

Low vitamin d serum level increases symptoms severity in schizophrenic patients measured by Positive and Negative Symptoms Scale (PANSS) in Batak Tribe Sumatera Utara, Medan-Indonesia



Novi Prasanty,^{1*} Mustafa Mahmud Amin,² Elmeida Effendy,² Muhammad Joesoef Simbolon^{2,3}

ABSTRACT

Background: Schizophrenia is the most common psychotic disorder found in population. It is a severe form of psychotic disorders and tends to be chronic. Nearly 1% people suffer from schizophrenia. It has been proved that vitamin D plays crucial roles in neuroprotection and neurodevelopment, therefore low levels are commonly associated with schizophrenia.

Methods: A total of 54 schizophrenic patients, Batak tribe, male, and female are diagnosed with semistructured MINI ICD-X. A Positive and Negative Syndrome Scale (PANSS) was used to evaluate disease activity and serum vitamin D level was measured using ELFA. Regression linear

was used to analyze the relationship between serum vitamin D level and disease's symptom.

Results: There was a negative correlation between serum levels of vitamin D and the PANSS score in schizophrenic patients with $r = -0.686$ ($p < 0.001$) for positive PANSS score, $r = -0.773$ ($p < 0.001$) for negative PANSS score, $r = -0.448$ ($p < 0.001$) for general psychopathology, and $r = -0.631$ ($p < 0.001$) for total PANSS score.

Conclusion: There was a negative correlation between serum vitamin D levels and the total score of PANSS, the lower the serum levels of vitamin D, the higher the total score of the PANSS.

Keywords: PANSS, Schizophrenia, Serum Vitamin D levels, symptoms

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BACKGROUND

Schizophrenia is a chronic mental disorder consists of heterogenous symptoms and cognitive impairment. Based on epidemiological data, imaging, and post-mortem analysis, a hypothesis of neurological and dopamine development has become the main theory of schizophrenia. Another theory stated that genetic factors or environmental effect in the early phase of life and lack of brain development will bring negative impacts toward mental health as adults.¹

Vitamin D is widely known for their role in calcium and bone hemostasis, cell proliferation, and the modulation of parathyroid hormone secretion. Another evidence shows that vitamin D and their receptors play an important part in brain, such as nerve protection and immunity modulation. Vitamin D also maintain anti proliferation activity that acts as an important regulator from brain cell proliferation and differentiation, which is involved in brain development.^{2,3}

During perinatal period, vitamin D deficiency has been thought to improve the risk of schizophrenia. The development of vitamin D deficiency hypothesis came from the observation that there

is an increase of risk in individu born in winter, spring, live far away from the equator, and towards them who stayed in urbanization or ruralization area. These areas are known to be less exposed to sunlight, thereby reducing production of vitamin D.⁴

Many have suggested that there is a positive correlation between levels of vitamin D deficiency and the severity of schizophrenia on adults, although it's just newly studied. It has been found that schizophrenic patients have less vitamin D level compared to healthy people or people with depression. In another data, it is also found that teenager patients with 3.5 times lower vitamin D level than normal have more psychotic features.⁵ A 25 – ODH3 deficiency on adolescence has 3 times more risk to develop psychotic features, which adjusted with race, Body Mass Index (BMI), society living in city or rural, and seasonal change.²

Vitamin D is also said to cause negative symptoms and worsen cognitive features. A retrospective study done in Finland-born group found that vitamin D3 supplement which given in the first year of life is able to decrease the risk of schizophrenic as

¹Residence of Psychiatry, Faculty of Medicine, Universitas Sumatera Utara, Medan-Indonesia.

²Department of Psychiatry, Faculty of Medicine, Universitas Sumatera Utara, Medan-Indonesia.

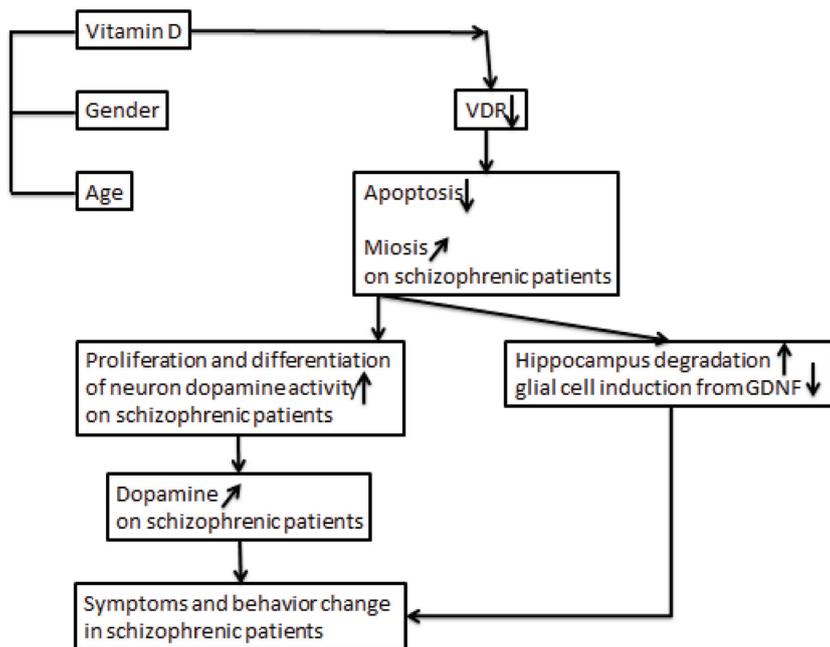
³Department of Psychiatry, Faculty of Medicine, Universitas Islam Sumatera Utara, Medan-Indonesia.

*Correspondence to: Novi Prasanty, Residence of Psychiatry, Faculty of Medicine, Universitas Sumatera Utara, Medan-Indonesia
novijalobet@gmail.com

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much as 77% on male. Another study shows that neonates with low 25 – ODH3 level is significantly linked with schizophrenia in Denmark population. Vitamin D not only play their part as external risk factor, but also affect many gene expressions as internal factors.²

METHODS

A total of 54 Batak tribe patients are diagnosed with schizophrenia using *Pedoman Penggolongan dan Diagnosis Gangguan Jiwa di Indonesia edisi III* (PPDGJ III) criteria. These patients are all in outpatient care of Prof. M. Ildrem Mental Hospital, ranged from 15 – 50 years old, in acute phase of treatment, and have received Risperidone 4mg/day as treatment for ≤ 8 weeks. The inclusion criterias for this study are not in menstruating condition, pregnant or breast-feeding, and not consuming vitamin or supplements. The exclusion criterias are having general medical condition history, comorbid with another psychotic disorders, and in an anxious condition. All patients are given the same sunlight exposure within 30 minutes between 10.00 – 13.00 Western Indonesian Time (peak sunlight exposure in Western Sumatra).

Symptoms severity is measured with PANSS. Confounding factors such as gender, age, tribe, sunlight exposure, medicine, and body mass index (BMI) have been controlled.

RESULTS

In table 1 of the demographic characteristics obtained that more male research subjects was found with 36 (65.5%) than female with 19 subjects (34.5%). The average age on male subjects is 31.167 ± 8.241 and 29.684 ± 5.478 on female subjects and there is no significant difference found (p = 0.430). Most education group found is Primary School in both male and female (p = 0.430).

Most marital status found is not married in male as much as 22 (61.1%) and married in female 11 (57.9%), but there is no significant difference between the two groups (p = 0.289). Average BMI is 23.317±1.132 for male and 23.612±1.203 for female with no significant difference between the two groups (p = 0.382). Both general PANSS psychopathology and PANSS total score on male and female have significant difference with (p = 0.001) and (p = 0.038) each.

Serum Vitamin D Levels

Average serum vitamin D levels on male subjects is 23.639 (4.990) and 18.300 (3.877) on female subjects, there is significant difference between male and female serum levels (p = 0.001, p < 0.05).

Table 1 Characteristics of Subjects

Variable	Male (n = 36)	Female (n = 19)	P
Age	31.167+8.241	29.684+5.478	0.430 ^a
Education			
Primary School	17 (65.4%)	9 (34.6%)	0.430 ^b
Junior High School	15 (68.2%)	7 (31.8%)	
Senior High School	4 (57.1%)	3 (42.9%)	
Occupation			
Working	10 (27.8%)	7 (41.2%)	0.700 ^c
Not Working	26 (72.2%)	12 (63.2%)	
Marital Status			
Married	14 (38.9%)	11 (57.9%)	0.289 ^c
Not Married	22 (61.1%)	8 (42.1%)	
BMI	23.317+1.132	23.612+1.203	0.382 ^a
PANSS			
Positive	30.861+1.944	30.579+2.194	0.654 ^b
Negative	21.611+2.346	22+2.517	0.719 ^b
General Psychopathology	37.111+1.801	33.790+1.134	0.001 ^b
Total Score	89.523+5.448	86.368+5.469	0.038 ^b

t-Independent test (p<0.05)
 b. Mann Whitney test U (p<0.05)
 c. Chi Square test (p<0.05)

Table 2 Serum vitamin D levels

	Average (SD)	p
Male	23.639 (4.990)	0.001
Female	18.400 (3.877)	

Table 3 Linear Regression Vitamin D Serum Level and Positive PANSS Score

	Constant	Coefficient	R ²	r	P
Vitamin D	36.528	-0.264	0.460	-0.686	0.001

Table 4 Linear Regression Vitamin D Serum Level and Negative PANSS Score

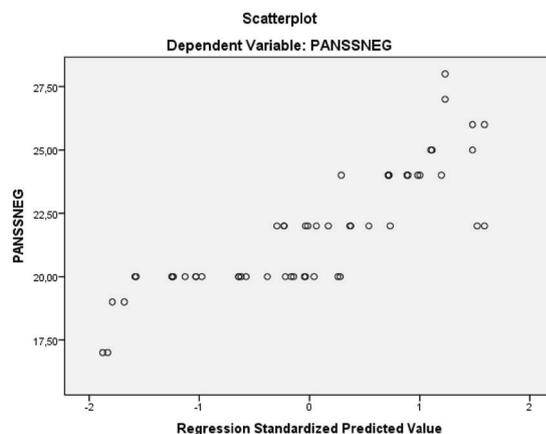
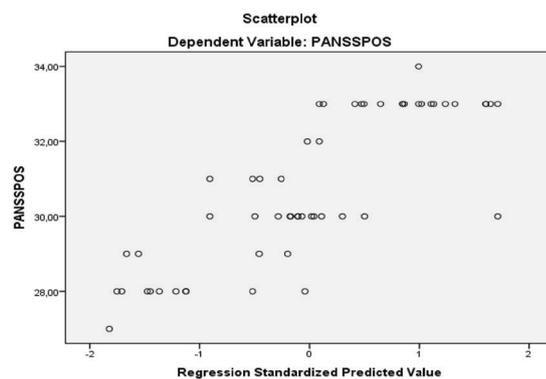
	Constant	Coefficient	R ²	r	P
Vitamin D	29.435	-0.352	0.589	-0.773	0.001

Table 5 Linear Regression Vitamin D Serum Level and General PANSS Psychopathology Score

	Constant	Coefficient	R ²	r	p
	et al.		0.642		0.001
Vitamin D		-0.193		-0.448	

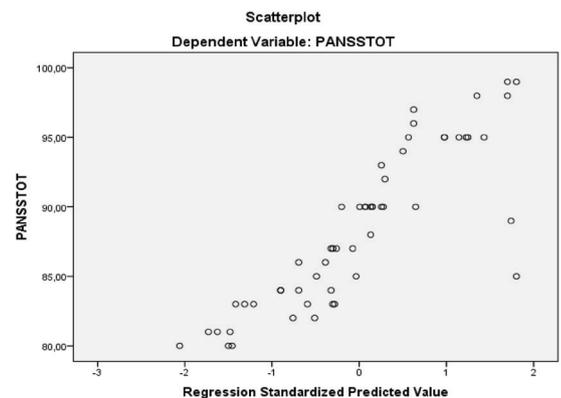
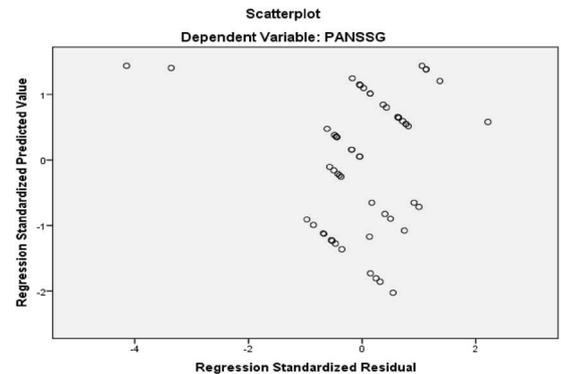
Table 6 Linear Regression Vitamin D Serum Level and PANSS Total Score

	Constant	Coefficient	R ²	r	p
	113.085		0.730		0.001
Vitamin D		-0.997		-0.631	



From table 3, it is found that there is a strong relationship from the result of linear regression analysis between vitamin D serum level and positive PANSS score with r value = 0.686 ($p < 0.001$) and $R^2 = 46\%$ with Positive PANSS Score = 27.903 – 0.264 vitamin D serum level.

From table 4, it is found that there is strong relationship from the result of linear regression analysis between vitamin D serum level and negative



PANSS score with r value = 0.773 ($p < 0.001$) and $R^2 = 58.9\%$ with Positive PANSS Score = 29.435 – 0.352 vitamin D serum level.

From table 5, it is found that there is a relationship between from linear regression analysis of vitamin D serum level and general PANSS psychopathology score with $r = -0.448$ ($p < 0.001$).

From table 5, it is found that there is a relationship between from linear regression analysis of vitamin D serum level and PANSS total score with $r = -0.631$ ($p < 0.001$).

DISCUSSION

In this study, we found negative correlation between serum vitamin D levels and positive PANSS score ($r = -0.686$, $p = 0.001$). Correlation between serum vitamin D levels and negative PANSS score in the study with $r = -0.773$ ($p = 0.001$). Correlation between serum vitamin D levels and total PANSS score with $r = -0.631$ ($p = 0.001$), this shows that there is a significant correlation between serum vitamin D levels and negative PANSS score, positive PANSS score, and also total PANSS score with negative correlation direction and strong correlation. Correlation between serum vitamin D levels and general psychopathology PANSS score obtained with $r = -0.448$ ($p = 0.001$), this shows that there is a significant correlation between vitamin D serum and general psychopathology PANSS score with negative correlation and medium correlation. The

higher serum vitamin D levels, the lower PANSS score in schizophrenic patients become.

A similar result was shown in a study conducted by Rabia et al. who found correlation between serum vitamin D levels and positive, negative, general psychopathology, and total PANSS score.⁶ Another study conducted by Kristina et al. also found correlation between serum vitamin D levels and positive and negative PANSS score.⁷

In contrast, a study conducted by Dganit et al. found there was no significant correlation found between serum vitamin D levels and positive, negative, general psychopathology, and total PANSS score.⁸ The same case occur with a study conducted by Laily et al showing that there is a negative correlation between serum vitamin D levels and positive, negative, and total PANSS score on psychotic patients, but the p value was not significant.⁹

Another study conducted by Hadded et al also shown that there was no significant differences between average positive, negative, general psychopathology, and total PANSS score on serum vitamin D levels < 25 nmol/L and serum vitamin D levels > 25nmol/L ($p = 0.55$), ($p = 0.748$), ($p = 0.422$), ($p = 0.32$).¹⁰

Morover, a study conducted by Suheyla et al about the relationship between serum vitamin D levels and positive and negative symptom score mean measured with *Scale for the Assessment of Positive Symptoms (SAPS)*, found a significant difference for each serum vitamin D levels categories. The study divided the serum vitamin D level into three categories, deficiency (10ng/mL), insufficiency (10-20ng/mL) and sufficiency (>20ng/mL) with $p = 0.015$ for positive symptom and $p = 0.019$ for negative symptoms.

Based on multivariate linear regression analysis, a strong relationship between positive, negative, general psychopathology, and total PANSS score and serum vitamin D levels was found. For every 1 ng/mL increase in serum vitamin D levels, it will decrease positive PANSS score as much as 0.264 ($p = 0.001$); negative PANSS score as much as 0.352 ($p = 0.001$), general psychopathology PANSS score as much as 0.193 ($p = 0.001$), and total PANSS as much as 0.997 ($p = 0.001$).

Another study conducted by Graham et al on the first episode of schizophrenic concluded that the relationship between serum vitamin D levels and positive PANSS score has $R^2 = 13.9\%$ with $p = 0.20$, relationship between vitamin D and negative PANSS score has $R^2=14.8\%$ with $p =0.04$, and relationship between vitamin D serum levels and PANSS total score has $R^2=18.4\%$ with $p = 0.06$.⁵

The same study conducted by Jie Yin Yee et al looking at the relationship between serum vitamin

D levels and positive and negative PANSS score on the first episode of psychotic while controlling the gender, tribe, and length of illness without medication. The study found that R^2 value for positive PANSS score is 14.3% and R^2 value is 26.4% for negative PANSS score.¹²

From this study, we concluded that serum vitamin D levels affect each positive and negative symptom in schizophrenic patients. This was in line with several studies that have assessed serum vitamin D levels and each symptom of schizophrenic patients. Not only did it has an effect on each symptom, but vitamin D also gave an overview of metabolic problems from schizophrenic patients, related to medication. Low serum vitamin D levels as a newborn change the brain function and hippocampus volume, therefore it can predict any risk that triggers schizophrenia in babies. Vitamin D is also related to inflammation process of schizophrenic people.^{13,14,15}

In a normal condition, dopamine will be metabolized into dihydroxyphenylacetic acid (DOPAC) using inter nerve oxidative deamination with Monoamine Oxidase (MAO) as a by-product. Dopaminergic neurotransmissions are reduced in the ventral striatum, increased in the associative striatum, and reduced once more in the dorsolateral prefrontal cortex. Catechol-O-Methyl Transferase (COMT) is closely related to schizophrenia, especially those who consumed marijuana. Low serum vitamin D levels can cause COMT to decrease in frontal brain regulation and reduce Homovallinic Acid (HVA) concentration as an active marker of dopamine. Decreased levels of HVA in the pre-frontal cortex has been associated with poor work memory in schizophrenia.^{1,2}

Formulating the discovery of vitamin D receptors (VDRs) in neuron and glial cell, some studies have shown that vitamin D were critically important in the early stages of brain development and optimal brain function. In brain development, VDRs are associated with increased apoptosis and decreased mitosis. Thus, both in cellular levels and transcription, vitamin D plays a part in proliferation and death of brain cell. Structure and proliferation caused by vitamin D deficiency will be associated with abnormal neurochemistry and behavior in adults.^{1,16}

In vitamin D deficiency, a few histological changes in the dentate gyrus, hypothalamus, basal ganglia, amygdala, and cingulate gyrus can be seen. Vitamin D consistently initiates neuron differentiation in the hippocampus, decreases mitosis, and increases neuron growth factor (NGF) thus enabling the creation of axons and dendrites. Vitamin D neurotrophin factor affect NGF through

multiple pathways, for example, glial cell pathway through neurotrophic factor glial-cell derived neurotrophic factor (GDNF), synthesis of neurotrophin 3 (NT3) that decrease neurotrophin 4 (NT4) levels, neuroimmunomodulation, and glutamatergic effect.^{2,16}

When vitamin D deficiency happens before birth, NGF levels would fall 17% and GDNF would fall 25% at birth. Unlike GDNF, NGF would stay low after birth even after administration of vitamin D supplement. NGF is known to have trophic action on cholinergic neurons from the frontal brain that projected to the hippocampus, meanwhile, GDNF acts on dopaminergic neurons from basal ganglia. GDNF also control the apoptosis of dopaminergic neuron from grey matter at postnatal.²

Vitamin D affects dopamine differentiation and innervation through VDR expression. It can be found in neuro epithelium which coincide with monoamine cell peak in grey matter, hence the presence of VDR in the mesencephalon on peak period of dopamin neuron differentiation can evoke a consistent change. The absence of vitamin D is able to increase proliferation and differentiation of delayed dopamine neuron activity levels. In addition, evidence continues to demonstrate vitamin D in a positive way that is to increase GDNF levels in the mesencephalon. GDNF is an important factor that involved in survivability and function of dopamine neuron that can change dopaminergic area as the contributive factor toward adult behavior.¹

The association of dopamine and glutamate, which explains in terms of N-methyl-D-aspartate (NMDA) transmission reduction in the prefrontal cortex, appears to decrease dopamine transmission in mesocorticolimbic, thus exacerbates cognitive function. If this condition continue, it can lead to positive symptoms. Therefore, dopaminergic dysfunction has been suspected to be caused by abnormal glutamatergic transmission.²

Reduced NMDA transmission may cause both excessive cortical deficit and associative striatum dopamine. Otherwise, this dopamine abnormality deteriorate glutamatergic function and synaptic connectivity. The most important D1 receptor activity facilitates glutamatergic transmission, while D2 decreases it. Therefore, D1 modulation may arise as a new pharmacology target. Although the relationship between glutamate and vitamin D has not been found yet, the role of glutamate in schizophrenia cannot be ignored. Another theory mentions that an increasing amount GABA receptors has been found in the prefrontal cortex and the cingulate anterior cortex consistently in schizophrenic patients. Once a mother is having vitamin D deficient, the GABA levels are continuously dropped.²

A monozygotic twin experiment for schizophrenia showed bigger ventricle, and thinner cortex in anterior cingulate, posterior cingulate, perigenual, and medial occipital on the brain. Anterior cingulate cortex has an important part in compassion, motivation, attention, and selection response, which is the cognitive function in schizophrenic patients. Furthermore, vitamin D has been proven to have a role in hippocampus cell, specifically in smaller hippocampus volume and amygdala, thus neurons change and reduce functional activity and gene function.^{2,16}

Serum vitamin D levels are affected by sunlight exposure, nutritional factor, skin color, tribe, season, residential area, activity, and smoking habit. However, from the previous study, there was a slight difference regarding factors that may affect serum vitamin D levels. A study conducted by Dganit et al examining sunlight exposure intensity towards patients and nutritional or food uniformity consumed by schizophrenic patients found that there was no significant relationship between those factor and serum vitamin D levels.⁸

CONCLUSION

There is a correlation between serum vitamin D levels with symptoms' severity in schizophrenic patients. The higher serum vitamin D levels, the lower PANSS score in schizophrenic patients.

LIMITATION

Since this was a cross sectional study conducted in outpatient care, we could not control a few cofounding factors such as diet of the subjects, skin color, and residential area.

BIBLIOGRAPHY

1. Kesby JP, Cui Xiaoying, Burne THJ, Eyles DW, Altered Dopamine Ontogeny in The Developmentally Vitamin D Deficient Rat and Its Relevance to Schizophrenia. *Frontiers in Cellular Neuroscience*. 2013; Vol. 7. Article 111: p. 1-12.
2. Amaral AD, Calhau C, Coelho R, Schizophrenia : Implications of Vitamin D Deficit on Brain Development. *International Journal of Clinical Neurosciences and Mental Health*. 2014; Vol. 1. No. 16: p. 1-14.
3. Stewart A, Wong K, Cachat J, Elegante M, Gilder T, Mohnot S, et al, Neurosteroid Vitamin D System as a Nontraditional Drug Target in Neuropsychopharmacology. *ResearchGate Behavioural Pharmacology*. 2010; 21: p. 420-426.
4. Schoenrock SA, Tarantino RM, Developmental Vitamin D Deficiency and Schizophrenia : The Role of Animal Models. *John Wiley and Sons Ltd and International Behavioural and Neural Genetics Society*. 2016; 15: p. 45-61.
5. Graham KA, Keefe RS, Lieberman JA, Calikoglu AS, Lansing KM, Perkins DO. Relationship of low vitamin D status with positive, negative and cognitive symptom domains in people with first-episode schizophrenia. *Early Intervention in Psychiatry*. 2015; 9: 397-405.

6. Yüksel RN, Altunsoy N, Tikir B, Külük MC, Unal K, Goka S, Aydemir C, Goka E. Correlation between total vitamin D levels and psychotic psychopathology in patients with schizophrenia: therapeutic implications for add-on vitamin D augmentation. *Ther Adv Psychopharmacol* 2014; Vol. 4, No. 6: p. 268– 275.
7. Cieslak K, Feingold J, Antonius D, Messinger JW, Draxler R, Rosedale M, et al. Low Vitamin D Levels Predict Clinical Features of Schizophrenia. *National Institute of Health Public Acces.* 2015; 1 : p. 1-7.
8. Itzhaky D, Amital D, Gorden K, Bogomolni A, Arnson Y, Amital H. Low Serum Vitamin D Concentrations in Patients with Schizophrenia. *IMAJ* 2012; 14 : p. 88–92.
9. Lally J, Sood PG, Firdosi M, Lyegbe C, Stubbs B, Greenwood K, et al. Clinical Correlates of Vitamin D Deficiency in Established Psychosis. *Biomed Central Psychiatry.* 2016; 16:76. p. 1-9
10. Hadded C, Zoghbi M, Hallits S, Bou Assai T, Hashim M, Nabout R et al. Vitamin D Levels in Lebanese Patients with Schizophrenia : A Case-Control Study. *Annals of Nutritional Disorders and Therapy.* 2017; Vol 4(1): 1041. p. 1-6
11. Bulut SG, Bulut S, Atalan DG, Berkol T, Gurcay E, Turker T, et al. The Relationship Between Symptom Severity and Low Vitamin D Levels in Patients with Schizophrenia. *Plos One Journal.* 2016. p. 1-13
12. Yee YJ, See YM, Abdul Rashid NA, Neelamekam S, Lee J. Association Between Serum Levels of Bioavailable Vitamin D and Negative Symptoms in First- Episode Psychosis. *Elsevier Psychiatry Research.* 2016. 243. p. 390-394.
13. Shukurova M, Yuksek E, Emul M, Savrun M. Vitamin D Level in Schizophrenia and Association with Metabolic Syndrome Parameters. *Bulletin of Clinical Psychopharmacology.* 2015; 25(1). p. 529-530
14. Chiang M, Natarajan R, Fan X. Vitamin D in Schizophrenia: a Clinical Review. *Evid Based Mental Health.* Download from <http://ebmh.bmj.com/on> February 15, 2016 - Published by Group.bmj.com. p. 6-9.
15. Shivakumar V, Kalmady SV, Anekal AC, Jose D, Narayanaswamy JC, Agarwal SM, et al. Serum Vitamin D and Hippocampus Gray Matter Volume in Schizophrenia. *ResearchGate: Psychiatry Research : Neuroimaging.* 2015; Vol. 6. No. 006 : p. 1-13.
16. Almeras L, Eyles D, Benech P, Laffite D, Villard C, et al. Developmental Vitamin D deficiency Alters Brain Protein Expression In The Adult Rat : Implications For Neuropsychiatric Disorders. *Proteomics Journal.* 2007; (7): p. 769-780.



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