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Association between all-cause mortality and severity of depressive symptoms in patients with type 2 diabetes: Analysis from the Japan Diabetes Complications Study (JDCS)

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ABSTRACT

Objective: The aims of this study are to confirm whether the excess mortality caused by depressive symptoms is independent of severe hypoglycemia in patients with type 2 diabetes mellitus (T2DM) and to evaluate the association between all-cause mortality and degrees of severity of depressive symptoms in Japanese patients with T2DM.

Methods: A total of 1160 Japanese patients with T2DM were eligible for this analysis. Participants were followed prospectively for 3 years and their depressive states were evaluated at baseline by the Center for Epidemiologic Studies Depression Scale (CES-D). Cox proportional hazards model was used to evaluate the relative risk of all-cause mortality and was adjusted by possible confounding factors, including severe hypoglycemia, all of which are known as risk factors for both depression and mortality.

Results: After adjustment for severe hypoglycemia, each 5-point increase in the CES-D score was significantly associated with excess all-cause mortality (hazard ratio 1.69 [95% CI 1.26–2.17]). The spline curve of HRs for mortality according to total CES-D scores showed that mortality risk was slightly increased at lower scores but was sharply elevated at higher scores.

Conclusion: A high score on the CES-D at baseline was significantly associated with all-cause mortality in patients with T2DM after adjusting for confounders including severe hypoglycemia. However, only a small effect on mortality risk was found at relatively lower levels of depressive symptoms in this population. Further research is needed to confirm this relationship between the severity of depressive symptoms and mortality in patients with T2DM.

1. Introduction

Patients with type 2 diabetes mellitus (T2DM) are at a higher risk of depression than people without diabetes [1], and, furthermore, the mortality risk significantly increases with comorbid depression [2]. Hence, an evaluation of depression is very important in diabetes care.

Severe hypoglycemia is known to significantly increase the risk of cardiovascular disease and all-cause death in patients with T2DM [3,4].

Abbreviations: T2DM, Type 2 diabetes mellitus; CES-D, Center for Epidemiologic Studies Depression Scale; JDCS, Japan Diabetes Complications Study; JDS, Japan Diabetes Society; DPN, Diabetic peripheral neuropathy; DSPN, Diabetic sensorimotor polyneuropathy; PHQ-9, Patient Health Questionnaire-9

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Depression is an independent risk factor for severe hypoglycemia in patients with T2DM [5]. Therefore, the increased risk of death by comorbid depression in patients with T2DM may be mediated by severe hypoglycemia. However, it has not been clarified whether the excess mortality caused by depression is independent of severe hypoglycemia in diabetic patients.

A meta-analysis of 22 observational prospective studies showed that the risk of death increased in those with subthreshold depression defined by a self-report scale [6]. Moreover, a significant relationship was reported between depressive symptoms and mortality even in depressive symptoms with a lower degree of severity than the cutoff value in depression screening [7,8]. Therefore, regardless of the diagnostic criteria for depression, evaluation of how the risk of death varies with the degree of the depressive symptoms is important. However, previous research in T2DM has not shown sufficient data on the risk of death according to severity of depressive symptoms in patients with diabetes. These previous studies only evaluated the relationship between mortality and depression as a categorical variable or only assessed whether the depressive symptom score and mortality risk had a significant linear correlation [9–12].

Hence, we aimed to evaluate whether the association between depressive symptoms and all-cause mortality is independent of severe hypoglycemia and to determine variations in the relationships between the degree of depressive symptoms and all-cause mortality after consideration of severe hypoglycemia in patients with T2DM.

2. Methods

2.1. Study population

This analysis is part of the Japan Diabetes Complications Study (JDCS), a multicenter prospective study of the incidence of and risk factors for diabetic complications and mortality among Japanese patients with T2DM. The JDCS was originally planned as a randomized lifestyle intervention study, and half of the participants received structured counseling. Details have been published elsewhere [13].

Participants in this study were between 40 and 70 years old and already had been diagnosed with T2DM at the 1995 registration. At the time of registration, individuals whose HbA1c was > 6.5% and who did not have any history of cardiovascular disease, overt nephropathy, or proliferative retinopathy were recruited. Laboratory tests and clinical variables, including assessment of diabetic complications, were checked annually, and lifestyle surveys were conducted in 1995 and 2000.

The lifestyle survey in 2000 included assessment of depressive symptoms with the Center for Epidemiologic Studies Depression Scale (CES-D), and the baseline of the present study (i.e., time follow-up began) was therefore set as April 1, 2000. After excluding 973 patients without complete data for the CES-D or who were not followed after the baseline examination, 1060 patients (574 men and 486 women) out of the 2033 eligible patients were included in the present study.

Diabetes mellitus was diagnosed according to the 'Report of the Committee of the Japan Diabetes Society (JDS) on the Classification and Diagnostic Criteria of Diabetes Mellitus', which is almost identical in terms of thresholds for glucose levels to those of the World Health Organization. All enrolled patients provided written informed consent.

2.2. Clinical and laboratory measurements

Demographic, lifestyle, and comorbidity information was collected as part of the 2000 survey. Mean values for at least two measurements at the time of the baseline examination were obtained for HbA1c, fasting plasma glucose, and fasting serum lipids. HbA1c assays were performed according to procedures outlined by the Laboratory Test Committee of the JDS, which is known to be converted by the formula HbA1c (JDS) (%) = 0.98 × HbA1c (National Glycohemoglobin Standardization Program; NGSP) (%) + 0.25%. All other laboratory tests were done at each participating institute. Serum LDL-cholesterol was calculated using Friedeward's equation. All other measurements, including those for body weight and blood pressure, were performed at least once a year, although only baseline data were used in this study. Lifestyle evaluation was performed at the 2000 survey by a self-administered questionnaire, which included the CES-D, and that solicited information on the incidence of hypoglycemia. Hypoglycemia was evaluated by the question "Have you experienced hypoglycemia in the past year? (yes/no)", and "If you have experienced hypoglycemia in the past year, did you need medical care?". Severe hypoglycemia was defined as present in patients who answered "yes" to the latter question. Physical activity was assessed by Baecke's Total Physical Activity Index [14].

2.3. Vascular complications

Diabetic nephropathy, diabetic retinopathy, and macroangiopathy were annually assessed, and an assessment of diabetic peripheral neuropathy (DPN) was done at the first and fifth year of this study by the Achilles tendon reflex test and subjective symptoms of lower peripheral extremities. DPN was defined as 'possible diabetic sensorimotor polyneuropathy (DSPN)' or 'probable DSPN' by the Toronto DPN Expert Group [15]. Details were in our previous report [13].

2.4. Assessment of depressive symptoms

The CES-D is a self-report scale designed to measure depression in the general population [16]. The CES-D consists of 20 items that are designed to measure self-reported depressive symptoms in the prior two weeks. Each of the 20 items is assigned a value of 0–3, with four items positively worded and reverse scored. Total scores range from 0 to 60, with higher scores indicating more depressive symptoms. The CES-D is a valid and reliable instrument for assessing depression in community samples with high internal consistency, good construct and concurrent validity, and modest test-retest reliability. A score of ≥ 16 in the general US population is used to suggest the presence of a probable major depressive disorder [16]. Similarly, in a Japanese population, it was reported that a CES-D score of 16 points is the most appropriate cutoff value for a mood disorder with a sensitivity of 88.2% and a specificity of 84.8% [17]. Another report showed that a cutoff point of 19 was used to suggest the presence of clinical depression in Japanese workers [18]. Optimal cutoff values should differ according to sample populations because the meaning of terms is probably not the same among languages, cultures, races, ages, those with comorbid diseases, etc. Hence, we have used the total score of the CES-D itself to indicate the state of depressive symptoms in this analysis.

2.5. Outcome measures

Death and causes of death were obtained through annual report forms. The main outcome in this study was all-cause mortality.

2.6. Statistical analysis

All statistical analyses and data management were conducted at the central data center for the JDCS. Patient characteristics were described as mean ± SD, median and interquartile range, or percentage. Multivariate Cox regression analysis was used to calculate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) by the following confounding risk factors: age, sex, duration of diabetes, lifestyle factors including current smoking (yes/no), ethanol intake (g/day), physical activity (Baecke total index), sleep duration (< 6/6–8/≥ 9 h), clinical variables accounting for BMI (kg/m^2), waist circumference (cm), systolic blood pressure (mm Hg), HbA1c (%), LDL-cholesterol (mg/dl), HDL-cholesterol (mg/dl), triglycerides (mg/dl), diabetes treatment regimen (diet/oral hypoglycemic agents/insulin), and diabetes

complications composed of diabetic retinopathy, diabetic peripheral neuropathy, overt nephropathy, coronary artery disease, and stroke.

We considered severe hypoglycemia as an important confounding factor for mortality because it is a risk for mortality [19] and presents a higher risk in patients with depression [5]. Similarly, we took into account DPN and sleep duration as key modulators for this analysis. DPN has been related to mortality in patients with T2DM [20], and it is estimated that sleep duration mediates the association between depression and cardiovascular mortality [21]. Sleep duration and BMI have a U-shaped association with mortality [22,23]. Hence, we used these variables as categorical data. To evaluate the relationship between the degree of severity of depression indicated by the CES-D score and HRs for mortality, we showed the spline curve for this relationship with adjustment by all confounders. Our study population was selected from participants in the JDCS, which was comprised of those who received either traditional or strategic lifestyle interventions. We also conducted multi-variable Cox regression analysis according whether or not an intervention was provided. All *p*-values are two-sided, and the significance level is 0.05. All statistical analyses were conducted using SAS packages ver. 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Clinical characteristics of the 1060 patients with T2DM are shown in Table 1. The average CES-D score was 12.5 points (SD: 8.2, min: 0, max: 48) and prevalences of retinopathy, peripheral neuropathy, overt nephropathy, coronary artery disease, and stroke at baseline were 42.6%, 24.1%, 7.6%, 4.2%, and 2.7%, respectively. Therapeutic regimens for T2DM were diet only in 16.6%, oral hypoglycemic agents in 50.9%, and insulin in 32.5% of patients. The frequency of severe hypoglycemia during this study period was 1.2%. Supplemental Table 1 shows the baseline characteristics of both excluded and included participants. The prevalence of retinopathy and neuropathy was higher in the included group than that in the excluded group. Supplemental Table 2 shows baseline data according to whether or not an intervention was provided. The CES-D score did not differ significantly between the two groups.

Table 1
Baseline characteristics of 1060 patients with type 2 diabetes.

	Mean or %	SD
Age (year)	63.9	6.7
Women	45.8%	
Diabetes duration (year)	11.2	7.3
Body mass index (kg/m^2)	22.9	3.1
≤ 18.5	6.3%	
> 25	22.6%	
Waist circumference (cm)	80.4	9.1
Systolic blood pressure (mm Hg)	133.2	15.4
Diastolic blood pressure (mm Hg)	75.4	9.4
HbA1c (%, NGSP)	8.0	1.2
HbA1c (IFCC)	64.1	13.4
Fasting plasma glucose (mg/dL)	158.7	45.2
LDL-cholesterol (mg/dL)	120.7	27.7
HDL-cholesterol mg/dL)	59.2	17.4
Triglycerides (mg/dL)*	100.0	73.0
ACR (mg/gCr)*	19.7	38.9
eGFR (mL/min/1.73 m^2)	77.5	20.1
Current smoker	22.8%	
Ethanol intake (g/day)	88.5	153.1
Physical activity (Baecke's total index)	15.1	8.9
Sleep duration (hours)		
< 6	8.0%	
6	32.3%	
7	33.5%	
8	22.0%	
≥ 9	4.3%	
Treatment		
Diet	16.6%	
Oral hypoglycemic agents (OHA)	50.9%	
Insulin	32.5%	
Microangiopathy		
Retinopathy	42.6%	
Peripheral neuropathy	24.1%	
Overt nephropathy	7.6%	
Macroangiopathy	6.2%	
Coronary artery disease	4.2%	
Stroke	2.7%	
Total CES-D score	12.5	8.2

Continuous data are means (SD: standard deviation) or *median (interquartile range), categorical data are prevalence (%).
ACR: albumin/creatinine ratio, eGFR: estimated glomerular filtration rate.

Table 2
Hazard ratios for all-cause death according to 5-point increments in total CES-D scores.

	Hazard ratio	95% confidence interval		*p* Value	Number of deaths/patients
Crude model	1.33	1.10	1.60	< 0.01	26/1060
Model 1[a]	1.33	1.11	1.60	< 0.01	26/1056
Model 2[b]	1.42	1.13	1.76	< 0.01	18/762
Model 3[c]	1.69	1.26	2.25	< 0.01	13/675
Model 4[d]	1.69	1.26	2.25	< 0.01	13/675
Model 5[e]	1.69	1.26	2.27	< 0.01	13/639

[a] Adjusted for age, sex and duration of diabetes.
[b] Additionally adjusted for the variables in model 1 and lifestyle factors (current smoking, alcohol intake, physical activity, sleep duration).
[c] Additionally adjusted for the variables in model 2 and clinical variables (BMI, waist circumference, systolic blood pressure, HbA1c, LDL-cholesterol, HDL-cholesterol, triglycerides).
[d] Additionally adjusted for the variables in model 3 and use of OHA and insulin.
[e] Additionally adjusted for the variables in model 3 and complications of diabetes (severe hypoglycemia, retinopathy, overt nephropathy, peripheral neuropathy, macroangiopathy).

During the median follow-up interval of 3.6 years, there were 26 deaths (men, 18/574 deaths; women, 8/486 deaths). The 3-year follow-up rate was 91.4%. The total person-years studied were 3461 person-years (men, 1846 person-years; women, 1615 person-years). The crude all-cause mortality was 7.5 per 1000 person-years (men, 9.6; women, 5.0).

Table 2 shows the relationship between each 5-point increase in the total CES-D score and all-cause mortality risk by the multivariate Cox proportional hazards model. The relationship was statistically significant and these associations were seen even after the adjustment for severe hypoglycemia. Moreover, these relationships were not attenuated even after adjustment for multiple risk factors for death including known risk factors associated with atherosclerosis. Supplemental Table 3 shows the results of the multiple regression analysis according to whether or not the participant received an intervention. The HRs for all-cause death were higher in the control group compared with the intervention group.

Fig. 1 is a spline curve of HRs for mortality according to total CES-D scores. As shown in Fig. 1, sharp increases in all-cause mortality were observed at scores ≥ 24. The reanalysis using a CES-D cutoff value of 24 showed that depression defined by a CES-D score of ≥ 24 was significantly associated with all-cause mortality (Table 3). However, the attenuation of relationships was observed using a score of 16 as a cutoff point (Table 3).

4. Discussion

In the current study, the severity of depressive symptoms was significantly associated with all-cause mortality after adjustment for potential confounders including severe hypoglycemia. Severe depressive symptoms may be a risk factor for death independent of severe hypoglycemia in T2DM. Additionally, the risk of death increased slowly at the lower level of total CES-D scores and increased acceleratingly at higher levels in patients with T2DM.

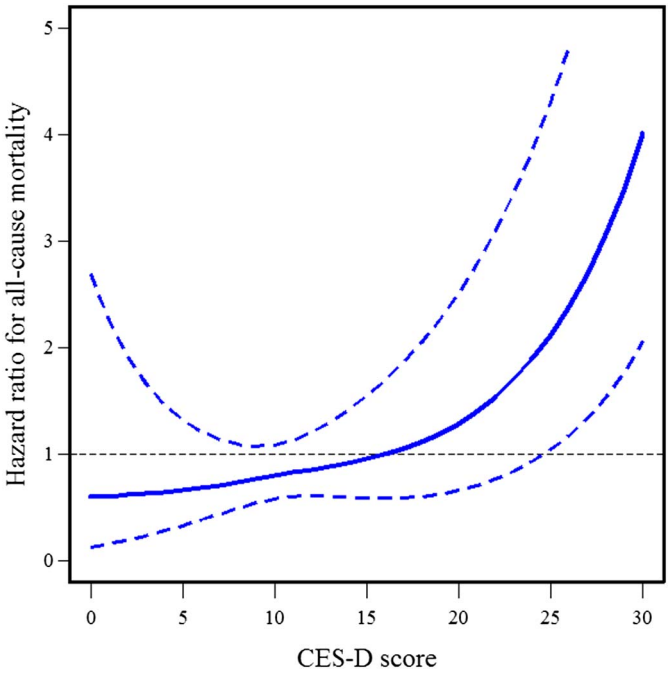

Fig. 1. Spline curve of hazard ratios with 95% confident intervals showing relationships between all-cause mortality and total CES-D scores.
Reference was set at the global cutoff value of a CES-D score of 16.

A meta-analysis revealed that the relative risk of death was significantly elevated in depressed patients [24]; however, only a few studies have investigated the association between psychological symptoms across the continuum of severity and mortality [8,25]. These studies, in which the characteristics were different, also showed an increased risk of mortality even in people with low depressive symptom scores, that is, equivalent to scores lower than the cutoff value for depression. Additionally, depressive symptoms scores and hazard ratios for mortality showed a linear and directly proportional relationship. Differently, our study showed that the risk of death increased slowly in the low score range, but that the risk curve dramatically heightened in the high-score range. These facts indicate that depression-related mortality is relatively low in those with a lower degree of depressive symptoms and that the risk of death becomes greater with higher levels of depressive symptoms in patients with T2DM.

The association between depression and excess mortality has been well established not only in the general population but also in patients with T2DM [2,26]. However, particularly in diabetic patients, there is a significant risk of death even without depression [12]. Moreover, it was suggested that the CES-D score tended to be higher in diabetic patients than in nondiabetic individuals because of the influence of diabetes-related distress such as visual impairment and neuropathy [27].

No study has evaluated the relationship between mortality risk and the degree of severity of depressive symptoms especially in a diabetic population. Only two studies assessed the association between all-cause mortality and depression categorized by severity of depressive symptoms [10,11]. In both studies, the depressive state was divided into two categories, minor depression and major depression, by using information from the Patient Health Questionnaire-9 (PHQ-9). Their results showed that major depression was significantly associated with an increased risk of all-cause death. However, the results related to minor depression were conflicting between these two studies. Though the reason for this discrepancy is unknown, the difference in study settings might be responsible. One study was conducted at primary care clinics and another at specialized clinical care centers, as was our study. Such differences in clinical situations could affect the outcome through differences in the characteristics of diabetic patients, therapeutic strategies, or screening for comorbidities. Furthermore, in our research and in the study in which minor depression was not associated with mortality [10], the major endpoint was cardiovascular disease and mortality. Therefore, the degree of precision in screening for cardiovascular disease might lead to differences among these studies [10,11]. However, it is difficult to conclude the effect of mild depressive symptoms on mortality from the results of these studies.

In our analysis, depression defined by a CES-D cutoff value of 24 was significantly associated with all-cause mortality whereas those relationships were attenuated and the statistical significance disappeared using a score 16 as a cutoff point. These findings indicate that the influence of depressive symptoms on all-cause mortality increases at higher CES-D scores in patients with T2DM. Unfortunately, we could not evaluate the impact of details of the CES-D score on mortality because the incidence of death was too low in our study population for a stratified analysis. Also, the influence of depression may be different in different stages of diabetes. In fact, the severity of diabetes complications has been associated with comorbid depression [28]. Further study is needed to evaluate the optimal cutoff value for clinical depression in patients with T2DM considering the severity of complications.

In the stratified analysis, the HRs for all-cause death were lower in the intervention group compared with the control group. Comprehensive therapies consisting of psychosocial interventions, particularly cognitive-behavior therapy, and collaborative care were reported to be effective in the treatment of depression in patients with diabetes [29], suggesting the effectiveness of intervention therapy for the prevention of death related to depressive symptoms in patients with T2DM. Future studies are needed to clarify the elements contributing to mortality reductions.

A total CES-D score of 16 is globally used as a valid cutoff value for depression in US and Japanese populations [16] [17]. A score of ≥ 16 is most suitable for detection of clinical depression by ROC analysis in Japanese workers [18]. In a report by Zhang et al. a score of 21 was

Table 3
Hazard ratios of all-cause death according to different CES-D cutoff scores indicating depression.

	CES-D score ≥ 16				CES-D score ≥ 24				
	Hazard ratio	95% confidence interval		*p* Value	Hazard ratio	95% confidence interval		*p* Value	Number of deaths/patients
Crude model	1.44	0.63	3.31	0.39	3.78	1.59	8.98	< 0.01	26/1060
Model 1[a]	1.44	0.63	3.32	0.39	3.91	1.64	9.34	< 0.01	26/1056
Model 2[b]	1.62	0.61	4.35	0.34	5.26	1.94	14.3	< 0.01	18/762
Model 3[c]	2.78	0.89	8.66	0.08	7.80	2.50	24.3	< 0.01	13/675
Model 4[d]	2.66	0.85	8.35	0.09	8.09	2.52	26.0	< 0.01	13/675
Model 5[e]	2.89	0.91	9.15	0.07	8.16	2.49	26.7	< 0.01	13/639

[a] Adjusted for age, sex and duration of diabetes.
[b] Additionally adjusted for the variables in model 1 and lifestyle factors (current smoking, alcohol intake, physical activity, sleep duration).
[c] Additionally adjusted for the variables in model 2 and clinical variables (BMI, waist circumference, systolic blood pressure, HbA1c, LDL-cholesterol, HDL-cholesterol, triglycerides).
[d] Additionally adjusted for the variables in model 3 and use of OHA and insulin.
[e] Additionally adjusted for the variables in model 3 and complications of diabetes (severe hypoglycemia, retinopathy, overt nephropathy, peripheral neuropathy, macroangiopathy).

shown to be an optimal cutoff point in predicting depression in Chinese patients with T2DM [30]. That is, the optimal cutoff score for depression may vary depending on race and underlying conditions. In our study 10% of participants had a CES-D score ≥ 24 points. A previous meta-analysis showed that the prevalence of depression assessed by diagnostic interviews was about 10% in patients with T2DM [1], which is consistent with our findings. These facts suggest that a CES-D score of 24 or more may be a useful diagnostic indicator of depression in patients with type 2 diabetes.

This study has several limitations. First, depressive symptoms were only measured at one point in time by self-report questionnaires. Therefore, information on a diagnosis of depression by clinical interviews or administration of antidepressants was not available in this study. Second, this study was essentially focused on the assessment of vascular complications and mortality in participants with diabetes. There was no accurate information at baseline on underlying non-vascular diseases among the study participants, such as cancer, respiratory diseases, etc. Third, cognitive function was not evaluated in this study although it is closely related to diabetes and depression [31]. On the other hand, our research has several strengths. JDCS is a nationwide study involving 59 institutes in Japan that specialize in diabetes care. Therefore, the accuracy and quality of the diagnosis of diabetes and its complications are assured. Another point is that in our analysis we adjusted for all relevant confounding factors. We considered many factors in this study; for example, vascular complications, severe hypoglycemia, sleep duration, diabetes therapy, etc. Furthermore, we used BMI as a categorical variable in the adjustment of confounders, whereas it was adjusted as a continuous variable in almost all past studies. This is because BMI showed a U-shaped relationship with mortality not a linear correlation in published data [22].

Recently, subclinical depression has been highlighted as a risk factor for mortality. However, the results of this study suggested that low-level depressive symptoms were only remotely related to the risk of all-cause death, at least in our study setting. On the other hand, our spline curve indicated that severe depressive symptoms revealed by a CES-D score of ≥ 24 had a serious effect on mortality in patients with T2DM. Depression is known to aggravate therapeutic adherence in diabetes care [32], while treatment for depression was shown to improve adherence to medications [33]. Therefore, there is no doubt that the evaluation of depressive symptoms is important in diabetes care. A further study is needed to determine the degree of depressive symptoms that we should treat specifically.

5. Conclusions

This study demonstrated that the severity of depressive symptoms was significantly associated with all-cause mortality in patients with T2DM independent of severe hypoglycemia. However, only a small effect on mortality risk was found at relatively lower levels of depressive symptoms in our study population. Further research is needed to clarify whether mild depressive symptoms are significantly associated with mortality in patients with T2DM.

Conflicts of interest

The authors declare that there is no duality of interest associated with this manuscript.

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Author contributions

S.M., S.T., K.F., O.H., M.H., J.N., Y.A., Y.O., N.Y., and H.S. contributed to the conception and design of the study, acquisition, analysis and interpretation of data, and drafting and editing the manuscript. All of the authors approved the final version of the manuscript. H.S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jpsychores.2017.05.020.

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