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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. 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 Scaleanalyzed by a five-factor model. The Calgary Depression Scale for Schizophrenia was used to assess depression and suicidal ideation. Blood samples were analyzed for S-25(OH)D, CRP, sTNF-R1, IL-Ra and OPG. We performed bivariate correlations and multiple 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 = −0.13, p = 0.02) and negative symptoms (rho = 0.14, p = 0.01), but did not act as a mediator. 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 patients with prominent negative or depressive symptoms.

1. Introduction

Vitamin D is a fat-soluble hormone that is important for neurodevelopment and neuropsychiatric disorders (Cui et al., 2015). Vitamin D passes the blood-brain barrier, and both vitamin D receptors (VDR) and the enzyme hydroxylasing S-25(OH)D into the active metabolite 1,25-dihydroxy-vitamin D ($1,25(OH)_2D$) are found in the human brain (Eyles et al., 2005).

The prevalence of vitamin D deficiency is higher in persons with psychotic disorders than in the general population (Belvederi Murri et al., 2013; Valipour et al., 2014). Low levels of S-25(OH)D is found in patients with acute psychotic episodes (Dealberto, 2013; Yuksel et al., 2014). Studies also find links between low S-25(OH)D and general negative symptoms (Graham et al., 2015) and passive apathetic withdrawal

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(Berg et al., 2010), while other find associations to higer levels of social anhedonia and poverty of speech only in males (Cieslak et al., 2014).

The strongest link between low S-25(OH)D and psychiatric symptomatology is found in depression (Anglin et al., 2013; Milaneschi et al., 2014) and suicide attempters have significantly lower S-25(OH)D than non-suicidal patients (Grudet et al., 2014). Depressive episodes are also prevalent in psychotic disorders (Romm et al., 2010) and findings indicate that low S-25(OH)D is associated with depression also in these disorders (Berg et al., 2010).

Inflammation is currently investigated as a potential disease mechanism in psychotic disorders (Goldstein et al., 2009; Potvin et al., 2008). Our research group has previously reported associations between psychotic symptomatology and increased levels of inflammatory markers (soluble tumor necrosis factor receptor 1 (sTNF-R1) and interleukin- 1 receptor antagonist (IL-1Ra)) (Hope et al., 2013) in 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). Vitamin D is a regulator of the immune system (Calton et al., 2015; Fernandes de Abreu et al., 2009). In line with this, low levels of S-25(OH)D has been found to be associated with high CRP in schizophrenia patients, compared to healthy controls (Zhu et al., 2015).

There are thus indications that low S-25(OH)D is associated with increased disease severity in psychotic disorders, potentially to specific symptom profiles. There are also indications that inflammatory pathways could be involved in the association between low S-25(OH)D and clinical symptoms. Our first aim was thus to investigate the associations between S-25(OH)D levels and specific symptom profiles in a large, well- categorized clinical sample of patients with psychotic disorders; more specifically to investigate if lower levels of S-25(OH)D was associated with higher levels of positive or negative symptoms as measured by the Positive and Negative Syndrome scale for Schizophrenia (PANSS) and/or with higher levels of depressive and suicidal symptoms as measured by the Calgary Depression Scale for Schizophrenia (CDSS). Our second aim was to investigate if the putative associations between S-25(OH)D and symptom profiles were influenced by the general level of inflammation as measured by C-reactive protein (CRP) or the level of specific inflammatory markers previously associated with higher levels of positive symptoms in psychotic disorders and with depression in bipolar disorders; i.e. sTNF-R1, IL-1Ra and OPG.

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, found to be appropriate in clinical samples of different cultural background (Wallwork et al., 2012) and in early psychosis (Langeveld et al., 2013). The Calgary Depression Scale for Schizophrenia (CDSS) is used to identify depression in patients with psychosis by excluding symptoms that overlap with negative symptoms of schizophrenia (Addington et al., 1994; Addington et al., 1990). We lacked CDSS information for 71 participants who 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 versus mild, moderate or severe suicidal ideation. Age of onset was set as age at 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 the majority population group (including participants with European ancestry) and the ethnic minority group (including participants with Asian, Latin-American and African ancestry). The participants went through a physical examination including blood sampling, height,weight and body mass index (BMI) (kg/m^2) using standardized procedures. Medication use (reported and prescriptions) were noted.

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 × (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). Standard (i.e. not high-sensitivity) CRP in plasma, serum–thyroxine (T4) and thyroid stimulating hormone (TSH) were analyzed at Department of clinical Biochemistry (Oslo University Hospital). Participants with CRP > 10 mg/L (i.e. suspect of intercurrent infection)(WHO, 2016) and two participants with known chronic infections (hepatitis) 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).

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Missing CDSS scores was imputed based on a regression model from a subsample of 146 patients with both IDS-C and CDSS scores, producing the following formula; (−0.314) + (IDS-C × 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).

To investigate the association between symptom profiles, S-25(OH)D, inflammatory markers, and other clinical characteristics, we started out examining their bivariate associations, followed up by multivariate analyses to investigate to which extent associations between S-25(OH)D and symptoms were mediated by other variables. Bivariate correlations were measured with Pearson's r for normally distributed continuous variables and Spearman's rho for variables with a skewed distribution. The positive and negative symptom factors from the PANSS were log-transformed while the CDSS total score was square root transformed, to enable us to use linear regression as the main analytic strategy. CRP was dichotomized into high (CRP ≥ 5 mg/L) or low (CRP < 5 mg/L) level in accordance with previous studies in clinical samples with psychosis (Dickerson et al., 2007; Stubbs et al., 2015).

We performed a hierarchal block-wise multiple linear regression analysis for each outcome variable to evaluate the effect of S-25(OH)D on the outcomes (positive symptom factor, negative symptom factor and depressive symptoms). Variables with bivariate correlations at the $p < 0.10$ 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, diagnosis 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 we entered S-25(OH)D as a continuous variable. The last step from the analyses is shown (Table 3). 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 multiple linear regressions, but we here also entered depressive symptoms at an additional step because of the high correlation ($r = 0.61$, $p < 0.001$) between depressive symptoms and suicidality. We finally performed follow-up analyses stratified by sex. 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 the subsample with available immune analyzes. There were significant correlations between CRP and S-25(OH)D and between CRP and negative symptoms (Table 2). We performed a regression analysis with negative symptoms as the outcome variable. Possible confounding variables were entered as described above but with CRP entered in the second last step to see how CRP influenced the association between S-25(OH)D and negative symptoms (Table 3). There was a significant correlation between IL-1Ra and negative symptoms but not S-25(OH)D, and we stopped further analyses at this step. There were no significant correlations between sTNF-R1 or OPG with S-25(OH)D and any of the outcome variables.

3. Results

Description of the participants is summarized in Table 1. In the bivariate analyses we found low S-25(OH)D to be significantly correlated with negative symptoms ($r = -0.18$, $p = 0.001$) and depressive symptoms ($r = -0.12$, $p = 0.02$); with a trend level for positive symptoms ($r = -0.09$, $p = 0.09$) and suicidal ideation ($t = 1.9$, $p = 0.06$). There were no significant 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 did not reach the level of statistical significance (Table 2).

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 = 322)	1.05 (9.4)

The final step from the multiple regressions 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 negative symptoms however remained significant (adjusted $R^2 = 0.113$, $F(6,357) = 8.58$, $p < 0.001$). The association between S-25(OH)D and negative symptoms was not altered significantly by entering CRP 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 possible confounding variables. The association between low S-25(OH)D and suicidal ideations however appeared to be mediated by depression. Follow-up analyses stratifying for sex indicated the same patterns of association in men and women (data not shown).

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 after controlling for potential confounding factors.

The significant association between low S-25(OH)D and higher negative symptoms expand the knowledge from two previous small studies that have found the same association (Cieslak et al., 2014; Graham et al., 2015). 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., 2013; Gardsjord et al., 2016; Mucci et al., 2016) and we lack possible treatment strategies (Aleman et al., 2016; Woodward et al., 2005).

Vitamin D is found to be important for normal function of the dopamine circuits implicated in the pathogenesis of positive symptoms in animal models (Eyles et al., 2013). The association between S-25(OH)D and positive symptoms in the current study was however not significant after controlling for education and diagnosis. Associations between low S-25(OH)D and positive symptoms have been found in studies of youth with psychiatric disorders (Gracious et al.,

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Table 2
Bivariate correlations between vitamin D (measured as 25(OH)D in serum) and major symptom factors in psychotic disorders.

	S-25(OH)D	PANSS positive symptom factor score	PANSS negative symptom factor score	Total CDSS symptom score	Suicidal ideations	N
	Pearson's r	Pearson's r	Pearson's r	Pearson's r	Pearson's r	
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
T4	0.13*	−0.06	−0.07	−0.12*	−0.02**	344
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	−0.13*	0.003	0.14*	0.07	0.08	322

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 from the Negative and Positive Syndrome Scale for Schizophrenia. CDSS; Calgary depression scale for schizophrenia. Suicidal ideations represent a score 1,2 or 3 on item 8 in the CDSS.
(*) $p < 0.1$.
* $p < 0.05$.
** $p < 0.01$.

2012) and in acute psychosis (Yuksel et al., 2014). The samples in these studies may however represent a subgroup of patients with more severe symptomatology since they were all inpatients. Associations with florid positive symptoms and atypical symptoms were also found in a sample recent refugees hypothesized to have a recent drop in vitamin D levels (Dealberto, 2013). These patients had no comprehensive clinical characterization, and we thus do not know if the association was confounded by factors such as diagnosis.

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 previous 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 line with previous studies (Grudet et al., 2014); the multiple linear regression analyses showed that this association mainly was mediated by depression. 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 initially hypothesized that inflammation was a

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

Variables	PANSS positive symptom factor score		PANSS negative symptom factor score		PANSS negative symptom factor score		Total CDSS symptom score		Suicidal ideation	Wald
	B(SE)	t	B(SE)	t	B(SE)	t	B(SE)	t	B(SE)	
Female gender	−0.03(0.05)	−0.64	−0.05(0.05)	−1.10	−0.01 (0.05)	−0.13	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)	−1.79				
Schizophrenia vs. non-schizophrenia spectrum	0.31(0.05)	6.04**	0.19(0.05)	4.01**	0.19(0.05)	3.68**				
Inpatient vs. Outpatient	0.07(0.05)	1.41	0.12(0.05)	2.54*	0.11(0.05)	2.26*				
Ethnic minority vs. Majority	−0.01(0.055)	−0.24	−0.001(0.05)	−0.98	−0.003 (0.06)	−0.06				
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					0.06 (0.10)	0.62				
S-25(OH)D	0.000(0.001)	−0.37	−0.002(0.001)	−2.27*	−0.002(0.001)	−2.01*	−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 $R^2 = 0.11$, $F(7,321) = 6.53$, $p < 0.001$		Total model: Adjusted $R^2 = 0.05$, $F(4,357) = 5.23$, $p < 0.001$		Total model: Nagelkerke $R^2 = 0.60$, $Chi^2 = 184.77(5)$, $p < 0.001$	

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 from the Negative and Positive Syndrome Scale for Schizophrenia. CDSS; Calgary depression scale for schizophrenia. Suicidal ideations represent a score 1,2 or 3 on item 8 in the CDSS.
* $p < 0.05$.
** $p < 0.01$.
[a] Variable only entered for the outcome suicidal ideations.

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mediating factor. We found that CRP was significantly correlated with both S-25(OH)D and negative symptoms, but did not mediate the association between S-25(OH)D and negative symptoms. IL-1Ra was associated with negative symptoms in bivariate analyses; in line with previous findings linking IL-1Ra to disease activity (Hope et al., 2011; Hope et al., 2013), but had no significant associations with S-25(OH)D. Our results imply an independent association between S-25(OH)D and symptomatology that is not mediated by pro-inflammatory pathways. The immune system is however complex and there could be other interactions between S-25(OH)D , inflammation and symptomatology that is not covered by our strategy or choice of inflammatory markers.

An alternate explanation for the associations between S-25(OH)D and symptoms is that disease related behavior may affect vitamin D levels (Belvederi Murri et al., 2013). It is possible that behavior based in negative and depressive symptomatology includes spending more time indoors and a poorer diet, i.e. the low S-25(OH)D could be interpreted as secondary to withdrawal symptoms. Since our data are cross sectional, we cannot conclude regarding direction of the associations.

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 suggesting that oxidative stress cause negative symptoms through an imbalance in the excitative-inhibitory glutamate-GABA responses (Albayrak et al., 2013; Sullivan and O'Donnell, 2012). There are also indications that vitamin D is involved in the pathogenesis of depression 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 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 the large, well- characterized sample. The participants are recruited from in- and outpatient clinics from a catchment area based health care system serving a broad spectrum of psychotic disorder with participants from all parts of society. 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 we were able to impute the missing values based on IDS-C. Only a subgroup had available immune measurements and it is possible that negative findings are based in lack of statistical power. We used ethnicity as a proxy for skin color; while more objective measures would have been preferable.

In conclusion, there are strong associations between lower S-25(OH)D and higher negative and depressive symptoms in psychotic disorders. Clinicians are encouraged to measure S-25(OH)D as part of assessments and randomized controlled trials should be performed to investigate the effect of vitamin D supplementation as a possible adjuvant treatment strategy in patients with low S-25(OH)D and a psychotic disorder with prominent negative or depressive symptoms.

Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

MN has designed the study and written the manuscript in close collaboration with IM and AOB. OAA contributed to biological data and coordinated protocol. LRK, ID, SH, SRD and MAW have provided clinical and biochemical data. KLR and AF have contributed to interpretation of results. All authors contributed to and have approved the final manuscript.

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