BJPsych | The British Journal of Psychiatry (2016) 208, 593–594

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Edited by Kiriakos Xenitidis and Colin Campbell

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Duration of depressive symptoms significantly related to increase in mortality

White *et al*[1] examined the relationship between the duration of depressive symptoms and mortality in adults aged 50 or older in a follow-up study. The authors assessed depressive symptom duration as the sum of screen-positive number by an eight-item Center for Epidemiologic Studies Depression Scale (CES-D) score of $\geqslant 3$. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of screen-positive depressive symptoms with numbers from 1 to 4 against never-reported symptoms for mortality were 1.41 (1.15–1.74), 1.80 (1.44–2.26), 1.97 (1.57–2.47) and 2.48 (1.90–3.23), respectively. The authors concluded that the duration of depressive symptoms was significantly associated with mortality in a dose–response manner. I have some concerns regarding their study.

First, the same authors recently investigated the association between depressive symptom severity and mortality.[2] Depressive symptom severity was assessed by the positive number of an eight-item CES-D score. Adjusted HRs (95% CIs) of 2, 4 and 8 positive scores on CES-D for mortality were 1.59 (1.40–1.82), 1.80 (1.52–2.13) and 2.27 (1.69–3.04), respectively. I understand that mortality risk existed at low levels of depressive symptoms, but the authors concluded that and the risk became a plateau thereafter. The authors conducted the risk assessment of duration and severity of depressive symptoms for subsequent mortality in these two papers, and there is a need of additional explanation for the relationship with and without a dose–response manner.

Second, there are reports that the time (duration) of depression was associated with subsequent mortality in patients with acute coronary syndrome.[3,4] These references handled different events, such as all-cause mortality and cardiac events. I recommend that White *et al* conduct a sensitivity analysis by dividing the cause of death such as neoplasms, cardiovascular disease and cerebrovascular disease (stroke).

Finally, the authors adopted Cox regression analysis, and evaluation of depressive symptoms by CES-D was repeatedly made. In this situation, I strongly recommend the authors conduct a time-dependent Cox model for their analysis, which had been reported.[5–7] Among them, Wassertheil-Smoller *et al*[7] reported that baseline depressive symptoms were not related to subsequent mortality, but Cox proportional hazards regression analyses with the CES-D scale as a time-dependent variable indicated a significant increase of death with increase in the CES-D score thereafter. As the significance of HR disappeared when all covariates were adjusted for the association between the number of screen-positive depressive symptoms and mortality, further study is needed to confirm the association.

1 White J, Zaninotto P, Walters K, Kivimäki M, Demakakos P, Biddulph J, et al. Duration of depressive symptoms and mortality risk: the English Longitudinal Study of Ageing (ELSA). *Br J Psychiatry* 2016; **208**: 337–42.

2 White J, Zaninotto P, Walters K, Kivimäki M, Demakakos P, Shankar A, et al. Severity of depressive symptoms as a predictor of mortality: the English longitudinal study of ageing. *Psychol Med* 2015; **45**: 2771–9.

3 Grace SL, Abbey SE, Kapral MK, Fang J, Nolan RP, Stewart DE. Effect of depression on five-year mortality after an acute coronary syndrome. *Am J Cardiol* 2005; **96**: 1179–85.

4 Parker G, Hyett M, Walsh W, Owen C, Brotchie H, Hadzi-Pavlovic D. Specificity of depression following an acute coronary syndrome to an adverse outcome extends over five years. *Psychiatry Res* 2011; **185**: 347–52.

5 Fan L, Sarnak MJ, Tighiouart H, Drew DA, Kantor AL, Lou KV, et al. Depression and all-cause mortality in hemodialysis patients. *Am J Nephrol* 2014; **40**: 12–8.

6 Scherrer JF, Garfield LD, Lustman PJ, Hauptman PJ, Chrusciel T, Zeringue A, et al. Antidepressant drug compliance: reduced risk of MI and mortality in depressed patients. *Am J Med* 2011; **124**: 318–24.

7 Wassertheil-Smoller S, Applegate WB, Berge K, Chang CJ, Davis BR, Grimm R Jr, et al. Change in depression as a precursor of cardiovascular events. SHEP Cooperative Research Group (Systoloc Hypertension in the elderly). *Arch Intern Med* 1996; **156**: 553–61.

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doi: 10.1192/bjp.208.6.593

Authors' reply: We thank Professor Kawada for his careful reading of our paper. He raises a number of issues that we address here. First, it is important to recognise that, while we used the same study (the English Longitudinal Study of Ageing, ELSA) in each of the papers he describes,[1,2] we asked very different questions of the data.

In the first paper,[2] we were interested in whether depression symptom *severity*, across the full range of scores measured on a single occasion, was related to later risk of all-cause mortality. If mortality effects are seen in people with mild-to-moderate depression, this could potentially point to the need for treatment at lower levels than is currently the case. Wishing to test whether the dose–response association we found for psychological distress (a combined measure of depression and anxiety) and all-cause mortality in the Health Surveys for England – Scottish Health Surveys collaboration was replicated using a depression-specific inventory,[3] we used an administration of the Center for Epidemiologic Studies Depression Scale (CES-D) during wave 1 of data collection in ELSA. On relating those scores (higher score indicated greater depression severity) to mortality experience over the following 9 years, after basic statistical adjustments, there was a stepwise effect that, as Kawada indicates, seemed to plateau in people reporting the most severe symptoms.

In the second paper, recognising that symptoms of depression tend to be, as Kawada points out, time-varying,[4,5] in order to better capture depression exposure we capitalised on the serial measurements made over 4 waves of data collection (8 years) in ELSA, which is rare in population-based studies. We found that the number of waves a study member was denoted as a 'case' (based on a score of $\geqslant 3$ on the CES-D) was positively associated with deaths occurring after the final wave of data capture. Again, we found evidence of a dose–response effect. Importantly, in both papers, taking into account differences across the depression groups in levels of physical activity, cognitive function, functional impairments and physical illness led to complete attenuation of any relationships. This suggests that these factors either confound or mediate the depression–mortality gradient.

Contrary to Kawada's view, we do not think that studies of sick populations – in the examples given, patients with cardiovascular disease (CVD) – offer any insight into the link between depression and the future occurrence of CVD events (aetiology). In our papers, concerns regarding a lack of statistical power (for analyses of depression duration) and space constraints (for analyses of depression severity) prevented us from reporting