Lack of association between erythropoietin treatment and risk of depression in patients with end-stage kidney disease on maintenance dialysis: a nationwide database study in Taiwan

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Abstract

Background: Patients with end-stage kidney disease (ESKD), have been associated with higher risk of developing depression. Erythropoietin (EPO), frequently used for the treatment of anemia in ESKD patients, has been shown to have neuroprotective and antidepressant effects. In this study, we examined whether EPO treatment changed the risk of depression in ESKD patients.

Methods: In a nationwide population-based cohort in Taiwan from 1998 to 2013, patients with a diagnosis of ESKD on maintenance dialysis and aged greater than 18 years were classified into EPO treatment group or non-EPO treatment group. All patients were followed up until the diagnosis of depressive disorder or the end of the study period.

Results: In this cohort (13,067 patients in the EPO and 67,258 patients in the non-EPO group), 5569 patients were diagnosed as depressive disorder in the follow-up period. We found the risk of depression in EPO group was not significantly different from that in non-EPO group (adjusted hazard ratio = 0.98, 95% confidence interval 0.92–1.04, $p = 0.499$) after adjusting for sex, age, certification year of catastrophic illness for ESKD, physical co-morbidities, and use of benzodiazepines.

Conclusion: In summary, using the nationwide reimbursement data in Taiwan, we found that EPO treatment in ESKD patients was not associated with their general risk of developing depression.

Keywords: big data, depression, dialysis, end-stage kidney disease, erythropoietin, National Health Insurance Research Database

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Introduction

Chronic kidney disease (CKD) is a global health burden, affecting around 11–13% of the world population,[1] and is associated with reduced life quality, huge financial burden, and shorter life expectancy in developed countries.[2] Anemia is a commonly diagnosed complication in patients with CKD,[3] especially in those with end-stage kidney disease (ESKD; stage 5 of CKD). Erythropoietin (EPO) has long been found to stimulate the differentiation of erythrocytes since the 1950s,[4,5] and was one of the standard treatments of anemia in ESKD patients.[3,6] In addition, in the past two decades, EPO was recognized to act on many other systems, including inflammatory response system,[7] immune cells,[8] endothelium cells,[9] cardiac tissues,[10] and pancreatic beta cells.[11] Moreover, EPO has been found to be

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expressed in the brain,[12] and is produced by neurons and astrocytes. Its combination with EPO receptor, acting through JAK2 and multiple downstream signaling pathways including STAT5, PI3K/Akt, NF-kappa B, and MAPK,[13] was shown to exert neurotrophic and neuroprotective effects.[14,15]

Hence, EPO has been examined for its possible effects on mood regulation and cognition in humans. One week after EPO administration in healthy volunteers, their neural and cognitive responses to fearful facial expression were reduced, similar to effects of conventional antidepressants.[16] Meanwhile, memory-relevant hippocampal response was enhanced in these subjects, consistent with increased hippocampal plasticity.[17] Next, these studies were extended to clinical subjects. Three days after administration in patients with major depression, EPO reduced amygdala–hippocampal response during encoding of negative affect-laden pictures[18] and neural and cognitive responses to fearful facial expression,[19] consistent with down-regulation of the negative memory bias in antidepressant mechanism.[20]

These findings suggested EPO as a candidate agent for future management of mood and cognitive symptoms in depression. In a double-blind, placebo-controlled randomized trial in patients with treatment-resistant depression, Miskowiak *et al.*[21] found that EPO 40,000 IU infusion per week was effective in reducing depressive symptoms, improving quality of life, verbal recall, and recognition after 9 weeks, and these effects were sustained at follow-up week 14. Such effects might be related to changes in plasma level of brain-derived neurotrophic factor.[22] Although promising, there is no double-blind placebo-controlled study examining clinical efficacy of EPO in the treatment of clinical depression. Also, it is still unclear whether EPO administration can reduce the risk of depression in vulnerable populations, such as patients with ESKD.

In this study, we used a claims database consisting of the nationwide population to determine whether EPO treatment changed the occurrence of depressive disorder in patients with ESKD on maintenance dialysis, with adjusting potential confounding factors in the population-based data sources.

Methods

Data source

Taiwan introduced a sole-payer National Health Insurance (NHI) program in 1995, and 99% of the 23 million Taiwanese population were enrolled in 2010. In 1996, the NHI in Taiwan established the *National Health Insurance Research Database* (*NHIRD*). The database from the NHI program constitutes the reimbursement medical claim files representative of the entire population in Taiwan. The *NHIRD* provides comprehensive information about the insured subjects, such as sex, date of birth, clinical diagnostic codes, visiting medical institutions, and prescription records. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) was used for diagnostic codes. All investigators signed an agreement guaranteeing patient confidentiality before using the database. All information from *NHIRD* that could be used to identify medical institutions or individual patients was scrambled to ensure confidentiality. A waiver was granted for informed consent due to the minimal risk to the privacy of the individual subjects. The protocol for this study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No: 201801214B0).

Patient selection and definition

ESKD patients on maintenance dialysis were defined as having certification of catastrophic illness (ICD-9-CM: 585) and receiving dialysis for more than 90 days. In Taiwan, the status of catastrophic illnesses enables the co-payment for the treatment of the disease to be waived, and it declares the high severity of the diseases in Taiwan. In this study, the certification year of catastrophic illness indicated the year that ESKD first occurred. We established the following exclusion criteria to eliminate the confounding effects: (1) patients who had mood disorders (ICD-9-CM: 296, 311, or 300.4) or dementia (ICD-9-CM: 290 or 331). Patients who had dementia were excluded because there is a significant association between depression and dementia[23] or cognitive decline.[24] (2) Patients who had the certification of catastrophic illness before January 1998 or after December 2012. (3) Patients who had been prescribed erythropoietin before they were issued the certification of catastrophic illness. (4) Patients on maintenance dialysis who were aged <18 years .

Demographic, clinical variables, and outcomes

We collected sex, age, certification year of catastrophic illness, physical comorbidity (hypertension, diabetes mellitus, dyslipidemia, vascular disease, and cancer), and benzodiazepines use, which increased the risk of depressive disorder.[25] The outcome of depressive disorders (ICD-9-CM: 296.2, 296.3, 311, or 300.4) was defined as diagnosed at least twice by psychiatrists based on their diagnostic interview and clinical judgment.

Statistical methods and sensitivity analyses

Descriptive statistics were used to compare patients' characteristics. We used independent *t*-tests and chi-square to compare continuous and categorical variables, respectively, between ESKD patients on maintenance dialysis without EPO (non-EPO) and with EPO treatment. For the outcome of depressive disorder, we constructed Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the occurrence of such outcomes, which were further adjusted for potential confounders with sex, age, certification year, physical comorbidities, and benzodiazepine use. Association between both the outcome (depressive disorder) and elevated mortality risk is well established in ESKD patients on maintenance dialysis.[26] Therefore, subsequent competitive risk analysis of the association between the outcome and mortality was performed solely in the included patients.

We performed four sensitivity analyses to assess the robustness of our results. First, to further improve the diagnostic validity and stability, the threshold for the inclusion criteria was raised to diagnosis of depressive disorder at least four times by board-certified psychiatrists in model 1. Second, to increase the specificity of the outcome definition, we considered only depressive patients treated with antidepressants in model 2. Third, to avoid the short follow-up period hindering the occurrence of potential outcomes, we restricted the entry year of the study cohort to between 2001 and 2005 and followed these patients until 31 December 2013, in model 3. Fourth, to decrease residual confounding factors that may lead to a bias, we implemented 1:1 propensity score matching (PSM)[27] for non-EPO and EPO cohorts in model 4. In addition, we conducted a dose-dependent analysis to assess the relation between EPO dose and risk of depression. In this part, we calculated the EPO average dose as a total EPO dose per week. We separated included EPO-treatment patients into low- (<500 IU per week), medium- (501–2000 IU per week), and high- (>2000 IU per week) dose groups, and used a low-dose group as a reference. All analyses were conducted with SAS 9.4 software (SAS Institute Inc., Cary, NC, USA), and a two-tailed $p < 0.05$ was considered statistically significant.

Results

Figure 1 depicts the processes to select the participants in the study cohort. From 176,982 patients having catastrophic illness certification of ESKD in the database, 161,690 were on dialysis for more than 90 days. After applying the exclusion criteria, 80,325 patients were included in the analysis. Of these patients, 13,067 were in the EPO group and 67,258 were in the non-EPO group. The basic characteristics of included subjects are described in Table 1. Compared with the non-EPO group, the EPO group were more likely to be female (non-EPO *versus* EPO: 46.8% *versus* 50.5%) and younger (non-EPO *versus* EPO: 61.0 years old *versus* 60.1 years old), but less likely to have co-morbid hypertension (non-EPO *versus* EPO: 83.9% *versus* 82.2%), diabetes mellitus (non-EPO *versus* EPO: 60.5% *versus* 58.3%), dyslipidemia (non-EPO *versus* EPO: 47.5% *versus* 44.3%), vascular disease (non-EPO *versus* EPO: 23.5% *versus* 22.2%), and benzodiazepines use (non-EPO *versus* EPO: 87.4% *versus* 85.8%). For cancer comorbidity, both groups had no significant difference.

In the 404,438 person-years of follow-up, 5569 ESKD patients during the follow-up period were diagnosed as depressive disorder, yielding a crude incidence rate of 13.77 per 1000 person-years. Table 2 demonstrates the occurrence of depressive disorder in the non-EPO and EPO groups. Compared with the risk of depressive disorder in the non-EPO group, we found that those with EPO treatment had no significant difference in adjusted HR [(aHR) 0.98 (95% CI 0.92–1.04), $p = 0.499$] after adjusting for sex, age, certification year, physical comorbidities, and benzodiazepine use, and competitive HR [(cHR) 0.99 (95% CI 0.93–1.05), $p = 0.757$] after considering mortality. In four sensitivity analyses, only the cHR of depressive disorder

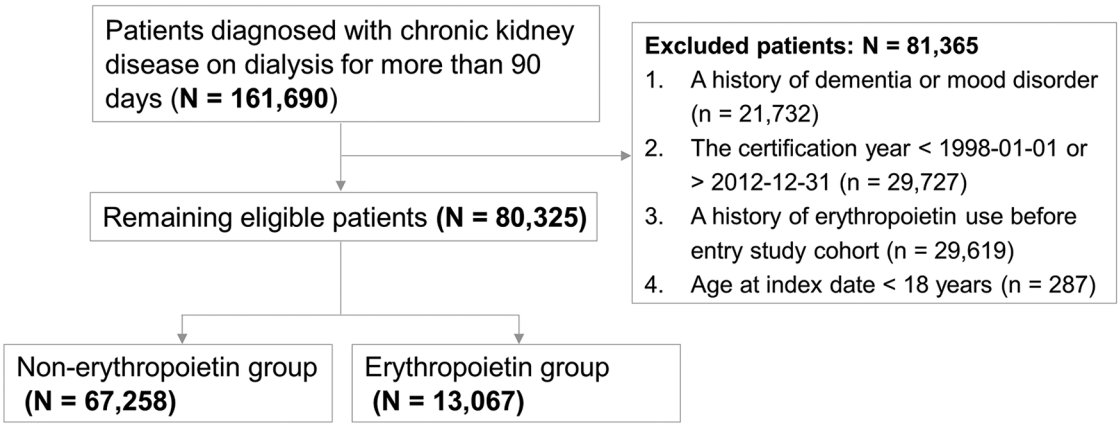

Figure 1. Flowchart showing the selection processes of study subjects.

Table 1. Characteristics of patients in non-erythropoietin and erythropoietin groups.

Characteristics	Non-EPO *n* = 67,258	EPO *n* = 13,067	*p*
Sex			<0.001
Male	35,785 (53.21)	6469 (49.51)	
Female	31,473 (46.79)	6598 (50.49)	
Age, years	60.99 ± 14.09	60.08 ± 14.31	<0.001
Certification year of catastrophic illness for ESKD			<0.001
1998–2002	21,530 (32.01)	5222 (39.96)	
2003–2007	21,388 (31.80)	4991 (38.20)	
2008–2012	24,340 (36.19)	2854 (21.84)	
Comorbidity			
Hypertension	56,432 (83.90)	10,741 (82.20)	<0.001
Diabetes mellitus	40,676 (60.48)	7615 (58.28)	<0.001
Dyslipidemia	31,958 (47.52)	5790 (44.31)	<0.001
Vascular disease	15,793 (23.48)	2900 (22.19)	0.001
Cancer	9131 (13.58)	1807 (13.83)	0.441
Benzodiazepines use	58,763 (87.37)	11,214 (85.82)	<0.001

Data were expressed as *n* (percentage) or mean ± standard deviation.
EPO, erythropoietin; ESKD, end-stage kidney disease.

with antidepressant use and cohorts after PSM were significantly lower in ESKD patients with EPO treatment [model 2: cHR 0.91 (0.86–0.97), $p = 0.004$; model 4: cHR 0.79 (0.72–0.86), $p < 0.001$]. However, we found no significant differences in other sensitivity analyses, regardless of using a model of aHR or cHR [model 1: aHR 1.03 (0.96–1.11), cHR 1.02 (0.95–1.10); model 3: aHR 0.98 (0.89–1.08), cHR 0.98 (0.89–1.08)]. In

Table 2. Primary outcome and four sensitive analyses of patients in non-erythropoietin and erythropoietin groups.

Outcome	No. of events	Person-years	Incidence rate of depressive disorder[a]	Adjusted HR[b,c]	*p*	Competitive HR[b]	*p*
Primary							
Non-EPO	4188	329,822	12.70 (12.32–13.09)	1.00 (Reference)		1.00 (Reference)	
EPO	1381	74,616	18.51 (17.56–19.51)	0.98 (0.92–1.04)	0.499	0.99 (0.93–1.05)	0.757
Model 1[d]							
Non-EPO	2938	329,822	8.91 (8.59–9.24)	1.00 (Reference)		1.00 (Reference)	
EPO	1017	74,616	13.63 (12.82–14.49)	1.03 (0.96–1.11)	0.409	1.02 (0.95–1.10)	0.555
Model 2[e]							
Non-EPO	3751	329,822	11.37 (11.01–11.74)	1.00 (Reference)		1.00 (Reference)	
EPO	1276	74,616	17.1 (16.19–18.07)	0.96 (0.90–1.03)	0.225	0.91 (0.86–0.97)	0.004
Model 3[f]							
Non-EPO	1669	129,323	12.91 (12.3–13.54)	1.00 (Reference)		1.00 (Reference)	
EPO	585	32,595	17.95 (16.55–19.46)	0.98 (0.89–1.08)	0.702	0.98 (0.89–1.08)	0.649
Model 4[g]							
Non-EPO	1186	70,163	16.90 (15.97–17.89)	1.00 (Reference)		1.00 (Reference)	
EPO	850	73,158	11.62 (10.86–12.43)	1.07 (0.98–1.17)	0.129	0.79 (0.72–0.86)	<0.001

[a]Incidence rate is expressed as event number per 1000 person-years.
[b]HR is expressed as ratio with 95% confidence interval.
[c]Adjusted for sex, age, certification year of catastrophic illness for end-stage kidney disease, all comorbidities, benzodiazepines use.
[d]Model 1 included only patients with depressive disorder who were diagnosed at least four times by board-certified psychiatrists.
[e]Model 2 included only patients with depressive disorder treated with antidepressants.
[f]Model 3 limited the entry year of the study cohort to between 2001 and 2005 and following these patients until 31 December 2013.
[g]Model 4 reanalyzed primary outcome after matching and non-EPO and EPO cohorts.
EPO, erythropoietin; HR, hazard ratio.

addition, the basic characteristics after PSM are shown in Supplemental material Table 1 online.

Table 3 shows the analysis of dose-dependent relationship of EPO average dose and depressive disorder in the erythropoietin group. The medium- and high-dose groups had a decreased risk in comparison with the low-dose group, but the result did not reach statistical significance [medium: HR 0.92 (0.82–1.04), aHR 0.92 (0.82–1.04); high: HR 0.95 (0.82–1.09), aHR 0.91 (0.79–1.05)].

Discussion

In the current study, the real-world evidence in Taiwan shows that long-term administration of EPO to ESKD patients with maintenance dialysis was not associated with general risk of developing depression in these patients. This result persisted after we adjusted for potential variables including the sex, age, certification year, physical comorbidities, and benzodiazepine use of included subjects. To our best knowledge, this is the first study exploring the association between EPO treatment and the risk of depression.

Accumulating evidence has suggested that EPO is a potential target for the treatment of depression, including mood and cognitive symptoms.[13,20] Although one study had found that recombinant human EPO infusion can improve depressive symptoms and some cognitive functions in patients with treatment-resistant depression,[21] there is no open trial or double-blind,

Table 3. Dose-dependent outcome of patients in erythropoietin group.

EPO average dose[a]	HR[b]	*p*	Adjusted HR[b,c]	*p*
1–500 IU	1.00 (Reference)		1.00 (Reference)	
501–5000 IU	0.92 (0.82–1.04)	0.192	0.92 (0.82–1.04)	0.178
>5000 IU	0.95 (0.82–1.09)	0.433	0.91 (0.79–1.05)	0.202

[a]EPO average dose is expressed as total EPO dose per week.
[b]HR is expressed as ratio with 95% confidence interval.
[c]Adjusted for sex, age, certification year of catastrophic illness for end-stage kidney disease, all comorbidities, benzodiazepines use.
EPO, erythropoietin; HR, hazard ratio; IU, international unit.

placebo-controlled study to examine the response and remission rate of EPO for treating depressive disorder. When looking at cognitive functions, EPO was found to improve memory functions and speed of complex cognitive processing in patients with treatment-resistant depression and remitted bipolar disorder,[28,29] and the efficacy was associated with baseline cognitive or memory impairment.[29,30] Consistently, one recent nationwide population-based study found EPO treatment was associated with lower risk of general dementia, vascular dementia, and unspecified dementia in patients receiving hemodialysis, but not with Alzheimer's disease.[31] Together with our study, although EPO has not been proved to have therapeutic or preventive effect for depressive disorder, its neurotrophic and neuroprotective functions may be related to improvement of depressive symptoms and cognitive functions in patients with neuropsychiatric deficits or systemic diseases, such as mood disorders and ESKD. In the dose-dependent analysis, we found the medium- and high-EPO dose groups had a decreased risk of depression in comparison with the low-dose group. Although not significant, this result suggests that a higher dose of EPO should be considered in future clinical studies examining its effect in reducing depressive symptoms.

Depression is one of the most frequent co-morbid conditions of CKD patients. According to one meta-analytic study by Palmer *et al.*,[32] the prevalence rate of interview-based depression was 22–26% in patients with CKD, and the rate of depressive symptoms by self- or clinician-administered rating scales was 26–39%. For both types of assessment, the prevalence rate is higher in patients with dialysis or with kidney transplantation than earlier stage CKD patients.[32] They suggested that self-report scales may overestimate the presence of depression, particularly in the dialysis setting. Also, the prevalence of depression is associated with the severity of CKD.[32,33] Early recognition and treatment of depression are important because it did not only reduce health-related quality of life,[34] but also increased the mortality rate in patients with CKD,[35] and in patients receiving long-term dialysis.[36]

Anemia is also a common complication in patients with CKD, and it develops gradually and gets more severe as kidney disease progresses.[37] Its prevalence is approximately 42% in patients with stage 3 CKD, increasing to approximately 76% in ESKD.[38] Erythropoiesis-stimulating agents (including EPO) and adjuvant iron therapy are the primary treatment for anemia in both dialysis and non-dialysis CKD patients.[39] In our study, we limited our included subjects to ESKD patients on maintenance dialysis, defined as having certification of catastrophic illness, to ensure an accurate diagnosis of severe CKD. The inclusion of only ESKD patients may result in a ceiling effect of EPO in changing the risk of subsequent depression. It is probably difficult to see a neurotrophic or neuroprotective effect of EPO in an environment with highly disordered metabolic homeostasis in ESKD patients with dialysis. This effect might be observed in CKD at an earlier stage.

The strength of this study is its population-based survey with large sample size, with good follow-up throughout. Also, this study utilized retrospective follow-up design and depression as a diagnosis done by a psychiatrist and not based on a self-rated questionnaire, thus providing a good schema to compare the outcome in patients with and without EPO treatment. However, several limitations should be noted when interpreting our

results. First, some anemic patients can be asymptomatic and thus might not visit the clinic, thereby eluding diagnosis; therefore, the incidence of EPO use in the non-anemic controls was probably overestimated because of the presence of these asymptomatic patients. Second, our study was observational in nature and cannot prove causal relation. Although we adjusted for common health conditions, it is possible that subclinical disease may also have contributed to depressive symptoms. Third, we limited the included subjects to ESKD patients with dialysis. It is not clear whether EPO treatment changes the risk of depressive disorder in CKD patients at an earlier stage. Fourth, the study used insurance claims database, so many important clinical characteristics, such as patients' socioeconomic status, family function, and smoking status, were not available. Moreover, we implemented a propensity score matching to decrease potential bias from the database, but bias could exist in the data. Finally, although our result did not support a preventive effect of EPO treatment from depression, EPO's multiple effects, including improving symptoms of anemia, reducing the number of patients needing blood transfusion, tissue protectors in multiple organs, and raising the quality of life, all may improve depressive symptoms in the clinical setting.

Conclusion

In summary, through the analysis of the nationwide-wide reimbursement data in Taiwan, we found that EPO treatment in patients with ESKD was not associated with their general risk of developing depressive disorder, and it did not provide a preventive effect from depression. These results could be an essential reference related to the clinical practice of taking care of patients with chronic renal disease. Clinicians should be careful about the possible high risk of depression even the ESKD patients have received EPO treatment.

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Author contributions

Pao-Yen Lin performed the research, analyzed the data, and wrote the manuscript. Pao-Yen Lin and Chih-Wei Hsu designed the experiments. Lung-Chih Li, Liang-Jen Wang, Yao-Hsu Yang, and Chih-Wei Hsu interpreted the data and revised the manuscript. Chih-Wei Hsu contributed to statistical analyses. Chih-Wei Hsu is co-corresponding author. All authors reviewed and approved the final version.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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References

1. Hill NR, Fatoba ST, Oke JL, *et al.* Global prevalence of chronic kidney disease - a systematic review and meta-analysis. *PLoS One* 2016; 11: e0158765.
2. Elshahat S, Cockwell P, Maxwell AP, *et al.* The impact of chronic kidney disease on developed countries from a health economics perspective: a systematic scoping review. *PLoS One* 2020; 15: e0230512.
3. Mikhail A, Brown C, Williams JA, *et al.* Renal association clinical practice guideline on anaemia

of chronic kidney disease. *BMC Nephrol* 2017; 18: 345.

4. Reissmann KR. Studies on the mechanism of erythropoietic stimulation in parabiotic rats during hypoxia. *Blood* 1950; 5: 372–380.
5. Plzak LF, Fried W, Jacobson LO, *et al.* Demonstration of stimulation of erythropoiesis by plasma from anemic rats using Fe59. *J Lab Clin Med* 1955; 46: 671–678.
6. Padhi S, Glen J, Pordes BA, *et al.* Management of anaemia in chronic kidney disease: summary of updated NICE guidance. *BMJ* 2015; 350: h2258.
7. Nairz M, Sonnweber T, Schroll A, *et al.* The pleiotropic effects of erythropoietin in infection and inflammation. *Microbes Infect* 2012; 14: 238–246.
8. Yuan R, Wang B, Lu W, *et al.* A distinct region in erythropoietin that induces immuno/inflammatory modulation and tissue protection. *Neurotherapeutics* 2015; 12: 850–861.
9. Kimáková P, Solár P, Solárová Z, *et al.* Erythropoietin and its angiogenic activity. *Int J Mol Sci* 2017; 18: 1519.
10. Talan MI and Latini R. Myocardial infarction: cardioprotection by erythropoietin. *Methods Mol Biol* 2013; 982: 265–302.
11. Choi D, Schroer SA, Lu SY, *et al.* Erythropoietin protects against diabetes through direct effects on pancreatic beta cells. *J Exp Med* 2010; 207: 2831–2842.
12. Marti HH, Wenger RH, Rivas LA, *et al.* Erythropoietin gene expression in human, monkey and murine brain. *Eur J Neurosci* 1996; 8: 666–676.
13. Ma C, Cheng F, Wang X, *et al.* Erythropoietin pathway: a potential target for the treatment of depression. *Int J Mol Sci* 2016; 17: 677.
14. Masuda S, Chikuma M and Sasaki R. Insulin-like growth factors and insulin stimulate erythropoietin production in primary cultured astrocytes. *Brain Res* 1997; 746: 63–70.
15. Genc S, Kuralay F, Genc K, *et al.* Erythropoietin exerts neuroprotection in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated C57/BL mice via increasing nitric oxide production. *Neurosci Lett* 2001; 298: 139–141.
16. Miskowiak K, O'Sullivan U and Harmer CJ. Erythropoietin reduces neural and cognitive processing of fear in human models of antidepressant drug action. *Biol Psychiatry* 2007; 62: 1244–1250.
17. Miskowiak K, O'Sullivan U and Harmer CJ. Erythropoietin enhances hippocampal response during memory retrieval in humans. *J Neurosci* 2007; 27: 2788–2792.
18. Miskowiak KW, Favaron E, Hafizi S, *et al.* Effects of erythropoietin on emotional processing biases in patients with major depression: an exploratory fMRI study. *Psychopharmacology (Berl)* 2009; 207: 133–142.
19. Miskowiak KW, Favaron E, Hafizi S, *et al.* Erythropoietin modulates neural and cognitive processing of emotional information in biomarker models of antidepressant drug action in depressed patients. *Psychopharmacology (Berl)* 2010; 210: 419–428.
20. Miskowiak KW, Vinberg M, Harmer CJ, *et al.* Erythropoietin: a candidate treatment for mood symptoms and memory dysfunction in depression. *Psychopharmacology (Berl)* 2012; 219: 687–698.
21. Miskowiak KW, Vinberg M, Christensen EM, *et al.* Recombinant human erythropoietin for treating treatment-resistant depression: a double-blind, randomized, placebo-controlled phase 2 trial. *Neuropsychopharmacology* 2014; 39: 1399–1408.
22. Vinberg M, Miskowiak K, Hoejman P, *et al.* The effect of recombinant erythropoietin on plasma brain derived neurotrophic factor levels in patients with affective disorders: a randomised controlled study. *PLoS One* 2015; 10: e0127629.
23. Holmquist S, Nordstrom A and Nordstrom P. The association of depression with subsequent dementia diagnosis: a Swedish nationwide cohort study from 1964 to 2016. *PLoS Med* 2020; 17: e1003016.
24. John A, Patel U, Rusted J, *et al.* Affective problems and decline in cognitive state in older adults: a systematic review and meta-analysis. *Psychol Med* 2019; 49: 353–365.
25. Chung KH, Li CY, Kuo SY, *et al.* Risk of psychiatric disorders in patients with chronic insomnia and sedative-hypnotic prescription: a nationwide population-based follow-up study. *J Clin Sleep Med* 2015; 11: 543–551.
26. Tuot DS, Lin F, Norris K, *et al.* Depressive symptoms associate with race and all-cause mortality in patients with CKD. *Kidney Int Rep* 2019; 4: 222–230.
27. Rassen JA, Shelat AA, Myers J, *et al.* One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol Drug Saf* 2012; 21(Suppl. 2): 69–80.

28. Miskowiak KW, Vinberg M, Macoveanu J, *et al.* Effects of erythropoietin on hippocampal volume and memory in mood disorders. *Biol Psychiatry* 2015; 78: 270–277.
29. Ott CV, Vinberg M, Kessing LV, *et al.* The effect of erythropoietin on cognition in affective disorders - associations with baseline deficits and change in subjective cognitive complaints. *Eur Neuropsychopharmacol* 2016; 26: 1264–1273.
30. Miskowiak KW, Rush AJ Jr, Gerds TA, *et al.* Targeting treatments to improve cognitive function in mood disorder: suggestions from trials using erythropoietin. *J Clin Psychiatry* 2016; 77: e1639–e1646.
31. Hung P-H, Yeh C-C, Sung F-C, *et al.* Erythropoietin prevents dementia in hemodialysis patients: a nationwide population-based study. *Aging (Albany NY)* 2019; 11: 6941–6950.
32. Palmer S, Vecchio M, Craig JC, *et al.* Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. *Kidney Int* 2013; 84: 179–191.
33. Jhee JH, Lee E, Cha MU, *et al.* Prevalence of depression and suicidal ideation increases proportionally with renal function decline, beginning from early stages of chronic kidney disease. *Medicine (Baltimore)* 2017; 96: e8476.
34. Wang W-L, Liang S, Zhu F-L, *et al.* The prevalence of depression and the association between depression and kidney function and health-related quality of life in elderly patients with chronic kidney disease: a multicenter cross-sectional study. *Clin Interv Aging* 2019; 14: 905–913.
35. Palmer SC, Vecchio M, Craig JC, *et al.* Association between depression and death in people with CKD: a meta-analysis of cohort studies. *Am J Kidney Dis* 2013; 62: 493–505.
36. Farrokhi F, Abedi N, Beyene J, *et al.* Association between depression and mortality in patients receiving long-term dialysis: a systematic review and meta-analysis. *Am J Kidney Dis* 2014; 63: 623–635.
37. Fehr T, Ammann P, Garzoni D, *et al.* Interpretation of erythropoietin levels in patients with various degrees of renal insufficiency and anemia. *Kidney Int* 2004; 66: 1206–1211.
38. McClellan W, Aronoff SL, Bolton WK, *et al.* The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin* 2004; 20: 1501–1510.
39. Bonomini M, Del Vecchio L, Sirolli V, *et al.* New treatment approaches for the anemia of CKD. *Am J Kidney Dis* 2016; 67: 133–142.