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Vitamin D and clinical symptoms in First Episode Psychosis (FEP): A prospective cohort study

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ABSTRACT

Background: There is a paucity of longitudinal research investigating vitamin D in people with early psychosis.
Method: Vitamin D levels were measured in 168 patients (64% (n = 108) male, mean age 29.3 (9.8) years) with first episode psychosis (FEP), along with measures of clinical state at baseline and at 12 months follow up. We assessed the a) cross sectional, and; b) longitudinal relationships between continuous and categorical 25-hydroxyvitamin D (25(OH)D) levels and clinical symptoms at first contact for psychosis and at 12 months.
Results: In FEP, 80% (n = 134) at baseline, and 76% at 12 months follow up, had suboptimal vitamin D levels (<20 ng/ml). Suboptimal levels of 25 (OH) D at baseline were not cross-sectionally associated with clinical symptoms. Higher vitamin D levels at baseline (n = 77) were significantly associated with better visual reproduction-immediate recall (β = 0.249, 95%CI = −0.012–0.871, p = 0.044).

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Higher baseline vitamin D levels were prospectively associated with lower total PANSS (β = −0.24, 95%CI = −0.47–0.01, p = 0.04) and PANSS negative symptom scores (β = −0.12, 95%CI = −0.23–0.01, p = 0.04) at 12 months.

Conclusion: We identified a prospective association between higher baseline serum Vitamin D levels and lower total psychotic symptoms and negative symptoms of psychosis at 12 months after first contact for psychosis. The results of this study require replication in larger prospective studies, and highlight the need for large randomised trials to assess the effect of vitamin D supplementation on symptoms of psychosis in FEP.

1. Introduction

Vitamin D is a secosteroid hormone which functions as a neuroprotective factor, with a role to play in neuroimmunomodulation, regulation of neurotrophic factors and brain development (Eyles et al., 2013; Harms et al., 2008). Vitamin D is primarily acquired through cutaneous synthesis under the action of ultraviolet (UV) sunlight (Holick, 2004) and to a variable but much lesser extent from nutritional sources. Vitamin D levels thus reflect ambient levels of sunlight (Hypponen and Power, 2007). An increased risk of developing schizophrenia is seen in settings where sunlight may be relatively low - higher latitudes (Gupta and Murray, 1992; Jongsma et al., 2018; Saha et al., 2006) and urban settings (Mortensen et al., 1999; Peen et al., 2010), with a higher prevalence of psychosis seen in Black African or Black Caribbean migrant groups in the UK (Fearon et al., 2006). Vitamin D during neurodevelopment may be important - Winter/Spring births confer a higher risk of psychosis (Davies et al., 2003), while a Danish longitudinal case-control study has found that vitamin D in neonates is associated with the risk of developing schizophrenia in adult life (McGrath et al., 2010).

Vitamin D levels are sub-optimal in people with established schizophrenia and other psychotic disorders (Adamson et al., 2017), being lower than matched controls even from the first episode of psychosis (Crews et al., 2013; Firth et al., 2017). In the two largest cross sectional studies of Vitamin D in established psychotic disorders, levels of suboptimal Vitamin D (vitamin D insufficiency and deficiency) of 90% (Lally et al., 2016) and 46% (Suetani et al., 2017) have been recorded. Suboptimal vitamin D in schizophrenia and psychotic disorders is increasingly recognised as a widespread problem (Valipour et al., 2014).

Relationships between vitamin D and psychotic symptoms, both positive and negative have been reported in established schizophrenia (Adamson et al., 2017; Berg et al., 2010; Cieslak et al., 2014; Dogan Bulut et al., 2016; Nerhus et al., 2016), though the largest cross sectional study of 324 patients with established psychotic disorders did not replicate these findings (Lally et al., 2016). The most consistent findings in people with mental disorders have been associations between lower vitamin D levels and depression (Anglin et al., 2013). Inverse correlations between vitamin D levels and depressive symptoms have been identified in some cross sectional studies in established psychosis (Berg et al., 2010; Nerhus et al., 2016), but this is an equivocal finding (Itzhaky et al., 2012; Lally et al., 2016).

Considerably less is known about clinical correlates of low vitamin D in FEP compared to those with established psychosis. Low vitamin D levels were associated with negative symptoms and more severe cognitive deficits in 20 people with first episode schizophrenia (FES) (Graham et al., 2015). These findings were supported by a cross sectional study of 31 FEP patients, in which a similar inverse correlation between vitamin D levels and negative symptoms was identified (Yee et al., 2016). A somewhat larger study with 71 FEP patients did not identify significant correlations between vitamin D and psychotic symptoms, but did identify significant correlations with depressive symptoms (Nerhus et al., 2015). Associations with clinical state have been demonstrated in adolescents who are 3.5 times more likely to have psychotic symptoms when vitamin D deficient (Gracious et al., 2012).

Cognitive deficits are a recognised feature of psychotic disorders, evident prior to the onset of illness and with impairment in processing speeds, verbal and working memory and executive functioning the most consistent deficits found (Fatouros-Bergman et al., 2014; Howes et al., 2015; Nerhus et al., 2017; Zanelli et al., 2010). The neurobiology underlying the cognitive impairment seen in psychotic disorders is unclear (Howes et al., 2015). The role of Vitamin D in brain development and functioning supports the hypothesis that hypovitaminosis D could contribute to cognitive impairments. While the relationship between low vitamin D levels and worse cognitive function is best established in the elderly (van der Schaft et al., 2013), the association in those with psychosis remains uncertain. A cross sectional association between Vitamin D insufficiency and more severe cognitive deficits (as measured by overall cognitive score) in twenty cases of FES was identified (Graham et al., 2015). Of the individual cognitive measures, only verbal fluency was related to low vitamin D status, although once adjusted for age, the relationship no longer remained significant. Cognitive function was not correlated with Vitamin D status in healthy controls. In a cross sectional study of 225 people with psychotic disorders, vitamin D deficiency was associated with decreased processing speed and decreased verbal fluency (Nerhus et al., 2017).

A major limitation of work to date exploring the relationship between vitamin D and clinical state in people FEP is that to the best of our knowledge no longitudinal study exists, precluding inferences on the directionality between vitamin D and clinical status. Further, while previous cross sectional studies of small sample size have assessed the relationship between vitamin D and psychotic and depressive symptoms, only one has explored the relationship with cognition.

1.1. Study aims

Clinical remission and recovery in FEP remains suboptimal (Lally et al., 2017a) and in the current study, we sought to clarify whether serum vitamin D (25-hydroxyvitamin D (25(OH)D)) levels are prospectively associated with psychotic and depressive symptoms at 12 months after first contact for FEP.

Given the paucity of research investigating vitamin D in people with early psychosis, we set out to examine a) the cross sectional relationship between vitamin D and clinical state and cognitive measures at first contact for psychosis; b) the relationship between baseline vitamin D status and depressive and psychotic symptoms at 12 months; and c) the prevalence of vitamin D deficiency and insufficiency during the first year of treatment for psychosis.

We hypothesized that baseline 25(OH)D serum levels are cross sectionally associated with clinical state measures in FEP, and that lower vitamin D levels at baseline would be inversely associated with depressive and psychotic symptoms at 12 months.

2. Methods

2.1. Study participants and design

A prospective observational study of 168 adults (108 males) with a first episode psychosis (FEP), recruited as part of a prospective

observational cohort study, Physical health and substance Use Measures in first onset Psychosis (PUMP), part of the National Institute of Health Research funded IMPACT programme (grant RP-PG-0606-1049).

All participants were included in the study after written, informed consent and the study protocol was approved by the Research Ethics Committee (08/H0807/53) Patients were assessed at baseline and after 1 year of follow-up.

2.2. Eligibility criteria

Inclusion Criteria were as follows: a) aged between 18 and 65; b) met the ICD-10 criteria for FEP (codes F20–29 and F30–33) (World Health Organization, 1992) and; c) understood English and did not require an interpreter.

Patients were excluded if they: were pregnant or had a major medical illness or neurological disease; met the criteria for organic psychosis (F09) or presented with evidence of transient psychotic symptoms resulting from acute intoxication as defined by ICD-10; or diagnosed with a moderate or severe learning disability (as defined by ICD-10, World Health Organization, 1992) (World Health Organization, 1992); or had a history of previous contact with health (GP or psychiatric) services for psychosis (Lally et al., 2017b).

2.3. Recruitment

Patients were recruited as soon after first presentation as possible and were followed up prospectively over a twelve-month period during which they remained under the care of mental health teams. The baseline diagnoses were made from face-to-face interviews and mental health records according to ICD-10 criteria (World Health Organization, 1992) utilising the Operational Criteria Checklists (OPCRIT) (McGuffin et al., 1991). Individuals with comorbid substance use disorders were not excluded.

2.4. Outcome measures

2.4.1. Serum vitamin D measurement and categorisation

Serum Vitamin D levels (serum 25(OH)D) were measured at baseline and at one year, using chemiluminescence immunoassay (DiaSorin, S.P.A. Saluggia (Vercelli), Italy). Vitamin D insufficiency was defined as vitamin D levels between 10 and 20 ng/ml while levels below 10 ng/ml were classed as vitamin D deficiency (Dawson-Hughes et al., 2010). A serum level of >20 ng/ml (equivalent to >50 nmol/L) was considered optimal (Pearce and Cheetham, 2010). We further categorised vitamin D as quartiles, replicating previous work (Jovanova et al., 2017), to ensure that we were able to assess the effects vitamin D across its range of values.

2.4.2. Demographic data and clinical outcome measures

Baseline data included demographics, age, sex, ethnicity (self-report), and diagnoses. Clinical state measures were recorded at baseline and at 12 months follow up. The severity of psychopathology was rated on the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1989) and by the Global Assessment of Functioning (GAF) scale at first presentation for psychosis. Mood symptoms were assessed using the Calgary Depression score (Addington et al., 1990), and the Young Mania Rating Scale (YMRS) (Young et al., 1978).

The assessment of psychopathology and cognition was completed blind to vitamin D status.

2.4.3. Neurocognitive assessment

A subset of 88 patients at baseline were administered a neurocognitive battery to assess cognitive functioning. The battery comprised assessments from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) and the Wechsler Memory Scale – Third Edition (WMS-III). The following tests were used from the WAIS-III battery: block design; matrix reasoning; digit symbol coding; information; and digit span. The following tests were used from the WMS-III battery: verbal fluency; trail making; logical memory; visual reproduction; and spatial span. Two subtasks from the computerised Cambridge Neuropsychological Test Automated Battery (CANTAB) were administered to 54 patients within the subset: the Stockings of Cambridge (SoC) (Sahakian and Owen, 1992) and the Spatial Working Memory (SWM) (Sahakian and Owen, 1992) task. The SoC is a spatial planning task measuring executive function. The SWM is a test of working memory and in particular measures an individual's ability to retain and manipulate stored information. The National Adult Reading Test (NART) (Nelson and Willison, 1991) was used as an estimate of general IQ.

2.5. Confounding factors

The following proposed confounding factors were evaluated: gender, age, and season of sampling. We used the season of blood sampling as a proxy for sunlight irradiation, as it is a factor which will affect the duration and intensity of sunlight exposure. We defined the seasons as follows: Summer: June to August; Autumn: September–November; Winter: December to February; Spring: March–May.

2.6. Data analysis

2.6.1. Multiple imputation

Serum 25(OH)D level (ng/ml), ethnicity and gender were the only variables in the dataset that did not have any missing information. It has now been recognised that complete case analysis without adequate handling of missing data may lead to biased results, or reduced power and precision of estimates (Zhao and Long, 2016). We assumed that the missing variables were missing at random (MAR). The assumption is that the propensity for missingness in our dataset was not linked to the unobserved values, and only dependent on observed data. We imputed the missing values using multiple imputation by chained equations (MICE) (Deng et al., 2016). MICE has been shown to be a robust method for dealing with missing data across empirical and longitudinal studies (He et al., 2011; Zhao and Long, 2016). In the MICE procedure a series of regression models are run whereby each variable with missing data is modelled according to its distribution (Azur et al., 2011); for continuous variables, this would be a multivariable linear regression; and for binary variables, a logistic regression. To increase the precision of the imputed data and subsequent perditions, we imputed all variables of interest including outcomes and confounding variables (Schafer and Graham, 2002) and additionally included auxiliary variables (Collins et al., 2001) such as baseline diagnoses and ethnicity. We used 25 sets of imputations (White et al., 2011); each imputed dataset was then analysed separately using standard complete-data analysis methods and the results were combined across all imputed datasets using Rubin's rule (Rubin, 1996). In the present study, we conducted multiple imputation using the MICE package (Van Buuren and Groothuis-Oudshoorn, 2011) in R. The proportion of outcome measures imputed compared to observed is shown in Supplementary table 1.

2.6.2. Descriptive and association analyses

Between groups comparisons were made using X^2 test for categorical variables; independent student's *t*-test for continuous variables, or the Mann-Whitney *U* test if variables were not normally distributed. Linear regression was used to test the hypothesis that baseline vitamin D levels were related to clinical state at 12 months, by examining the association between baseline serum vitamin D levels and the 12-month PANSS, GAF, CDRS, and YMRS scores controlling for potential confounding factors of gender, age, season of sampling at baseline, and the corresponding baseline clinical variable. Statistical significance was defined as $p < 0.05$. All analyses were conducted in RStudio version 0.99.486 (Integrated Development for R. RStudio, Inc., Boston, MA).

Of the subset of 88 patients administered the neurocognitive battery at baseline, 76 had baseline 25(OH)D serum levels recorded. An exploratory analysis was conducted examining the linear correlation between each individual baseline neurocognitive test and baseline 25(OH)D serum levels using Pearson's correlation coefficient. For those neurocognitive tests which were significantly correlated ($p < 0.05$) with 25(OH)D serum levels, separate linear regressions were run adjusting for age, gender and season of sampling as potential confounding factors.

3. Results

Demographic and clinical characteristics of participants and the relationships with Vitamin D status are shown in Table 1 and Table 2. Nearly half the participants were of white ethnicity (n = 78; 46%), with a large minority of participants of black ethnicity (n = 61; 36%). Forty two percent (n = 71) were vitamin D deficient (<10 ng/ml) at study recruitment, 37.5% (n = 63) were vitamin D insufficient (10–20 ng/ml), and 20.2% (n = 34) had sufficient vitamin levels (>20 ng/ml). The mean 25-OHD serum level was 13.8 (SD 9.3) ng/ml (range 4.0–67.9 ng/ml).

Those with suboptimal vitamin D levels at study recruitment were more likely to be of Black ethnicity (n = 57; 93% with suboptimal vitamin D levels) ($X^2 = 15.73$, $p < 0.001$) and to have had blood sampling in winter (n = 32; 97% with suboptimal vitamin D levels) ($X^2 = 12.65$, $p = 0.005$).

Those who were inpatients at baseline had a significantly higher mean vitamin D level (15.8 (11.6)) ng/ml than outpatients (mean level = 12.2 (6.9) ng/ml) ($t = 2.039$, $p = 0.044$).

3.1. Neurocognition subgroup

The associations between 25-OHD levels and demographic and clinical features in the subgroup in which neurocognitive measures were performed at baseline (n = 76) are shown in Supplementary table 2. The mean 25-OHD serum level was 12.95 (SD 8.1) ng/ml (range 4.0–41.3 ng/ml).

3.2. Vitamin D status at 12 months

Eighty four percent had suboptimal vitamin D levels at 12 months follow up; 45.8% (n = 77) with vitamin D deficiency ((<10 ng/ml); 36.9% (n = 62) with vitamin D insufficiency (25-OHD level of 10–20 ng/ml) and 17.3% (n = 29) with optimal vitamin D levels). The mean serum vitamin D level at 12 months was 12.2 (SD = 8.5) ng/ml (range = 4.0–71.9 ng/ml).

3.3. Cross sectional analysis at baseline

The cross-sectional analysis of the relationship between baseline 25(OH)D serum levels and baseline clinical state, including depressive and psychotic symptoms is presented in Table 1. We did not identify any association between 25(OH) D serum levels, analysed either as a binary variable (optimal and suboptimal vitamin D) or as quartiles, and clinical state measures.

Cross-sectional analysis of the relationship between baseline 25(OH)D serum levels and neurocognitive assessments yielded statistically significant unadjusted associations with seven cognitive tests encompassing verbal memory, non-verbal memory and executive functioning (Supplementary table 3). When adjusted for age, gender and season of sampling, only an association between higher vitamin D levels and visual reproduction - immediate recall (predominantly testing non-verbal memory) remained statistically significant ($\beta = 0.249$, 95% CI = −0.012–0.871, $p = 0.044$).

3.4. Longitudinal analysis

Next, we assessed the longitudinal relationship between baseline 25(OH)D serum levels (as a continuous measure and quartiles) and 12-month depressive and psychotic symptoms, as well as general functioning at 12 months after study recruitment (see Tables 3–4).

Higher levels of 25 (OH) D at baseline were associated with reduced total PANSS score (B = −0.24, 95%CI = −0.47 to −0.01, p = 0.04) and reduced PANSS negative symptom scores ((B = −0.12, 95%CI = −0.23 to −0.01, p = 0.04)) at 12 months (Table 3).

Table 1
Clinical and demographic baseline characteristics by vitamin D quartiles.

Clinical and demographic baseline characteristics	Total	*Baseline vitamin D levels*				Test Statistics		
		19.05–67.9	11.3–19.04	7.05–11.2	4–7.04			
	Mean(SD)/n(%)	Mean(SD)/n(%)	Mean(SD)/n(%)	Mean(SD)/n(%)	Mean(SD)/n(%)	t/X^2	df	p-Value
	N = 168	n = 42 (25.0%)	n = 43 (25.6%)	n = 41 (24.4%)	n = 42 (25.0%)			
Age (years)	29.3 (9.8)	29.6 (11.9)	29.2 (9.7)	29.7 (7.7)	28.9 (9.9)	0.05	134	0.99
Gender						3.76	3	0.29
Female	60 (35.7)	20 (47.2)	14 (32.6)	14 (34.2)	12 (28.6)			
Male	108 (64.3)	22 (52.4)	29 (67.4)	27 (65.8)	30 (71.4)			
Ethnicity						28.3	6	<0.001
White	78 (46.4)	31 (39.7)	24 (30.8)	12 (15.4)	11 (14.1)			
Black	61 (36.3)	5 (8.2)	13 (21.3)	22 (36.1)	21 (34.4)			
Other	29 (17.3)	6 (20.7)	6 (20.7)	7 (24.1)	10 (34.5)			
Season of blood intake						14.97	9	0.09
Autumn	56 (34.4)	18 (32.1)	14 (25.0)	12 (21.4)	12 (21.4)			
Spring	31 (19.0)	2 (6.5)	8 (25.8)	7 (22.6)	14 (45.2)			
Summer	31 (19.0)	6 (19.4)	9 (29.0)	10 (32.3)	6 (19.4)			
Winter	45 (27.6)	15 (33.3)	11 (24.4)	11 (24.4)	8 (17.8)			
Psychopathology								
Total PANSS	58.4 (13.7)	60.2 (15.2)	57.0 (12.5)	58.0 (10.7)	58.1 (16.7)	0.30	123	0.83
PANSS positive	14.4 (5.5)	14.2 (4.4)	13.8 (5.6)	14.5 (4.6)	14.9 (7.3)	0.21	131	0.89
PANSS negative	14.5 (5.8)	14.7 (6.2)	14.1 (4.9)	15.0 (6.4)	14.0 (5.8)	0.23	130	0.87
PANSS psychopath	29.3 (6.8)	31.3 (7.4)	29.2 (5.9)	28.2 (5.8)	28.4 (7.8)	1.45	129	0.23
GAF disability	30.8 (16.6)	31.5 (15.4)	32.7 (17.6)	27.3 (14.4)	31.3 (18.8)	0.79	164	0.50
GAF symptoms	28.0 (12.6)	29.3 (14.1)	29.9 (14.2)	26.5 (10.2)	26.5 (11.8)	0.66	131	0.58
Calgary total score	5.5 (5.1)	5.5 (5.4)	5.5 (5.4)	5.9 (4.7)	5.0 (4.8)	0.16	127	0.92
YMRS	5.3 (5.2)	5.4 (4.6)	4.8 (4.5)	5.4 (5.1)	5.7 (6.5)	0.16	127	0.92

Table 2
Demographic characteristics and differences in mean baseline vitamin D by season of sampling, age categories, ethnicity & diagnoses.

	Total sample n = 168	Female n = 60 (35.7%)	Male n = 108 (64.3%)			
Mean Age (SD)	29.3 (9.8)	31.0 (10.5)	28.4 (9.3)			
Mean vitamin D level	13.8 (9.3)	16.4 (12.0)	12.4 (7.2)			
Range vitamin D level	(4–67.9)	(4–67.9)	(4–38.4)			
	Mean 25-OHD level (ng/ml) ± SD				f	df	p-Value
Ethnicity	Black (n = 61) 9.7 ± 4.9[3]	White (n = 78) 17.8 ± 10.9[3]	Asian (n = 8) 12.7 ± 9.4	Mixed/Other (n = 21) 11.5 ± 6.8	10.78	167	<0.001*
Season sampling	Autumn (n = 56) 16.0±11.9	Winter (n = 31) 10.0 ± 7.4[1]	Spring (n = 31) 12.9 ± 7.2[2]	Summer (n = 45) 14.8 ± 7.6	3.06	162	0.03*

Analysis of variance (ANOVA) was conducted to assess for differences in serum 25-OHD between groups. The *values represent the significant difference with $p < 0.05$.
[1, 2]Mean serum 25-hydroxyvitamin D (25-OHD) levels were significantly decreased in those who had blood sampling in Winter compared to Summer or Autumn and were significantly decreased in Spring compared to Summer or Autumn. [3]Mean 25-OHD levels were significantly decreased in those of black ethnicity compared to those of white ethnicity.

When analyzing 25 (OH) D serum level in quartiles, we found no significant prospective relationship with 12-month clinical state measures, including psychotic and depressive symptoms (Table 4).

Longitudinal changes in serum 25(OH) D levels were not associated with clinical state outcome scores at 12 months (see Supplementary table 4). There was no significant association between the change in serum 25 (OH) levels and changes in psychotic symptoms as measured by the PANSS or depressive symptoms as measured by the Calgary Depression Scale score over the first 12 months of illness, when adjusting for gender, age, and season of baseline 25(OH) D sampling.

4. Discussion

4.1. Vitamin D and clinical symptoms

This is the first longitudinal study to assess the relationship between serum vitamin D at first presentation with psychosis and clinical state measures 12 months later. In our longitudinal analysis, we identified a significant inverse relationship between baseline serum vitamin D levels and both total psychotic symptoms, and negative symptoms of psychosis at 12 months follow up. This is the first report of an association between higher baseline vitamin D levels and improved clinical outcomes at one year. Further we conducted the largest cross sectional analysis of vitamin levels and clinical symptoms in FEP, in which we failed to identify a cross sectional relationship between depressive or psychotic symptoms and mean serum vitamin D levels or vitamin D deficiency, unlike earlier studies.

The lack of an association between vitamin D levels (both categorical and continuous) and negative symptoms of psychosis at baseline, but the identified association with negative symptoms at 12 months, raise the possibility that low vitamin D at onset of psychosis may be associated with the later emergence of negative symptoms. Like previous work in FEP, we failed to identify a cross sectional relationship between vitamin D levels and positive (Graham et al., 2015; Nerhus et al., 2015; Yee et al., 2016) or negative symptoms (Nerhus et al., 2015).

4.2. Vitamin D and negative symptoms

We identified that higher baseline vitamin D levels were associated with improved negative symptoms at 12 months follow up. Vitamin D is thought to be neuroprotective, with brain antioxidant properties, and anti-inflammatory effects, potentially improving negative symptoms secondary to unmitigated oxidative stress (Mitra et al., 2017; Nerhus et al., 2016; Wrzosek et al., 2013). There remains a significant unmet need in the management of negative symptoms, with no treatment having consistent replicated efficacy in treating negative symptoms. Though preliminary, our findings raise the prospect of benefits of optimising vitamin D levels in early psychosis and ameliorating negative symptoms of psychosis.

4.3. Vitamin D and cognitive function

Our exploratory study on the cross-sectional relationship of cognitive functioning and baseline vitamin D levels is likewise an important addition to earlier work. At unadjusted levels, the statistically significant neurocognitive test correlates were consistent with existing associations of decreased processing speeds, memory deficits and poor executive functioning in those with psychotic illness. However, we did not replicate the previously identified association between vitamin D and reduced verbal fluency in those with FEP (Graham et al., 2015; Nerhus et al., 2017). When adjusted, we demonstrated a statistically significant association between higher levels of vitamin D and improved nonverbal memory. A randomised trial (n = 82) investigating the effects of high dose vitamin D supplementation on cognition in healthy adults demonstrated significantly improved performance in nonverbal (visual) memory tasks with high dose vitamin D supplementation, more so than in

Table 3
Unadjusted and adjusted associations between baseline Vitamin D level (continuous variable) and mental state outcomes at follow up.

Mental state measures at follow up	Unadjusted				Adjusted			
	β	95%CI		p-Value	β	95%CI		p-Value
PANSS total	−0.26	−0.49	−0.03	0.03	−0.24	−0.47	−0.01	0.04
PANSS positive	−0.06	−0.14	0.03	0.21	−0.03	−0.13	0.06	0.50
PANSS Negative	−0.10	−0.21	0.00	0.06	−0.12	−0.23	−0.01	0.04
PANSS Psychopathology	−0.10	−0.23	0.03	0.14	−0.09	−0.23	0.06	0.23
GAF disability	0.27	−0.05	0.58	0.10	0.23	−0.12	0.59	0.20
GAF symptoms	0.12	−0.24	0.48	0.52	0.16	−0.28	0.60	0.92
Calgary total score	−0.07	−0.17	0.03	0.16	−0.08	−0.18	0.02	0.13
YMRS	0.02	−0.08	0.12	0.70	0.04	−0.08	0.16	0.48

β, beta coefficient; CI, confidence intervals.
Adjusted for gender, age, season of baseline vitamin D level and corresponding baseline psychopathology.

Table 4
Unadjusted and adjusted associations between baseline Vitamin D quartiles and mental state outcomes at follow up.

Mental state measures at follow up	Unadjusted				Adjusted			
	β	95%CI		p-Value	β	95%CI		p-Value
PANSS total								
19.05–67.9	–	–	–	–	–	–	–	–
11.3–19.04	4.31	−1.96	10.58	0.17	4.59	−1.79	10.96	0.16
7.05–11.2	2.43	−3.94	8.80	0.45	3.07	−2.78	8.93	0.30
4–7.04	3.71	−2.63	10.04	0.25	4.66	−2.28	11.60	0.18
PANSS positive								
19.05–67.9	–	–	–	–	–	–	–	–
11.3–19.04	0.90	−1.50	3.30	0.46	0.62	−1.73	2.98	0.60
7.05–11.2	−0.03	−2.35	2.29	0.98	−0.13	−2.64	2.37	0.92
4–7.04	1.08	−1.45	3.62	0.40	0.70	−1.91	3.32	0.59
PANSS negative								
19.05–67.9	–	–	–	–	–	–	–	–
11.3–19.04	1.58	−1.39	4.56	0.29	1.56	−1.25	4.36	0.27
7.05–11.2	1.40	−1.35	4.16	0.31	1.39	−1.55	4.34	0.35
4–7.04	1.92	−1.31	5.15	0.24	2.63	−0.74	5.99	0.12
PANSS psychopathology								
19.05–67.9	–	–	–	–	–	–	–	–
11.3–19.04	1.78	−1.69	5.24	0.31	2.14	−1.63	5.90	0.26
7.05–11.2	1.01	−2.98	5.00	0.61	1.65	−2.36	5.65	0.41
4–7.04	0.74	−2.74	4.22	0.67	1.08	−3.09	5.24	0.60
GAF disability								
19.05–67.9	–	–	–	–	–	–	–	–
11.3–19.04	−2.79	−11.34	5.77	0.52	−2.79	−11.97	6.40	0.55
7.05–11.2	−0.25	−9.01	8.51	0.96	0.59	−8.95	10.13	0.90
4–7.04	−4.82	−13.37	3.74	0.27	−5.03	−14.58	4.52	0.30
GAF symptoms								
19.05–67.9	–	–	–	–	–	–	–	–
11.3–19.04	−0.69	−10.45	9.08	0.89	−0.67	−10.31	8.96	0.89
7.05–11.2	1.18	−8.67	11.04	0.81	0.67	−9.39	10.74	0.89
4–7.04	−1.96	−10.96	7.03	0.67	−2.21	−12.62	8.20	0.67
Calgary total score								
19.05–67.9	–	–	–	–	–	–	–	–
11.3–19.04	1.13	−1.54	3.81	0.40	1.36	−1.40	4.11	0.33
7.05–11.2	−0.22	−2.99	2.56	0.88	−0.25	−3.38	2.89	0.88
4–7.04	1.87	−0.95	4.69	0.19	1.89	−1.20	4.97	0.22
YMRS								
19.05–67.9	–	–	–	–	–	–	–	–
11.3–19.04	2.06	−0.77	4.89	0.15	1.94	−1.58	5.46	0.27
7.05–11.2	−2.23	−5.16	0.70	0.13	−1.75	−5.00	1.50	0.28
4–7.04	−0.19	−3.65	3.26	0.91	−0.95	−4.40	2.50	0.58

β, beta coefficient; CI, confidence intervals.
Adjusted for gender, age, season of baseline vitamin D level and corresponding baseline psychopathology.

other cognitive domains (Pettersen, 2017). An RCT investigating he use of high dose oral vitamin D in people with schizophrenia treated with clozapine found that those treated with 14,000 IU of vitamin D (n = 24) had significantly improved delayed recall (memory) and attention scores, though this effect was lost after correcting for multiple comparisons compared to placebo treated cases (n = 23) (Krivoy et al., 2017). The identified association between 25(OH)D serum levels and nonverbal memory in our study replicates findings from previous general population observational studies (Darwish et al., 2015; Kuzma et al., 2016). It is postulated that the association reflects nonverbal memory's greater cognitive demand and dependence upon executive functioning (Pettersen, 2017).

4.4. Prevalence of vitamin D insufficiency/deficiency

We identified that 80% (n = 134) had suboptimal vitamin D levels (<20 ng/ml) at first contact for psychosis, a much higher proportion than the previously reported 50% (n = 10) with vitamin D levels < 30 ng/ml at FEP (Graham et al., 2015). We identified a mean vitamin D level of 13.8 ng/ml (n = 168) at study recruitment, much lower than the previously identified mean vitamin D levels in FEP of 28.2 ng/ml (n = 20) (Graham et al., 2015), 61.7 ng/ml (n = 31) (Yee et al., 2016) and 44.8 ng/ml (n = 71) (Nerhus et al., 2015). This finding may be a reflection of the ethnicity distribution of our sample.

4.5. Strengths and limitations

A major strength of this study is the prospective study design, allowing for inference to be made on the association between vitamin D and total and negative symptoms of psychosis. The association between higher vitamin D levels at onset with fewer total and negative psychotic symptoms one year later is suggestive of a possible casual association, and the longitudinal association reduces the likelihood of reverse causality as an explanation for the finding. However, as this is an exploratory study, we did not employ a strategy to account for multiple comparisons (Althouse, 2016; Rothman, 1990). Being a hypothesis driven exploratory study, we sought to limit the possibility of type II errors (incorrect confirmation of the null hypothesis), which multiple testing will increase while reducing the risk of type I errors. Further, as clinical symptoms are mutually correlated, the use of Bonferroni correction would not be appropriate as it assumes independence of the performed assessments (Bender and Lange, 2001). However, as an exploratory study, our findings require replication in large prospective cohorts. There are also several confounding factors that we did not control for, including antipsychotic adherence and measures of diet and physical activity. In established psychosis lower vitamin D levels are associated with less intense physical activity and reduced time spent outdoors (Lally et al., 2016). How this translates to FEP populations is not yet clear, and to the best of our knowledge has not been

investigated (Adamson et al., 2017). Further, we did not identify a significant difference in negative symptom scores between those with higher and lower vitamin D levels. The study lacked power to confidently detect potential real effects of findings of smaller statistically significant difference. Nevertheless, we report on the largest sample size of FEP patients with vitamin D data to date, with 168 people included compared to sample sizes ranging from 20 to 71 in earlier cross sectional studies (Graham et al., 2015; Nerhus et al., 2015; Yee et al., 2016).

5. Conclusion

Suboptimal vitamin D is highly prevalent in FEP, and remains so 12 months after first contact for psychosis. We found that higher baseline vitamin D levels were associated with fewer total and negative psychotic symptoms at one year after first contact for psychosis, suggesting that vitamin D may have relevance to the course of psychotic disorders. Randomised controlled trials to investigate the potential of vitamin D supplementation in ameliorating general outcomes, negative symptoms and cognitive impairment in early psychosis are called for.

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Declaration of interest

MDF has received honoraria for lectures from Janssen and Sunovian.

ASD has received honoraria from Janssen and Roche Pharmaceuticals.

RMM has received honoraria for lectures from Lundbeck, Otsuka, Janssen and Sunovian.

OH has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organised by. Astra-Zeneca, Autifony, BMS, Eli Lilly, Heptares, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand and Roche.

FG has received honoraria for advisory work and lectures or CME activity support from Roche, BMS, Lundbeck, Otsuka, Janssen and Sunovion, is a collaborator on a NHS Innovations project co-funded by Janssen and has a family member with professional links to Lilly and GSK, including shares.

All other authors (JL, OA, NS, PGS, BS, DS, SS) declare they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.08.011.

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