Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2021 Jun 21; 9(T3):212-222.
https://doi.org/10.3889/oamjms.2021.6303
eISSN: 1857-9655
Category: *T3 - Thematic Issue "Neuroscience, Neurology, Psychiatry and General Medicine"*
Section: *Psychiatry*

Factors Associated with Cognitive Score in People with Schizophrenia at Prof. Dr. M. Ildrem Mental Hospital Medan

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Edited by: Branislav Filipović
Citation: Siagian JM, Loebis B, Camellia V, Effendy E. Factors Associated with Cognitive Score in People with Schizophrenia at Prof. Dr. M. Ildrem Mental Hospital Medan. Open Access Maced J Med Sci. 2021 Jun 21; 9(T3):212-222. https://doi.org/10.3889/oamjms.2021.6303
Keywords: Schizophrenia; Cognitive; Montreal Cognitive Assessment Ina
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Received: 27-Apr-2021
Revised: 07-Jun-2021
Accepted: 11-Jun-2021

Funding: This research did not receive any financial support
Competing Interest: The authors have declared that no competing interest exists

Abstract

BACKGROUND: Schizophrenia is characterized by being a condition with complex symptomatic dimensions. Its prognosis is poor due to the impairment of multiple cognitive functions, which handicaps the adequate social, academic, or employment reintegration of the patient. Cognitive impairment refers to the loss of cognitive functions, specifically memory, attention, and speed of information processing. A wide range of cognitive functions is affected, particularly memory, attention, motor skills, executive function, and intelligence.

METHODS: This study is a multivariate predictive conceptual framework study with a cross-sectional approach to 120 subjects at the Prof. Dr. M Ildrem Mental Hospital Medan in May 2020–July 2020 using a sample that is a consecutive sampling. The test conducted in this study consisted of a bivariate test and a multivariate linear regression test to determine the factors that were associated with the cognitive score. The measuring instrument used is the Montreal Cognitive Assessment (MoCA) Ina.

RESULTS: In the bivariate test, in gender variable (p = 0.644) and age variable (p = 0.255) were not statistically significant, so the variables were not included in the multivariate test. In marital status variable (p = 0.0001), type of antipsychotic (p = 0.193), income/month (p = 0.0001), length of education (p = 0.0001), length of illness (p = 0.0001), frequency hospital admission (p = 0.0001), duration of untreated psychosis (DUP) (p = 0.0001), positive and negative syndrome scale (PANSS) scale (p = 0.141), and negative PANSS scale (p = 0.0001) were found statistically significant for the total MoCA Ina score on the bivariate test. After multivariate linear regression testing, the statistically significant variables on the total MoCA Ina score were negative PANSS scale (p = 0.001), income/month (p = 0.0001), length of education (p = 0.001), length of illness (p = 0.0001), DUP (p = 0.028), and marital status (p = 0.0001).

CONCLUSION: By knowing the factors related to the total score of MoCA Ina, it is expected that clinicians can be more careful in giving treatment interventions for people with schizophrenia who are at risk for cognitive impairment.

Introduction

Schizophrenia is a psychotic disorder with an unknown cause, which is described by disorders of thinking, mood, and behavior. Clear awareness and intellectual abilities are usually maintained, although certain cognitive impairments may develop later [1], [2]. A poor prognosis exists in some cognitive functions resulting in difficulties in social, academic, and adequate work adaptation. Cognitive impairment refers to the loss of cognitive function particularly memory, attention, and information processing speed. Cognitive onset and changes proceed with a slow, gradual decline that most often begins before the first episode of psychosis [3].

Negative symptoms in schizophrenia, such as blunt effects, emotional withdrawal, poor rapport, passivity and apathy, difficulty in abstract thinking, stereotypical thinking, and reduced spontaneity, are generally considered a decrease in normal functioning and are associated with length of stay and poor social functioning. It is interesting to note that the negative symptoms of schizophrenia determine whether people with schizophrenia (PWS) end up functioning well or have poor outcomes. Cognitive impairment is a known feature of schizophrenia and it has been discussed by Kraepelin for a long time that mental efficiency always decreases to a sufficient degree to cause PWS to be confused and inattentive [4], [5].

Cognitive impairment is significantly more common in PWS, impacting up to 75% of PWS. Various cognitive functions that have an impact are memory, attention, motor skills, executive function, and intelligence. The major disturbance in the memory portion is an indication that the disturbance in the structure of the hippocampal and medial temporal lobes is the precursor to the cognitive changes seen in the disease [6]. There are several methodological limitations to this cognitive assessment. The simple, fast, easy to use, valid, and reliable cognitive screening test called the Montreal Cognitive Assessment (MoCA) is designed as a rapid test for "mild cognitive impairment" among the elderly. The cognitive domains assessed by the MoCA include visuospatial skills, language, attention, memory, executive functioning,

abstraction, computation, and orientation. In a study conducted by Ramirez *et al*., in 2014, in Mexico, to assess the validity of the MoCA in detecting cognitive impairment in PWS and the results were obtained that the MoCA showed adequate psychometric ability to be used as a screening instrument to detect mild cognitive impairment in PWS [3], [7].

In a study conducted by Talreja *et al*., in 2018, in India, conducted a study on 100 PWS (54 men and 46 women) to assess the relationship of cognitive function to socio-demographic factors using a measuring tool to assess cognitive function, namely, Addenbrooke's Cognitive Examination Revised (ACER) and the Mini-Mental Status Examination (MMSE). Using the Chi-square test analysis test and univariate logistic regression, with demographic variables including age, sex, marital status, socio-economic status, residence, diagnosis, duration of schizophrenia, the total duration of treatment, current episodes of schizophrenia, and cognitive impairment. Using the ACER measurement tool, significant results were obtained on the variable of residence (village) (odds ratio [OR] = 0.343, 95% confidence intervals [CI] = 0.135–0.875, p = 0.025) and the length of illness was over 2 years. (OR = 3.87, 95% CI = 1.054–14.12, p = 0.041) but there was no significant relationship found on the variables age, gender, marital status, socioeconomic status, diagnosis, length of treatment, and other treatments used. Furthermore, using the MMSE measurement tool, significant results were obtained on the cognitive impairment variable (OR = 7.526, 95% CI = 2.33–24.35, p = 0.001) and on the variable marital status (not married) (OR = 0.33, 95% CI = 0.137–0.79, p = 0.013) but there was no significant relationship found in the variables age, sex, socioeconomic status, diagnosis, length of treatment, and other treatments [6].

In a study conducted by Arunpongpaisal *et al*., in 2013, in Thailand, conducted a study on 75 PWS using MoCA Thai to evaluate cognitive impairment in PWS with a cross-sectional study design using univariate analysis, with demographic variable data between another gender, marital status, and length of education and with clinical variables including age onset in years, duration of illness, type of schizophrenia, type of antipsychotic, and previous history of electroconvulsive therapy (ECT) and significant results were obtained on the variable length of education <12 years (OR = 9.25, 95% CI = 1.90–45.03, p = 0.002) and variables receiving typical and combination antipsychotic treatment (OR = 5.97, 95% CI = 1.66–21.55, p = 0.005) [7].

In a study conducted by Chang *et al*., in 2013, in Hong Kong, conducted a study on 93 PWS to assess the impact of duration of untreated psychosis (DUP) on cognitive and negative symptoms in the first episode of schizophrenia, using the ANCOVA analysis test. The results show that DUP is significantly associated with the severity of negative symptoms and impaired logical memory and literature, showing that cognitive function is correlated with negative symptoms in schizophrenia and there is a relationship between logical memory and negative symptoms where negative symptoms correlate with immediate logical memory ($r = -0.35$, $p = 0.001$) and also with delayed logical memory ($r = -0.36$, $p \leq 0.001$). There were also significant results between DUP with immediate logical memory ($p < 0.05$) and delayed logical memory ($p < 0.05$). Thus, DUP exerts different effects on different cognitive domains, with memory deficits most associated with DUP and also prolonged DUP being associated with more severe impairment of visual memory. DUP is usually defined as the time between the first positive symptom of psychosis and the start of psychiatric treatment (e.g., medication or hospitalization) [8], [9].

Methods

Population and demographic studies

This research is a multivariate study with a predictive conceptual framework with a cross-sectional approach, namely, analyzing the relationship between several independent and dependent variables using the MoCA-Ina instrument [10], [11]. Where the research was carried out was Prof. Dr. M Ildrem Mental Hospital Medan with research time starting from May 2020 to July 2020. The research sample was PWS who went to the outpatient installation of Prof. Dr. M Ildrem Mental Hospital Medan from May 2020 to July 2020 which met the inclusion and exclusion criteria and how to select samples with non-probability sampling type consecutive sampling.

The inclusion criteria were 18–60 years old whose diagnosis of schizophrenia was enforced using Pedoman Penggolongan dan Diagnosis Gangguan Jiwa di Indonesia III, who have ideal body weight (body mass index = 18.5–24.99), with at least complete elementary school education and willing to be a respondent and can be interviewed. Exclusion criteria were having general medical disorders and/or other comorbidities, having a first family history of cognitive impairment, having a history of substance use (except caffeine and nicotine), and having a history of ECT.

MoCA

The MoCA was designed as a rapid screening tool for mild cognitive impairment. MoCA's are useful for detecting a mild cognitive decline in a variety of conditions including Alzheimer's disease, vascular cognitive impairment, Parkinson's disease, Lewy body, frontotemporal dementia, multiple sclerosis, Huntington's disease, brain tumors, amyotrophic

lateral sclerosis, sleep apnea, failure, heart, substance abuse schizophrenia, human immunodeficiency virus, and head trauma. The time to administer the MoCA is approximately 10 min. The total score is 30 points; a score of 26 or above is considered normal. MoCA has a sensitivity of 90%, and a specificity of 87% for assessing cognitive function. In Indonesia, MoCA has been validated into Indonesian by Husein *et al*., in 2009, and is referred to as MoCA-Ina. The Indonesian version of the MoCA test (MoCA-Ina) is valid according to transcultural validation rules and is trusted so that it can be used [3], [12].

Positive and negative syndrome scale (PANSS)

The hypothesis about a positive symptom in schizophrenia is a result of dopamine hyperactivity in the mesolimbic dopamine pathway. The hypothesis about negative symptoms for cognitive and executive function is the result of a dopamine deficit in the mesocortical dopamine pathway to the dorsolateral prefrontal cortex. The hypothesis about negative symptoms for effect and other negative symptoms is the result of a dopamine deficit in the mesocortical dopamine pathway to the ventromedial prefrontal cortex. The Positive and Negative Syndrome Scale was developed by Kay *et al*., in 1987. The Positive and Negative Syndrome Scale consists of 30 items which are divided into three subscales. The subscales are the positive symptom, negative symptoms, and psychopathology scale. The positive symptom scale consists of seven items, the negative symptom scale consists of seven items, and the psychopathology scale consists of sixteen items [4], [13].

Procedure

To obtain the number of samples in this study, a preliminary study has been conducted and 120 subjects have been obtained. Furthermore, PWS who was brought for treatment by his family to the outpatient installation section of Prof. Dr. M Ildrem Mental Hospital Medan who met the inclusion and exclusion criteria will then be given informed consent and asked to sign the informed consent. After that, anamnesis and structured interviews with PWS and family will be carried out, as well as assessing the PANSS score on the positive scale and PANSS on the negative scale, and then followed by assessing the cognitive score on the PWS using the MoCA-Ina measurement tool, then filling in each domain consisting of eight domains (visuospatial, executive function, language, attention, concentration, working memory, memory, and orientation). Then, the cognitive score was assessed from the total number of each domain. After that, the research data will be collected and interpreted, and processed further [14].

Statistical analysis

The analytical test used in this study is the linear regression analysis can only be used if the requirements of the linear regression test are met, while the linear regression requirements include the most important requirements for linearity, as well as other requirements, namely, the residual requirement of normal distribution (proof with histogram graphs, plots, and normality test), mean 0 (descriptive proof), no outliers (proof by case wise diagnostic), constant/homoscedasticity (with evidence with a scatter graph between residues and independent variables), and independent (proof by Durbin-Watson). For the independent variable, there is no multicollinearity (proof by Pearson correlation test and tolerance test). For the dependent variable and the independent variable, the terms are linear (proof with a scatter graph between the independent variable and the dependent variable) [11]. The steps of the linear regression test for numerical independent variables are to test for normality using the Kolmogorov–Smirnov test if at least one of the independent variables or numerical variables are normally distributed, the Pearson test will be carried out. If the numerical independent variable correlation has a $p < 0.25$, then the independent variable meets the requirements for inclusion in the multivariate linear regression analysis. After that, if the comparison of categorical independent variables has $p < 0.25$, then the independent variable meets the requirements to be included in the multivariate linear regression analysis [11], [15].

Analysis of categorical independent variables using descriptive analysis and normality test, then bivariate analysis with independent t-test, then multivariate analysis, then resume analysis, and report analysis. Analysis using numerical independent variables using descriptive analysis and normality test, then bivariate analysis using the Pearson test, then multivariate analysis, then resume analysis and report the analysis for analysis using SPSS version 23 data.

Results

This study took 120 PWS who came to the outpatient installation of Prof. Dr. M Ildrem Mental Hospital Medan who met the inclusion and exclusion criteria where the categorical variables discussed in Table 1 were the gender of PWS, marital status of PWS, and type of antipsychotic PWS. Categorical data are presented in numbers (n) and percentages (%) [15]. While the numerical variables discussed in Table 1 are the age of PWS, monthly PWS income, duration of PWS education, duration of PWS illness, frequency of hospital admission to PWS, DUP PWS, PANSS scale positive PWS, and PANSS negative PWS scale. Numerical data are presented in the center (median) and

Table 1: Demographic characteristics of PWS and clinical conditions of PWS

	Value
Age (in years)	
Median (min-max)	29 (20–45)
Gender (total and percentages)	
Male	64 (53.3%)
Female	56 (46.7%)
Marital Status (total and percentages)	
Married	49 (40.8%)
Unmarried	71 (59.2%)
Salary per month (in million)	
Median (min-max)	2.5 (0.8–5)
Length of Education (in years)	
Median (min-max)	10 (6–15)
Length of sickness (in years)	
Median (min-max)	5 (1–12)
Hospital admission frequency (times)	
Median (min-max)	3 (1-6)
Antipsychotic type (total and percentages)	
Typical	43 (35.8%)
Atypical	77 (64.2%)
DUP (in months)	
Median (min-max)	3 (1–18)
PANSS positive scale	
Median (min-max)	22 (16–32)
PANSS negative scale	
Median (min-max)	24 (18–36)

spread (minimum and maximum) because the data are not normally distributed, with the Kolmogorov–Smirnov test (n = 120), where $p < 0.05$ for each variable [15].

Table 2: Bivariate analysis of independent variables categorical scale

Variable	mean ± s.d.	n	p
MoCA Ina score	21.87 ± 4.12		
Gender			
Male	21.70 ± 4.06	64	
Female	22.05 ± 4.21	56	0.644[a]
Marital status			
Married	25.22 ± 2.84	49	0.0001[a]
Unmarried	19.55 ± 3.16	71	
Antipsychotic type			
Typical	21.21 ± 4.53	43	
Atypical	22.23 ± 3.86	77	0.193[a]

[a]T-independent test.

From Table 1, it can be seen that the most sex variable of PWS is male, 64 subjects (53.3%), of the variable PWS marital status the most are unmarried, namely, 71 subjects (59.2%) and in the variable type of antipsychotic PWS, the most is atypical, namely, 77 subjects (64.2%). Table 1 also shows that the median age of the PWS variable is 29 years with a minimum value of 20 years and a maximum of 45 years. Furthermore, the median in the PWS monthly income variable is 2.5 million with a minimum value of 0.8 million and a maximum of 5 million. Furthermore, the median for the PWS length of education variable was 10 years with a minimum value of 6 years and a maximum of 15 years. Furthermore, the median for the PWS length of illness variable was 5 years with a minimum value of 1 year and a maximum value of 12 years. Furthermore, the median on the PWS hospital admission frequency variable was 3 times with a minimum value of 1 time and a maximum value of 6 times. Furthermore, the median on the DUP PWS variable was 3 months with a minimum value of 1 month and a maximum value of 18 months. Furthermore, the median on the PANSS variable on the positive PWS scale is 22 with a minimum value of 16 and a maximum value of 32. Furthermore, the median on the PANSS variable on the negative PWS scale is 24 with a minimum value of 18 and a maximum value of 36.

Table 3: Bivariate analysis of independent variables with numeric scale

Variable	mean±s.d	r	n	p
Moca Ina score	21.87±4.12			
PwS age				
Median (min-max)	29 (20–45)	−0.105	120	0.255[a]
PWS salary per month				
Median (min-max)	2.5 (0.8–5)	0.719	120	0.0001[a]
PWS length of education				
Median (min-max)	10 (6–15)	0.688	120	0.0001[a]
PWS length of sickness				
Median (min-max)	5 (1–12)	−0.711	120	0.0001[a]
PWS hospital admission frequency				
Median (min-max)	3 (1–6)	−0.738	120	0.0001[a]
PWS DUP				
Median (min-max)	3 (1–18)	−0.644	120	0.0001[a]
PWS positive PANSS				
Median (min-max)	22 (16–32)	−0.135	120	0.141[a]
PWS negative PANSS				
Median (min-max)	24 (18–36)	−0.677	120	0.0001[a]

[a]Pearson correlation test

Table 4: Model summary of third multivariate linear regression

Model summary					
Model	R	R square	Adjusted R square	Std. error of the estimate	Durbin-Watson
1	0.904[a]	0.817	0.806	1.816	
2	0.904[b]	0.817	0.807	1.811	1.672

Bivariate analysis (Pearson correlation test and independent t-test)

Tables 2 and 3 shows the Bivariate analysis of independent variables with categorical scale and numeric scale. Bivariate analysis, in this study, because the dependent variable was numerical in scale, the multivariate analysis was chosen linear regression and with a predictive conceptual framework. The steps taken for multivariate linear regression analysis are descriptive and normality test analysis, bivariate analysis, multivariate analysis, resume analysis, and finally, the results report. The requirement for the independent variables to be included in the multivariate linear regression analysis is that for the bivariate analysis, the p-value must be <0.25. As for this study, there are 11 independent variables, including three independent variables with a categorical scale and eight independent variables with a numerical scale (Pearson Correlation Test and independent t-test [11], [15].

Table 5: Residual statistics of multivariate linear regression analysis

Residuals statistics					
	Minimum	Maximum	Mean	Std. deviation	n
Predicted value	14.15	29.39	21.87	3.723	120
Residual	−5.051	4.179	0.000	1.765	120
Std. predicted value	−2.073	2.022	0.000	1.000	120
Std. residual	−2.789	2.308	0.000	0.974	120

a. Dependent Variable: MocA-Ina total score.

Multivariate analysis of predictive linear regression

After the bivariate analysis is carried out, the multivariate analysis is continued, if it has met the requirements for conducting linear regression tests, the most important is the linearity requirements, as well as other requirements, namely, the residual requirements,

Table 6: Resume of multivariate linear regression analysis

Third multivariate		
Model	The model obtained consists of PANSS negative PWS scale, monthly PWS income, duration of PWS education, duration of illness in PWS, DUP PWS, and PWS marital status	This model was obtained after the frequency variable entered the PWS Hospital, the type of antipsychotic PWS, and PANSS positive scale PWS was issued gradually using the backward method
Assumption Testing	Linearity: Fulfilled. Normality: Fulfilled. Residual mean zero: Fulfilled. The residue of no outliers: Fulfilled. Residual constant: Fulfilled. Independent: Fulfilled. There is no multicollinearity: Fulfilled.	Scatter gives a linear impression. The histogram and plot graphs give a normal impression. Average = 0. Residue value ranges from − 3 to d. 3 standard deviations. Graphics do not form a specific pattern. The Durbin-Watson score is close to 2. Tolerance > 0.4.
Regression Equations	MoCA Ina score = 23.23–0.16 * PANSS negative scale PWS + 1.02 * PWS monthly income + 0.33 * PWS education period - 0.29 * PWS duration of illness - 0.12 * PWS DUP - 1.88 * PWS marital status	
Adjusted R^2	80.7%	The ability of PANSS on the negative scale of PWS, monthly PWS income, length of PWS education, length of illness in PWS, DUP PWS, and PWS marital status to explain the MoCA Ina score of 80.7%
Correlation Coefficient	PANSS negative scale PWS = −0.18 PWS monthly income = 0.25 PWS length of education = 0.19 Duration of illness PWS = −0.22 PWS DUP = −0.12 PWS Marital Status = −0.23	The strength of the correlation is very weak and the direction is negative. Weak correlation strength and positive direction. Very weak correlation strength and positive direction. Weak correlation strength and negative direction. The strength of the correlation is very weak and the direction is negative. Weak correlation strength and negative direction.

normal distribution, mean 0, no outliers, independent, and constant. For the independent variables, there is no multicollinearity (Pearson correlation test and tolerance test). For the dependent variable and the independent variable, the terms are linear (independent and dependent variable scatter graph) [11].

Multivariate analysis of third linear regression

After repeated linear regression multivariate analysis excluded insignificant variables, then from Table 4, it can be seen that model 2 is the model with the highest coefficient of determination, namely, 80.7%. Then, the results show that model 2 is a fit model because there is no multicollinearity where the tolerance value is >0.4 and all independent variables have $p < 0.05$ [11].

For the condition of the residue, the distribution of the residue must be normal, the residual mean is 0, and there are no outliers, constant/homoscedasticity and independent. From the histogram and plot graphs, it can be seen that the distribution gives a normal impression, coupled with the normality test using the Kolmogorov–Smirnov also shows a value of $p = 0.2$ (above 0.05). Therefore, it can be concluded that the residual distribution is normal [11].

From Table 5, it can be seen that the residual mean is 0; therefore, the residual average requirement of 0 has been fulfilled. From Table 5, it can also be seen that the minimum value is −2789 and the maximum value is 2308; therefore, the condition for no outliers is also fulfilled, namely, the range value is not less than −3–3. Furthermore, it is seen that the Durbin Watson value in Table 4 is 1.672 so that the independent condition of the residue is met, which is around number 2. It can also be seen from the scatter graph between the residue and the independent variable that it is constant/homoscedasticity, which is not forming a specific pattern [11].

Then, for the requirements of the dependent variable (MoCA Ina score) that met the requirements, multivariate linear regression analysis was carried out because it was normally distributed using the Kolmogorov–Smirnov test with $p = 0.081$. The relationship between the independent variable and the dependent variable is also linear so that this requirement has been fulfilled [11].

When performing multivariate linear regression analysis with a predictive conceptual framework it is recommended to use the backward method, which means that the SPSS program will filter data from independent variables that have multicollinearity and are not statistically significant until the most suitable model is found (model fit). It can also be seen in the statistical results that the ANOVA value is <0.0001, which means that there is at least one statistically significant independent variable. Therefore, we then proceed to look at the model summary and in Table 4 it can be seen that model 2 has the best coefficient of determination [11].

Multivariate analysis of linear regression reports

From Table 6, by analyzing the backward method, a linear regression equation is obtained based on the resume above, namely, MoCA Ina Score = 23.23–0.16 * PANSS negative scale PWS + 1.02 * monthly income PWS + 0.33 * length of education PWS - 0.29 * length of illness PWS - 0.12 * DUP PWS - 1.88 * PWS marital status. All linear regression assumptions, namely, linearity, normality, mean zero residues, no outliers residue, independent, constant/homoscedasticity, and no multicollinearity have been met [11].

Results of multivariate analysis of factors associated with the MoCA Ina score

The results of this study concluded that all the variables attached to Table 7 are associated with the MoCA Ina score with $p < 0.05$ [11].

Table 7: Final results of multivariate analysis

MoCA Ina score	Correlation coefficients	Multivariate regression β	p
Variable			
Constant		23.23	0.0001
PWS PANSS Negative Scale	–0.18	–0.16	0.001
PWS Monthly Income	0.25	1.02	0.0001
PWS Education Period	0.19	0.33	0.001
PWS Length of sickness	–0.22	–0.29	0.0001
PWS DUP	–0.12	–0.12	0.028
PWS Marital Status	–0.23	–1.88	0.0001

Adjusted R^2 80.7%

Discussion

This study is an observational analytic study. Based on the number of independent variables, this study is a multivariate study because it assesses the relationship between several independent variables and one dependent variable. Based on time, this study is a cross-sectional study. The research diagnosis in this study is a linear regression with a predictive conceptual framework because this study seeks to find the relationship of several factors on the independent variable and the dependent variable, where the dependent variable in this study is a numerical scale, namely, the MoCA Ina score [10], [16].

This study was conducted at Prof. Dr. M Ildrem Mental Hospital Medan from May 2020 to July 2020, where the subjects in this study were 120 subjects PWS who went to the outpatient installation of Prof. Dr. M Ildrem Mental Hospital Medan during May 2020–July 2020. The sample size of the research subjects was determined based on a preliminary study [17]. The sampling method in this study is non-probability sampling, namely, by consecutive sampling, where each research subject who comes consecutively meets the inclusion and exclusion criteria and agrees to participate in this study, after being given informed consent will be entered in this study [16]. Furthermore, in this study, confounding variables were successfully controlled utilizing restrictions [10].

In this study, when performing multivariate linear regression analysis, in addition to numerical correlative relationships, there is also a relationship between numerical and categorical variables (numerical comparative). Therefore, for multivariate linear regression analysis that is appropriate for these conditions is to create a variable, where later this variable will be included in the multivariate linear regression analysis. Dummy variables can be created manually or by using SPSS. Based on the considerations of this study, dummy variables were created using SPSS version 23. In this study, for each category variable, only one dummy variable was made, because the categorical data consisted of only two groups.

MoCA Ina score

In this study, it can be seen that the PWS negative scale PANSS variable, PWS monthly income, PWS education period, PWS illness duration, PWS DUP, and PWS marital status are related to the MoCA Ina score on PWS. Meanwhile, on the PWS gender categorical scale-independent variable, after the independent t-test was carried out there was no significant relationship with $p = 0.644$ ($p > 0.25$). Likewise, with the PWS age numerical scale-independent variable, after the Pearson correlation test was carried out there was no significant relationship with $p = 0.255$ ($p > 0.25$). Therefore, the two variables were considered not related to the MoCA Ina score (statistically) and did not qualify for inclusion in the multivariate linear regression analysis [11]. Meanwhile, for other variables, in this multivariate analysis study, the backward method is used in the analysis, which means that a model that has the highest coefficient of determination will be sought by removing the variables that have multicollinearity and also the least significant variables, which are continued until the fittest model is found with the highest determination coefficient [11].

Biological plausibility

In this study, it can be seen that the PWS negative scale PANSS variable, PWS monthly income, PWS education period, PWS illness duration, PWS DUP, and PWS marital status are related to the MoCA Ina score on PWS. Therefore, these variables deserve to be considered as a factor that can cause cognitive impairment in PWS, where damage occurs in most of the cognitive aspects, including, verbal learning and memory, secondary memory, working memory, and executive function [18].

Furthermore, according to the results of this study, it was found that the PWS monthly income variable had the highest correlation coefficient value, so there was a possibility of interference with executive function, where the executive function was found to be very important for work outcomes and independent living. In the work domain, a person's inability to plan daily work, prioritize activities, and use problem-solving skills, can reduce one's job prospects. In terms of living independently, the executive function is involved in all areas from planning for the future and setting goals to solving problems that arise in life [19].

The term "executive function" is used to denote a group of higher cognitive functions in the prefrontal cortex and has been used synonymously with the term "frontal-lobe functions." The current definition of the executive function includes several subprocesses and the response is that not all executive processes are uniquely maintained by the frontal cortex. In particular, some executive processes can be sustained by a network of cortical distributions, not by unique frontal

regions that may or may not be associated with the frontal lobe. Executive function refers to the will, planning, purposeful action, and self-monitoring behavior. It describes processes of the highest order cognitive that allow flexible modification of thinking and behavior in response to changing cognitive or environmental conditions. PWS exhibit executive function deficits and these deficits are associated with treatment-refractory symptoms such as negative symptoms, poor functional outcomes. Executive dysfunction may contribute to decreased working memory and attention [5]. It is known that a common mechanism that contributes to cognitive impairment in various domains in schizophrenia is the inability to actively describe target information on working memory, which is required to guide behavior and the presence of deficits has illustrated the decline in function of the dorsolateral lateral prefrontal cortex, where it interacts with areas of the brain others such as the parietal cortex, thalamus, and striatum and the influence of the neurotransmitter system such as dopamine, GABA, and glutamate [20].

Prolonged sickness equals more severe cognitive impairment which is predictive of a lack of response to treatment leading to worse outcomes for chronic patients with dominant cognitive symptoms [21], whereas an excessive decrease in intelligence quotient (IQ) in PWS is associated with a progressive decrease in gray matter associated with duration of illness [22].

Hence, according to this study, it can be attributed that a prolonged DUP association with worse cognitive outcomes, one possible explanation is that DUP may be biologically damaging to the brain. There is some evidence to suggest that a longer DUP is associated with a greater reduction in the volume of gray matter, including the hippocampus, an area of the brain that is critically involved in the memory system. Thus, it is plausible that prolonged DUP might result in larger brain structural deficits with more pronounced cognitive impairment [9].

Also according to the results of this study, hypoactivity in the mesocortical dopamine pathway may be hypothesized to mediate the negative and cognitive symptoms of schizophrenia, which may arise from deficits in dopamine transmission at D1 receptors in the prefrontal cortex (decreased cerebral blood flow to the frontal cortex is the best evidence for this of hypofrontality and dysfunction in brain areas in schizophrenia) [23]. It can also be seen that glutamatergic-mediated cognitive impairment, in turn, can be controlled by the acetylcholine (ACH) system and specifically by the α7 receptor. In the central nervous system, acetylcholinergic neurotransmission is completely involved in aspects of memory formation, as well as motivational and volitional behavior, all of which are disrupted in schizophrenia. These cognitive and behavioral functions are thought to be modulated by the α7 ACh receptor. Therefore, changes in the neurotransmission of ACh may contribute to the cognitive and behavioral symptoms of schizophrenia [24]. Therefore, cognitive impairment in PWS is associated with poor functioning and low quality of life [25].

In this study for PWS age, the median (min-max) value was obtained, namely, 29 (20–45) years, also in this study the PWS age variable was not related to the MoCA Ina score ($p = 0.255$), at the time of the bivariate analysis, so that the variable PWS age did not qualify for entry into the multivariate linear regression analysis, because the requirements for $p < 0.25$ were not met. The results in this study are by the study of Talreja *et al*., in 2018 in India, the mean value was ± s.d. PWS age was 33.96 ± 9.89 years and in that study, there was no significant association between PWS age and cognitive impairment (assessed from ACER score or MMSE score) [6]. Likewise with a study conducted by Arunpongpaisal *et al*., in 2013 in Thailand, the mean value was ± s.d. PWS age was 36.2 ± 9.4 years and in that study, there was no significant association between PWS age and cognitive impairment (assessed by MoCA Thai score) [7].

Abnormalities in gray matter and white matter structure are consistently observed in schizophrenia and it is known that they develop during the disease, particularly during the early stages of the disorder. Correspondingly, it is known that dynamic changes in brain structure occur with normal brain development, maturation, and aging. Despite consistent observations of reduced gray matter and white matter volume in schizophrenia, it remains unclear whether this deficit becomes exaggerated with increasing age or duration of illness [26].

In this study, the majority of PWS sex was male 53.3%, also in this study, the PWS gender variable was not related to the MoCA Ina score ($p = 0.644$), at the time of bivariate analysis, so the PWS gender variable has not met the requirements for entry into the multivariate linear regression analysis, because the requirements for $p < 0.25$ were not met. The results of this study are by the study of Talreja *et al*., in 2018, in India, it was found that the most sex were male 54% and 46% female in that study, there was no significant relationship between the sex of PWS with cognitive impairment (assessed by the MMSE score) [6]. Sex differences in the cognitive domain are still a controversial issue. Some authors say that men score worse on attention, language, and executive function than women. While some other authors say women function better on neuropsychological performance than men, except for the attention category and other authors also say that women perform better than men in learning and verbal memory. However, there is another study that found no gender difference in the assessment of the cognitive domain [25].

As in a study conducted by Moriarty *et al*., in 2001, in New York, it was found that the male sex was 89 people and the female sex was 116 people in that study, there was no significant relationship between gender

and cognitive function. that is p > 0.01 (assessed by the MMSE score) [27]. Furthermore, in a study conducted by Galderisi *et al*., in 2011, in Italy, it was found that male gender was 156 people and female gender was 120 people and in that study there was no significant relationship with social function (assessed from several psychosocial measuring instrument indicators), wherein the study the negative effects of schizophrenia explain that there are large differences in social functioning, suggesting that there may be large differences in the severity of negative symptoms mediating the effect of sex on social functioning [28].

In this study, the majority of PWS marital status was unmarried 59.2%, also in this study, there was a relationship between the PWS marital status variable and the MoCA Ina score, also very significant results with p = 0.0001 with r = –0.23 (weak correlation strength and negative direction) after multivariate linear regression analysis. Where being unmarried compared to being married has a negative correlation coefficient on the MoCA Ina score, which means that being unmarried is higher associated with a lower MoCA Ina score than being married. The results in this study are following the study of Talreja *et al*., in 2018, in India, it was found that there was a relationship between PWS marital status that not married had a significant relationship with cognitive impairment, namely, p < 0.05 (assessed from the MMSE score) [6]. This is different from a study conducted by Arunpongpaisal *et al*., in 2013, in Thailand, which stated that there was no relationship between PWS marital status and cognitive impairment [7].

Marital status has been recognized as one of the best predictors of schizophrenia development. Being married turns out to be able to make for premorbid psychosocial adaptation associated with better prognosis, it has also been explained that the risk of hospitalization in single (unmarried) patients increases with age. However, this condition is not observed in married patients and the fact that unmarried status is associated with lower quality of life in the intrapsychic domain (sexual activity, life goals, curiosity, empathy, and interaction) [29].

In this study, the PWS monthly income obtained a median (min-max) value of 2.5 (0.8–5) million, also in this study, there was a relationship between the PWS monthly income variable and the MoCA Ina score, also obtained very significant results with a p = 0.0001 with a value of r = 0.25 (weak correlation strength and positive direction) after multivariate linear regression analysis, where the PWS high monthly income is associated with an increase in the MoCA Ina score. The results in this study differ from the study of Talreja *et al*., in 2018, in India, it was found that the socio-economic level variable was not related to cognitive impairment (assessed from the ACER score or the MMSE score) [6].

Cognitive impairment is evident in the emotional, social, educational, functional, and occupational fields of PWS daily life; therefore, cognition is associated with work outcomes/abilities (and therefore loss of productivity). Cognitive functions that are affected include memory, attention, problem solving, learning, executive function, processing speed, and social cognition. Cognitive disorders have an impact on the ability of individuals to carry out activities of daily life, work productively, function socially, and adhere to treatment, which results in direct or indirect economic consequences. Schizophrenia is an expensive psychiatric disorder to treat, and its annual average cost is reported to be significantly higher than other mental health conditions. Cognitive function is the main determinant of functional and work-related outcomes in schizophrenia with more than positive or negative symptoms [18].

In this study, the PWS education period obtained a median (min-max) value of 10 (6–15) years, also in this study, there was a relationship between the PWS length of education variable and the MoCA Ina score, also obtained significant results with p = 0.001 with a value of r = 0.19 (very weak correlation strength and positive direction), where the high length of PWS education is associated with an increase in the MoCA Ina score. These results are consistent with a study conducted by Arunpongpaisal *et al*., in 2013, in Thailand, there was a significant relationship in the variable length of education <12 years (OR = 9.25, 95% CI = 1.90–45.03, p = 0.002) with cognitive impairment (assessed by MoCA Thai score) [7].

In a study conducted by Cardosa *et al*., in 2005, in Brazil, they found an association between lower schooling in schizophrenia and quality of life, where better levels of education were associated with better psychopathological status in the course of the disease and better rates of life. The social functioning adjustment also led to better satisfaction rates in life as well as in another study from Brazil that assessed social adjustment in schizophrenia in areas closely related to the quality of life, where low schooling was predicted as poor social functioning which remained associated with low quality of life in the social domain [29].

In this study, for the duration of PWS illness, the median value (min-max) was obtained, namely, 5 (1–12) years, also in this study, there was a relationship between the PWS length of illness and the MoCA Ina score = 0.0001 with a value of r = –0.22 (weak correlation strength and negative direction) after multivariate linear regression analysis, where the prolonged PWS illness duration is associated with a decrease in the MoCA Ina score. The results in this study are by the study of Talreja *et al*., in 2018, in India, there was a significant relationship between the length of illness over 2 years (OR = 3.87, 95% CI = 1.054–14.12, p = 0.041) with cognitive impairment (assessed by ACER score) [7]. The results of this study are different from the study conducted by Arunpongpaisal *et al*., in 2013 in Thailand, which stated that there was

no relationship between the duration of PWS illness and cognitive impairment [7]. Prolonged illness duration equals more severe cognitive impairment which is predictive of a lack of response to treatment leading to worse outcomes for chronic patients with dominant cognitive symptoms, where cognitive impairment and length of illness are associated with poor outcomes, while predominantly positive symptoms are associated with a good prognosis [30].

In this study, the PWS hospital admission frequency obtained a median (min-max) value of 3 (1–6) times, also in this study, there was a relationship between the PWS hospital admission frequency variable with the MoCA Ina score, also obtained very significant with p = 0.0001, at the time of bivariate analysis. However, when the first linear regression multivariate analysis was carried out, it was found that there was multicollinearity in the PWS hospital admission frequency variable with a tolerance value <0.4, so the variables had to be excluded sequentially. Therefore, the results of this study state that the PWS hospital admission frequency variable is not a factor related to the MoCA Ina score. The results of this study are different from studies from Talreja *et al*., in 2018, in India and also a study conducted by Arunpongpaisal *et al*., in 2013 in Thailand, because in that study they did not assess the variable frequency of hospital admission as clinical variables to see the relationship with cognitive impairment [6], [7].

There is minimal evidence that prolonged or brief hospitalizations lead to cognitive and functional changes, but rather that these hospitalizations may be the basis of cognitive and functional decline. Recurrence prevention and knowing about treatment is to help patients with resistant symptoms and can reduce the risk of lifelong cognitive and functional decline in PWS. Continuous hospital stay appears to have the potential to cause adverse effects on function, but current treatment exemplifies that there is an increased risk for medication non-adherence and psychotic relapse [31].

In this study, the most PWS type of antipsychotic was atypical 64.2%, also in this study, there was a relationship between the PWS antipsychotic type variable and the MoCA Ina score, with significant results with p = 0.193, at the time of bivariate analysis. However, when the first linear regression multivariate analysis was carried out, it was found that the PWS type of antipsychotic variable was automatically excluded in model 3 because it was considered insignificant with a p > 0.05. Therefore, the results of this study state that the variable type of PWS antipsychotic is not a factor associated with the MoCA Ina score. The results of this study are different from a study conducted by Arunpongpaisal *et al*., in 2013 in Thailand, which stated that there was a relationship between the types of PWS antipsychotics and cognitive impairment [7]. Pharmacological therapy with antipsychotics is the most important in the treatment of schizophrenia. However, in general, it has been observed that antipsychotics have a much more significant effect on positive symptoms than negative symptoms or cognitive impairment. Indeed, second-generation antipsychotic drugs do not appear to be sufficient in reducing negative symptoms [32].

In this study, for the PWS DUP, the median (min-max) value was 3 (1–18) months, also in this study, there was a relationship between the DUP PWS variable and the MoCA Ina score, also obtained significant results with p = 0.028 with an r value = –0.12 (very weak correlation strength and negative direction) after multivariate linear regression analysis, where a prolonged PWS DUP is associated with a decrease in the MoCA Ina score. The results in this study are from a study by Chang *et al*., in 2013, in Hong Kong, there was a significant relationship between prolonged DUP and more severe disturbances in visual memory and verbal memory (p = 0.001) [9].

The association between prolonged DUP and the unfavorable outcome can be explained by brain development, which continues from early fetal development to adulthood. Especially the time between the onset of schizophrenia has been observed as an active time in the brain change process. One hypothesis as to the unfortunate consequences of untreated psychosis is that untreated psychosis is harmful, even toxic, to the brain. Also without treatment, this process can become chronic and cause permanent damage. Correspondingly, changes in brain tissue can be avoided with early intervention, including concurrent treatment with other treatments. This could explain why shorter DUP have been associated with better outcomes in some studies. However, research on this subject is still conflicting in terms of results and conclusions as well as the toxicity of DUP are still under study [8].

In this study, for the PANSS positive scale PWS, the median value (min-max) was obtained, namely, 22 (16–32), also in this study, there was a relationship between the PANSS positive scale PWS variable and the MoCA Ina score p = 0.141, at the time of the bivariate analysis. However, when the first linear regression multivariate analysis was carried out, it was found that the PANSS variable on the positive scale of PWS was automatically excluded in model 3 because it was considered insignificant with a value of p > 0.05. Therefore, the results of this study state that the PANSS positive scale PWS variable is not a factor associated with the MoCA Ina score. The results of this study are different from those of Talreja *et al*., in 2018, in India and also a study conducted by Arunpongpaisal *et al*., in 2013 in Thailand, because in that study they did not assess the positive scale PANSS variable as a variable clinical to see its relationship with cognitive impairment [6], [7].

In the study for the negative scale PANSS PWS, the median value (min-max) was obtained, namely, 24 (18–36), also in this study, there was a relationship between the PANSS negative scale PWS variable and

the MoCA Ina score, also obtained significant results with p = 0.001 with a value of r = –0.18 (very weak correlation strength and negative direction) after multivariate linear regression analysis, where the high PANSS negative PWS scale is associated with a decrease in the MoCA Ina score. The results in this study are consistent with a study by Chang *et al*., in 2013, in Hong Kong, there was a significant relationship between the negative PANSS scale and cognitive function (logical memory) p = 0.001 [9]. One of the most common clinical rating scales used for schizophrenia is PANSS. This scale examines the various symptoms of schizophrenia. Interestingly, some aspects of the disease that is visible with basic characteristics such as cognitive (e.g., deficits in abstract thinking, stereotypical thinking, inattention) are defined as negative or generalized symptoms of schizophrenia by PANSS and contribute to the total score on these symptom dimensions [33].

The strength of this study is that it is based on the knowledge of researchers assessed from several literature reviews, studies with similar measurement methods and tools, which have never been carried out in Sumatra (important + applicable). The determination of the minimum sample size in this study is based on a preliminary study and the number of subjects in this study is also by the minimum sample size and an appropriate analytical test is carried out (analysis validity). This study also managed to get 120 research subjects (external validity 1b); therefore, at least the results of this study can be generalized to the target population. This study also controls for confounding variables that are considered to influence the study results, namely, using restrictions and can be explained academically how the pathophysiology (internal validity causes) [21]. The limitation of this study is that this study was not conducted in a multicenter due to limited resources (external validity), due to limited resources as well, this study only allows to be carried out in a cross-sectional manner, where the temporality requirement is not fulfilled because the initial identification is not clear (internal validity causes) [21].

Conclusion

After linear regression analysis was carried out, it was found that there was a relationship between PWS marital status and MoCA Ina score on PWS, there was a relationship between PWS monthly income and MoCA Ina score on PWS, there was a relationship between PWS education length and MoCA Ina score on PWS, there was a relationship between PWS pain and MoCA Ina score on PWS, there is a relationship between DUP PWS and MoCA Ina score on PWS and there is a relationship between PANSS negative scale PWS and MoCA Ina score on PWS with linear regression equation, namely, MoCA Ina Score = 23.23–0.16 * PANSS negative scale PWS + 1.02 * monthly income PWS + 0.33 * length of education PWS - 0.29 * length of illness PWS - 0.12 * DUP PWS - 1.88 * PWS marital status (Adjusted R^2 80.7%).

References

1. Sadock BJ, Sadock VA, Ruiz P. Kaplan and Sadock's Synopsis of Psychiatry Behavioral Sciences/Clinical Psychiatry. 11th ed. Philadelphia, PA: Wolters Kluwer; 2015. p. 300-23. https://doi.org/10.1097/00004850-198907000-00008
2. Departemen Kesehatan Republik Indonesia. Pedoman Penggolongan dan Diagnosis Gangguan Jiwa di Indonesia III (PPDGJ-III). Jakarta: Departemen Kesehatan Republik Indonesia; 1993. https://doi.org/10.6066/jtip.2013.24.2.121
3. Bores-Ramirez LR, Saracco-Alvarez R, Escamilla-Orazco R, Orellana AF. Validity of the Montreal cognitive assessment scale (MoCA) for the detection of cognitive impairment in schizophrenia. Salud Mental. 2014;37(6):517-22. https://doi.org/10.17711/sm.0185-3325.2014.062
4. Stahl SM. Psychosis and schizophrenia. In: Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application. 4th ed. Cambridge: Cambridge University Press; 2013. p. 155-214.
5. Bhattacharya K. Cognitive function in schizophrenia: A review. J Psychiatry. 2015;18(1):1-8.
6. Talreja BT, Shah S, Kataria L. Cognitive function in schizophrenia and its association with socio-demographics factors. Ind Psychiatry J. 2018;22:47-53. https://doi.org/10.4103/0972-6748.123619
   PMid:24459374
7. Arunpongpaisal S, Sangsirilak A. Using MoCA Thai to evaluate cognitive impairment in patients with schizophrenia. J Med Assoc Thailand. 2013;96(7):860-5.
   PMid:24319859
8. Penttila M. Duration of untreated psychosis. Association with clinical and social outcomes and brain morphology in schizophrenia. Acta Univ Ouluensis D Med. 2013;1206:1-130.
9. Chang WC, Hui CL, Tang JY, Wong GH, Chan SK, Lee EH, *et al*. Impacts of duration of untreated psychosis on cognition and negative symptoms in first episode schizophrenia: A 3 year prospective follow up study. Psychol Med. 2013;43(9):1883-93. https://doi.org/10.1017/s0033291712002838
   PMid:23217676
10. Dahlan MS. Langkah-Langkah Membuat Proposal Penelitian Bidang Kedokteran Dan Kesehatan. Jakarta: Sagung Seto; 2014.
11. Dahlan MS. Regresi Linier. 2nd ed. Jakarta: Epidemiologi Indonesia; 2018.
12. Husein N, Lumempouw N, Ramli Y, Herqutanto. Uji Validitas dan Reabilitas Montreal Cognitive Assessment versi Indonesia (MoCA-Ina) untuk Skrining Gangguan Kognitif; 2010. Available from: http://www.mru.fk.ui.ac.id. [Last accessed on 2015 Sep 20]. https://doi.org/10.26891/jik.v11i1.2017.12-18
13. Mortimer AM. Symptom rating scales and outcome in schizophrenia. Br J Psychiatry. 2007;191(Suppl 50):s7-14. https://doi.org/10.1192/bjp.191.50.s7
   PMid:18019038
14. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, *et al*. The Montreal cognitive

assessment, MoCA: A Brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9. https://doi.org/10.1111/j.1532-5415.2005.53221.x

PMid:15817019

15. Dahlan MS. Statistik untuk Kedokteran dan Kesehatan. Jakarta. Epidemiologi Indonesia; 2014.
16. Sastroasmoro S, Ismael S. Dasar-Dasar Metodologi Penelitian Klinis. 3rd ed. Jakarta: Sagung Seto; 2008.
17. Dahlan MS. Besar Sampel dan Cara Pengambilan Dalam Penelitian Kedokteran dan Kesehatan. 5th ed. Jakarta: Epidemiologi Indonesia; 2019.
18. Kitchen H, Rofail D, Heron L, Sacco P. Cognitive impairment associated with schizophrenia: A review of the humanistic burden. Adv Ther. 2012;29(2):148-62. https://doi.org/10.1007/s12325-012-0001-4

PMid:22351433

19. Sharma T, Antonova L. Cognitive function in schizophrenia deficits, functional consequences and future treatment. Psychiatr Clin North Am. 2003;26(1):25-40.

PMid:12683258

20. Barch DM, Ceaser A. Cognition in schizophrenia: Core psychological and neural mechanisms. Trends Cogn Sci. 2012;16(1):27-34. https://doi.org/10.1016/j.tics.2011.11.015

PMid:22169777

21. Dahlan MS. Membaca dan Menelaah Jurnal Klinis. Jakarta: Salemba Medika; 2010.
22. Kahn RS. On the specificity of continuous cognitive decline in schizophrenia. Am J Psychiatry. 2019;176(10):774-6.

PMid:31569987

23. Gao WJ. Dopaminergic and glutamatergic dysfunctions. In: The Neuropathophysiology of Schizophrenia. Philadelphia, PA: Department of Neurology and Anatomy, Drexel University College of Medicine; 2009.
24. Malhotra AK, Marder SR, Weiden PJ. Cognitive Impairment in Schizophrenia: Understanding the Neurobiology and its Implications for Future Management. 2015. p. 1-7. Available from: http://www.currentpsychiatry.com/cognition. [Last accessed on 2015 Sep 25].
25. Ochoa S, Usall J, Cobo J, Labad X, Kulkarni J. Gender differences in schizophrenia and first episode psychosis: A comprehensive literature review. Schizophr Res Treatment. 2012;2012:916198. https://doi.org/10.1155/2012/916198

PMid:22966451

26. Cropley VL, Klauser P, Lenroot RK, Bruggemann J, Sundram S, Bousman C, *et al*. Accelerated gray and white matter deterioration with age in schizophrenia. Am J Psychiatry. 2017;174(3):286-95. https://doi.org/10.1176/appi.ajp.2016.16050610

PMid:27919183

27. Moriarty PJ, Lieber D, Bennett A, White L, Parella M, Harvey PD, *et al*. Gender differences in poor outcome patients with longlife schizophrenia. Schizophr Bull. 2001;27(1):103-13. https://doi.org/10.1093/oxfordjournals.schbul.a006850

PMid:11215540

28. Galderisi S, Bucci P, Ucok A, Peuskens J. No gender differences in social outcome in patients suffering from schizophrenia. Eur Psychiatry. 2012;27(6):406-8. https://doi.org/10.1016/j.eurpsy.2011.01.011

PMid:21616645

29. Cardoso CS, Caiaffa WT, Bandeira M, Siqueira AL, Abreu MN, Fonseca JO. Factors associated with low quality of life in schizophrenia. Saúde Pública. 2005;21(5):1338-48. https://doi.org/10.1590/s0102-311x2005000500005

PMid:16158138

30. Buoli M, Caldiroli A, Panza G, Altamura AC. Prominent clinical dimension, duration of illness and treatment response in schizophrenia: A naturalistic study. Korean Neuropsychiatr Assoc. 2012;9(4):354-60. https://doi.org/10.4306/pi.2012.9.4.354

PMid:23251199

31. Harvey PD, Loewenstein DA, Czaja SJ. Hospitalization and psychosis: Influences on the course of cognition and everyday functioning in people with schizophrenia. Neurobiol Dis. 2013;15:18-25. https://doi.org/10.1016/j.nbd.2012.10.022

PMid:23123218

32. Kaneko K. Negative symptoms and cognitive impairments in schizophrenia: Two key symptoms negatively influencing social functioning. Yonago Acta Med. 2018;61(2):91-102. https://doi.org/10.33160/yam.2018.06.001

PMid:29946215

33. Harvey PD, Koren D, Reichenberg A, Bowie CR. Negative symptoms and cognitive deficits: What is the nature of their relationship? Schizophr Bull. 2006;32(2):250-8. https://doi.org/10.1093/schbul/sbj011

PMid:16221995