A preliminary investigation of the clinical and cognitive correlates of circulating vitamin D in bipolar disorder

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Highlights

- 27% of the Australian sample were vitamin D deficient.
- There was no difference in the vitamin D levels and deficiency status between bipolar disorder patients with low grade mood symptomatology and healthy controls.
- Number of past mood episodes, illness duration, seasonal mood pattern, mood symptom severity and global cognition appear to be independent of vitamin D levels in BD.
- Use of vitamin D supplements to remedy vitamin D deficiency may have no direct effects on the clinical and cognitive features of bipolar disorder.

Abstract

The role that vitamin D plays in the cognitive and clinical characteristics of bipolar disorder (BD) is unclear. We examined differences in the levels and deficiency status of vitamin D in an Australian sample of BD patients compared to healthy controls; and determined the extent to which vitamin D is associated with clinical variables and cognitive function in the sample. 22 healthy controls and 55 stable outpatients with diagnosis of BD and low-grade mood symptomatology provided a sample of blood and completed cognitive tests and clinical measures. Plasma concentrations of 25-hydroxyvitamin D were assayed and used to segregate participants into subgroups with sufficient or deficient levels of vitamin D. Subgroups were then compared in terms of global cognition and a range of sociodemographic and clinical factors (number of past mood episodes, illness duration, seasonal mood pattern, mood symptom severity), while mean levels of vitamin D were compared between patients and controls. Although almost 27% of the current sample were vitamin D deficient, no significant differences in mean vitamin D levels or the prevalence of vitamin D deficiency were evident between BD patients and controls. Vitamin D was not associated with global cognition in either patients or controls, nor any of the clinical measures assessed in the study.

In conclusion, we observed no difference in the vitamin D levels and deficiency status of an Australian sample of healthy individuals and BD patients with low grade mood symptomatology compared to controls. Clinical symptoms and global cognition also appear to be independent of vitamin D levels in BD.

Keywords: 25-hydroxyvitamin D; global cognition; mood disorders; illness duration; seasonal mood pattern

1. Introduction

Vitamin D is a hormone implicated in calcium homeostasis, insulin signalling, and immune response modulation (Aranow, 2011; Berridge, 2017; Schwalfenberg, 2011). Approximately 20-40% of the population are estimated to be vitamin D deficient at any given time (Amrein et al., 2020). This may owe to inadequate dietary vitamin D intake, or variations in exposure to sunlight or the use of sunscreen, both of which affect endogenous vitamin D synthesis (Dunlop et al., 2022; Matsuoka et al., 1987; Tsiaras and Weinstock, 2011; van der Mei et al., 2007). Low vitamin D is a known risk factor for obesity and hypertension (Martini and Wood, 2008; Soares et al., 2012). There are also high rates of vitamin D insufficiency in mental health cohorts generally, and those with mood disorders specifically (Berk et al., 2008; Berk et al., 2007). It also has a relatively well-characterised role in the onset of diabetes and other cardiovascular illnesses (Grandi et al., 2010), which are prevalent in bipolar disorder (BD) at elevated rates compared to the general population (Goldstein et al., 2020). Despite this link, research focussing on the relationship between vitamin D and BD is sparse, with only a few studies having been published on the topic to date (Altunsoy et al., 2018; Belzeaux et al., 2015; Boerman et al., 2016; Grønli et al., 2014; Humble et al., 2010; Marsh et al., 2017; Menkes et al., 2012; Petrov et al., 2018; Sikoglu et al., 2015).

A recent review of this literature found that while sub-threshold vitamin D deficiency was reasonably common in BD, mean levels of vitamin D did not consistently differ between BD patients and healthy controls (Cereda et al., 2021). Acute mood symptomatology — indexed by psychiatric hospitalisation status — may moderate these between-group differences however, since lower mean vitamin D levels tended to be found in inpatient versus outpatient samples (Cereda et al., 2021). It is unclear whether this is because inpatients are likely to spend more time indoors and be exposed to less sunlight, or whether vitamin-D

is actually an intrinsic marker of clinical severity. Indeed, the extent to which vitamin D acts as a mediator, marker or moderator of the association with psychopathology is unclear, (Cui et al., 2021), with few studies having explicitly analysed whether vitamin D level or vitamin D deficiency status varies with the presence or severity of BD's characteristics mood symptoms. Whether vitamin D is associated with other clinical characteristics of BD, including number of past mood episodes, seasonal pattern or illness duration, is also unknown.

In the general population, vitamin D levels have been found to influence neural development and cognitive functioning (McGrath, 1999), with low vitamin D specifically related to poor cognitive outcomes (Anastasiou et al., 2014; Goodwill and Szoeke, 2017). Relevantly, a large proportion of patients with BD experience persistent cognitive dysfunction that adversely impacts psychosocial functioning and quality of life (Van Rheenen et al., 2020; Van Rheenen et al., 2017; Van Rheenen et al., 2021). While the catalysts and maintaining factors for this dysfunction remain unclear, emerging evidence suggests that it links to cardiometabolic disease risk factors, for which low vitamin D has also been implicated (Bora et al., 2019; Ringin et al., Under review; Sánchez-Ortí et al., 2022; Van Rheenen TE et al., 2021). Despite this, there is almost a complete absence of data on the association between vitamin D and cognitive dysfunction in BD, with only one small study having examined this potential link. In that study of an inpatient psychogeriatric sample of mixed diagnoses including 11 patients with BD, no association between vitamin D levels and a crude measure of global cognitive function was evident (Lapid et al., 2013).

Given the paucity of existing literature, it is clear that our understanding of the relationship between vitamin D and BD is in its infancy, particularly in terms of the role that vitamin D may play in the cognitive and clinical characteristics of the disorder. In this study we sought to address this, by examining differences in the levels and deficiency status of the

active form of vitamin D (25-hydroxyvitamin D) in an Australian sample of BD patients compared to healthy controls; and determining the extent to which vitamin D is associated with clinical variables and cognitive function in the sample.

2. Materials and Methods

This study was approved by the relevant Human Ethics Review Board and abided by the Declaration of Helsinki.

2.1 Participants

The sample comprised 55 stable outpatients with a DSM-IV-TR confirmed diagnosis of BD (type I = 52; type II = 3) and 22 healthy controls. Eighty-two percent of the sample was Caucasian in ethnicity. All participants were recruited via general advertisement (full sample) and/or community support groups or outpatient clinics (BD) as part of a multidimensional study incorporating neuroimaging and cognitive assessments for which vitamin D was not the primary focus. Participants were assessed in Victoria, Australia, during both Autumn/Winter and Spring/Summer months. Psychiatric diagnosis and healthy control status were assessed using the MINI-International Neuropsychiatric Interview (MINI) and MINI screen (Sheehan et al., 1998). No BD patient met criteria for a mood episode at the time of assessment (as determined by the MINI), and none reported that they had experienced a mood episode in the 3 weeks prior. All BD patients had been on a stable medication regime for a period of at least 2 months (i.e. no non-trivial changes in dose/type). Current mood symptoms were assessed with the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) and the Young Mania Rating Scale (YMRS; Young et al., 1978). Thirty-six of the BD patients were euthymic (MADRS and YMRS $\leq$ 8) and 18 displayed mild-to-moderate symptoms (i.e., 16 with MADRS scores > 8 but less than 32 and

3 with YMRS scores > 8 but less than 18)[1]. No control participant had a current diagnosis or previous history of psychiatric illness, or an immediate family history of mood or psychiatric disorder. All participants were between the ages of 18 and 65 years of age, fluent in English, and provided informed consent. Those who had recently received ECT, were dependent on alcohol or illicit substances in the last three months, had significant visual or verbal impairments, or a history of intellectual disability, dementia or a known neurological disorder, were excluded.

2.2. Measures

Vitamin D

Participant venepuncture was performed by trained personnel, with each whole blood sample centrifuged at 4000rpm for 10 minutes. Once separated, a 500µl aliquot of plasma was isolated and stored at -80°C until use. Plasma concentrations of 25-hydroxyvitamin D (Vitamin D) were measured using a standard ELISA array, per manufacturer's instructions. Concentrations were obtained from data that was normalised based on the average of standard curves run in duplicate. The intra assay variability was <10% and the inter assay variability was <5%. Participants were dichotomised into groups based on vitamin D status, with deficiency defined by the Endocrine Society of Australia as <20ng/ml (50 nmol/l) and sufficiency defined as ≥20ng/ml[2] (Nowson et al., 2012).

Cognitive assessment

All participants completed the Wechsler Test of Adult Reading (WTAR; Wechsler, 1997) as a measure of estimated premorbid intelligence, as well as the MATRICS Consensus

[1] Note that one BD participant was missing YMRS/MADRS data.

[2] Given evidence that a vitamin D level of ≥30ng/ml may be beneficial for cognitive function (Annweiler et al., 2015), analyses were re-run with deficiency defined as <30ng/ml. Results were unchanged and thus findings are not presented for brevity.

Cognitive Battery (MCCB; Nuechterlein and Green, 2006), which has been previously validated in BD samples (Burdick et al., 2011; Sperry et al., 2015; Van Rheenen and Rossell, 2014). The MCCB assesses six cognitive domains — processing speed, attention, working memory, visual learning, executive function, and social cognition. Raw MCCB test scores were converted to domain *t*-scores that were age and gender corrected based on a normative sample of 300 healthy controls (Kern et al., 2011). A composite score, reflecting *global cognition* was used in the subsequent analyses to circumvent multiple testing given the relatively modest size of the sample.

Clinical variables

In addition to clinical symptoms measured by the MADRS and YMRS as described above, participants also self-reported their lifetime history of mood episodes, illness duration, and seasonal pattern of mood symptoms.

2.3. Statistical Analysis

All analyses were completed using the Statistical Package for the Social Sciences (SPSS) version 27 (IBM). Fisher's exact test and one-way analyses of variance (ANOVA) were used to examine group differences in demographic variables, as well as mean vitamin D levels and vitamin D status (vitamin D deficient or sufficient)[3]. Univariate ANCOVAs were used to examine cognitive (all participants) and clinical (BD-only) variables as a function of vitamin D status. A vitamin D status x group interaction term was included in the analysis of

[3] As participants were recruited as part of a multi-dimensional study in which vitamin D was not the primary focus, we were liberal in our inclusion of participants taking vitamin D supplements for logistical and practical reasons. Six participants included in the current analyses reported taking vitamin D supplements (4 BD patients, 2 healthy controls). To assess the extent to which these participants were confounding the results, we removed them and re-ran the analyses. This made no difference to the findings, and for brevity, the results of these precautionary analyses are not included below.

cognition to identify any diagnosis-specific effects. Season of blood draw[4] was set as a covariate in all models *a-priori,* WTAR score in the model of global cognition[5], and age and sex in the models assessing clinical variables[6]. To assess the extent to which findings were influenced by current mood, all procedures were conducted again in secondary analyses excluding non-euthymic BD patients. A false discovery rate of $p < .05$ was applied to the models assessing clinical variables to account for multiple comparisons using the Benjamini-Hochberg method. Bivariate correlations (using a conservative alpha of $p = <.01$) were also conducted in the BD group to cross-check the extent to which cognitive and clinical factors were associated with vitamin D levels when measured continuously.

3. Results

Participant characteristics by vitamin D deficiency status are displayed in Table 1 and Supplementary Table S1, while participant characteristics by diagnostic status are displayed in Supplementary Tables S2 and S3. With the exception of the full BD group having lower premorbid IQ scores than controls, there were no significant differences between any groups on any demographic variables. Vitamin D deficiency was evident in ~26% of BD patients and ~32% of controls, but the proportion of individuals with a vitamin D deficiency versus those without did not differ by diagnostic group. Vitamin D deficient and sufficient

[4] Season of blood draw was initially dichotomised to summer/spring and winter/autumn given the increased/decreased sunlight during those seasons and as evidence has shown an increase in 25-hydroxyviatmin-D levels during spring and summer compared to autumn and winter (Holick, 1995). However, there is also evidence that vitamin D levels are higher in summer *and* autumn and lower in winter *and* spring (Maxwell, 1994), so analyses were re-run with season dichotomised to summer/autumn and winter/spring. Results were unchanged and thus the findings presented here include only the summer/spring, winter/autumn dichotomy, for brevity.

[5] Age and sex were not included as covariates in the cognitive model as the global cognitive score was age and gender corrected based on norms for the MCCB. However, given there was a trend for a sex distribution difference in vitamin D deficiency status, we conducted sex-stratified analyses of global cognition as a function of vitamin D status. As there were no significant effects, these results are not reported.

[6] Ethnicity is typically considered an importance covariate when assessing vitamin D levels, however it was not included in the current analyses as there was little variability in ethnicity in the sample (82.1% Caucasian/European).

individuals did not differ in terms of ethnicity, season of blood draw or employment status[7]. Mean vitamin D levels also did not significantly differ by diagnostic group, although a small size effect was evident favouring higher scores in the BD patients (p = .18, Cohen's d = 0.37).

Primary analysis of vitamin D status differences in cognitive and clinical variables in the full BD sample compared to controls

Diagnostic and/or vitamin D status comparisons and interactions for cognitive functioning and clinical variables (in the full sample of BD patients) are shown in Table 2. A main effect of diagnostic group on global cognition was evident, with worse cognitive performance in BD patients compared to controls. There was no main effect of vitamin D status or vitamin D status *by* group interaction on global cognition (see Table 3 for effect sizes of diagnostic group differences in global cognition by vitamin D status). In the BD group, no main effects of vitamin D status were found for any of the clinical variables.

Secondary analyses of the strictly euthymic subsample compared to controls

Exclusion of non-euthymic BD patients in the secondary analyses made no meaningful difference to any of the above results. These analyses are reported in supplementary Table S4.

Correlations

[7] These variables were assessed given that vitamin D has been shown to differ by seasonality, skin pigmentation and sunlight exposure (employed people or students *may* have more incidental or occupational sun exposure than unemployed people)(Maxwell, 1994).

The results of the bivariate correlational analyses are presented in Supplementary Tables S5 and S6. No significant correlations (at $p < .01$) were found between mean vitamin D levels and the cognitive or clinical variables of interest in the BD group.

Discussion

In this study we measured the active form of vitamin D, 25-hydroxyvitamin D, in a group of individuals with BD and healthy controls. We found that 27% of our sample were vitamin D deficient, which is consistent with broader community estimates of vitamin D deficiency in the range of 20-30% of the Australian population (Daly et al., 2012; Gill et al., 2014). However, no significant differences in mean vitamin D levels or the prevalence of vitamin D deficiency was evident between BD patients and controls; a finding that held irrespective of whether the analyses included only euthymic BD patients or those with sub-threshold symptoms of mania or depression as well.

The limited range of past studies comparing vitamin D in BD patients and controls have produced mixed findings. Nonetheless, there does appear to be some indication that vitamin D levels track with symptom severity and psychiatric hospitalisation status, since lower levels of vitamin D have been found in those with more severe BD symptoms as well as in samples of inpatients but not outpatients with BD (Cereda et al., 2021). In our data however, we found no evidence that vitamin D is associated with mania or depressive symptomatology, though the absence of effects here may relate to the low symptom burden of our outpatient sample. Indeed, no BD patient met criteria for a current mood episode or reported one in the three weeks prior to assessment. Approximately two-thirds of the sample were also considered to be strictly euthymic with YMRS and MADRS scores ≤ 8, while the remainder of patients had subthreshold symptoms in the mild-moderate range (only 3 with low-level mania symptoms).

In our data, vitamin D deficiency was not linked to illness duration, number of past mood episodes, or the presence of a seasonal pattern of mood symptoms. Global cognitive performance also did not differ according to vitamin D status in patients *or* controls. This latter finding is inconsistent with that of a recent comprehensive review that indicated evidence of cognitive deficits in otherwise healthy individuals with low vitamin D levels (Goodwill and Szoeke, 2017). The absence of a cognitive association here is curious, given vitamin D has neuroprotective properties resulting from its ability to regulate glutathione and calcium signalling in the brain as well as induce neurotrophin biosynthesis (Garcion et al., 2002; Kalueff et al., 2004). These processes are involved in antioxidant defence, neural detoxification, neuritogenesis and brain plasticity, which underpin learning and memory (Schinder and Poo, 2000). Approximately 75% of those in our sample had vitamin D levels considered to be adequate in Australia, and for which it could be argued these neuroprotective properties might be at play (Nowson et al., 2012). Despite this, the BD group was still found to have lower global cognitive scores than controls. While a global cognitive deficit in BD is consistent with the literature, its presence in the context of sufficient vitamin D levels in most of our BD patients does appear to indicate that cognition in BD is independent of circulating vitamin D. The absence of a statistical correlation between vitamin D and global cognitive scores when the data was analysed continuously supports this notion. It is also aligns with recent evidence from a systematic review of psychosis-spectrum disorders –which share several phenotypic and genetic similarities with BD - indicating that the correlation between vitamin D and cognition is attenuated when relevant confounders are considered (Tsiglopoulos et al., 2021).

It should be noted that the absence of significant vitamin d status differences in the variables of interest likely reflect this study being underpowered to detect the *small effects* that we observed for most comparisons (Cohen's d ranging from 0.02-0.22). Indeed, post-hoc

power-analyses conducted in our quest to make sense of the results indicated that this study had less than 14% power to detect *significant* effects of a magnitude of f=0.1, which is equivalent to d=0.2 (the top end of the effect-size magnitudes observed in our data). An *a-priori* g*power analysis further indicated that future studies would need to include 787 participants to obtain significant differences of small effect with 3 covariates (age, sex, season of blood draw) and power set at 80%. Given these numbers, significant vitamin d status differences may be clinically meaningless. Nonetheless, the aforementioned information does raise the possibility that our results represent a false negative for a *small subset* of patients in whom vitamin D deficiency may be integral to their illness. Our results should be interpreted with this in mind.

To our knowledge, this is the first study to examine vitamin D in BD in the context of well-characterised clinical variables and a measure of global cognition derived from a comprehensive battery of cognitive tests. Other strengths of the study relate to our statistical exploration or covariation of a range of potentially confounding variables, including symptom status, vitamin D supplementation use, and season of assessment. Some limitations should also be considered, including the cross-sectional nature of the study which precluded our ability to assess the role of vitamin D according to suggested clinical staging models in BD (e.g. see Kupka et al., 2021) or in relation to cognitive decline. The modest sample size also limited our ability to explore associations between vitamin D and the cognitive subdomains that constituted the global cognitive score. Further, although BD patients had been on a stable medication regime for at least 2 months, there was a range of psychotropic medications and polypharmacy in use and the extent to which this pharmacological heterogeneity affected the study findings is not clear. Finally, although we assessed vitamin D supplement use in the sample, we did not explicitly assess hours of sun exposure or dietary vitamin D intake, which are among the factors affecting circulating vitamin D. However, it is

notable that vitamin D in either group did not differ according to the season in which assessments were conducted, which is a proxy for a sun exposure.

In sum, our findings show no difference in the vitamin D levels and deficiency status of an Australian sample of healthy individuals and BD patients with low grade mood symptomatology. Number of past mood episodes, illness duration, seasonal mood pattern, mood symptom severity and global cognition also appear to be independent of vitamin D levels in BD. In light of this, our work raises the possibility that the use of vitamin D supplements to remedy the vitamin D deficiency that is present in a subset of BD patients will have no direct effects on the clinical and cognitive features of the disorder. This is in line with clinical trial data indicating that vitamin D supplementation is ineffective in preventing depressive symptoms in the general population (Okereke et al., 2020), and of uncertain value in the treatment of depression itself (Gowda et al., 2015; Mikola et al., 2022). Researchers may wish to confirm this in future clinical trials for BD, as well as to replicate the findings observed here in larger samples.

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Table 1. Characteristics of BD and healthy control participants by vitamin D status

	Vit D deficient				**Vit D sufficient**				**Comparison**	
	BD		**HC**		**BD**		**HC**		***F/Fisher's, p*[a]**	**Post-hoc***
	N (%)	*M, SD*	*n*	*M, SD*	*n*	*M, SD*	*n*	*M, SD*		
Age		37.6 ± 10.3		30.1 ± 10.0		37.8 ± 8		37.5 ± 10.8	F = 1.0 p = 0.407	----
WTAR		106.5 ± 10.3		114.9 ± 8.6		108.5 ± 11.4		113.9 ± 10.4	F = 1.9, p = 0.146	----
YMRS total		3.6 ± 3.4		----		3.8 ± 3.6		----	F = 0.01, p = 0.906	
MADRS total		8.6 ± 9.2		----		8.1 ± 7.1		----	F = 0.05, p = 0.821	
Medication load		1.7 ± 1.3				1.8 ± 1.3			F = 0.08, p = 0.783	
Mean vitamin D (ng/ml)		15.3 ± 3.4		13.2 ± 3.2		34.3 ± 9.4		30.9 ± 8.1	F = 29.0, p < 0.001*	vit D deficient (BD and HC) < vit D sufficient (BD and HC)
Vitamin D status (deficient/sufficient)	14 (25.5)		7 (31.8)		41 (74.5)		15 (68.2)		p = 0.582	----
Sex										
Male	12 (85.7)		3 (42.9)		20 (48.8)		10 (66.7)		p = 0.067	----
Female	2 (14.3)		4 (57.1)		21 (51.2)		5 (33.3)			
Ethnicity										
Caucasian	12 (85.7)		3 (50.0)		36 (87.8)		12 (80.0)		p = 0.158	----
Non-caucasian	2 (14.3)		3 (50.0)		5 (12.2)		3 (20.0)			
Employment status[b]										
Employed/student	11 (78.6)		4 (57.1)		30 (73.2)		12 (80.0)		p = 0.698	----
Not employed	3 (21.4)		3 (42.9)		11 (26.8)		3 (20.0)			
Season of blood draw										
Autumn / Winter	9 (64.3)		4 (57.1)		21 (51.2)		10 (66.7)		p = 0.731	----
Spring / Summer	5 (35.7)		3 (42.9)		20 (48.8)		5 (33.3)			

Table 1. Characteristics of BD and healthy control participants by vitamin D status

	Vit D deficient				**Vit D sufficient**				**Comparison**	
	BD		**HC**		**BD**		**HC**		***F/Fisher's, p*[a]**	**Post-hoc***
	N (%)	*M, SD*	*n*	*M, SD*	*n*	*M, SD*	*n*	*M, SD*		
Medication (using)										
Lithium	5 (35.7)		--		15 (36.6)		--		p = 1.000	----
Lamotrigine	3 (21.4)		--		6 (14.6)		--		p = 0.678	
Sodium valproate	3 (21.4)		--		11 (26.8)		--		p = 1.000	
Anticonvulsants	6 (42.9)		--		22 (53.7)		--		p = 0.547	
Typical antipsychotic	0 (0.0)		--		2 (4.9)		--		p = 1.000	
Atypical antipsychotic	6 (42.9)		--		19 (46.3)		--		p = 1.000	
Mood stabiliser	8 (57.1)		--		28 (68.3)		--		p = 0.522	
Antidepressant	5 (35.7)		--		14 (34.1)		--		p = 1.000	
Benzodiazepine	0 (0.0)		--		7 (17.1)		--		p = 0.172	
Anticholinergic	0 (0.0)		--		0 (0.0)		--		--	

Note that vitamin D was measured as circulating 25-hydroxyvitamin D; BD; bipolar disorder, HC; healthy control, WTAR; Wechsler's Test of Adult Reading, YMRS; Young Mania Rating Scale, MADRS; Montgomery-Asberg Depression Rating Scale; missing data for ethnicity (n = 1 HC)

[a] Fisher's Freeman Halton exact test is reported when cells are greater than 2x2.

[b] Not employed constitutes unemployed, retired, volunteer work, and disability/pension.

---- Data not applicable

*Significant at $p < 0.05$

Table 2. Association of Vitamin D status with variables of interest

Domain[a]		Comparisons[b]	Group	M[c]	SD	d
Global cognition						
Full Sample	Vitamin D status	F (1,67) = 0.72, p = 0.410	Sufficient	48.43	11.47	-0.22
			Deficient	46.00	10.58	
	Diagnostic group	F (1,67) = 4.49, p = 0.038*	HC	50.39	11.22	-0.54
			BD	44.04	12.23	
	Vitamin D status *by* diagnostic group[f]	F (1,67) = 1.93, p = 0.170	HC Sufficient	53.62	10.40	----
			HC Deficient	47.16	10.31	
			BD Sufficient	43.25	10.25	
			BD Deficient	44.83	10.36	
YMRS total						
BD sample only	Vitamin D status	F (1,49) = 0.18, p = 0.672	Sufficient	3.87	3.64	-0.14
			Deficient	3.37	3.75	
MADRS total						
BD sample only	Vitamin D status	F (1,49) = 0.008, p = 0.929	Sufficient	8.18	7.80	-0.03
			Deficient	8.41	8.04	
Illness duration						
BD sample only	Vitamin D status	F (1,44) = 0.14, p = 0.711	Sufficient	16.07	7.69	-0.12
			Deficient	15.12	7.88	
Lifetime mood episodes						
BD sample only	Vitamin D status	F (1,43) = 0.004, p = 0.947	Sufficient	23.18	24.23	0.02
			Deficient	23.74	25.04	
Seasonal pattern, N[e]						
BD sample only	Vitamin D status	Fisher's, p = 1.000	Sufficient SP	19	----	Cramer's V = 0.01
			Sufficient NSP	7		
			Deficient SP	20		
			Deficient NSP	7		

Table 3. Size of diagnostic group differences in global cognition by vitamin D status

Group	M[a]	SD	d
BD sufficient	43.25	10.25	-0.15
BD deficient	44.83	10.36	
HC sufficient	53.62	10.40	0.62
HC deficient	47.16	10.31	
BD sufficient	43.25	10.25	-1.00
HC sufficient	53.62	10.40	
BD deficient	44.83	47.16	-0.23
HC deficient	10.36	10.31	

BD; Bipolar disorder, HC; Healthy control.
[a] Values are adjusted for season of blood draw and Wechsler Test of Adult Reading (WTAR) scores.