Schizophrenia Research 195 (2018) 513–518

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The relation of vitamin D, metabolic risk and negative symptom severity in people with psychotic disorders

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ARTICLE INFO

Article history:
Received 10 May 2017
Received in revised form 30 August 2017
Accepted 31 August 2017
Available online 18 September 2017

1. Introduction

People with psychotic disorders have an increased metabolic risk and their mean life expectancy is reduced with circa 28 years (Olfson et al., 2015).Predictors of this increased metabolic risk are genetic predisposition (Liu et al., 2013), lifestyle factors such as unhealthy diet, physical inactivity and smoking (Bobes et al., 2010), and the side effects of antipsychotic medication (Werner and Coveñas, 2014;Chadda et al., 2013). Low vitamin D status might also contribute to an increased metabolic risk (Ginde et al., 2009;Kendrick et al., 2009;Kilkkinen et al., 2009;Ford et al., 2009) and all-cause mortality by promoting atherosclerosis, hypertension, inflammation and activation of the renin-angiotensin system (Wang et al., 2012;Garland et al., 2014;Lee et al., 2008). Also, one review demonstrated cardiovascular mortality rates in the general population were higher during winter than in summer (Zittermann et al., 2005).

Vitamin D interacts with dopaminergic, cholinergic and noradrenergic neurotransmitter systems, which have all been implicated in experiencing psychotic symptoms (Eyles et al., 2013). When vitamin D is low, dopamine signalling in the brain appears to decrease (Eyles et al., 2013;Cui et al., 2015;Cui et al., 2013;Groves et al., 2014), which in its turn could lead to more severe negative symptoms of psychosis (Buchanan et al., 2007). Indeed, several studies found that vitamin D insufficiency was strongly associated with negative symptoms of psychosis (Graham et al., 2015;Yüksel et al., 2014;Cieslak et al., 2014;Ottesen Berg et al., 2010).

Vitamin D is thus associated with both metabolic risk and negative symptom severity. Negative symptoms have also been shown to interfere with patients' ability to be physically active and make healthy lifestyle choices, which can increase their metabolic risk (Bergqvist et al., 2013). Negative symptom severity may therefore mediate the association between low vitamin D and increased metabolic risk in people with a psychotic disorder.

Vitamin D is mostly produced in the skin by exposure to ultraviolet-B radiation in sunlight (Brown et al., 1999;Holick, 2007). Absorption of vitamin D and levels of circulation differ among individuals and can be influenced by determinants such as latitude, season, time of day, skin color (Holick et al., 2011), bodyweight, age, calcium intake (Zittermann et al., 2014), diet and genetics (Mazahery and von Hurst, 2015).

Vitamin D shows a natural fluctuation throughout the year, with vitamin D insufficiency more likely to occur during winter than in summer (Rosecrans and Dohnal, 2014). A recent study suggests seasonality may also affect clinical symptoms of schizophrenia, although the underlying mechanism is unknown (Byrne et al., 2015).

In this study we aim to investigate whether vitamin D levels are associated with metabolic risk in people with psychotic disorders and whether this effect was mediated by negative symptoms. We hypothesize that vitamin D levels may influence the severity of metabolic disturbances and negative symptoms. As vitamin D levels naturally fluctuate throughout the seasons (Rosecrans and Dohnal, 2014), we examine whether metabolic risk and negative symptom severity follow a similar seasonal fluctuation pattern. Furthermore, we investigate whether the

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http://dx.doi.org/10.1016/j.schres.2017.08.059
0920-9964/

severity of metabolic risk and negative symptoms differ between patients using and patients not using vitamin D supplementation. In this cross-sectional study, seasonal patterns and differences with regard to supplementation may indicate an interdependent and potentially causal connection between vitamin D, metabolic risk and negative symptom severity.

2. Materials and methods

2.1. Study design

All patients participated in the Pharmacotherapy Monitoring and Outcome Survey (PHAMOUS), an ongoing Dutch survey in four mental health institutions in the northern Netherlands, between 2012 and 2014 (Bruins et al., 2016). Mental and physical health of people with a psychotic disorder are yearly assessed for health evaluation purposes as part of regular clinical practice. PHAMOUS procedures are fully explained to participants, after which they are free to opt-out for the use of their anonymized data in the research database. The procedures are in accordance with the Declaration of Helsinki and local and international ethical standards, as confirmed by the ethical committee of the University Medical Center of Groningen, the Netherlands.

Inclusion criteria for the current study were: i) available laboratory test data of serum 25-hydroxyvitamin D (25(OH)D); ii) diagnosis of a psychotic disorder (i.e. schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, substance induced psychosis or psychosis NOS), iii) available outcome data of at least one of the MetS components (i.e. waist circumference, blood pressure [BP], high-density lipoprotein cholesterol [HLD-C], triglycerides and fasting glucose).

2.2. Measurements

Demographic information was collected with an interview. Patients' diagnostic information, use of antipsychotic medication and use of other medication (antihypertensive, lipid-lowering or antidiabetic) were also recorded and/or collected from their medical records. Antipsychotics were recorded as dosage in chlorpromazine equivalents (Gardner et al., 2010) for analyses that included psychotic symptom severity, and as high (olanzapine, clozapine), medium (risperidone, quetiapine, chlorprothixene, paliperidone, pipamperone, levemopromazine) and low in metabolic side effects (aripiprazole, haloperidol, bromperidol, flupentixol, pimozide, sulpiride, zuclopenthixol) for analyses that included metabolic risk (Leucht et al., 2013). When patients had no prescription for antipsychotics they were categorized as no metabolic side effects.

The Positive And Negative Syndrome Scale (PANSS) was used to assess the severity of psychotic symptoms (Kay et al., 1987). It consists of a Positive Symptom (e.g. delusions and hallucinations), Negative Symptom (e.g. blunted affect and social withdrawal) and General Psychopathology scale (e.g. mannerisms and unusual thought content). Each of the 30 items was scored on a 7-point Likert-scale: (1 means absent symptom and 7 severe). The PANSS Negative subscale was used in the analyses.

Waist circumference (in cm) was measured between the lower rib and the upper edge of the hipbone, using a flexible measuring tape. The tape was read at the end of a regular exhalation. Seated systolic and diastolic BP (SBP and DBP in mmHg) were measured twice with an interval of 15 sec using a manometer. The mean of the two measurements was reported.

A fasting blood sample was collected to determine HDL-C (mmol/l), triglycerides (mmol/l), fasting glucose (mmol/l), glycated hemoglobin (HbA_{1c} in %) and serum 25(OH)D (nmol/l) (Holick, 2007;Jones, 2012). When serum 25(OH)D was reported as <10, the outcome was set at 9.9 for analyzing purposes. Vitamin D insufficiency was defined as serum 25(OH)D < 50 nmol/l. Participants were asked to refrain from caloric intake for 8 h before their blood sample was collected. If patients had not fasted, this was noted on the lab form.

MetS was defined as the presence of three or more of the following NCEP-ATP-III criteria (Grundy et al., 2005): 1) waist circumference ≥ 88/102 cm (female/male); 2) BP ≥ 130/85 mmHg or being prescribed antihypertensives; 3) HDL-C < 1.30/1.03 mmol/l (female/male) or receiving lipid-lowering drugs; 4) triglycerides ≥1.7 mmol/l or receiving triglyceride-lowering drugs 3); 5) fasting glucose ≥ 6.1 mmol/l, being prescribed antidiabetics (Forouhi et al., 2006;WHO, 2006). When glucose levels were not available (2.0%, n = 36) or patients had not fasted (16.4%, n = 302), a previous diagnosis of diabetes mellitus (11.4%) or HbA_{1c} > 6.5% (reported in 78.4% of the patients without fasting glucose) were used as MetS criterion. Individual components were standardized and combined to create a continuous MetS variable as marker for metabolic risk (Eisenmann, 2008). Blood pressure was standardized using mean arterial pressure (MAP). Means and standard deviations of the patients ranging within healthy reference values were used to standardize HDL-C (1.1–2.0 mmol/l in female and 0.9–1.7 mmol/l in male patients), triglycerides (≤2.2 mmol/l) and fasting glucose (≤7.1 mmol/l) or HbA_{1c} (<8.0%) (Pekelharing et al., 2016). For patients with diabetes without available measure of fasting glucose or HbA_{1c}, a fasting glucose level of 7.1 (threshold for diabetes mellitus) was used for standardization. A clustered MetS *Z*-score was created by dividing the sum of all standardized components by five (Eisenmann, 2008), where HDL-C was reversed because higher scores represent a better outcome.

2.3. Statistical analysis

Values of serum 25(OH)D and the PANSS Negative subscale had a non-normal distribution and were log transformed to approach normality. Independent Sample *t*-tests and Chi^2 tests were used to examine baseline differences and distributions of subcategories between patients with and without vitamin D insufficiency.

Laboratories used either the liquid chromatography–mass spectrometry technique (LC-MS) or the Roche Diagnostic method to determine serum 25(OH)D. Differences in median and range of serum 25(OH)D between the LC-MS and Roche method were inspected. Differences in mean serum 25(OH)D were evaluated with an Independent Sample t-test and ANOVA, where each season of assessment was included as a covariate to check consistencies in the two measurement methods.

Individual associations between serum 25(OH)D (independent variable), PANSS Negative subscale (mediator) and MetS Z score (dependent variable) were examined using linear regression analysis. In the mediation model both serum 25(OH)D and PANSS Negative subscale were included as predictors of MetS Z score. The association models were corrected for age, gender, season of assessment and antipsychotic medication since they are considered confounders for the association of vitamin D and metabolic risk. In case the negative subscale is significantly associated with metabolic risk, corrected for vitamin D, the Sobel test will be used to test for an indirect effect of the of serum 25(OH)D on MetS *Z*-score (Sobel, 1982).

To examine whether metabolic risk and negative symptom severity follow the same seasonal trend as vitamin D, differences between seasons in mean serum 25(OH)D, PANSS Negative subscale, MetS Z-score and individual MetS components were examined using One-Way ANOVA with contrast analyses, using Bonferroni corrections for multiple testing. Independent Sample *t*-tests were used to examine differences in mean serum 25(OH)D, MetS Z-score and PANSS Negative subscale between patients with (15.4%, n = 284) and without (84.6%, n = 1556) vitamin D supplementation.

3. Results

Laboratory test data of serum 25(OH)D was present in 43% of all patients with PHAMOUS assessments between 2012 and 2014, leading to

the inclusion of 1840 patients in this study. Information on all five MetS components was present in 88.7% (n = 1632) of the patients, 6.7% (n = 124) had information on four risk factors and 4.6% (n = 84) had information on three risk factors or less. Scores on the PANSS Negative subscale were present for 62.7% (n = 1154) of the patients. Vitamin D levels peaked between July and September and were lowest between January and March. Seasons were therefore categorized as winter (January–March), spring (April–June), summer (July–September) and fall (October–December) (Rosecrans and Dohnal, 2014). An overview of baseline characteristics and differences between patients with and without vitamin D insufficiency is presented in Table 1.

Vitamin D was insufficient in 62.7% (n = 1154) of the overall sample and in 83% of the patients from African European descent. Patients with vitamin D insufficiency had higher scores on the MetS *Z*-score and PANSS Negative subscale and were more likely to take antihyperglycemic medication. Moreover, they were more often measured in winter or spring than in summer. Compared to patients with sufficient vitamin D, there was a higher prevalence of schizophrenia and a lower prevalence of schizoaffective- and delusional disorder as diagnosis among patients with insufficient vitamin D. Illness duration, illness severity and type of antipsychotic medication did not differ between patients with or without vitamin D insufficiency.

Patients measured with the LC-MS method (n = 136) had a lower mean (F = 5.75, p = 0.017), median, range and smaller standard deviation of serum 25(OH)D than patients measured with the Roche method (n = 406), see Supplementary Table 1. However, only 5.1% of the patients in the LC-MS method group were assessed during summer, as opposed to 36.0% of the patients in the Roche method group. After correcting for season of assessment, the adjusted mean serum 25(OH)D levels were not significantly different between the two methods (p = 0.231).

3.1. Associations between serum 25(OH)D, negative symptoms and MetS

Adjusted for covariates, logarithmic serum 25(OH)D was negatively associated with the MetS *Z*-score (B = −0.211, 95% CI = −0.309:−0.113, p < 0.001, n = 1494, with antipsychotics categorized by metabolic risk) and the logarithmic PANSS Negative subscale (B =

Table 1
Baseline characteristics and differences patients with and without vitamin D insufficiency.

	Total sample (n = 1840)	Vit D insufficiency (n = 1154)	No vit D insufficiency (n = 686)	Chi2/t	p
	%(n)/M(SD)	%(n)/M(SD)	%(n)/M(SD)		
Age	45.0 (11.8)	44.7 (11.9)	45.4 (n = 11.8)	−1.34	0.180
Gender (% male)	63.8 (n = 1174)	67.2 (n = 776)	58.0 (n = 398)	15.86	<0.001**
Ethnicity	(n = 1840)	(n = 1154)	(n = 686)		
Caucasian	88.0 (1620)	85.5 (n = 987)	92.3 (n = 633)	18.6	<0.001**
African European	4.1 (n = 75)	5.4 (n = 62)	1.9 (n = 13)	13.31	<0.001**
Other	7.9 (n = 145)	9.1 (n = 105)	5.8 (n = 40)	6.33	0.012*
Illness duration	17.7 (11.1)	17.6 (10.9)	17.8 (11.4)	−0.47	0.640
Diagnosis	(n = 1840)	(n = 1154)	(n = 686)		
Schizophrenia	66.2 (n = 1218)	69.2 (n = 799)	61.1 (n = 419)	12.80	<0.001**
Schizoaffective disorder	14.9 (n = 275)	12.8 (n = 148)	18.5 (n = 127)	10.95	0.001**
Schizophreniform disorder	2.1 (n = 38)	2.2 (n = 25)	1.9 (n = 13)	0.16	0.692
Delusional disorder	2.0 (n = 36)	1.4 (n = 16)	2.9 (n = 20)	5.24	0.022*
Substance induced psychosis	0.4 (n = 7)	0.2 (n = 2)	0.7 (n = 5)	3.50	0.061
Psychosis NOS	14.5 (n = 266)	14.2 (n = 164)	14.9 (n = 102)	0.15	0.698
Antipsychotic medication	(n = 1588)	(n = 1050)	(n = 634)		
Not using antipsychotics	13.7 (n = 252)	15.0 (n = 158)	14.8 (n = 94)	0	0.995
Low metabolic side-effects	21.6 (n = 398)	22.3 (n = 234)	25.9 (n = 164)	3.34	0.067
Medium metabolic side-effects	18.1 (n = 333)	19.4 (n = 204)	20.3 (n = 129)	0.37	0.544
High metabolic side-effects	38.1 (n = 701)	43.2 (n = 454)	39.0 (n = 247)	2.03	0.154
Chlorpromazine equivalent (mg)	334.1 (493.7)	336.0 (506.6)	330.9 (471.4)	0.21	0.831
Antihypertensive medication	13.9 (n = 255)	14.4 (n = 164)	13.5 (n = 91)	0.34	0.559
Lipid-lowering medication	13.3 (n = 245)	14.6 (n = 166)	11.7 (n = 79)	3.13	0.077
Antidiabetic medication	9.7 (n = 178)	11.6 (n = 132)	6.8 (n = 46)	11.13	0.001**
Serum 25 (OH)D	45.8 (27.4)	29.0 (11.1)	74.1 (23.1)	−56.30	<0.001**
Vitamin D supplements	15.4 (n = 284)	8.3 (n = 96)	27.4 (n = 188)	120.08	<0.001**
Clinical Chemical method	(n = 542)	(n = 310)	(n = 232)		
LC-MS method	7.4 (n = 136)	7.4 (n = 85)	7.4 (n = 51)	0	0.957
Roche Method	22.1 (n = 406)	19.5 (n = 225)	26.4 (n = 181)	11.87	0.001**
Seasons	(n = 1836)	(n = 1153)	(n = 683)		
Winter	28.0 (n = 515)	36.0 (n = 415)	14.6 (n = 100)	97.62	<0.001**
Spring	23.9 (n = 439)	27.2 (n = 314)	18.3 (n = 125)	19.13	<0.001**
Summer	24.0 (n = 442)	14.7 (n = 169)	40.0 (n = 273)	149.12	<0.001**
Fall	23.9 (n = 440)	22.1 (n = 255)	27.1 (n = 185)	5.61	0.018*
Z-score Metabolic syndrome					
Overall Z-score	0.29 (1.13)	0.39 (1.15)	0.13 (1.06)	4.49	<0.001**
Z-score waist circumference	0.00 (1.00)	0.08 (1.03)	−0.14 (0.92)	4.59	<0.001**
Z-score MAP	0.00 (1.00)	0.04 (1.04)	−0.07 (0.93)	2.17	0.030*
Z-score HDL-C (inversed)	−0.44 (2.40)	−0.35 (2.41)	−0.58 (2.38)	1.96	0.050
Z-score triglycerides	1.23 (2.82)	1.39 (2.83)	0.96 (2.78)	3.15	0.002**
Z-score fasting glucose	0.74 (2.44)	0.86 (2.55)	0.54 (2.22)	2.78	0.006**
PANSS scores					
Total score	51.9 (16.1)	52.2 (15.6)	51.4 (16.8)	0.74	0.460
Positive subscale	12.0 (4.8)	12.1 (4.8)	12.0 (4.7)	0.49	0.627
Negative subscale	14.3 (6.2)	14.7 (6.3)	13.6 (6.1)	2.93	0.003**
General Psychopathology scale	25.9 (7.9)	25.8 (7.6)	26.1 (8.4)	−0.57	0.569

M = mean. SD = standard deviation. N = number of patients. NOS = not otherwise specified.
MAP = mean arterial pressure. HDL-C = high-density lipoprotein cholesterol. PANSS = Positive and Negative Syndrome Scale.
* Significant at 0.05 level.
** Significant at 0.01 level.

−0.073, 95% CI = −0.114:-0.032, p < 0.001, n = 1154, antipsychotics in chlorpromazine equivalents). The logarithmic PANSS Negative subscale was not significantly associated with the MetS *Z*-score (B = 0.127, 95% CI = −0.035:0.290, p = 0.125, n = 1054, unadjusted for covariates). Therefore, the logarithmic PANSS Negative subscale did not mediate the association between logarithmic serum 25(OH)D and the MetS Z-score and there was no need for using a Sobel test on an indirect effect of serum 25(OH)D on MetS Z-score.

3.2. Seasonal differences

Serum 25(OH)D levels were significantly different in all seasons; they were lowest during the winter (n = 515) and highest during summer (n = 442) (see Table 2 and Fig. 1). Vitamin D insufficiency was prevalent in 80.6% (n = 415) of the patients measured during winter, in 71.5% (n = 314) of the patients measured in spring, in 38.2% (n = 169) of the patients measured during summer and in 58.0% (n = 255) of the patients measured in fall. Compared to winter, negative symptoms were significantly less severe during the spring (p = 0.023) and fall (p = 0.002). There were no significant differences in MetS *Z*-score between the seasons, but waist circumference was larger during winter than in summer (p = 0.003) and fall (p = 0.017). Also, compared to spring, HDL-C was significantly lower in summer (p = 0.019) and fall (p = 0.017). After Bonferroni correction, the differences between negative symptom severity in winter and fall (p = 0.012), waist circumference in winter and summer (p = 0.017) and HDL-C in spring and summer (p = 0.045) remained significant.

3.3. Vitamin D supplementation

Patients using vitamin D supplementation had significantly higher serum 25(OH)D levels (mean difference = 22 nmol/l, $t = 11.60$, p < 0.001) than patients not using supplementation. Mean serum 25(OH)D levels of patients using supplementation fluctuated throughout the seasons (F = 3.46, p = 0.017), but were never <50 nmol/l (insufficient), nor >75 nmol/l (threshold for optimal vitamin D, see Table 2). There were no significant differences in logarithmic PANSS Negative subscale scores ($t = 0.37$, p = 0.710, n = 1154) or MetS *Z*-scores ($t = -1.00$, p = 0.317, n = 1631) between patients with and without supplementation.

3.4. Posthoc analyses

The prevalence of vitamin D insufficiency was different between people with schizophrenia, schizoaffective- and delusional disorders. We examined the possibility that the type of diagnosis influenced the association between negative symptoms and vitamin D. We repeated the linear regression analysis and included diagnosis of schizophrenia, schizoaffective- and delusional disorders as additional, dichotomous covariates. The association between logarithmic serum 25(OH)D and the logarithmic PANSS Negative subscale remained significant (B = −0.055, 95% CI = −0.093:−0.017, p = 0.005). Only a diagnosis of schizophrenia was of significant influence (B = 0.17, p < 0.001).

Similarly, the use of antidiabetic medication differed between patients with and without vitamin D insufficiency, which could influence the association between vitamin D and metabolic risk. The repeated linear regression analysis showed a significant contribution of antidiabetic medication as additional covariate (B = 1.20, p < 0.001), but the association of logarithmic serum 25(OH)D with the MetS *Z*-score remained statistically significant (−0.154, 95% CI = −0.241:−0.066, p = 0.001).

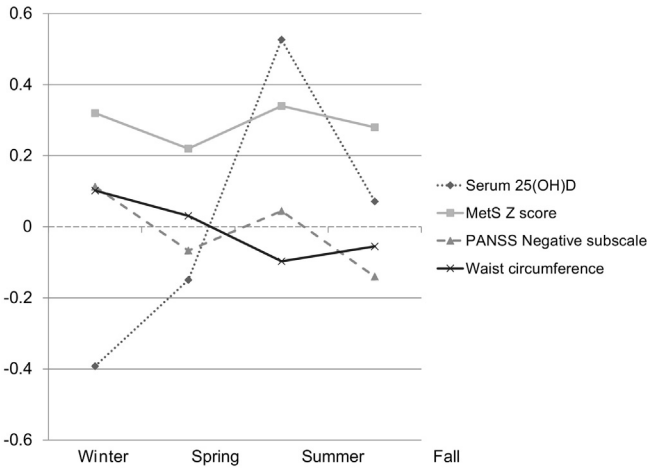

Fig. 1. Seasonal pattern of vitamin D, negative symptoms, metabolic risk and waist circumference.

4. Discussion

The prevalence of vitamin D insufficiency in this study (62.7%) is comparable to the prevalence found in a large review of people with schizophrenia (65.3%(Valipour et al., 2014) and much higher than in the general Dutch adult population (40%, (Verkaik-Kloosterman et al., 2011)). Vitamin D insufficiency was associated with increased metabolic risk, which is consistent with findings in the general population (Geleijnse, 2011;Jorde and Grimnes, 2011;Saneei et al., 2013;Scragg et al., 2007;Scragg et al., 2004). This study also supports previous findings with regard to the inverse relation between vitamin D and negative symptoms (Graham et al., 2015;Yüksel et al., 2014;Cieslak et al., 2014;Ottesen Berg et al., 2010). However, the association between vitamin D and metabolic risk was not mediated by negative symptoms. Therefore, other factors than negative symptom severity may be of greater importance in the complex relation between vitamin D and

Table 2
Differences in mean serum 25(OH)D, PANSS-N and metabolic syndrome Z-score throughout the seasons.

	Winter	Spring	Summer	Fall		
	M (SD)	M (SD)	M (SD)	M (SD)	F	p
Serum 25(OH)D nmol/l	35.0 (22.8)	41.7 (23.6)	60.2 (28.9)	47.7 (27.6)	80.69	<0.001**
Serum 25(OH)D nmol/l (with suppl.)	61.7 (33.9)	56.6 (32.2)	73.4 (26.8)	64.6 (33.1)	3.46	0.017*
PANSS Negative subscale	15.0 (6.3)	13.8 (5.9)	14.5 (6.8)	13.4 (6.0)	3.8	0.010*
Z-score metabolic syndrome	0.32 (1.2)	0.22 (1.1)	0.34 (1.1)	0.28 (1.2)	0.83	0.475
Waist circumference (cm)	103.7 (16.9)	102.5 (15.4)	100.6 (14.5)	101.2 (15.8)	3.57	0.014*
MAP	97.9 (13.3)	98.3 (12.9)	96.9 (12.2)	98.4 (12.8)	1.29	0.278
HDL-C (mmol/l)	1.31 (0.65)	1.38 (0.86)	1.26 (0.61)	1.26 (0.44)	2.99	0.030*
Triglycerides (mmol/l)	1.81 (1.23)	1.86 (1.17)	1.92 (1.42)	1.85 (1.35)	0.45	0.717
Fasting glucose (mmo/l)	6.09 (1.73)	6.02 (1.62)	5.91 (1.41)	5.89 (1.72)	1.35	0.256

M = mean. SD = standard deviation. PANSS = positive and negative syndrome scale.
MAP = mean arterial pressure. HDL-C = high-density lipoprotein-cholesterol.
* Significant at 0.05 level.
** Significant at 0.01 level.

metabolic risk. Recent animal studies for example, suggested vitamin D insufficiency to exacerbate the metabolic side effects of antipsychotic medication and vitamin D supplementation to prevent antipsychotic-induced metabolic risk (Dang et al., 2015;Nagashima et al., 2016). Indeed, antipsychotic drugs can contribute to patients' increased metabolic risk and may also aggravate negative symptoms by their sedative and subjective side-effects (Werner and Coveñas, 2014;Chadda et al., 2013;Bushe et al., 2013). This in turn may prohibit patients from being physically active and from making healthy lifestyle choices, thereby further contributing to patients' increased metabolic risk (Bergqvist et al., 2013). Along the same line, sedative side effects can limit sun exposure by preventing patients from actively going outside, thus affecting vitamin D production in the body. As the majority of the patients in our sample is using antipsychotics, this could partially explain our findings of overall increased metabolic risk and low vitamin D status. Also, it has been suggested that vitamin D insufficiency may not have a disease- or organ-specific impact, but that it is a marker of general morbidity (Meems et al., 2015).

Serum 25(OH)D levels fluctuated throughout the seasons, while negative symptom severity and metabolic risk did not show the same seasonal fluctuation. Waist circumference was smaller in summer than winter, the inverse of vitamin D. Such differences might be explained by increased physical activity and time spent outside on days with more sunshine and higher temperatures, affecting both vitamin D production and metabolic risk (O'Connell et al., 2014;Witham et al., 2013). The other risk factors did not show a similar seasonal trend in our study, which does not support the hypothesis of a causal relation between vitamin D and other metabolic risk factors. Indeed, a recent study found that increased levels of outdoor recreational activity lowered cardiovascular mortality, but this relation was not substantially influenced by vitamin D (Donneyong et al., 2016). Negative symptoms did show a seasonal pattern, partially mimicking the fluctuation trend in vitamin D levels, but the differential severity over seasons was too small to be considered clinically relevant. To the best of our knowledge, previous studies have concentrated on psychotic symptom severity in relation to season of birth (Córdova-Palomera et al., 2015), but no studies to date examined seasonal variations in psychotic symptom severity.

Although not designed as a clinical trial, this study did demonstrate that patients using supplementation had serum 25(OH)D levels above the cut-off for vitamin D insufficiency in all seasons as expected. However, mean vitamin D never reached the optimal serum 25(OH)D levels of at least 75 nmol/l (Holick, 2007;SACN (Scientific Advisory Committee on Nutrition), 2007;Bischoff-Ferrari et al., 2006). We found no differences in negative symptom severity or metabolic risk between patients with and without supplementation, which is in line with multiple randomized controlled trials that have found little or no effect of supplementation of vitamin D on metabolic risk in the general population (Geleijnse, 2011;Challoumas, 2014;Jorde and Figenschau, 2009;Pittas et al., 2007).

People with a diagnosis of schizophrenia more often had insufficient vitamin D, whereas people with a diagnosis of schizoaffective- or delusional disorder more often had sufficient vitamin D levels. This finding is in contrast with current literature, where the relation of vitamin D are either discussed in general without separating different diagnoses (Adamson et al., 2017) or where no differences between diagnoses are found (Boerman et al., 2016;Grønli et al., 2014), and most likely attributable to season of assessment.

4.1. Strengths and limitations

The PHAMOUS cohort enabled us to examine vitamin D levels and their association with metabolic risk and negative symptom severity in a large sample of people with psychotic disorders in a real world setting. Although the design was cross-sectional, the large number of patients allowed for examination of differences in vitamin D levels, metabolic risk and negative symptom severity between seasons and between patients with and without supplementation. This gave us an indication of the directionality of the associations between vitamin D levels, metabolic risk and negative symptom severity.

An important limitation of this study is the fact that one third of the patients had missing data on the PANSS Negative subscale and that the prevalence of the MetS was lower in these patients (44% in patients without PANSS scores vs. 53% in patients with PANSS scores, $p = 0.001$). This limitation may be a potential bias in our sample, as it may have influenced our findings on the relation between negative symptom severity and metabolic risk. However, as serum 25(OH)D levels were not significantly different between patients with or without PANSS data ($M = 45.8$ vs. $M = 45.7$, $p = 0.948$), we were able to adequately examine the relation between negative symptom severity and vitamin D levels.

Another limitation was the lack of information regarding certain other factors that could have influenced the relation between vitamin D and metabolic risk. Physical activity, dietary intake and the amount of sun exposure may play a moderating role in the association between vitamin D and metabolic risk, but these factors were not properly assessed in the PHAMOUS cohort.

4.2. Conclusion

Although the nature of this study does not allow to speculate about potential causality, our study does emphasize the complexity of the relation between vitamin D and metabolic risk in people with psychotic disorders. Longitudinal research focusing on the role of antipsychotics, clinical features such as apathy and a poor lifestyle in general, with detailed information about sun exposure, physical activity and dietary intake, may be able to provide answers.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.08.059.

Funding/support

This study is supported by investments of the mental health institutions participating in the Rob Giel Research center: GGZ Friesland Mental Health Organization, Lentis Mental Health Organization, GGZ Drenthe Mental Health Organization, Mediant, Dimence Groep, and the University Center for Psychiatry at the University Medical Center Groningen.

Contributors

JB, FJ, GMHP and RB have designed the study and JB has written the manuscript. EC and FAJM provided expertise on metabolic risk and vitamin D and worked in close collaboration with JB. ERH contributed to the analysis plan.

Conflict of interest

The authors report no conflict of interest.

Acknowledgements

We thank Dr. A. Stellinga for her efforts to have a vitamin D measure included in the PHAMOUS screenings and her assistance in the early stages of preparing this manuscript.

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