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Letter to the Editor

LETTER TO THE EDITOR

Reply to 'Depression and clinical outcomes in CKD: do anti-depressants play a role? (EQUAL Study)'

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We would like to thank Chilcot and colleagues for their compliments and kind remarks regarding our recently published study. We appreciate their comments and suggestions for future research. The authors have raised very interesting issues and we are thankful for the opportunity to respond to these issues.

First, Chilcot and colleagues discuss that the Mental Health Inventory (MHI-5) is not the most optimal measure to assess depressive symptoms. We agree with the authors on this issue, as the MHI-5 is initially designed to measure psychological distress. As we described in our discussion: a more optimal measure for diagnosis of depressive symptoms would have been, for example, the Beck Depression Inventory [1]. However, that being said, the MHI-5 has been examined in a large cohort of elderly people (aged 65 years or higher), where it demonstrated a good sensitivity and specificity (sensitivity 78.7%, specificity 72.1%) in the detection of a major depressive episode [2]. As also discussed in our article, the MHI-5 has been validated for the detection of depressive symptoms in a wide range of populations, including several countries that participated in our cohort [3]. Furthermore, our study greatly contributes to the knowledge about this under-researched topic in elderly people with chronic kidney disease (CKD) in the pre-dialysis phase.

Following the official SF-36 guidelines, we calculated the MHI-5 scores when a minimal of three out of the five questions were answered [4]. Based on the suggestion of Chilcot *et al.*, we repeated our Cox regression analyses after multiple imputation of missing MHI-5 items, thereby enabling us to include the entire cohort ($N = 1708$) in our analysis. As shown in Tables 1 and 2, most of the results are similar to the results of our primary

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Table 1. Association of the presence of depressive symptoms at baseline with time until start of dialysis, all-cause mortality and a combined adverse event, after imputation of MHI-5 score and baseline confounders

	Entire cohort		Males		Females	
Outcome	Crude HR (95% CI) $N = 1708$	Adjusted HR[a] (95% CI) $N = 1708$	Crude HR (95% CI) $N = 1114$	Adjusted HR[a] (95% CI) $N = 1114$	Crude HR (95% CI) $N = 594$	Adjusted HR[a] (95% CI) $N = 594$
Start of dialysis	1.02 (0.83–1.24)	1.01 (0.79–1.28)	1.10 (0.87–1.40)	1.01 (0.77–1.33)	1.09 (0.73–1.62)	1.19 (0.78–1.82)
All-cause mortality	1.31 (1.03–1.66)*	1.20 (0.93–1.55)	1.48 (1.10–1.99)**	1.22 (0.92–1.60)	1.15 (0.78–1.69)	1.06 (0.71–1.56)
Combined adverse outcome[b]	1.14 (0.97–1.33)	1.10 (0.91–1.32)	1.25 (1.04–1.50)*	1.13 (0.92–1.39)	1.12 (0.84–1.49)	1.11 (0.81–1.51)

The hazard ratio (95% confidence interval) indicates the increased rate of an event (start of dialysis, all-cause mortality and combined adverse outcome) for the presence of depressive symptoms at baseline (i.e. a score $\leq$70 on the MHI-5).

[a]Adjusted for: age, gender, ethnicity, level of education, primary kidney disease (PKD), Charlson Comorbidity Index (CCI), body mass index (BMI), smoking status, subjective global assessment (SGA), estimated glomerular filtration rate (eGFR) at baseline, and plasma albumin and urea levels.

[b]Combined adverse outcome: either start of dialysis or all-cause mortality.

*$P < 0.05$, **$P < 0.01$.

Table 2. Association of the mental health score at baseline with time until start of dialysis, all-cause mortality and a combined adverse event, after imputation of MHI-5 and baseline confounders

	Entire cohort		Males		Females	
Outcome	Crude HR (95% CI) $N = 1708$	Adjusted HR[a] (95% CI) $N = 1708$	Crude HR (95% CI) $N = 1114$	Adjusted HR[a] (95% CI) $N = 1114$	Crude HR (95% CI) $N = 594$	Adjusted HR[a] (95% CI) $N = 594$
Start of dialysis	1.02 (0.97–1.07)	1.01 (0.96–1.07)	1.04 (0.98–1.10)	1.02 (0.95–1.09)	1.04 (0.94–1.15)	1.03 (0.93–1.14)
All-cause mortality	1.08 (1.02–1.14)**	1.05 (0.96–1.11)	1.12 (1.05–1.20)**	1.08 (1.00–1.15)*	1.04 (0.95–1.14)	0.99 (0.89–1.09)
Combined adverse outcome[b]	1.04 (1.01–1.08)**	1.03 (0.99–1.07)	1.07 (1.03–1.12)**	1.04 (0.99–1.09)	1.04 (0.98–1.11)	1.01 (0.94–1.08)

The hazard ratio (95% confidence interval) indicates the increased rate of an event (start of dialysis, all-cause mortality and combined adverse outcome) for every 10 points decrease on the MHI-5.

[a]Adjusted for: age, gender, ethnicity, level of education, PKD, CCI, BMI, smoking status, SGA, eGFR at baseline, and plasma albumin and urea levels.

[b]Combined adverse outcome: either start of dialysis or all-cause mortality.

*$P < 0.05$, **$P < 0.01$.

analyses. The adjusted hazard of all-cause mortality in males with depressive symptoms compared with males without depressive symptoms did lose significance {adjusted hazard ratio (HR) 1.22 [95% confidence interval (CI) 0.92–1.60]}. However, when depressive symptoms were considered as continuous parameter, a significant association was still found between an increase in depressive symptoms and a higher hazard of all-cause mortality in males [adjusted HR 1.08 (95% CI 1.00–1.15)].

Second, Chilcot *et al.* discuss our suggestion that anti-depressants may potentially improve survival in men given the observed association between depressive symptoms and mortality in this subgroup. We agree with the authors that more research is needed to explore the beneficial role and safety of anti-depressants in this population. Particularly, randomized clinical trials are needed to investigate whether anti-depressant treatment improves survival in this population [5]. Additionally, we believe it is important to emphasize that depressive symptoms may influence survival of patients with CKD and that treatment of depressive symptoms should always be considered during the treatment of CKD. Furthermore, the authors suggest to additionally adjust for the use of anti-depressant medication in our analyses. We respectfully disagree with this suggestion, as we believe that anti-depressant medication is a mediator rather than a confounder in the pathway between depressive symptoms and all-cause mortality. Use of anti-depressant medication is 'caused' by depressive symptoms and should therefore not be considered as a confounder. We do believe it would be very interesting to further investigate the effect of anti-depressants on our outcome measures and are eager to further explore this question in future research.

Finally, Chilcot and colleagues point out that anti-depressants with QT-prolonging potential increase the risk of cardiac sudden death in patients on hemodialysis compared with patients on anti-depressants without QT-prolonging potential [6]. We agree with the authors that, especially in the vulnerable population of patients with CKD, prescription of medication should be evaluated thoroughly. Considering risks (e.g. QT-prolongation) and benefits (e.g. improvement of depressive symptoms) is of great importance, and advantages and disadvantages should be weighed against each other with great care and by means of shared decision-making. Furthermore, it is important to note that there are also numerous examples of anti-depressants with a low or non-existant risk of QT-prolonging potential (e.g. paroxetine and fluoxetine) [7] and that depressive symptoms may also be treated using non-pharmacological interventions (e.g. cognitive behavioral therapy) [8]. Although randomized clinical trials on the effect of anti-depressant medication on all-cause mortality in patients with CKD are needed, we would like to stress the importance of adequate treatment of depressive symptoms in this population.

We would like to thank our colleagues again for their interest in our study.

CONFLICT OF INTEREST STATEMENT

None declared.

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