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Oestrogen receptor polymorphisms and late-life depression

Joanne Ryan [1 2 *] **, Jacqueline Scali** [1] **, Isabelle Carrière** [1] **, Karine Peres** [3] **, Olivier Rouaud** [4] **, Pierre-Yves Scarabin** [5] **, Karen A. Ritchie** [1 6] **, Marie-Laure Ancelin** [1]

[1] *Neuropsychiatrie : recherche épidémiologique et clinique INSERM : U1061 , Université Montpellier I , Hôpital La Colombière , 39 Avenue Charles Flahault - BP 34493 - Pav 42 Calixte Cavalier 34093 Montpellier Cedex 05, FR*

[2] *Fondation Fondamental Hôpital Albert Chenevier, Assistance publique - Hôpitaux de Paris (AP-HP) , 40 rue de Mesly 94000 Créteil, FR*

[3] *Epidémiologie et Biostatistique INSERM : U897 , Université Victor Segalen - Bordeaux II , Institut de Santé Publique, d'Épidémiologie et de Développement (ISPED) , 146, rue Léo-Saignat 33076 Bordeaux, FR*

[4] *Neuroépidémiologie INSERM : U708 , Université Paris VI - Pierre et Marie Curie - GH Pitié-Salpetriere, Assistance publique - Hôpitaux de Paris (AP-HP) , 47, Boulevard de L'Hopital 75651 Paris Cedex 13, FR*

[5] *CESP, Centre de Recherche en Epidémiologie et Santé des Populations INSERM : U1018 , Université Paris XI - Paris Sud , Hôpital Paul Brousse , Assistance publique - Hôpitaux de Paris (AP-HP) , 16 avenue Paul Vaillant Couturier 94807 Villejuif Cedex, France, FR*

[6] *Epidemiology Faculty of Medicine, St Mary's Hospital, Imperial College London , South Kensington Campus, London SW7 2AZ, GB*

* Correspondence should be addressed to: Joanne Ryan <joanne.ryan@inserm.fr >

Abstract

Background

Evidence suggests a role for estrogen in depression but the involvement of estrogen receptor (ER) polymorphisms remains unknown.

Aims

To determine the association between ER polymorphisms and late-life depression and the modifying effect of hormone treatment (HT).

Method

Depression was assessed using the Mini-International Neuropsychiatric Interview, according to DSM-IV criteria and the Centre for Epidemiologic Studies-Depression Scale. The association between ER-α and ER-β polymorphisms with severe depression was examined in 6017 community-dwelling elderly using multivariate logistic regression.

Results

In women, the ER-α rs2234693 and rs9340799 polymorphisms were significantly associated with the risk of late-life depression. The A allele of ER-β rs1256049 increased the risk of depression, but only for non-current users of HT. In men, only the ER-β rs4986938 polymorphism showed a weak association with depression risk.

Conclusions

ER polymorphisms are associated with severe late-life depression risk in women only.

MESH Keywords Age Factors ; Aged ; Aged, 80 and over ; Alleles ; Depressive Disorder, Major ; epidemiology ; genetics ; Effect Modifier, Epidemiologic ; Estrogen Replacement Therapy ; Female ; Gene Frequency ; Genetic Predisposition to Disease ; epidemiology ; Genotype ; Humans ; Logistic Models ; Longitudinal Studies ; Male ; Multivariate Analysis ; Polymerase Chain Reaction ; Polymorphism, Single Nucleotide ; Postmenopause ; psychology ; Psychiatric Status Rating Scales ; Receptors, Estrogen ; genetics

INTRODUCTION

Depression is a major public health problem with high prevalence rates worldwide and an increased risk of comorbidity and mortality, especially in the elderly. Family studies provide evidence that there is a genetic component to depressive disorders, although only a small number of candidate genes have been identified[1]. Several lines of evidence suggest a role for estrogen in depression. Depression results from a disruption in the normal brain neurochemistry, including depletion in the levels of serotonin, and estrogen has been shown to modulate neurotransmitter turnover and enhance serotonergic activity[2]. Numerous epidemiological studies support these observations, linking estrogen with depressed mood and antidepressant response (see for review[3]). Estrogen-containing hormone treatment (HT) is also effective in improving the depressed mood of perimenopausal women[4], although its use in older postmenopausal women remains more controversial. However given that the actions of estrogen occur in large part through intracellular activation of the estrogen receptors (ER-α and ER-β), it is surprising that very few studies have examined whether ER polymorphisms can modify the risk of depression. Polymorphisms of these receptors have been associated previously, although not consistently, with estradiol levels[5], vasomotor

symptoms[6], and other brain disorders like Alzheimer's disease [7 ,8]. Genetic variation in the ER may also influence a person's susceptibility to developing depression and may modify estrogen signalling and thus the effect of HT on mood, but this has not been examined previously. This current study aimed to investigate the association between severe late-life depression and five ER-α and ER-β polymorphisms. Given the lack of data in this field, we did not hypothesize which genotypes would be most frequent in depressed participants. Analysis will be stratified by gender so that individual associations in men and women can be identified, and the potential modifying effect of HT use in women can be evaluated.

METHODS AND MATERIALS

Study Population

This analysis uses data collected at baseline from the Three City Study (3C), an ongoing multi-centre longitudinal study involving the French cities Bordeaux, Dijon and Montpellier[9]. Recruitment of the cohort took place between 1999 and 2001 with eligible participants (aged over 65 years and non-institutionalised) being randomly selected from the electoral rolls in the three cities. Thirty-seven percent of contacted people agreed to participate and were administered interviews by trained staff and underwent a number of clinical examinations. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre (France) and participants provided written informed consent. Of the 9097 dementia-free participants initially recruited in the 3C study, those who were not assessed for current and past psychiatric symptomatology (n=953), or who did not provide blood samples for genotyping analysis (n=1291) could not be included in this analysis. We also excluded participants with incomplete genotyping data (n=237) or missing data concerning the key covariates (n=599), such that all of the analyses presented are based on the same population sample. Participants excluded from this analysis were significantly more likely to have current depression (χ^2_1 =73.9, p<0.0001), and were more likely to be female (χ^2_1 =38.7, p<0.001), however there was no significant difference in terms of the distribution of ER polymorphism genotypes.

Depression Measures

The Mini-International Neuropsychiatry Interview (MINI), a standardized psychiatric examination which has been validated in the general population[10], was used for the diagnosis of current and past major depressive disorder (MDD), according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Severity of depressive symptoms was assessed with the Centre for Epidemiology Studies Depression Scale (CES-D)[11]. Participants with a DSM-IV diagnosis of current MDD or those scoring above the clinical cut-off for “probable” cases of depression (CES-D≥23)[12],were classified as having current severe depression in this analysis. Current use of antidepressants, validated by presentation of the prescription or the medication itself, was also considered as a covariate in the analysis.

Estrogen Receptor Polymorphisms

Fasting venous blood samples were taken from the participants at baseline. Blood was collected on EDTA and DNA was extracted from white blood cells (Puregene kit, Qiagen, France) and stored at −80°C. Genotyping was performed by Kbiosciences (Hoddesdon Herts, UK) using their competitive allele-specific PCR Single-Nucleotide Polymorphism (SNP) genotyping system (KASPar). The amplified PCR products were analysed by fluorescence scanning in a BMG labtech Pherastar scanner and the results were interpreted with their KlusterCaller 1.1 software. The error rate for the KASPar assay system is less than 0.3%.

Five SNPs were examined which have shown potential causal associations with diseases and other hormone-related health outcomes in some previous studies, including Alzheimer's disease[7 ,8], cognitive function[13], cardiovascular disease[14 ,15], bone mineral density[16 ,17], breast cancer[18], vasomotor symptoms[6] and estradiol levels[19]. ER-α rs2234693 (otherwise known as *Pvu* II) and rs9340799 (*Xba* I), and ER-β rs1256049 (*Alu* I), rs4986938 (*Rsa* I) and rs1271572 (in the promoter region of the gene)

Other measures

At inclusion, information was obtained on socio-demographic and lifestyle characteristics, as well as overall health. Body mass index (BMI) was calculated as weight (kg) divided by the height squared (m^2). Participants unable to complete at least two tasks from either the Instrumental Activities of Daily Living (IADL)[20] or the Activities of Daily Living (ADL)[21] scales, were classified as having physical limitations. Cognitive impairment was defined as having a Mini-Mental State Examination (MMSE) score less than 26 and questionnaires concerning sleeping habits were used to define insomnia[22]. Current use of HT at the time of the baseline interview was validated by presentation of the prescription or the medication itself.

Information on the participant's health was obtained through detailed medical questionnaires, a complete inventory of all drugs used within the preceding month and from fasting blood samples. These questionnaires included their history of vascular diseases (angina pectoris, myocardial infarction, stroke, cardiovascular surgery, bradycardia or palpitations), other chronic illnesses (asthma, diabetes [

fasting glucose ≥7.0 mmol/l or reported treatment], hypercholesterolemia [total cholesterol ≥6.2 mmol/l], hypertension [resting blood pressure ≥160/95 mm Hg or treated] and thyroid problems) or cancer diagnosis within the last two years. Participants were classified as having comorbidity if they suffered from vascular disease, more than 1 chronic illness or a recent cancer.

Statistical Analysis

A χ^2 test was used to compare the observed allele frequencies with those expected under the Hardy–Weinberg equilibrium. The association between baseline socio-demographic and clinical variables with both depression and ER polymorphisms was examined using *t* -tests, ANOVA and chi-squared tests. Due to the statistically significant interactions between gender and depression, all subsequent analyses were undertaken separately for males and females. Genotype frequencies of the ER polymorphisms were compared between depressed and non-depressed participants using logistic regression models. Adjustment was made for covariates that were significantly associated with depression in this sample and which remained significant in the final multivariate models. The potential interaction between ER polymorphisms and the use of estrogen-containing HT in women was also considered, based on our *a priori* hypothesis that ER polymorphisms could mediate the effect of estrogen on depression. There was no indication of collinearity between the covariates in the adjusted models. SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina, USA) was used for all of the analyses and all tests were two-tailed, with a significance level of $p<0.05$.

RESULTS

Participant's characteristics

Baseline characteristics of the 6017 participants are summarized in Table 1 . They ranged in age from 65 to 96 years with a mean of 73 years. Men and women differed significantly on all socio-demographic and health variables examined, with the exception of age. Women were significantly more likely to use antidepressants, to have current depressive symptoms and to have a current or past diagnosis of MDD (Table 1). Overall 564 participants were diagnosed with current severe depression (CES-D≥23 or current MDD), with a higher prevalence rate in women compared to men (12.9% vs. 4.4% respectively, $\chi^2_1=123$, $p<0.001$).

Polymorphism frequencies according to depression status

The overall distribution of genotypes in both sexes was not significantly different from those predicted by the Hardy-Weinberg equilibrium, except in the case of the ER-β rs1271572 polymorphisms in women ($\chi^2_1=5.7$, $p=0.02$). The ER-α polymorphisms are known to be in strong linkage disequilibrium with one another[16], as are the three ER-β polymorphisms examined[15]. Genotype frequencies for each of the ERs according to the participant's depression status are given in Table 2 . There was no significant difference in the genotype distribution between men and women, although women were more likely to be heterozygous for ER-β rs4986938 (49.6% of women overall had the GA genotype compared with 46.6% of men, $\chi^2_2=5.7$, $p=0.06$). For both sexes, the frequency of the AA genotype for ER-β rs1256049 was very small so these participants were grouped with those heterozygous GA for subsequent analysis.

ER polymorphisms and depression

The results of the multivariate logistic regression analyses for the associations between ER polymorphisms and depression are shown in Table 3 . In men the only borderline significant association was a 1.7 times increase in current severe depression with the AA versus the GG genotype of ER-β rs4986938. None of the other polymorphisms showed any significant association with depression in men.

Amongst women however, those homozygous CC for the ER-α rs2234693 polymorphism were 40% less likely to have current severe depression compared to homozygous TT women. The findings concerning the rs9340799 polymorphism were almost identical, with women having the GG genotype significantly less likely to have late-life depression compared to women with the AA genotype. In terms of the ER-β, women with at least one A allele of the rs1256049 polymorphism were more likely to have current severe depression, but this was at the limit of statistical significance. The other two ER-β polymorphisms were not associated with late-life depression.

ER x HT interaction

When the potential modifying effect of HT use on the association between these ER polymorphisms and severe depression in women was examined, there was a non-significant trend for an interaction between ER-β rs1256049 and current HT (interaction term, $p=0.08$ in the multivariate adjusted model shown on Table 3). Subsequent analysis stratified by current HT use revealed that women who were not using treatment (n=2986) were significantly more likely to have current severe depression with the GA/AA genotype (OR: 1.72, 95% CI: 1.17–2.50, $p=0.005$). In stark contrast, among women who were using HT (n=539), the GA/AA genotype was not associated with the risk of severe depression (OR: 0.69, 95% CI: 0.23–2.08, $p=0.51$).

DISCUSSION

In this older population-based cohort, we have found significant gender-specific associations between polymorphisms of the ERs α and β with severe late-life depression. The results also provide some evidence of an interaction between HT and one of the ER-β polymorphisms, which modified a woman's risk of depression.

Association between ER-α polymorphisms and severe depression in women

Of the few previous studies which have investigated the association between depression and ERα polymorphisms in women, the results have been mixed, and this may relate to differences in study sizes (smaller studies may lack statistical power), and populations (e.g. age, menopausal status, HT use), as well as the criteria for depressive symptomatology. The SWAN study of 1538 pre- and peri-menopausal women from four different ethnic groups[23] and the Rotterdam study of 2468 elderly women[24], have both reported no significant association between the rs2234693 and rs9340799 polymorphisms and moderate depressive symptoms (CES-D≥ 16). In two small studies of young postmenopausal women, differential findings have been reported in unadjusted analysis. No association was found between these same ER-α polymorphisms and depressed mood in 177 Mexican women[6], yet significant associations were found in a study of 106 Korean women [25]. The only previous study to examine the association between ER polymorphisms and MDD (based on the Hamilton Scale and DSM-IV criteria) reported that the frequency of the rs2234693 CC genotype was significantly higher in 126 midlife Chinese women (mean age 46.7) than in the 89 controls[26]. In our larger study of 3525 elderly women however, the CC and GG genotypes of the rs2234693 and rs9340799 polymorphisms respectively were associated with a significant decrease in current severe depression (defined as a current MDD based on DSM-IV criteria or severe depressive symptoms using a CES-D score of 23 or greater). In post-hoc analysis we did not find a significant association with these ER-α polymorphisms and moderate depressive symptoms alone (CES-D≥ 16, supplementary data). Our findings thus relate specifically to a severe clinical level of current depression.

Potential interaction between ER-β polymorphism and HT

The association between the ER-β and depression has been insufficiently studied. There is one report of a non significant association between another polymorphism (rs1256030) and moderate depressive symptoms (CES-D≥ 16) in 1435 midlife women[23] and in a Korean study of 43 women with post-menopausal depression and 63 controls, no significant association was found with rs1256049 or rs4986938 [25]. Here we find that the ER-β rs1256049 polymorphism was significantly associated with an increased likelihood of severe depression in women, but only for those non-HT users. No significant association was observed for women who were currently using HT. It has been shown previously that ER polymorphisms and HT can interact to influence health outcomes in women[14 ,16]. To our knowledge however, no study has examined whether such an interaction can modify the risk of depression, despite several RCTs demonstrating the psycho-protective effects of HT[4]. Our finding provides some preliminary evidence that HT could be beneficial for certain genetically vulnerable women, by reducing the risk of depression associated with the ER-β rs1256049 polymorphism.

ER polymorphisms and depression in men

We found no significant association between ER-α polymorphisms and moderate or severe depression in men (Table 3 and Supplementary Table), in accordance with the two previous studies that have been conducted[24 ,26]. The rs2234693 and rs9340799 polymorphisms were not associated with MDD in a small case-control study of middle-aged Chinese men[26], nor in the Rotterdam study of depressive symptoms[24]. Neither of these studies however, examined associations with ER-β. We report here that the AA allele of the ER-β rs4986938 may increase the likelihood of depression specifically in men, although this was of borderline significance. In a similar manner, one of the few prior studies examining this polymorphism reported a higher frequency of the A allele in men with Alzheimer's disease, but no such association in women[27].

Biological hypothesis linking ER and depression

ER-α and ER-β classically function as ligand-activated transcription factors and can affect hundreds of genes, including regulation of the synthesis and metabolism of various neurotransmitters in the brain[2]. The mechanisms by which ER could influence depression are thus complex. It remains uncertain what precise effects the polymorphisms examined here may have on receptor expression. Although silent mutations, they can still affect mRNA structure, stability and receptor synthesis, and thus have potentially important functional consequences. At least in terms of rs2234693 and rs9340799, they have been shown to regulate the expression of the ER-α and they may alter transcription factor binding[28 ,14]. These polymorphisms may also be in linkage disequilibrium with other functional polymorphisms which have not yet been identified. The ER-α polymorphisms examined in our study have been associated with other brain disorders, such as cognitive decline[13] and Alzheimer's disease[7], although not consistently. These polymorphisms have also shown significant associations with estradiol levels in postmenopausal women (lower estradiol with the T (rs2234693) and A (rs9340799) alleles)[19], and in a similar manner with bone density and fractures (higher bone mass density and lower fractures for the rs9340799 genotype GG) (see for meta-analysis[17]). This would support earlier findings that estrogen may have a protective effect against depression[29].

Our data suggest distinct genetic vulnerability to depression for men and women. Different polymorphisms of the ER-β increased the likelihood of severe depression in men and women, while in women only the ER-α polymorphisms were associated with late-life

depression. There are numerous mechanisms which could help explain these sex differences (see for review[30]). Although male and females have a similar distribution of ER-α and β in the brain, there appears to be differences in the level of expression of these receptors in various regions. Our results may partly account for gender differences in depression prevalence and highlight the need for a sex-specific approach to the development of novel hormone-based therapies.

Study limitations and strengths

Limitations to this study include the relatively low response rate, which limits the ability to generalise these findings as study volunteers tend to be better educated and healthier than the overall population. Participants diagnosed with probable/possible dementia at inclusion (n=217) were excluded from this analysis to minimise recall bias, however as such participants may have higher rates of depressive symptoms, this could have decreased the overall power of the study and possibly underestimating the associations found. Possible prescription bias in relation to women who are given HT should also be taken into account, although we have controlled for numerous potential confounding factors in the analysis. The results of this analysis were not adjusted for multi-comparisons, as there was a strong *a priori* biological rationale for investigating these five specific associations, given the extensive scientific literature supporting a role for estrogen in depression. The usefulness of a Bonferroni correction in this study is thus questionable[31] and would result in an inflated type 2 error rate, especially given that the correction assumes independence of the tests, but both ER-α polymorphisms are in strong linkage disequilibrium[16], as are the three ER-β polymorphisms[15]. It remains likely however, that based on the 5% significance level, one of the significant associations found occurred merely by chance. Finally, it should be noted that in this study we report associations between ER polymorphisms and the prevalence of late-life depression, but have not differentiated the independent associations with depression incidence and disease duration.

This study is strengthened by its sample size and population-based design, as well as the inclusion of both men and women to enable the assessment of independent sex-specific associations. Depression was assessed by trained staff using two distinct measures, including a structured diagnostic interview, which have been validated in the general population[10]. Severity ratings allowed us to examine separately the relationship between moderate depressive symptoms and severe depression, with ER genotypes. Although our analyses have adjusted for a large range of socio-demographic and health variables, including past depressive episodes, it is still possible that there are unrecognised factors which could help explain our findings. Replication of our findings in other large population-based studies is needed.

We report here that polymorphisms of the ER-α in particular are associated with depression in older women. In addition, there was some evidence that current HT modified the association between ER-β rs1256049 and severe depression in women. These findings suggest the possibility that some women may be genetically more susceptible than others to the psycho-protective effects of HT. This could have important clinical applications, suggesting the potential for offering tailored hormonal therapies based on genetic markers for the treatment of mood disorders in women and perhaps men, via the development of ER selective effectors.

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Footnotes:

Declaration of interest: None.

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TABLE 1

Comparison between the characteristics of 6017 elderly community dwelling men and women, who participated in the 3C Study.

Characteristic	**Men (n = 2492)**	**Women (n = 3525)**	**Test for gender difference**	
		Mean (SD)	**t test**	**p**
Age (years)	73.4 (4.9)	73.5 (4.9)	−0.89	0.37
BMI (kg/m^2)	26.3 (3.4)	25.3 (4.2)	9.2	< 0.001
		%	χ^2 **(df)**	**p**
≥ 12yrs schooling	38.8	24.9	133 (1)	< 0.001
Married or living with others	83.2	48.1	767 (1)	< 0.001
Current heavy drinker (≥ 24 grams each day)	34.6	4.1	956 (1)	< 0.001
Heavy smoker (10 pack years)	8.3	3.8	57.1 (1)	< 0.001
Physical activity limitations	5.3	7.5	11.2 (1)	< 0.001
At least three current medications	48.0	56.1	38.0 (1)	<0.001
Cognitive impairment	21.7	26.4	17.7 (1)	<0.001
Insomnia	15.1	31.2	204 (1)	<0.001
History of cerebro- and cardio-vascular disease	22.3	11.4	128 (1)	<0.001
Comorbidity[a]	50.8	46.9	9.1 (1)	0.003
Current use of hormone treatment	n/a	15.3	n/a	n/a
Current use of antidepressants	3.4	7.8	50.0 (1)	<0.001
Severe depressive symptoms (CES-D≥23)	4.3	12.2	113 (1)	<0.001
Current MDD	0.6	2.0	18.1 (1)	<0.001
Past MDD[b]	6.9	14.4	83.6 (1)	<0.001
Centre			0.72 (2)	0.70
Bordeaux	22.3	22.0		
Dijon	53.0	54.1		
Montpellier	24.7	23.9		

a Includes cerebro- and cardio-vascular disease, more than one chronic illnesses (high blood pressure, high cholesterol, diabetes, thyroid problems, asthma), or cancer diagnosed within the last 2 years.

TABLE 2

ER polymorphism genotype frequencies according to current depression status.

Polymorphism & genotype	MEN		WOMEN	
	No depression (n=2382)	Severe current depression (n=110)	No depression (n=3071)	Severe current depression (n=454)
ER-α rs2234693:				
TT	29.8	32.7	30.0	33.9
CT	50.8	48.2	49.9	51.1
CC	19.4	19.1	20.1	15.0
ER-α rs9340799:				
AA	41.6	48.2	41.5	44.5
GA	46.4	38.2	46.5	46.7
GG	12.0	13.6	12.0	8.8
ER-β rs1256049:				
GG	91.4	90.9	92.2	89.7
GA	8.4	8.2	7.7	10.1
AA	0.2	0.9	0.1	0.2
ER-β rs4986938:				
GG	38.1	31.8	36.3	34.1
GA	46.5	47.3	49.2	52.0
AA	15.4	20.9	14.5	13.9
ER-β rs1271572:				
GG	32.6	31.8	32.7	30.6
TG	49.2	52.7	49.8	54.6
TT	18.2	15.5	17.5	14.8

TABLE 3

Adjusted[a] logistic regression models for the associations between ER polymorphisms and current severe depression.

	MEN		WOMEN	
Polymorphism & genotype	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
ER-α rs2234693:				
TT	1		1	
CT	0.89 (0.57–1.40)	0.62	0.88 (0.69–1.11)	0.27
CC	0.85 (0.48–1.51)	0.58	0.61 (0.44–0.84)	0.003
ER-α rs9340799:				
AA	1		1	
GA	0.72 (0.47–1.10)	0.13	0.90 (0.72–1.13)	0.37
GG	0.99 (0.53–1.83)	0.97	0.60 (0.41–0.88)	0.009
ER-β rs1256049:				
GG	1		1	
GA or AA	1.11 (0.55–2.22)	0.77	1.44 (1.01–2.05)	0.05
ER-β rs4986938:				
GG	1		1	
GA	1.30 (0.82–2.05)	0.26	1.08 (0.85–1.35)	0.54
AA	1.74 (1.00–3.06)	0.05	1.01 (0.72–1.40)	0.97
ER-β rs1271572:				
GG	1		1	
TG	1.12 (0.72–1.74)	0.63	1.19 (0.94–1.51)	0.15
TT	1.11 (0.55–2.22)	0.68	0.91 (0.66–1.27)	0.58

a Adjusted for age, education, centre, marital status, physical limitations, cognitive impairment, current medications, comorbidity, insomnia and past MDD.