Low vitamin D is associated with negative and depressive symptoms in psychotic disorders

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Abstract

Background: There are indications that low S-25(OH)D is associated with increased disease severity in psychotic disorder, but there is still uncertain whether low levels are associated with a specific symptom profile. Our first aim was to investigate the relations between low S- 25(OH)D and positive, negative and depressive symptoms. Our second aim was to explore if associations between S-25(OH)D and symptoms were influenced by levels of inflammatory markers.

Methods: Participants (N=358) with a medical history of one or more psychotic episodes were recruited. Current symptomatology was assessed by The Structured Interview for the Positive and Negative Syndrome Scale and The Calgary Depression Scale for Schizophrenia. Blood samples were analyzed for S-25(OH)D, CRP, sTNF-R1, IL-Ra and OPG. We performed bivariate correlations and multivariate regression models to evaluate the effect of S-25(OH)D on the outcomes.

Results: Low S-25(OH)D was significantly associated with negative symptoms (adjusted R^2 =0.113, F(6,357)=8.58, p<0.001) and with depression (adjusted R^2 =0.045, F(4,357)=5.233, p<0.001) when adjusting for possible confounding factors (i.e. gender, education, diagnose, hospitalization status, ethnicity, season and thyroid status). CRP was correlated with both S-25(OH)D (rho=-0.12, p= 0.03) and negative symptoms (rho=0.12, p=0.03), but did not mediate the association between vitamin D and negative symptoms. The correlations between S-25(OH)D and the inflammatory markers sTNF-R1, IL-Ra and OPG were not significant.

Conclusion: There is a strong association between low S-25(OH)D and higher negative and depressive symptoms in psychotic disorders. Randomized controlled trials should be performed to investigate the effect of vitamin D supplementation as adjuvant treatment strategy in this patient group.

Key words: S-25(OH)D, schizophrenia, psychosis, symptomatology, inflammation

1. Introduction

Vitamin D is a fat-soluble hormone that recent years has been found important for neurodevelopment and for neuropsychiatric disorders (Cui et al., 2015). It passes the blood-brain barrier, and both the vitamin D receptor (VDR) and the enzyme that hydroxylates the circulating form S-25(OH)D into the active metabolite 1,25-dihydroxy-vitamin D ($1,25(OH)_2$ D) are found in the human brain (Eyles et al., 2005). The prevalence of vitamin D deficiency is reported to be high in psychotic disorders (Belvederi Murri et al., 2013; Valipour et al., 2014) and this could infuence on symptoms.

Low S-25(OH)D has been found in patients with acute psychotic episodes compared to patients in remission (Yuksel et al., 2014) and in acute psychosis with excitement or stupor, bizarre and disorganized behaviour (Dealberto, 2013). There has been proposed sex differenses where low vitamin D has been found associated with negative symptoms in males, and to increased anti-social aggression in females (Cieslak et al., 2014a). Low vitamin D levels have also been found associated with higher degree of negative symptoms like social anhedonia and poverty of speech in males (Cieslak et al., 2014a) and the total negative symptom factor in a first episode sample (Graham et al., 2014). The strongest link between low S- 25(OH)D and psychiatric symptomatology has been found in depression (Anglin et al., 2013; Milaneschi et al., 2014). In line with this, suicide attempters have significantly lower S- 25(OH)D compared to non-suicidal patients (Grudet et al., 2014). Many patients with psychotic disorders experience depressive episodes (Romm et al., 2010) and previous findings indicate that low S- 25(OH)D is associated with depression also in psychotic disorders (Berg et al., 2010).

Vitamin D is found to be a regulator of the immune system (Calton et al., 2015; Fernandes de Abreu et al., 2009) and low S-25(OH)D has been found associated with increased inflammation in schizophrenia patients compared to controls. Inflammation is investigated as a potential general disease mechanism in severe psychotic disorders (Goldstein et al., 2009; Potvin et al., 2008). In animal models vitamin D is considered to have anti-inflammatory neuroprotective properties in the

brain through recruitment of microglia (Garcion et al., 1998) and immune-regulation through dendritic cells (Bscheider and Butcher, 2016), and it is possible that the relation between low S-25(OH)D and clinical symptoms could be influenced by inflammatory pathways (Autier et al., 2014). Previous publications from our research group have shown associations between psychotic symptomatology and increased levels of the inflammatory markers soluble tumor necrosis factor receptor 1 (sTNF-R1) and interleukin- 1 receptor antagonist (IL-1Ra) (Hope et al., 2013) in both schizophrenia and bipolar disorder, and between depressed mood and low levels of the inflammatory markers osteoprotegerin (OPG), sTNF-R1 and IL-1Ra in bipolar disorder (Hope et al., 2011).

There are thus indications that low S-25(OH)D is associated with increased disease severity in psychotic disorder, but there is still uncertain whether low levels are associated with a specific symptom profile . It is also uncertain whether the associations between vitamin D and disease activitity is associated with levels of inflammatory markers. Our first aim was to investigate the relations between low S- 25(OH)D and symptom profiles in a large, well- categorized clinical sample of patients with psychotic disorders. We more specifically wanted to test if low S- 25(OH)D was associated with increased positive or negative symptoms as measured by the Positive and Negative Syndrome scale for Schizophrenia (PANSS) and with increased depressive and suicidal symptoms as measured by the Calgary Depression Scale for Schizophrenia (CDSS). Our second aim was to explore if associations between S-25(OH)D and symptom profiles were influenced by general inflammation measured by C-reactive protein (CRP) or the level of the inflammatory markers; sTNF-R1, IL-1Ra and OPG, markers found to be related to positive symptoms in psychotic disorder and with depression in bipolar disorder.

2. Methods

Participants were recruited consecutively between 2003 and 2014 from in- and out-patient psychiatric units in the catchment areas of the five major hospitals in South Norway, as part of the larger Thematically Organized Psychosis (TOP) Study. The Regional Committee for Medical Research Ethics approved the study and our research methodology followed The Code of Ethics of the World Medical Association, Helsinki Declaration. Participation is based on informed consent.

2.1. Participants

For the current study we included participants with available vitamin D measurements and with a history of one or more psychotic episodes. To ensure that S-25(OH)D reflected the serum level at the time for symptom assessments, participants with symptom assessments and blood sampling within the same season or with a maximum of three weeks discrepancy were included. The final sample consisted of 358 participants with following diagnostic distribution: Schizophrenia, schizophreniform- and schizoaffective disorder, N=232 (schizophrenia group); delusional disorder, brief psychotic episode, psychotic depressive disorder, psychosis NOS, psychotic bipolar disorder I, psychotic bipolar disorder II and psychotic bipolar disorder NOS, N= 126 (non-schizophrenia group).

2.2 Procedures

2.2.1. Clinical

Information about demographic and clinical variables, and use of medication, was obtained by clinical interviews and by conferring with medical records. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used for diagnostic purposes. Current symptomatology was assessed by The Structured Interview for the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). PANSS scores were analyzed using Wallwork's five -factor model, (Wallwork et al., 2012). This five-factor model is found to be appropriate in clinical samples of different cultural background (Wallwork

et al., 2012) and in early psychosis (Langeveld et al., 2012). It can be difficult to distinguish between depressive and negative symptomatology in patients with psychotic disorders. The Calgary Depression Scale for Schizophrenia (CDSS) was developed to identify depression in patients with psychosis by excluding symptoms that overlap with negative symptoms of schizophrenia (Addington et al., 1992; Addington et al., 1990) and it thus differentiates better than other depression scales (Addington et al., 1994). We lacked CDSS information for 71 participants who instead had been assessed using the clinician-rated Inventory of Depressive Symptomatology (IDS-C) (Rush et al., 1996). Their IDS-C scores were used to impute the missing data (see paragraph 2.3). Current suicidal ideation was derived from item 8 from CDSS and item 18 from IDS-C and subsequently dichotomized into no suicidal ideation as "0" and mild, moderate and severe suicidal ideation as "1". Age of onset was set as age at the time of the first psychotic episode, and duration of illness was calculated as age at inclusion into the study minus age of onset. The seasons were dichotomized into winter (December – May) and summer (June- November) (Porojnicu et al., 2007). Ethnicity was determined by asking for country of birth for the participant and his/her parents and was used to divide the participants into two groups; the majority population group (including participants with European ancestry) and the ethnic minority group (including participants with Asian, Latin -American and African ancestry). At inclusion the participants went through a physical examination including blood sampling; a standard procedure was used to measure height and weight and body mass index (BMI) calculated by kg/m^2. The participants were asked for their total use and prescriptions of medications.

2.2.2. Biochemical variables

From September 2012; total S- 25(OH)D (a sum of 25(OH)D2 and 25(OH)D3) was determined using a liquid chromatography- tandem mass spectrometry (LC-MS/MS) method developed at the Hormone laboratory (Oslo University Hospital, Aker) (Nerhus et al., 2015). Until September 2012, S-25(OH)D was measured by radioimmunoassay (RIA kit from Diasorin) (Holvik et al., 2005). The regression equation LC-MS/MS = 1.16 x (RIA) -9 was obtained at the laboratory during method comparison. It

was used to convert all S-25(OH)D concentrations obtained by LC-MS to equivalent concentrations obtained by RIA, which are used in the analyses.

The plasma levels of sTNF-R1, OPG and IL1-Ra were measured at the laboratory at Research Institute of Internal Medicine (Oslo University Hospital, Rikshospitalet) using enzyme immunoassays (EIA) obtained from R&D systems (Minneapolis, MN, USA). The inflammatory markers were selected based on earlier findings in our research group considered to represent distinct inflammatory pathways with stable markers showing little diurnal fluctuations (Hope et al., 2015). IL-1Ra is a regulator of IL-1α activity; sTNF-R1 is a marker of activity in upstream inflammatory pathways and OPG is a soluble member of the tumor necrosis family (Dieset et al., 2012). CRP in plasma, serum –thyroxine (T4) and thyroid stimulating hormone (TSH) were analyzed at Department of clinical Biochemistry (Oslo University Hospital, Ullevaal). Three participants had CRP >20 mg/L (i.e. suspect of inter-current infection) and two had known chronic infections (hepatitis) and were removed from the analysis for the second research aim.

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics v. 22 (IBM Corp. 2014). The level of significance was preset to $p < 0.05$ (two-tailed). For the participants missing CDSS scores, the score was imputed based on a regression model developed from a subsample of 146 patients with both IDS-C and CDSS scores, producing the following formula; (-0,314) + (IDS-C x 0,282) (adjusted R^2 = 67.1). We used mean substitution for missing data (4 missing for years of education, 3 missing hospitalization status and 14 missing T4 measurements). The bivariate correlations were evaluated with Pearson's r for the dichotomous and continuous variables with normal distribution and with Spearman's rho for the variables with skewed distribution. The positive and negative symptom factors from the PANSS and CRP were log-transformed, and the CDSS total score was square root transformed to be able to use regression as the main analytic strategy in multivariate analyses.

We performed a hierarchal block-wise linear regression model for each of the outcome variables to evaluate the effect of S-25(OH)D on the outcomes i.e. positive symptom factor, negative symptom factor and depressive symptoms. Only the last step from the analyses is shown in table 3. Variables with bivariate correlations at the $p < 0.01$ level with both S-25(OH)D and the dependent variable in question were entered into the model in the following way: Variables with known clinical associations with the dependent variables were entered in the first block if they also were correlated with S-25(OH)D; i.e. gender, education, diagnose and hospitalization status. In the second block, we entered the variables that based on the bivariate analyzes showed associations with both S-25(OH)D and either of the dependent variables, i.e. ethnicity, season of the year, serum- thyroxine (T4) and substance abuse. In the third and final step, we entered S- 25(OH)D as a continuous variable to test our hypotheses. The residual plots showed satisfactory model fits. We then performed a hierarchal block-wise binary logistic regression analysis for suicidality, following the same general principles as for the linear regressions, but we here also entered depressive symptoms at an additional step because of the high correlation between depressive symptoms and suicidality ($r=0.61$, $p<0.001$). For the second research aim, we first investigated the bivariate correlations between S- 25(OH)D and the inflammatory markers CRP, sTNF-R1, IL- 1Ra and OPG in a subsample with available immune analyzes. There were significant correlations between CRP and S-25(OH)D and between CRP and negative symptoms. We therefore performed an additional regression analysis with negative symptoms as the outcome variable. The possible confounding variables were entered as described above and CRP was entered in the second last step of the regression model to see how that affected the association between S-25(OH)D and negative symptoms (table 3). There was a significant correlation between IL-1Ra and negative symptoms, but as IL-1Ra was not correlated with S-25(OH)D and we therefore did not continue further multivariate analyses with this variable. There were no correlations between sTNF-R1 and OPG with S-25(OH)D or any of the outcome variables, thus we did not continue multivariate analyses.

3. Results

Description of the participants is summarized in table 1. From the bivariate correlation analyses we found Low S-25(OH)D was bivariate significantly associated with negative symptoms (r= -0.18, p=0.001) and depressive symptoms (r= -0.12, p=0.02) and on a trend level with positive symptoms (r= -0.09, p=0.09) and suicidal ideation (t=1.9, p=0.06). There were no bivariate correlations between vitamin D and excited (r=0.03, P=0.6) or disorganized (r= -0.06, p=0.3) symptoms. Low S-25(OH)D was significantly correlated with CRP, while the correlations between vitamin D and the inflammatory markers sTNF-R1, IL-Ra and OPG were not significant(table 2).

The final step from the multivariate analyses is shown in table 3. The association between S-25(OH)D and positive symptoms was not significant after controlling for potential confounding variables. The association between low S-25(OH)D and high score on negative symptoms however remained significant (adjusted R^2 =0.113, F (6,357) =8.58, p<0.001) after adjusting for the possible confounding variables with bivariate correlations both with S-25(OH)D and the outcome, i.e. gender, years of education, diagnosis and ethnic background. The association between S-25(OH)D and negative symptoms was not altered significantly by entering CRP as an additional step in the model. Both the models for negative symptoms (with and without CRP) are shown in table 3. Low S-25(OH)D remained significantly associated with depression (adjusted R^2 =0.045, F (4,357) =5.233, p<0.001) after adjusting for the possible confounding variables; gender, season of the year and T4. The association between low S-25(OH)D and suicidal ideations however, was not significant in the multiple regression, but appeared to be mediated by depression.

We performed additional analysis straftified by gender and found a trend for bivariate correlation between low vitamin D and higher score on the disorganized symptom factor in women (Pearson's r=-0.14, p=0.06), however in multiple regression this association was non-significant (t=-0.13, p=0.90).

4. Discussion

Our main finding from this large sample of participants with broad DSM-IV psychotic disorders was that low S-25(OH)D was associated with higher levels of negative symptoms and of depression, also when controlling for potential confounding factors.

The significant association between low S-25(OH)D and higher negative symptom factor expand the knowledge from two previous small studies that have found the same association (Cieslak et al., 2014b; Graham et al., 2014). The findings are of great clinical relevance since negative symptoms have an even higher impact on impaired quality of life than positive symptoms (Faerden et al., 2009; Fervaha et al., 2014) and we lack possible treatment strategies (Tsapakis et al., 2015).

The association between S-25(OH)D and positive symptoms was not l significant after controlling for education and diagnosis. Associations between low S-25(OH)D andpositive symptoms have been found in studies of youths with psychiatric disorders (Gracious et al., 2012) and in acute psychosis (Yuksel et al., 2014), but the samples from these particular studies may represent a subgroup of patients with more severe symptomatology or other confounders as they were all inpatients. Associations with florid positive symptoms and atypical syptoms were found in a sample of immigrants with recent refugee background hypothesized tohave a recent drop in vitamin D levels (Dealberto, 2013). In this particular study however the patients were not yet diagnosed and education level was not taken into account, factors that according to our study are confounders of the association between vitamin D and positive symptoms.

In the current study we also found a significant association between low S-25(OH)D and higher scores for depressive symptoms. This is in line with results from clinical samples of psychotic disorder (Berg et al., 2010) and depressive disorders (Milaneschi et al., 2014). Suicidal ideations were also associated with low S-25(OH)D in the current study in line with another study (Grudet et al., 2014) and the multivariate analyses showed that this association mainly was mediated by depression as

expected. In a clinical setting, this could support vitamin D as adjuvant therapy in treating co- morbid depressions in psychotic disorders.

There are several possible explanations for the strong associations between low S-25(OH)D and higher scores on negative and depressive symptoms. We hypothesized that inflammation was a mediating factor. We found that CRP was significantly correlated with both S-25(OH)D and negative symptoms, but the association between S-25(OH)D and negative symptoms was not mediated by CRP in multiple regression. IL-1Ra was bivariate correlated with negative symptoms in line with earlier findings linking IL-1Ra to disease activity (Hope et al., 2011; Hope et al., 2013), but had no significant association with S-25(OH)D. Our results imply an independent associations between S-25(OH)D and symptomatology not mediated by pro-inflammatory markers. The immune system is however very complex and there could be other interactions between S-25(OH)D , inflammation and symptomatology that is not covered by our analytic strategy or choice of inflammatory markers.

An alternate explanation for the associations between S-25(OH)D and symptoms is that disease behavior may affect vitamin D levels (Belvederi Murri et al., 2013). It is possible that illness behavior from both negative and depressive symptomatology includes spending more time indoor and having less focus on diet, and the low S-25(OH)D could be interpreted as secondary to the symptomatology. In our analyses we have controlled for diagnose, hospitalization status and ethnic background, but our data are cross sectional and we cannot conclude regarding direction of the associations. Randomized controlled trials have been performed in relation to depression. The results are ambiguous, however vitamin D appear to have an anti-depressive effect (Li et al., 2014; Spedding, 2014).

There are however indications that vitamin D could be more directly involved in the pathogenesis of specific symptoms. Vitamin D is considered neuroprotective properties through its prevention of oxidative stress in the central nerve system (Wrzosek et al., 2013) and there are hypothesis how oxidative stress may cause negative symptoms (Albayrak et al., 2013), possibly by imbalance in the

excitative-inhibitory glutamate-GABA responses (Sullivan and O'Donnell, 2012) There are also indications that vitamin D is involved in the pathogenesis of depression, possible through the serotonin system, as vitamin D recently has been discovered as a regulator of the serotonin synthesis (Patrick and Ames, 2014). The observed seasonality in affective disorders also implicates an important role for sun exposure and vitamin D in depression (Akhter et al., 2013; Geoffroy et al., 2014).

An important strength of the current study is that we have a large, well- characterized sample. The participants are recruited from in- and outpatient clinics from a catchment area based health care system providing a broad spectrum of psychotic disorder with participants from all parts of the society. This makes the sample representative and we can adjust for possible confounding factors. Important limitations are that two different assays were used for S-25(OH)D measurements and we did not have full datasets available for all the variables incorporated in the analyses. For CDSS however we were able to impute the missing values based on IDS-C. Only a subgroup had available immune measurements and a partial effect from the inflammatory markers cannot be excluded.

In conclusion, there are strong associations between lower S-25(OH)D and increased negative and depressive symptoms in psychotic disorders. Randomized controlled trials should be performed to investigate the effect of vitamin D supplementation as a possible adjuvant treatment strategy in this patient group.

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Table 1 Demographic and clinical characteristics of the sample

	N (%)
Schizophrenia spectrum	232 (64.8)
Bipolar spectrum	126 (35.2)
First treatment psychotic disorder	143 (29.9)
First treatment bipolar disorder	30 (8.4)
Male gender	217 (60.6)
Ethnic minority status	123 (34.4)
Summer season	175 (48.9)
Regular use of psychopharmacological medication	313 (87.4)
Hospitalized	119 (33.2)
Substance abuse	79 (22.1)
Suicidal ideation	107 (29.9)
	mean (SD)
Age	30.0 (9.1)
Age at onset	24.6 (8.0)
BMI kg/m2	26.1 (4.9)
S- 25(OH)D (reference value >50 nmol/L)	44.4 (22.8)
TSH (reference value 0.5-3.6 mIU/L)	2.3 (1.3)
T4 (reference value 8-21 pmol/L)	14.4 (2.5)
PANSS positive symptom factor	2.3 (1.1)
PANSS negative symptom factor	2.0 (0.9)
CDSS total symptom score	5.0 (4.8)
	median (range)
Duration of untreated psychosis in weeks	43 (1352)
Duration of illness in years	3 (33)
sTNF-R1 (ng/mL) (N= 231)	1.91 (5.59)
IL-1Ra (ng/mL)(N= 232)	248 (7975)
OPG (ng/mL)(N= 232)	1.36 (6.14)
CRP (mg/L)(N=336)	1.1 (18.8)

Table 2. Bivariate correlations

	S-25(OH)D	PANSS positive symptom factor score	PANSS negative symptom factor score	Total CDSS symptom score	Suicidal ideations	
	Pearson r	**Pearson r**	**Pearson r**	**Pearson r**	**Pearson r**	**N**
S-25 OH D		-0.09(*)	-0.18**	-0.12*	-0.10(*)	358
Female gender	0.13**	-0.10(*)	-0.12*	0.13*	0.09	358
Age	0.02	-0.002	-0.08	0.01	-0.09(*)	358
Ethnic minority vs. Majority	-0.38**	0.10*	0.12*	0.06	0.07	358
Years of education	0.15(*)	-0.27**	-0.18**	-0.05	-0.13*	354
Premorbid social function	0.015	0.18**	0.20**	0.19**	0.14*	344
Premorbid academic function	0.009	0.22**	0.07	0.09(*)	0.13*	342
Schizophrenia vs. non-schizophrenia spectrum	-0.13*	0.37**	0.28**	0.06	0.03	358
Substance abuse	0.11(*)	0.05	0.03	0.03	0.17**	358
BMI	-0.10(*)	0.01	0.08	-0.04	-0.02	358
Winter vs. Summer	-0.16**	0.04	0.01	-0.10(*)	-0.01	358
Inpatient vs. Outpatient	-0.09(*)	0.17**	0.20**	-0.08	0.02	355
Duration of illness in years	0.03	0.05	-0.03	0.12*	0.03	357
Current use of medication	0.01	-0.08	-0.01	-0.03	-0.04	333
S-T4	0.13*	-0.06	-0.07	-0.12*	-0.02**	344
S-TSH	-0.03	-0.10(*)	-0.04	0.02	-0.09(*)	343
	Spearman's rho	**Spearman's rho**	**Spearman's rho**	**Spearman's rho**	**Spearman's rho**	
sTNFR1	0.10	-0.02	0.06	-0.001	-0.05	231
IL1RA	-0.03	0.04	0.14*	0.10	0.03	232
OPG	0.09	0.06	-0.09	-0.007	-0.03	232
CRP	-0.12*	0.02	0.12*	0.08	0.07	336

(*)p<0.1, *p<0.05, **p<0.01. PANSS positive factor score represents the mean score from item P1, P3, P5 and G9 and the negative factor score represents the mean score from item N1, N2, N3, N4, N6 and G7

Table 3. Results from the last step of the multivariate regression analyses with symptom profiles as the outcome variables. Only variables with bivariate correlations with both S-25(OH)D and the outcome variable in question are entered in the analyses.

	PANSS positive symptom factor score		PANSS negative symptom factor score		PANSS negative symptom factor score		Total CDSS symptom score		Suicidal ideation	
Variables	**B(SE)**	**t**	**B(SE)**	**t**	**B(SE)**	**t**	**B(SE)**	**t**	**B(SE)**	**Wald**
Female gender	-0.03(0.05)	-0.64	-0.05(0.05)	-1.10	-0.03(0.05)	-0.62	0.33(0.13)	2.58*	-0.09(0.06)	2.52
Years of education	-0.03(0.01)	-3.29**	-0.11(0.01)	-1.42	-0.01(0.01)	-1.55				
Schizophrenia vs. non-schizophrenia spectrum	0.31(0.05)	6.04**	0.19(0.05)	4.01**	0.19(0.05)	3.76**				
Inpatient vs. Outpatient	0.07(0.05)	1.41	0.12(0.05)	2.54*	0.12(0.05)	2.41*				
Ethnic minority vs. Majority	-0.01(0.055)	-0.24	-0.001(0.05)	-0.98	0.001(0.05)	0.01				
Winter vs. Summer							-0.28(0.12)	-2.29*		
S-T4							-0.04(0.03)	-1.60	-0.14(0.07)	4.21*
Substance abuse									1.10(0.42)	6.98**
Total CDSS symptom score[a]									2.14(0.26)	69.89**
CRP					0.03(0.04)	0.75				
S-25(OH)D	0.000(0.001)	-0.37	-0.002(0.001)	-2.27*	-0.002(0.001)	-2.10*	-0.01(0.003)	-2.71**	-0.006(0.008)	0.67
	Total model: Adjusted R^2=0.16, F(6,357)=12.50, p<0.001		Total model: Adjusted R^2=0.11, F(6,357)=8.58, p<0.001		Total model: Adjusted R^2=0.11, F(7,328)=6.75, p<0.001		Total model: Adjusted R^2=0.05, F(4,357)=5.23, p<0.001		Total model: Nagelkerke R^2=0.60, Chi^2=184.77(5), p<0.001	

***p<0.05, **p<0.01, [a] Variable only entered for the outcome suicidal ideations.**