposure, Comparison, Outcome (PECO) framework (Morgan, Whaley, Thayer, & Schünemann, 2018). The criteria were developed with clinical and research experts and Patient and Public Involvement (PPI) representatives.

The review includes studies of (a) adult patients (≥18 years) with ESKF or CKD, (b) data on pro and anti-inflammatory biomarkers (c) depression measured by standardised clinical interviews, or by administered or self-report validated psychometric instruments. We included case-control, cohort (prospective and retrospective), and cross-sectional studies; and non-randomised intervention studies and randomised controlled trials (RCTs). Exclusion criteria included preclinical studies, non-English language studies and studies published in non-peer reviewed journals. Studies investigating the effects of antidepressants or supplements on inflammation, which did not provide baseline data on inflammation in depressed and non-depressed patients were excluded. Given the sparsity of evidence, we excluded studies of kidney transplant or acute kidney injury patients.

Study selection

References, titles and abstracts from electronic database searches were exported into Rayyan QCRI (Ouzzani, Hammady, Fedorowicz, & Elmagarmid, 2016). Titles and abstracts were screened independently by two reviewers (SJa and SJe). Screening of titles and abstracts against the inclusion and exclusion criteria was piloted on the first 100 abstracts and revealed that in 50% of publications, information on inflammatory biomarkers was not mentioned in the abstract. Therefore, abstracts meeting all other inclusion criteria underwent full text screening. Full text articles were checked independently by SJa and SJe against the inclusion and exclusion criteria. Authors of studies and potentially relevant conference abstracts were contacted to secure full text articles. After one month to respond, one re-contact was attempted. Inter-rater reliability for the full-text screening indicated good agreement between reviewers (κ 0.89). Uncertainties were resolved by consensus and unresolved discrepancies were referred to a third reviewer (KB).

Data extraction

A data extraction table was piloted on 10 studies and refined (see supplement document for data extraction fields). Study data were extracted independently by two reviewers (SJa and SJe) and charted in an Excel spreadsheet. Study characteristics extracted included study authors, year published, sample description, methodological characteristics, demographics (age, gender, ethnicity), depression

definition and cut-off scores, type and levels of inflammatory biomarkers and main results. Statistical information extracted included means/medians, standard deviations/range/interquartile range for outcome and exposure of interest, N for depressed and non-depressed groups, test-statistic and p-values. Discrepancies were discussed and resolved between the two reviewers (95.2% agreement). If data was not available on the outcome/exposure of interest, then corresponding authors were contacted and those that responded within a month were included in the meta-analysis.

Methodological quality and risk of bias

The risk of bias was assessed independently by two reviewers (SJe and SJa). Study quality and risk of bias are presented in supplementary material. RCT's were assessed using the 'Risk of Bias 2'(RoB 2) (Sterne et al., 2019), Non-randomised interventional studies (NRIS) were assessed using the 'Risk Of Bias In Non-randomized Studies - of Interventions' (ROBINS-I) (Sterne et al., 2016).

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of cohort studies (CS) (Wells et al., 2014). Study quality is rated as good, fair, or poor across selection, comparability and exposure categories. Studies were awarded one point for ascertainment of exposure if information was provided on how inflammatory biomarkers were measured. For assessment of outcome, studies were awarded one point if depression was diagnosed through a structured clinical interview or if data was obtained from medical records; no points were allocated for self-report measures or no description.

Cross-sectional studies (CSSs) were assessed using the AXIS tool designed specifically for CSSs (Downes, Brennan, Williams, & Dean, 2016). 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. Cohort studies from which cross-sectional data from one time-point were used, were assessed on the AXIS tool.

Data analysis

Where number of studies permitted a meta-analysis was conducted, otherwise, a narrative synthesis of the studies was undertaken (overview of narrative synthesis is presented in supplementary materials.

Meta-analysis

Studies providing baseline or longitudinal data on cytokine levels in patients with or without depression were included in the meta-analysis and in bivariate subgroup analysis. A minimum of three studies per inflammatory marker were considered sufficient for meta-analysis (Ryan, 2016). For continuous data outcomes a weighted mean difference and 95% confidence intervals (CIs) were calculated using a random effects model which also allows suspected heterogeneity between studies (Higgins et al., 2019). Forest plots were generated, and pooled effect sizes were calculated using Comprehensive Meta-Analysis (CMA, version 3) (Borenstein, Hedges, Higgins, & Rothstein, 2009). The standardised mean-difference (SMD) was computed from studies providing means and standard deviations (SD) for cytokine levels in patients with or without depression. Where required SD were calculated from CIs or standard errors (SE) using a verified formula (Wan, Wang, Liu, & Tong, 2014). If a study provided a median, interquartile range (including the first and third quartile) and sample size, this was converted into an estimated sample mean and SD using a formula (Wan et al., 2014). Where studies provided a correlation coefficient and a sample size instead of a means and SD, this was entered into CMA to compute the effect size. Where studies did not provide means and SD or correlation coefficient a standardised or unstandardised regression coefficient with SD and sample sizes for patients with or without depression with 95% CIs, were entered into CMA to compute the effect size (Wilson, 2001). All effect sizes were calculated such that positive values demonstrate higher levels of inflammatory markers in depressed patients, and negative values indicated the opposite. Where adequate data was not provided, study authors were contacted for additional data and were given 3 weeks to respond. Ten percent (5/50) of authors contacted provided the additional data required for the study to be included in the meta-analysis.

Quality check

To investigate heterogeneity, subgroup and sensitivity analysis were carried out for all inflammatory markers. Within group heterogeneity was assessed using Higgin's I^2 with a ≥50% cut-off for 'substantial heterogeneity' (Wan et al., 2014). Cochrane's Q with p values <0.05 was also reported to indicate significant within and between group heterogeneity. Likely sources of heterogeneity

investigated included the way in which depression was defined (structured clinical interview or validated self-report depression tool) and the type of data provided by studies which was used to calculate the effect size. Sensitivity analyses was carried out on study design for each inflammatory marker (cross-sectional; longitudinal; RCT) and study quality (poor; fair; good). Currently there is no gold standard method to analyse inflammatory markers. The majority of the studies used either ELISA, multiplex or nephelometric methods.

Meta-regression investigating age, gender and ethnicity was considered for inflammatory markers with more than 10 studies, however, this data was reported for the total sample rather than for patients with or without depression rendering it inappropriate (Wan et al., 2014). Publication bias using Egger's test for funnel plot symmetry was assessed for inflammatory makers containing more than 10 studies (CRP; IL-6; TNF-a). In all analyses, statistical significance was set at $p \leq 0.05$.

Results

A meta-analysis was conducted in a search which yielded 9001 citations (see PRISMA, Figure 1). Fifty-three studies met our inclusion criteria, and seven additional studies were identified by citation tracking: 60 entered the review.

Study characteristics

Studies which are included in the review are outlined in supplementary Table 1. One study used an RCT design and reported depression severity in comparison with controls (Zhao, Ma, Yang, & Xiao, 2017). Three were cohort (CS), and 56 were cross-sectional (CSS). Most studies included haemodialysis (HD) patients (32/60), followed by mixed sample of HD and Peritoneal dialysis (PD) patients (11/60), PD patients (12/60), CKD patients (3/60) and mixed sample of CKD and HD or PD patients (2/60).

Majority of studies used a self-report depression scale to measure the presence of depressive symptoms or severity (52/60). The self-report depression scales used by studies included the Hospital and Anxiety Depression Scale (Depression subscale) (HADS-D), Beck's Depression Inventory (BDI), Hamilton Depression Rating Scale (HAM-D), Mental Health Inventory (MHI), Geriatric Depression Scale (GDS), Patient Health Questionnaire (PHQ), Center for Epidemiologic Studies Depression Scale (CES-

D), Cognitive Depression Index (CDI); Zung Self-Rating Depression Scale (SDS) and Allgemeine Deperessionskala-Langform (ADS-L).

CRP was measured most often (53/60), followed by IL-6 (25/60), TNF-a (12/60), IL-10 (7/60) and a range of other biomarkers (IL-1β, fibrinogen, IL-17, IL-18 and IL-12p70; (note hs-CRP and CRP are referred to as CRP). Thirty (30/60) specifically aimed at investigating the association between inflammatory markers and depression in CKD/ESKF patients or an intervention and are referred to as 'fit for purpose' (supplementary table 1). Forty-eight percent of studies (29/60) reported that patients with active infections and/or inflammatory illnesses were excluded. Seventeen percent of studies (10/60) excluded patients on anti-inflammatory medication, majority of studies did not report this information. Study quality is presented in supplementary table 2.

Cross-sectional meta-analyses

Meta-analysis of cross-sectional associations between CRP and depression

Fifty-one studies analysed cross-sectional data on major depression (MD) or DS and CRP levels (8370 patients). Overall, there was significantly elevated level of CRP in those with depression compared to those without depression (SMD = 0.50 [95% CI 0.28-0.72]; p<0.0001) (figure 2). There was significant heterogeneity (I^2=95%; Chi^2=1046.47, df=50; p<0.0001; Tau^2=0.76). Seven (7/51) used a structured clinical interview to diagnose MD, while most studies (44/51) used a self-report screening tool to measure DS. Amongst these seven studies (613 patients) which used structured clinical interview to diagnose depression, overall CRP levels had only a trend significance between MD and non-MD groups (SMD= 0.56 [95% CI -0.043 – 1.16]; p=0.08), with moderate significant heterogeneity (I^2=55%; Chi^2=13.44, df=6; p=0.037; Tau^2=0.07) (supplementary table 3) (Armaly et al., 2012; Atalay et al., 2010; Choi et al., 2013; Cilan et al., 2013; Kalender et al., 2007; Kalender, Ozdemir, & Koroglu, 2006; Wang et al., 2016). Four (4/7) were fit for purpose. Numbers of MD patients included from all studies were small and ranged from 10-47 individuals.

Amongst studies which used self-report tools as diagnostic for DS, 44 analyses of (from 40 studies; 7757 patients) found significantly higher levels of CRP in the group with DS compared to no DS group (SMD= 0.49 [95% CI 0.25-0.73]; p<0.001) (Armaly et al., 2012; Atalay et al., 2010; Barros, Costa, Mottin, & d'Avila, 2016; Bornivelli, Aperis, Giannikouris, Paliouras, & Alivanis, 2012; Bossola et al., 2010;

Bossola, Di Stasio, Giungi, Rosa, & Tazza, 2015; Boulware et al., 2006; Chilcot et al., 2017; Choi et al., 2013; Cilan et al., 2013; Dogan, Erkoc, Eryonucu, Sayarlioglu, & Agargun, 2005; Dong et al., 2016; Fan et al., 2014; Gok Oguz et al., 2016; Guenzani et al., 2019; Gyamlani et al., 2011; Güney et al., 2008; Haverkamp et al., 2018; Haverkamp et al., 2019; Hsu et al., 2009; Hung et al., 2011; Jong et al., 2017; Kalender et al., 2007; Kalender et al., 2006; Kim, Kim, Kim, & Song, 2012; Ko et al., 2010; Kusztal et al., 2018; Li et al., 2011; Malhotra et al., 2017; Micozkadioglu et al., 2006; Mok et al., 2019; Nie et al., 2019; Nowak, Adamczak, & Więcek, 2013; Park et al., 2012; Park et al., 2010; Schricker et al., 2019; Simic Ogrizovic et al., 2009; Su et al., 2012; Taraz et al., 2012; Tufan, Yıldız, Dogan, Yıldız, & Sevinir, 2015; Uglešić et al., 2015; Wang et al., 2016; Yavuz et al., 2015; Zhang et al., 2014). Significant heterogeneity was detected (I^2=96%; Chi^2=1032.71, df=43; p<0.0001; Tau^2=0.79). There were no between-group differences when comparison only retained studies using structured clinical interviews for MD or a validated self-report measure of DS (Q-value=0.47, df=1; p=0.83). There was no difference for total between-group heterogeneity when comparing effect size calculation formats (supplementary table 5) or study quality (supplementary table 6). There was no difference for total between-group heterogeneity when comparing studies that excluded patients with active infections/inflammatory diseases (supplementary table 7) or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). However, significantly higher levels of CRP were reported in patients with depression for studies that did not exclude patients on NSAIDs compared to those that did (supplementary table 8).

Meta-analysis of cross-sectional associations between IL-6 and depression

Twenty-nine analyses from 27 studies (5140 patients) were appropriate for inclusion in the meta-analyses investigating cross-sectional associations between IL-6 and depression (Alshogran, Khalil, Oweis, Altawalbeh, & Alqudah, 2018; Bossola et al., 2010; Bossola et al., 2015; Boulware et al., 2006; Brys et al., 2020; H. Cilan et al., 2012; Cilan et al., 2013; Damayanti, Nasution, & Lubis, 2018; Dervisoglu, Kir, Kalender, Eraldemir, & Caglayan, 2008; Guenzani et al., 2019; Haverkamp et al., 2018; Haverkamp et al., 2019; Hung et al., 2011; Jong et al., 2017; Kalender et al., 2007; Knuth et al., 2014; Kusztal et al., 2018; Nie et al., 2019; Nowak et al., 2013; Schricker et al., 2019; Ogrizovic et al., 2009; Sonikian et al., 2010; Taraz et al., 2012; Uglešić et al., 2015; Wang et al., 2016; Zhao et al., 2017). Overall, there was significantly higher levels of IL-6 in patients with depression compared to patients

without depression (SMD = 0.67 [95% CI 0.35-0.99]; p<0.001). There was significant heterogeneity (I^2=96%; Chi^2=696.72, df=28; p<0.001; Tau^2=0.71) (figure 3). Four studies (317 patients) used a structured clinical interview to diagnose MD. Amongst these, no significant differences in IL-6 levels were found between MD and non-MD groups (SMD= 0.23 [95% CI-0.66 – 1.12]; p=0.62) (Cilan et al., 2012; Cilan et al., 2013; Kalender et al., 2007; Wang et al., 2016); and no significant heterogeneity (I^2=0%; Chi^2=1.10, df=3; p=0.78; Tau^2=0.00). Sample sizes of patients with depression were very small in all (9 to 11 people with MD) (Cilan et al., 2012; Cilan et al., 2013; Kalender et al., 2007). Among studies which used self-report DS, twenty-five analyses (from 22 studies; 4823 patients) found significant differences in IL-6 levels in individuals with increased DS compared to no DS (SMD = 0.74, CI^{95}=-0.39 – 1.08, p<0.001) (Alshogran et al., 2018; Bossola et al., 2010; Bossola et al., 2015; Boulware et al., 2006; Brys et al., 2020; Damayanti et al., 2018; Dervisoglu et al., 2008; Guenzani et al., 2019; Haverkamp et al., 2018; Haverkamp et al., 2019; Hung et al., 2011; Jong et al., 2017; Knuth et al., 2014; Kusztal et al., 2018; Nie et al., 2019; Nowak et al., 2013; Schricker et al., 2019; Ogrizovic et al., 2009; Sonikian et al., 2010; Taraz et al., 2013; Uglešić et al., 2015; Zhao et al., 2017). All 25 analyses showed significant considerable heterogeneity (I^2=97%; Chi^2=692.92, df=24; p<0.001; Tau^2=0.75) (supplementary table 3). Comparison of total between group heterogeneity comparing structured clinical interviews with depression defined using a validated self-report measure reported no significant heterogeneity (Chi^2=1.08, df=1; p=0.30).

Significantly higher IL-6 levels in depressed were found irrespective of how effect sizes were calculated and there was significant heterogeneity (supplementary table 5). Regardless of study design, both cross-sectional and RCT data reported significantly higher IL-6 levels in MD/DS compared to non-MD/DS groups (supplementary table 4). Significant considerable heterogeneity was reported for cross-sectional studies but not RCT's, furthermore total between group heterogeneity was found to be significant when comparing cross-sectional to RCT's. Only good quality cross-sectional studies (21 analyses) reported significantly higher levels of IL-6 in depressed compared to non-depressed groups (supplementary table 4) (Alshogran et al., 2018; Bossola et al., 2010; Bossola et al., 2015; Brys et al., 2020; Cilan et al., 2012; Cilan et al., 2013; Damayanti et al., 2018; Dervisoglu et al., 2008; Guenzani et al., 2019; Haverkamp et al., 2018; Haverkamp et al., 2019; Hung et al., 2011; Jong et al., 2017; Knuth et al., 2014; Kusztal et al., 2018; Nie et al., 2019; Nowak et al., 2013; Taraz et al., 2012; Uglešić et al., 2015; Wang et al., 2016). These results were not replicated in fair quality studies (Kalender et al., 2007;

Schricker et al., 2019; Ogrizovic et al., 2009; Sonikian et al., 2010); both fair and good quality studies reported considerable heterogeneity. There was no difference for total between-group heterogeneity when comparing studies that excluded patients with active infections/inflammatory diseases (supplementary table 7) or NSAIDs. However, significantly higher levels of IL-6 were reported in patients with depression for studies that did not exclude patients on NSAIDs compared to those that did (supplementary table 8).

Meta-analysis of cross-sectional associations between TNF-a and MD/DS

Eleven analyses from 11 studies (1838 patients) were included in the meta-analyses (Cilan et al., 2012; Cilan et al., 2013; Dervisoglu et al., 2008; Guenzani et al., 2019; Haverkamp et al., 2018; Haverkamp et al., 2019; Jong et al., 2017; Kalender et al., 2007; Ko et al., 2010; Taraz et al., 2012; Y. Wang et al., 2016). Overall, these found a trend for higher TNF-a levels in the MD/DS group compared to non-MD/DS group (SMD= 0.38, [95% CI -0.02-0.78]; p=0.07). All 11 analyses showed significant heterogeneity (I^2=93%; Chi^2=139.03, df=10; p<0.001; Tau^2=0.4) (figure 4).

Four studies (317 patients) used a structured clinical interview to diagnose MD. These found no significant differences in TNF-a levels between MD and non-MD group (SMD= 0.01 [95% CI -0.72–0.73]; p=0.99) (Cilan et al., 2012; Cilan et al., 2013; Kalender et al., 2007; Wang et al., 2016). The 4 analyses showed no significant differences in heterogeneity (I^2=0%; Chi^2=2.22, df=3; p=0.53; Tau^2=0.00) (supplementary table 3). The sample sizes of depressed patients were very small in all (9-11 MD individuals) (Cilan et al., 2012; Cilan et al., 2013; Kalender et al., 2007) but in one study (Wang et al., 2012).

Among studies which used self-report DS (1521 patients), there was significantly higher levels of TNF in the high DS group compared to the no DS (SMD= 0.59 [95% CI 0.07 – 1.12]; p=0.03) (Dervisoglu et al., 2008; Guenzani et al., 2019; Haverkamp et al., 2018; Haverkamp et al., 2019; Jong et al., 2017; Ko et al., 2010; Taraz et al., 2012). All 7 analyses showed significant heterogeneity (I^2=96%; Chi^2=136.58, df=6; p<0.0001; Tau^2=0.51) (supplementary table 3).

Comparison of studies defining depression using structured clinical interviews with those using a validated self-report measure reported no significant heterogeneity (Chi^2=1.65, df=1; p=0.20). The

type of effect size did not account for the findings (supplementary table 5). Both fair and good quality studies reported non-significant findings in TNF-a levels between MD/DS and non- MD/DS groups with significant heterogeneity reported for good quality studies (supplementary table 4). There was significant total between -group heterogeneity no when comparing studies that excluded patients with active infections/inflammatory diseases or NSAIDs. Studies excluding patients with infections/inflammatory diseases reported significantly higher levels of TNF-a in depressed patients compared to non-depressed patients (supplementary table 7 and 8).

Meta-analysis of cross-sectional associations between IL-10 and depression

Six analyses from 6 studies (1427 patients) were appropriate for inclusion in the meta-analyses investigating cross-sectional associations between IL-10 and depression (Guenzani et al., 2019; Haverkamp et al., 2018; Haverkamp et al., 2019; Ko et al., 2010; Ogrizovic et al., 2009; Taraz et al., 2012)(figure 5). All used a validated self-report measure to define the high DS group. IL-10 levels were significantly lower in the DS compared to the non-DS group (SMD= -0.57 [95% CI -1.09-0.06]; $p<0.0001$). All 6 analyses showed significant heterogeneity (I^2=95%; Chi^2=95.02, df=5; $p<0.0001$; Tau^2=0.38). Effect size calculation format showed no effect on the findings, however significant heterogeneity was reported only for effect size calculations using means and SD (supplementary table 5). Only good quality studies (5 analyses) reported significantly lower levels of IL-10 in depressed compared to non-depressed groups (supplementary table 4) (Guenzani et al., 2019; Haverkamp et al., 2018; Haverkamp et al., 2019; Ko et al., 2010; Taraz et al., 2012). No significant total-between group heterogeneity reported for studies excluding patients with infections/inflammatory diseases or NSAIDs, compared to those that did not. However, significantly lower levels of IL-10 were reported in studies that excluded patients with infections/inflammatory diseases (supplementary table 7). The opposite was observed in studies that did not exclude patients on NSAIDs, where levels of IL-10 were significantly lower in patients with depression (supplementary table 8).

Meta-analysis of cross-sectional associations between IL-1B and depression

Three analyses from three studies (1086 patients) were appropriate for inclusion in the meta-analysis (Haverkamp et al., 2018; Haverkamp et al., 2019; Taraz et al., 2012) (supplementary figure 1). All used a validated self-report toll to define depressive symptom group. There were no significant differences in IL-1B levels in high compared to the no-DS group (SMD= -0.01 [95% CI -0.13-0.11] p=0.093). All 3 analyses showed no significant heterogeneity (I^2=0%; Chi^2=0.98, df=2; p=0.61; Tau^2=0.00) and were of good quality. Effect size calculation format reported no significant influence on reported IL-1B levels in DS compared to no-DS groups (supplementary table 5). There were no significant differences in levels of IL-1B in studies that excluded patients with infections/inflammatory diseases or NSAIDs, compared to those that did not (supplementary table 7 and 8).

Meta-analysis of cross-sectional associations between fibrinogen and depression

Four analyses from 4 studies (297 patients) were appropriate for inclusion (Bossola et al., 2012; Bossola et al., 2015; Ko et al., 2010)(supplementary figure 2). All used a validated self-report measure to define the DS group. Significantly higher levels of fibrinogen were reported in high depressive symptoms compared to no-DS group (SMD= 0.64, [95% CI 0.33-0.95]; p<0.0001). There was no significant heterogeneity (I^2=35%; Chi^2=4.67, df=3; p=0.19; Tau^2=0.036). Effect size calculation format showed no effect (supplementary table 5). No significant total-between group heterogeneity reported for studies excluding patients with infections/inflammatory diseases, compared to those that did not and both groups reported significantly higher levels of fibrinogen in patients with depression compared to patients without (supplementary table 7).

Longitudinal associations between DS and inflammatory cytokines

Narrative Synthesis

There were three longitudinal studies which investigated inflammatory markers and future DS (Barros et al., 2016; Bossola et al., 2012; Haverkamp et al., 2019). There weren't sufficient studies for each inflammatory marker for meta-analysis, thus a narrative review was executed.

All studies were similar in terms of dialysis modality (HD patients), depression definition (BDI) and percentage of females (ranging from 39.4% - 41%). There was one fit for purpose study (Haverkamp et al., 2019) that investigated whether higher levels of inflammation were associated with the development of future DS in CKD/ESKF patients (Haverkamp et al., 2019). They found that CRP was an independent predictor for an increase in DS. Patients with higher baseline serum CRP levels, compared to patients with lower serum CRP levels, had increased DS at 12-months, but not at 6-months follow up (Haverkamp et al., 2019). Haverkamp et al. (2019) (Haverkamp et al., 2019) found no significant longitudinal associations between DS, as measured by BDI, and IL-6, TNF-α, IL-10 and IL-1β (Haverkamp et al., 2019). Barros et al. (2016) did not report a change of inflammatory levels and association with worsening depression in HD patients. Bossola et al. (2012) reported that fibrinogen levels are not associated with increased DS at follow-up in HD patients. In cross-sectional analysis, both Barros et al. (2016) and Haverkamp et al. (2019) reported significantly higher CRP levels in DS patients at the 12-month follow up compared to the no DS group.

Discussion

Depression is the most prevalent psychosocial factor in patients with CKD/ESKF and is associated with increased morbidity and mortality (Rosenthal Asher, Ver Halen, & Cukor, 2012). Accumulating evidence suggests that inflammation may be causal to the development of DS (Khandaker et al., 2019). Whether inflammation has a role in depressed CKD/ESKF patient is not yet clear. Higher levels of inflammation may point towards those who may particularly benefit from shared preventive approaches and better inform treatment strategies.

There is one other systematic review and meta-analysis which investigated depression and inflammation in kidney disease (Gregg et al., 2020). Their review only included studies with the biomarker albumin as their focus was on protein/energy wasting biomarker and consequent inflammation, thus our studies – despite similarities - differ in inclusion criteria and aim. This is the first systematic review and meta-analysis specifically investigating inflammatory biomarkers in depressed patients with CKD/ESKF. We found evidence of higher levels of pro-inflammatory cytokines and acute inflammatory markers e.g. CRP, IL-6, TNF, fibrinogen, but not for IL-1β, and lower levels of the anti-inflammatory cytokine IL-10 in CKD patients with increased DS in cross-sectional studies. Pooled

studies were statistically significant for higher CRP and IL-6, and a trend for TNF in CKD/ESKF patients with MD/DS. There was only a trend significant association for higher levels of CRP and clinical depression, and not for the other inflammatory markers. We believe the lack of association is most likely due to power since only few studies included patients with major depression as assessed by clinical structured interview. Similar results were also reported in an umbrella review of depression and peripheral inflammatory biomarkers in a population without chronic illness (Lee et al., 2021). Lee et al. (2021), reported significant association between increased DS and CRP, IL-6 and TNF, however this association was no longer significant with chronic MD patients.

Most studies investigated inflammatory markers using validated self-report tools for DS. Fewer studies, a total of 7 for CRP, and 4 for IL-6 and TNF - investigated cross-sectional associations using structured clinical interviews to diagnose depression. Most of these studies had very few patients and did not find associations between inflammatory cytokines and major depression. Reasons for this is most likely lack of power. Inflammation is observed in ~30% of patients with major depression in the absence of chronic physical illness (Miller & Raison, 2016), and in ~50% of patients with ESKF (Cobo, Lindholm, & Stenvinkel, 2018). Among the few studies which used structured clinical interview to diagnose depression, number of depressed patients were small (range 10-47 for CRP and even fewer for other markers), which would have limited our power to detect associations. More generally, there is an absence of studies that looked at inflammatory markers and major depression in CKD. No studies investigated the effect of starting dialysis on inflammation and the association with depression. There is variation between studies on when inflammatory parameters were collected in relation to time of dialysis. It is possible that inflammatory levels vary considerably before, during and after dialysis.

Longitudinal studies are lacking in CKD/ESKF. There were three longitudinal studies of inflammatory markers and DS, and only one particularly investigated whether inflammatory markers at baseline predict development of future DS (Haverkamp et al., 2019). Haverkamp et al. (2019) found a positive association for CRP, but not for other inflammatory markers, and future DS (G. L. G. Haverkamp et al., 2019). They also included patients with acute infection, which may have skewed the results. Barros et al. (2016) did not report on longitudinal associations of inflammatory markers at baseline and future DS. In individuals without chronic physical illnesses, there is evidence that chronic inflammation predicts DS (Bell et al., 2017; Zalli, Jovanova, Hoogendijk, Tiemeier, & Carvalho, 2016).

Inflammation in patients with depression seems to be particularly important in chronically ill individuals (Nikkheslat et al., 2015). There is preliminary evidence to show that inflammation is a shared pathway likely causal between depression and cardiovascular disease (CVD) (Khandaker et al., 2019). More research is needed to confirm whether inflammation is a shared factor partly explaining the high prevalence of depression in the chronic physically ill, and in CKD/ESKF specifically. It is possible that both CVD and depression are underpinned by one (or more) shared pathophysiological mechanism(s) which manifests as distinct conditions in different organs (e.g. brain and kidneys). Indeed, ESKF commonly arises in patients experiencing hypertension and diabetes; and depressive illness is known to be a co-morbid complication of medical disorders. There is the need for higher quality, larger, longitudinal studies for evidence to be conclusive of the role of inflammation in CKD/ESKF patients with depression.

We identified marked heterogeneity in study designs, but overall, the type of outcome measure used (self-report vs structured instrument), duration and method of dialysis, methods to measure effect size appeared to have some influence. There were no studies that reported whether dialysis efficacy or duration was associated with higher inflammation and depression. Future studies should focus on CRP, IL6, and TNF and more explicitly investigate whether there are co-morbid medical conditions and include measures of a range of severity of depressive illness in ESKF. The timing of onset of depressive illness is also important to clarify, as a previous history of depression may predispose to later depression in the face of a medical condition or life event with little specificity for ESKF and related inflammation. Our study could not investigate cause or effect as most studies were conducted cross-sectionally. It is possible that DS triggered increased inflammation. Both directions have been seen in the literature. Indeed, histories and contemporary experiences of adversity and trauma also make depression more likely and raise inflammatory markers. Furthermore, ESKF and dialysis are demanding and may lead to adjustment reactions, and pessimism that may not meet criteria for depression but may reflect other life stressors, such as social isolation, fear of loss and death, concerns about dependents, and uncertainty, not to mention the need for lifetime dialysis and a schedule which is dictated by health needs. This will make enjoyment of everyday life more difficult, for example, taking holidays or travel and risks of new onset conditions complicating an already challenging medical condition. Psychological flexibility and adjustment to the diagnosis and treatment are predictors of better outcomes and might be the mechanism by which therapeutic efforts might be helpful (Iida et al., 2020). Indeed, acceptance and

commitment therapy encourages psychological flexibility and is being tested in many chronic conditions including cancer survivors, and may have a place in the care of dialysis patients living with uncertainty (Fernandez-Rodriguez, Gonzalez-Fernandez, Coto-Lesmes, & Pedrosa, 2020).

Limitations

There is limited evidence and few studies that reported on the same inflammatory markers using similar sample sizes. Longitudinal and experimental studies are needed, testing whether inflammation is a shared factor for the development of depression and chronic physical illnesses which could be a target for prevention. Many studies reported here were not fit for purpose, not designed to evaluate our research question. We acknowledge that some medications taken for CKD or related-conditions may have anti-inflammatory properties (Salazar, Ennis, & Koh, 2016; Silva, de Figueiredo, & Rios, 2019; Webster, Nagler, Morton, & Masson, 2017), which could have influenced the results of our study. As studies included in this review did not specify which medications were taken their effect of the levels of inflammatory marker is unknown. In any case, this bias would contribute to findings towards the null, which was not what we observed here.

It is still unknown whether inflammation is particularly associated to a particular aetiology of CKD/ESKF and depression. There is a need for psychological interventions, social support, and anti-inflammatory drugs to investigate its effects on inflammation to observe whether inflammation could be a mechanism. Larger multicentre studies are needed focusing on specific patient groups, and those with specific co-morbidities (Kiecolt-Glaser, Derry, & Fagundes, 2015). Lastly, it is important to mention in this context directionality of the relationship. As most studies presented here were cross-sectional it is still unclear in the CKD/ESKF population whether inflammation is indeed causally related to development of DS. It is equally possible that inflammation follows DS.

In conclusion, we found evidence for a cross-sectional association of higher levels of pro-inflammatory cytokines and DS or clinical depression in patients with CKD/ESKF. Research is needed to investigate whether inflammation is a target for prevention and treatment of CKD/ESKF patients with depression.

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References

Alshogran, O. Y., Khalil, A. A., Oweis, A. O., Altawalbeh, S. M., & Alqudah, M. A. Y. (2018). Association of brain-derived neurotrophic factor and interleukin-6 serum levels with depressive and anxiety symptoms in hemodialysis patients. *General hospital psychiatry, 53*, 25-31. doi:10.1016/j.genhosppsych.2018.04.003

Armaly, Z., Farah, J., Jabbour, A., Bisharat, B., Qader, A. A., Saba, S., . . . Bowirrat, A. (2012). Major depressive disorders in chronic hemodialysis patients in Nazareth: identification and assessment. *Neuropsychiatric Disease and Treatment, 8*, 329-338. doi:10.2147/ndt.S31903

Atalay, H., Solak, Y., Biyik, M., Biyik, Z., Yeksan, M., Uguz, F., . . . Turk, S. (2010). Sertraline treatment is associated with an improvement in depression and health-related quality of life in chronic peritoneal dialysis patients. *International urology and nephrology, 42*, 527-536. doi:10.1007/s11255-009-9686-y

Barros, A., Costa, B. E., Mottin, C. C., & D'Avila, D. O. (2016). Depression, quality of life, and body composition in patients with end-stage renal disease: a cohort study. *Brazilian Journal of Psychiatry, 38*, 301-306. doi:10.1590/1516-4446-2015-1681

Bell, J. A., Kivimaki, M., Bullmore, E. T., Steptoe, A., Consortium, M. R. C. I., & Carvalho, L. A. (2017). Repeated exposure to systemic inflammation and risk of new depressive symptoms among older adults. *Translational Psychiatry, 7*, e1208. doi:10.1038/tp.2017.155

Bikbov, B., Purcell, C. A., Levey, A. S., Smith, M., Abdoli, A., Abebe, M., . . . Murray, C. J. L. (2020). Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet, 395*, 709-733. doi:10.1016/S0140-6736(20)30045-3

Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. (2009). Comprehensive Meta-analysis (version 2) [*Computer program]*. Retrieved from https://www.meta analysis.com/index.php?cart=BQYJ7015021

Bornivelli, C., Aperis, G., Giannikouris, I., Paliouras, C., & Alivanis, P. (2012). Relationship between depression, clinical and biochemical parameters in patients undergoing haemodialysis. *Journal of Renal Care, 38*, 93-97. doi:https://doi.org/10.1111/j.1755-6686.2012.00259.x

Bossola, M., Ciciarelli, C., Di Stasio, E., Conte, G. L., Antocicco, M., Rosa, F., & Tazza, L. (2012). Symptoms of depression and anxiety over time in chronic hemodialysis patients. *Journal of Nephrology, 25*, 689-698. doi:10.5301/jn.5000042

Bossola, M., Ciciarelli, C., Di Stasio, E., Conte, G. L., Vulpio, C., Luciani, G., & Tazza, L. (2010). Correlates of symptoms of depression and anxiety in chronic hemodialysis patients. *General Hospital Psychiatry, 32*, 125-131. doi:10.1016/j.genhosppsych.2009.10.009

Bossola, M., Di Stasio, E., Giungi, S., Rosa, F., & Tazza, L. (2015). Fatigue is associated with serum interleukin-6 levels and symptoms of depression in patients on chronic hemodialysis. *Journal of Pain and Symptom Management, 49*, 578-585. doi:10.1016/j.jpainsymman.2014.07.009

Boulware, L. E., Liu, Y., Fink, N. E., Coresh, J., Ford, D. E., Klag, M. J., & Powe, N. R. (2006). Temporal relation among depression symptoms, cardiovascular disease events, and mortality in end-stage renal disease: contribution of reverse causality. *Clinical Journal of the American Society of Nephrology, 1*, 496-504. doi:10.2215/cjn.00030505

Bramer, W. M., Rethlefsen, M. L., Kleijnen, J., & Franco, O. H. (2017). Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. *Systematic Reviews, 6*, 245. doi:10.1186/s13643-017-0644-y

Brys, A. D. H., Di Stasio, E., Lenaert, B., Sanguinetti, M., Picca, A., Calvani, R., . . . Bossola, M. (2020). Serum interleukin-6 and endotoxin levels and their relationship with fatigue and depressive symptoms in patients on chronic haemodialysis. *Cytokine, 125*, 154823. doi:https://doi.org/10.1016/j.cyto.2019.154823

Chilcot, J., Friedli, K., Guirguis, A., Wellsted, D., Farrington, K., & Davenport, A. (2017). C reactive protein and depressive symptoms in hemodialysis patients: A questionable association. *Hemodialysis International, 21*, 542-548. doi:https://doi.org/10.1111/hdi.12500

Choi, M. J., Seo, J. W., Yoon, J. W., Lee, S. K., Kim, S. J., Lee, Y. K., . . . Koo, J. R. (2013). The malnutrition-inflammation-depression-arteriosclerosis complex is associated with an increased risk of cardiovascular disease and all-cause death in chronic hemodialysis patients. *Nephron - Clinical Practice, 122*, 44-52.

Cilan, H., Oguzhan, N., Unal, A., Turan, T., Koc, A. N., Sipahioglu, M. H., . . . Oymak, O. (2012). Relationship between depression and proinflammatory cytokine levels in hemodialysis patients. *Renal Failure, 34*, 275-278. doi:10.3109/0886022x.2011.647292

Cilan, H., Sipahioglu, M. H., Oguzhan, N., Unal, A., Turan, T., Koc, A. N., . . . Oymak, O. (2013). Association between depression, nutritional status, and inflammatory markers in peritoneal dialysis patients. *Renal failure, 35*, 17-22. doi: 10.3109/0886022X.2012.741643

Cobo, G., Lindholm, B., & Stenvinkel, P. (2018). Chronic inflammation in end-stage renal disease and dialysis. *Nephrology Dialysis Transplantation, 33*, 35-40. doi:10.1093/ndt/gfy175

Damayanti, I., Nasution, H. H., & Lubis, W. H. (2018). Correlation of Depression Symptoms and Interleukin-6 in Chronic Renal Disease with Regular Hemodialysis Patients. *Sumatera Medical Journal, 1*, 19-26. doi:10.32734/sumej.v1i1.442

Dervisoglu, E., Kir, H. M., Kalender, B., Eraldemir, C., & Caglayan, C. (2008). Depressive symptoms and proinflammatory cytokine levels in chronic renal failure patients. *Nephron Clinical Practice, 108*, 272-277. doi:10.1159/000126907

Dogan, E., Erkoc, R., Eryonucu, B., Sayarlioglu, H., & Agargun, M. Y. (2005). Relation between depression, some laboratory parameters, and quality of life in hemodialysis patients. *Renal Failure, 27*, 695-699. doi:10.1080/08860220500242728

Dong, J., Pi, H.-c., Xiong, Z.-y., Liao, J.-l., Hao, L., Liu, G.-l., . . . Zheng, Z.-x. (2016). Depression and cognitive impairment in peritoneal dialysis: a multicenter cross-sectional study. *American Journal of Kidney Diseases, 67*(1), 111-118. doi:10.1053/j.ajkd.2015.06.025

Downes, M. J., Brennan, M. L., Williams, H. C., & Dean, R. S. (2016). Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *Bristish Medical Journal Open, 6*, e011458. doi:10.1136/bmjopen-2016-011458

Ekrikpo, U. E., Kengne, A. P., Bello, A. K., Effa, E. E., Noubiap, J. J., Salako, B. L., . . . Okpechi, I. G. (2018). Chronic kidney disease in the global adult HIV-infected population: A systematic review and meta-analysis. *PLoS One, 13*, e0195443. doi:10.1371/journal.pone.0195443

Fan, L., Sarnak, M. J., Tighiouart, H., Drew, D. A., Kantor, A. L., Lou, K. V., . . . Weiner, D. E. (2014). Depression and All-Cause Mortality in Hemodialysis Patients. *American Journal of Nephrology, 40*, 12-18. doi:10.1159/000363539

Farrokhi, F., Abedi, N., Beyene, J., Kurdyak, P., & Jassal, S. V. (2014). Association between depression and mortality in patients receiving long-term dialysis: a systematic review and meta-analysis. *American Journal of Kidney Diseases, 63*, 623-635. doi:10.1053/j.ajkd.2013.08.024

Fernandez-Rodriguez, C., Gonzalez-Fernandez, S., Coto-Lesmes, R., & Pedrosa, I. (2020). Behavioral Activation and Acceptance and Commitment Therapy in the Treatment of Anxiety and Depression in Cancer Survivors: A Randomized Clinical Trial. *Behaviour Modification*, 45, 822-859. doi:10.1177/0145445520916441

Foreman, K. J., Marquez, N., Dolgert, A., Fukutaki, K., Fullman, N., McGaughey, M., . . . Murray, C. J. L. (2018). Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet, 392*, 2052-2090. doi:10.1016/s0140-6736(18)31694-5

Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. (2020). *Lancet, 395*, 709-733. doi:10.1016/s0140-6736(20)30045-3

Oguz, E.G., Akoglu, H., Ulusal Okyay, G., Yayar, O., Karaveli Gursoy, G., Buyukbakkal, M., . . . Ayli, M. D. (2016). Serum apelin is associated with affective disorders in peritoneal dialysis patients. *Renal Failure, 38*, 1059-1066. doi:10.1080/0886022x.2016.1193873

Gregg, L. P., Carmody, T., Le, D., Martins, G., Trivedi, M., & Hedayati, S. S. (2020). A Systematic Review and Meta-Analysis of Depression and Protein–Energy Wasting in Kidney Disease. *Kidney International Reports, 5*, 318-330. doi:10.1016/j.ekir.2019.12.009

Guenzani, D., Buoli, M., Caldiroli, L., Carnevali, G. S., Serati, M., Vezza, C., . . . Vettoretti, S. (2019). Malnutrition and inflammation are associated with severity of depressive and cognitive symptoms of old patients affected by chronic kidney disease. *Journal of Psychosomatic Research, 124*, 109783. doi:10.1016/j.jpsychores.2019.109783

Guirguis, A., Chilcot, J., Almond, M., Davenport, A., Wellsted, D., & Farrington, K. (2020). Antidepressant Usage in Haemodialysis Patients: Evidence of Sub-Optimal Practice Patterns. *Journal of Renal Care, 46*, 124-132. doi:10.1111/jorc.12320

Gyamlani, G., Basu, A., Geraci, S., Lee, F., Moxey, M., Clark, M., & Dubbert, P. M. (2011). Depression, screening and quality of life in chronic kidney disease. *American Journal of the Medical Sciences, 342*, 186-191. doi:10.1097/MAJ.0b013e3182113d9e

Güney, İ., Biyik, M., Yeksan, M., Biyik, Z., Atalay, H., Solak, Y., . . . Türk, S. (2008). Sleep Quality and Depression in Peritoneal Dialysis Patients. *Renal failure, 30*, 1017-1022. doi:10.1080/08860220802406419

Harris, D. C. H., Davies, S. J., Finkelstein, F. O., Jha, V., Donner, J. A., Abraham, G., . . . Zuniga, C. (2019). Increasing access to integrated ESKD care as part of universal health coverage. *Kidney International, 95*, S1-S33. doi:10.1016/j.kint.2018.12.005

Haverkamp, G. L., Loosman, W. L., Schouten, R. W., Franssen, C. F., Kema, I. P., van Diepen, M., . . . Honig, A. (2018). Differences in the association of inflammation and tryptophan with depressive symptoms between white and non-white chronic dialysis patients. *General Hospital Psychiatry, 50*, 76-82. doi:10.1016/j.genhosppsych.2017.10.003

Haverkamp, G. L. G., Loosman, W. L., Schouten, R. W., Franssen, C. F. M., Kema, I. P., van Diepen, M., . . . Siegert, C. E. (2019). Longitudinal Associations Between Inflammation and Depressive Symptoms in Chronic Dialysis Patients. *Psychosomatic Medicine, 81*, 74-80. doi:10.1097/psy.0000000000000649

Hedayati, S. S., Gregg, L. P., Carmody, T., Jain, N., Toups, M., Rush, A. J., . . . Trivedi, M. H. (2017). Effect of Sertraline on Depressive Symptoms in Patients With Chronic Kidney Disease Without Dialysis Dependence: The CAST Randomized Clinical Trial. *Journal of the American Medical Association, 318*, 1876-1890. doi:10.1001/jama.2017.17131

Higgins, J. P., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (2019). *Cochrane handbook for systematic reviews of interventions*. (2nd edition). UK: John Wiley & Sons.

Hsu, H. J., Chen, C. K., Hsiao, C. C., Wu, I. W., Sun, C. Y., Chou, C. C., . . . Wu, M. S. (2009). Lack of association between plasma dehydroepiandrosterone sulfate (DHEA-S) levels and depression in hemodialysis patients: a cross-sectional study. *Experimental Gerontology, 44*, 733-739. doi:10.1016/j.exger.2009.08.009

Hsu, H. J., Chen, C. K., & Wu, M. S. (2009). Lower prevalence of depression in hemodialysis patients who use polysulfone dialyzers. *American Journal of Nephrology, 29*, 592-597. doi:10.1159/000193144

Hung, K. C., Wu, C. C., Chen, H. S., Ma, W. Y., Tseng, C. F., Yang, L. K., . . . Lu, K. C. (2011). Serum IL-6, albumin and co-morbidities are closely correlated with symptoms of depression in patients on maintenance haemodialysis. *Nephrology Dialysis Transplantation, 26*, 658-664. doi:10.1093/ndt/gfq411

Iida, H., Fujimoto, S., Wakita, T., Yanagi, M., Suzuki, T., Koitabashi, K., . . . Kurita, N. (2020). Psychological Flexibility and Depression in Advanced CKD and Dialysis. *Kidney Medicine, 2*, 684-691 e681. doi:10.1016/j.xkme.2020.07.004

Jong, I.-C., Tsai, H.-B., Lin, C.-H., Ma, T.-L., Guo, H.-R., Hung, P.-H., & Hung, K.-Y. (2017). Close correlation between the ankle-brachial index and symptoms of depression in hemodialysis patients. *International urology and nephrology, 49*, 1463-1470. doi:10.1007/s11255-017-1598-7

Kalender, B., Dervisoglu, E., Sengul, E., Ozdemir, A. C., Akhan, S. C., Yalug, I., & Uzun, H. (2007). Depression, nutritional status, and serum cytokines in peritoneal dialysis patients: is there a relationship? *Peritoneal Dialysis International, 27*, 593-595. Retrieved from https://pubmed.ncbi.nlm.nih.gov/17704454/

Kalender, B., Ozdemir, A. C., & Koroglu, G. (2006). Association of depression with markers of nutrition and inflammation in chronic kidney disease and end-stage renal disease. *Nephron Clinical Practice, 102*, 115-121. doi:10.1159/000089669

Khandaker, G. M., Zuber, V., Rees, J. M. B., Carvalho, L., Mason, A. M., Foley, C. N., . . . Burgess, S. (2019). Shared mechanisms between coronary heart disease and depression: findings from a large UK general population-based cohort. *Molecular Psychiatry*, 25, 1477–1486. doi:10.1038/s41380-019-0395-3

Kiecolt-Glaser, J. K., Derry, H. M., & Fagundes, C. P. (2015). Inflammation: depression fans the flames and feasts on the heat. *Am J Psychiatry, 172*, 1075-1091. doi:10.1176/appi.ajp.2015.15020152

Kim, J. K., Kim, S. G., Kim, H. J., & Song, Y. R. (2012). Serum S100B protein is associated with depressive symptoms in patients with end-stage renal disease. *Clinical Biochemistry, 45*, 1573-1577. doi:10.1016/j.clinbiochem.2012.08.014

Knuth, B., Radtke, V., Rocha, P., da Silva, K. S., Dalsóglio, F., Gazal, M., . . . Oses, J. P. (2014). Prevalence of depression symptoms and serum levels of interleukin-6 in hemodialysis patients. *Psychiatry and Clinical Neurosciences, 68*, 275-282. doi:10.1111/pcn.12130

Knuth, B., Radtke, V., Rocha, P., da Silva, K. S., Dalsóglio, F., Gazal, M., . . . Oses, J. P. (2014). Prevalence of depression symptoms and serum levels of interleukin-6 in hemodialysis patients. *Psychiatry and Clinical Neurosciences, 68*, 275-282.

Ko, G. J., Kim, M. G., Yu, Y. M., Jo, S. K., Cho, W. Y., & Kim, H. K. (2010). Association between depression symptoms with inflammation and cardiovascular risk factors in patients undergoing peritoneal dialysis. *Nephron Clinical Practice, 116*, c29-35. doi:10.1159/000314548

Kusztal, M., Trafidło, E., Madziarska, K., Augustyniak-Bartosik, H., Karczewski, M., Weyde, W., . . . Klinger, M. (2018). Depressive symptoms but not chronic pain have an impact on the survival of patients undergoing maintenance hemodialysis. *Archives of Medical Science, 14*, 265-275. doi:10.5114/aoms.2016.59765

Lee, S., Lee, K. H., Park, K. M., Park, S. J., Kim, W. J., Lee, J., . . . Fusar-Poli, P. (2021). Impact of data extraction errors in meta-analyses on the association between depression and peripheral inflammatory biomarkers: an umbrella review. *Psychological Medicine*. Advance online publication. doi:10.1017/S0033291721003767

Levey, A. S., Eckardt, K. U., Dorman, N. M., Christiansen, S. L., Hoorn, E. J., Ingelfinger, J. R., . . . Winkelmayer, W. C. (2020). Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. *Kidney International, 97*, 1117-1129. doi:10.1016/j.kint.2020.02.010

Li, Z. J., An, X., Mao, H. P., Wei, X., Chen, J. H., Yang, X., . . . Yu, X. Q. (2011). Association between depression and malnutrition-inflammation complex syndrome in patients with continuous ambulatory peritoneal dialysis. *International urology and nephrology, 43*, 875-882. doi:10.1007/s11255-011-9917-x

Liyanage, T., Ninomiya, T., Jha, V., Neal, B., Patrice, H. M., Okpechi, I., . . . Perkovic, V. (2015). Worldwide access to treatment for end-stage kidney disease: a systematic review. *Lancet, 385*, 1975-1982. doi:10.1016/s0140-6736(14)61601-9

Lunyera, J., Mohottige, D., Von Isenburg, M., Jeuland, M., Patel, U. D., & Stanifer, J. W. (2016). CKD of Uncertain Etiology: A Systematic Review. *Clinical Journal of the American Society of Nephrology, 11*, 379-385. doi:10.2215/cjn.07500715

Malhotra, R., Persic, V., Zhang, W., Brown, J., Tao, X., Rosales, L., . . . Kotanko, P. (2017). Tryptophan and Kynurenine Levels and Its Association With Sleep, Nonphysical Fatigue, and Depression in Chronic Hemodialysis Patients. *Journal of Renal Nutrition, 27*, 260-266. doi:10.1053/j.jrn.2017.01.024

Micozkadioglu, H., Micozkadioglu, I., Zumrutdal, A., Erdem, A., Ozdemir, F. N., Sezer, S., & Haberal, M. (2006). Relationship between depressive affect and malnutrition-inflammation complex syndrome in haemodialysis patients. *Nephrology, 11*, 502-505. doi:10.1111/j.1440-1797.2006.00664.x

Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nature Reviews Immunology, 16*, 22-34. doi:10.1038/nri.2015.5

Mok, M. M. Y., Liu, C. K. M., Lam, M. F., Kwan, L. P. Y., Chan, G. C. W., Ma, M. K. M., . . . Chan, T. M. (2019). A Longitudinal Study on the Prevalence and Risk Factors for Depression and Anxiety, Quality of Life, and Clinical Outcomes in Incident Peritoneal Dialysis Patients. *Peritoneal Dialysis International, 39*, 74-82. doi:10.3747/pdi.2017.00168

Morgan, R. L., Whaley, P., Thayer, K. A., & Schünemann, H. J. (2018). Identifying the PECO: A framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. *Environment International, 121*, 1027-1031. doi:10.1016/j.envint.2018.07.015

Mosleh, H., Alenezi, M., Al Johani, S., Alsani, A., Fairaq, G., & Bedaiwi, R. (2020). Prevalence and Factors of Anxiety and Depression in Chronic Kidney Disease Patients Undergoing Hemodialysis: A Cross-sectional Single-Center Study in Saudi Arabia. *Cureus Journal of Medical Science, 12*, e6668. doi:10.7759/cureus.6668

Nie, X. D., Wang, Q., Zhang, Y. H., Xiong, Z. Y., Liao, J. L., Hao, L., . . . Dong, J. (2019). Depression at Baseline Is an Independent Risk Factor for Cognitive Decline in Patients on Peritoneal Dialysis: A Multicenter Prospective Cohort Study. *Peritoneal Dialysis International, 39*, 465-471. doi:10.3747/pdi.2018.00239

Nikkheslat, N., Zunszain, P. A., Horowitz, M. A., Barbosa, I. G., Parker, J. A., Myint, A. M., . . . Pariante, C. M. (2015). Insufficient glucocorticoid signaling and elevated inflammation in coronary heart disease patients with comorbid depression. *Brain Behavaviour and Immunity, 48*, 8-18. doi:10.1016/j.bbi.2015.02.002

Nowak, Ł., Adamczak, M., & Więcek, A. (2013). Is inflammation a new risk factor of depression in haemodialysis patients? *International urology and nephrology, 45*, 1121-1128. doi:10.1007/s11255-012-0269-y

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan—a web and mobile app for systematic reviews. *Systematic Reviews, 5*, 210. doi:10.1186/s13643-016-0384-4

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., . . . Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Systematic Reviews, 10*, 89. doi:10.1186/s13643-021-01626-4

Palmer, S. C., Vecchio, M., Craig, J. C., Tonelli, M., Johnson, D. W., Nicolucci, A., . . . Strippoli, G. F. (2013). Association between depression and death in people with CKD: a meta-analysis of cohort studies. *American Journal of Kidney Disease, 62*, 493-505. doi:10.1053/j.ajkd.2013.02.369

Park, H. C., Lee, H., Lee, J. P., Kim, D. K., Oh, K. H., Joo, K. W., . . . Oh, Y. K. (2012). Lower residual renal function is a risk factor for depression and impaired health-related quality of life in Korean peritoneal dialysis patients. *Journal of Korean Medical Science, 27*, 64-71. doi:10.3346/jkms.2012.27.1.64

Park, H. C., Yoon, H. B., Son, M. J., Jung, E. S., Joo, K. W., Chin, H. J., . . . Oh, Y. K. (2010). Depression and health-related quality of life in maintenance hemodialysis patients. *Clinical nephrology, 73*, 374-380. doi:10.5414/cnp73374

R, R. (2016). Cochrane Consumers and Communication Group: meta-analysis. Retrieved from http://cccrg.cochrane.org

Rapa, S. F., Di Iorio, B. R., Campiglia, P., Heidland, A., & Marzocco, S. (2019). Inflammation and Oxidative Stress in Chronic Kidney Disease-Potential Therapeutic Role of Minerals, Vitamins and Plant-Derived Metabolites. *International journal of molecular sciences, 21*, 263. doi:10.3390/ijms21010263

Rosenthal Asher, D., Ver Halen, N., & Cukor, D. (2012). Depression and nonadherence predict mortality in hemodialysis treated end-stage renal disease patients. *Hemodialysis International, 16*, 387-393. doi:10.1111/j.1542-4758.2012.00688.x

Salazar, J. J., Ennis, W. J., & Koh, T. J. (2016). Diabetes medications: Impact on inflammation and wound healing. *Journal of diabetes and its complications, 30*, 746-752. doi:10.1016/j.jdiacomp.2015.12.017

Schricker, S., Heider, T., Schanz, M., Dippon, J., Alscher, M. D., Weiss, H., . . . Kimmel, M. (2019). Strong Associations Between Inflammation, Pruritus and Mental Health in Dialysis Patients. *Acta Dermato-Venereologica, 99*, 524-529. doi:10.2340/00015555-3128

Silva, I. V., de Figueiredo, R. C., & Rios, D. R. (2019). Effect of Different Classes of Antihypertensive Drugs on Endothelial Function and Inflammation. *International Journal of Molecular Sciences, 20*. doi:10.3390/ijms20143458

Simic Ogrizovic, S., Jovanovic, D., Dopsaj, V., Radovic, M., Sumarac, Z., Bogavac, S. N., . . . Nesic, V. (2009). Could depression be a new branch of MIA syndrome? *Clinical nephrology, 71*, 164-172. doi:10.5414/cnp71164

Simone Jayakumar, K. B., Jessica Schofield, Amy Ronaldson, Magdi Yaqoob, Livia Carvalho. (2019). The association between depression and inflammation in patients with chronic kidney disease(CKD) or End Stage Renal Disease (ESRD): a systematic review of the literature. Retrieved from https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019141305

Sonikian, M., Metaxaki, P., Papavasileiou, D., Boufidou, F., Nikolaou, C., Vlassopoulos, D., & Vlahakos, D. V. (2010). Effects of interleukin-6 on depression risk in dialysis patients. *American Journal of Nephrology, 31*, 303-308. doi:10.1159/000285110

Sterne, J. A., Hernán, M. A., Reeves, B. C., Savović, J., Berkman, N. D., Viswanathan, M., . . . Higgins, J. P. (2016). ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *British medical journal, 355*, i4919. doi:10.1136/bmj.i4919

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., . . . Higgins, J. P. T. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *British medical journal, 366*, l4898. doi:10.1136/bmj.l4898

Su, S. F., Ng, H. Y., Huang, T. L., Chi, P. J., Lee, Y. T., Lai, C. R., . . . Lee, C. T. (2012). Survey of depression by Beck Depression Inventory in uremic patients undergoing hemodialysis and hemodiafiltration. *Therapeutic Apheresis and Dialysis, 16*, 573-579. doi:10.1111/j.1744-9987.2012.01094.x

Taraz, M., Khatami, M. R., Dashti-Khavidaki, S., Akhonzadeh, S., Noorbala, A. A., Ghaeli, P., & Taraz, S. (2013). Sertraline decreases serum level of interleukin-6 (IL-6) in hemodialysis patients with

depression: results of a randomized double-blind, placebo-controlled clinical trial. *International Immunopharmacology, 17*, 917-923. doi:10.1016/j.intimp.2013.09.020

Taraz, M., Khatami, M. R., Gharekhani, A., Abdollahi, A., Khalili, H., & Dashti-Khavidaki, S. (2012). Relationship between a pro- and anti-inflammatory cytokine imbalance and depression in haemodialysis patients. *European Cytokine Network, 23*, 179-186. doi:10.1684/ecn.2013.0326

Tufan, F., Yıldız, A., Dogan, I., Yıldız, D., & Sevinir, Ş. (2015). Urea to creatinine ratio: a forgotten marker of poor nutritional state in patients undergoing hemodialysis treatment. *Aging Male, 18*, 49-53. doi:10.3109/13685538.2014.908281

Uglešić, B., Ljutić, D., Lasić, D., Jeličić, I., Višić, V., Glavina, T., . . . Meter, A. (2015). Depression and serum interleukin-6 levels in patients on dialysis. *Psychiatria Danubina, 27*, 168-173.

Wan, X., Wang, W., Liu, J., & Tong, T. (2014). Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *British Medical Council Medical Research Methodology, 14*, 135. doi:10.1186/1471-2288-14-135

Wang, L. J., Wu, M. S., Hsu, H. J., Wu, I. W., Sun, C. Y., Chou, C. C., . . . Chen, C. K. (2012). The relationship between psychological factors, inflammation, and nutrition in patients with chronic renal failure undergoing hemodialysis. *The International Journal of Psychiatry in Medicine, 44*, 105-118. doi:10.2190/PM.44.2.b

Wang, Y., Liu, Y., Lian, Y., Li, N., Liu, H., & Li, G. (2016). Efficacy of High-Dose Supplementation With Oral Vitamin D3 on Depressive Symptoms in Dialysis Patients With Vitamin D3 Insufficiency: A Prospective, Randomized, Double-Blind Study. *Journal of Clinical Psychopharmacology, 36*, 229-235. doi:10.1097/jcp.0000000000000486

Webster, A. C., Nagler, E. V., Morton, R. L., & Masson, P. (2017). Chronic Kidney Disease. *Lancet, 389*, 1238-1252. doi:10.1016/s0140-6736(16)32064-5

Wells, G., Shea, B., O Connell, D. L., Peterson, J., Welch, Losos, M., . . . Petersen, J. (2014). *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. Retrieved from https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Wilson, D. B. (2001). Practical meta-analysis effect size calculator. Retrieved from https://campbellcollaboration.org/escalc/html/EffectSizeCalculator-Home.php.

Yavuz, R., Yavuz, D., Altunoglu, A., Canoz, M. B., Sezer, S., Yalcin, B. M., & Demirag, M. D. (2015). Depression, Inflammation, and Social Support in Hemodialysis Patients. J*ournal of clinical and analytical medicine, 6, 801-805.* doi:10.4328/JCAM.3679

Zalli, A., Jovanova, O., Hoogendijk, W. J., Tiemeier, H., & Carvalho, L. A. (2016). Low-grade inflammation predicts persistence of depressive symptoms. *Psychopharmacology, 233*, 1669-1678. doi:10.1007/s00213-015-3919-9

Zhang, J., Zhang, P., Ni, X., Bao, B., Huang, C., Wu, Y., . . . Chen, J. (2014). Vitamin D status in chronic dialysis patients with depression: a prospective study. *British Medical Council Psychiatry, 14*, 125. doi:10.1186/1471-244X-14-125

Zhao, C., Ma, H., Yang, L., & Xiao, Y. (2017). Long-term bicycle riding ameliorates the depression of the patients undergoing hemodialysis by affecting the levels of interleukin-6 and interleukin-18. *Neuropsychiatric Disease and Treatment, 13*, 91-100. doi:10.2147/ndt.S124630