

Predictive Factors of Low HDL-C in Patients with Schizophrenia

Yu-Chi Huang¹, Chi-Fa Hung¹, Yu Lee¹, Pao-Yen Lin¹, Liang-Jen Wang²¹Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan;²Department of Child and Adolescent Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

Correspondence: Yu-Chi Huang, Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan, Tel +886-7-7317123 ext. 8753, Fax +886-7-7326817, Email ychuang01@gmail.com

Objective: Schizophrenia patients engage in more sedentary life activities and endure a higher risk of metabolic syndrome than general population. Evidence on investigating the predictors in relation to low HDL-C in schizophrenia is still lacking.

Methods: This cross-sectional study recruited 133 schizophrenia patients from a tertiary hospital; 13 patients were not included (12 refused participation and 1 had missing data). Blood samples were collected to determine plasma levels of total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol. Atherogenic index of plasma was calculated using $\log_{10}(\text{TG}/\text{HDL-C})$. The physical capacity was measured by 6-minute walk test (6MWT). The group of low HDL-C was categorized according to the sex-specific HDL-C thresholds (male: < 40 mg/dL; female: < 50 mg/dL); the reference category was the group of normal HDL-C. Three logistic regression models were performed to identify if sex, hospitalization times, 6MWT distances and TG levels were the significant predictors of low HDL-C. We examined the model performances using the area under the receiver operating characteristics curve (AUC) and calculated accuracy, sensitivity and specificity. *P* value of FDR < 0.05 was considered statistically significant after correcting for multiple comparisons.

Results: Model 1 (AUC = 0.79, accuracy/sensitivity/specificity = 0.73/0.60/0.81) and Model 2 (AUC = 0.82, accuracy/sensitivity/specificity = 0.75/0.66/0.81) controlled without or with education years. Model 3 (AUC = 0.82, accuracy/sensitivity/specificity = 0.76/0.64/0.84) controlled educational years, height and body mass index and showed relatively optimal accuracy and specificity with similar performance of Model 2. All models found that female, hospitalization times, 6MWT distances and TG levels were significant predictors associated with low HDL-C after multiple comparisons (all *p* < 0.05).

Conclusion: The results provide the clinical importance to assess low HDL-C, especially for female schizophrenia with more hospitalization, shorter 6MWT distances or higher TG levels due to increased susceptibility to cardiometabolic risks.

Keywords: 6-minute walk test, HDL-C, hospitalization, lipid, metabolic syndrome, physical capacity, schizophrenia

Introduction

Schizophrenia is a major chronic psychiatric disease that profoundly impacts on various aspects of patients' functional domains and results in their living with disability.¹ In comparison to the general population, schizophrenia patients are also at an increased risk to comorbid with ageing-related physical illnesses, such as metabolic syndrome, diabetes mellitus, and cardiovascular disease, as well as premature mortality following deleterious physical health.^{2,3} Since cardiovascular disease contributes to the most essential cause for the premature mortality of schizophrenia,⁴ it is clinically important to early assess the risk of cardiovascular disease in order to help schizophrenia patients to decrease physical morbidities and related mortality gap.

During the development course of metabolic syndrome, lipid abnormalities usually occurs earlier⁵ and have been suggested as important markers of cardiovascular disease.^{6,7} Among the abnormalities of lipid profiles, low high-density lipoprotein cholesterol (HDL-C) and high triglycerides (TG) contribute to the two major components of metabolic syndrome regarding atherogenic dyslipidemia.⁸ Low HDL-C is suggested to behave as the most powerful lipid parameter

to predict the risk and the treatment outcome of coronary heart disease.⁹ On the other hand, the atherogenic index of plasma (AIP), defined as the ratio of TG to HDL-C post logarithmical transformation, acts as a marker for evaluating cardiometabolic risk¹⁰ and shows the strongest association with metabolic syndrome superior to other atherogenic indices in the schizophrenia population.¹¹

On the other hand, schizophrenia patients tend to engage in sedentary lifestyles than general population, which is found to be associated with reduced functional exercise capacity and increased cardiometabolic concerns.¹² One study suggested schizophrenia patients with metabolic syndrome presents poorer physical capacity measured by 6-minute walk test (6MWT) and manifests significantly different levels of four in five metabolic syndrome components, including waist circumference, blood pressure, glucose and TG than those without metabolic syndrome, except the levels of HDL-C.¹³ However, according to the criteria of low HDL-C in metabolic syndrome, females have higher HDL-C threshold levels than males.¹⁴ The prior work showed 6MWT differences by metabolic syndrome but not specified by low HDL-C based on sex-different thresholds of HDL-C levels. Therefore, the knowledge gap regarding whether physical capacity and sex have independent influences on low HDL-C remains unclear. Due to the important health impact of HDL-C and its multi-factorial mechanisms,¹⁵ further study is warranted to evaluate the possible modifiable risk factors with regard to low HDL-C to present the hints in order to correct the HDL-C abnormality is clinically important.

To date, the predictors associated with low HDL-C in schizophrenia patients have not been established. The overall aims of the cross-sectional study were to adopt logistic regression analyses to 1) investigate the significant predictors of low HDL-C diagnosed by sex-specified HDL-C thresholds, 2) and compare three model performances by controlling for potential confounding factors.

Methods

Participant

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB No. 202100168B0) and complied with the Declaration of Helsinki. After providing a detailed explanation of the study, written informed consent was obtained from all participants. Eligible patients with schizophrenia were recruited from Kaohsiung Chang Gung Memorial Hospital if they met the following criteria: (1) 20–60 years of age, (2) having a diagnosis of schizophrenia as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5),¹⁶ (3) being treated with an antipsychotic drug at a stable dose for at least 1 month before the study and with relatively stable psychotic symptoms, as defined by a total score on the Positive and Negative Syndrome Scale (PANSS) of <95,¹⁷ (4) no history of major physical illnesses, such as cardiovascular disease, neuromuscular disorders or renal disorders, for safe exercise participation,¹⁸ and (5) no physical disability that caused difficulty in walking.

Sample Size

Given effect size = 0.7 and $\alpha = 0.05$, a minimum of 110 schizophrenia patients were required to achieve 95% of power using G*Power 3.1. software.

Baseline Assessments

Clinical Characteristics

The psychiatric diagnoses of the patients with schizophrenia were performed using the Mini International Neuropsychiatric Interview (MINI), which is a short and structured diagnostic interview for assessing psychiatric disorders.¹⁹ The MINI in Mandarin Chinese has been widely used in international researches with satisfactory reliability.²⁰ Patients' age at onset, duration of illness and hospitalization times were obtained through interviews with the patients and a review of their medical records. The psychopathology of patients with schizophrenia was evaluated using the PANSS, which consists of three subscales representing positive, negative, and general psychiatric symptoms.²¹ The use of hypolipidemic drugs use and diagnosis of diabetes mellitus were recorded.

Antipsychotic Treatment

The patients included were treated with a stable dose of an antipsychotic drug for at least 1 month before the study began. On the basis of the properties of the muscarinic-binding affinity antipsychotics were categorized into high (clozapine or olanzapine) and low (antipsychotics other than clozapine or olanzapine) groups.²² The dose of antipsychotic drugs was recalculated based on the defined daily dose recommended by the World Health Organization Collaborating Centre for Drug Statistics Methodology.²³

Biochemical Measures

Metabolic indices, including glucose and lipid profiles of HDL-C, TG, total cholesterol (TC) and low-density lipoprotein cholesterol (LDL), were measured by colorimetric method after 8–10 h of overnight fasting at the Laboratory of Medicine, Kaohsiung Chang Gung Memorial Hospital. Height (centimeter) and weight (kilogram) were measured by one research staff member. Body mass index (BMI, kg/m²) was calculated by weight (in kilogram) divided by height (in meter). Low HDL-C was defined as the presence the sex-specific HDL-C thresholds:¹⁴ HDL-C <40 mg/dL (1.0 mmol/L) in males or <50 mg/dL (1.3 mmol/L) in females. AIP was calculated using the following formula: $\log_{10}(\text{TG}/\text{HDL-C})$. Patients with schizophrenia were further categorized into a group with normal HDL-C and a group with low HDL-C.

6-Minute Walk Test (6MWT) Measures

The physical capacity was measured by 6MWT performed in a 25-m, flat and straight indoor corridor of the study hospital site to prevent external stimuli. 6MWT has been shown to be better tolerated and to demonstrate more daily activities than other exercise tests.²⁴ All participants were instructed to walk back and forth for six minutes as fast as possible without jogging or running according to the recommendations of the American Thoracic Society.²⁵ Although 30-m is standard corridor for 6MWT, non-standard 25-m corridor has good reliability of schizophrenia patients and is well adopted in schizophrenia researches.^{26,27} The total distances walked in meters were measured and recorded as the 6MWT distances for statistical analyses, with the greater 6MWT distances suggesting superior physical capacity. A cutoff of >366-meter was calculated by the mean value minus standard error.

Statistical Analysis

SPSS for Windows (version 21.0; SPSS, Inc., Chicago, IL, USA) and R software 4.5.2 were used to analyze data. Variables are presented as either mean $\pm$ standard deviation or frequency.

The chi-square test was used to compare categorical variables between groups. We checked the normality of variables by using Kolmogorov Smirnov Test. Descriptive statistics were calculated using the independent *t* test or Mann Whitney *u*-test to compare the continuous variables of demographic data and disease characteristics. The area under the receiver operating characteristics curve (AUC) was calculated to examine the model performance. We adopted logistic regression to determine the significant predictors correlated with low HDL-C among all participants with schizophrenia. The logistic regression modeling included variables (sex, hospitalization times, 6MWT distances, TG, education years, height and BMI) which were significantly different between groups. After using Durbin–Watson statistics, the value 1.793 indicated there was no autocorrelation. We then used variation inflation factor <10 to test multi-collinearity and found no collinearity. The predictors included sex, hospitalization times, 6MWT distances and TG, and the primary outcome was low HDL-C. Dummy codes were set for sex (female = 0, male = 1) and the group of HDL-C (normal HDL-C = 0, low HDL-C = 1). Male sex and the group of normal HDL-C were category references to female sex and the group of low HDL-C, respectively. Variables of education years, height and BMI were selected as covariates. The model fit was verified using the Hosmer–Lemeshow goodness-of-fit test, with a *p*-value >0.05 indicating a good fit. On the other hand, we used R software 4.5.2 with 1000 bootstrap resamples for model validation, assumption check, and calibration; accuracy, sensitivity and specificity were assessed. In Model 1, no covariates were selected to control. In Model 2, the covariate of education years was selected to control. In Model 3, the covariates of education years, height and BMI were selected to control. All three models had a good model fit according to the results of the Hosmer–Lemeshow goodness-of-fit test (all *p*-value > 0.05). The calibration curves of all three models also had a good fit between the predicted and

actual probabilities (Supplementary Figure 1). All continuous variables had liner fit with the log-odds of the primary outcome (Supplementary Figure 2). Unstandardized coefficients (B value), standard errors (SE) and Odds ratios (OR) with 95% confidence intervals (CIs) were computed. The False Discovery Rate (FDR) correction was adopted to adjust for multiple comparisons of all p -value. P value of FDR less than 0.05 was considered statistically significant after correcting for multiple comparisons. Standardized effect size was reported as the absolute value of Cohen's d .

Results

Between-Group Differences of Subjective Characteristics and Metabolic Indices

A total of 133 patients with schizophrenia were recruited; 12 patients refused to participate in the study. One patient had missing data and was removed from statistical analysis. The remaining 120 participants were categorized to the group with normal HDL-C ($n = 73$, 60.8%) or group with low HDL-C ($n = 47$, 39.2%) (Figure 1).

Table 1 presents a summary of the characteristics of the participants in the two groups. The group with low HDL-C had higher female proportion (76.6% vs 45.2%, $p < 0.01$), higher education years (13.9 ± 2.0 years vs 13.0 ± 2.2 years, $p < 0.05$, Cohen's $d = 0.391$), shorter height (161.6 ± 7.2 cm vs 164.9 ± 9.5 cm, $p < 0.05$, Cohen's $d = 0.386$), higher BMI (28.8 ± 6.0 kg/m² vs 26.2 ± 5.4 kg/m², $p < 0.05$, Cohen's $d = 0.464$) and higher hospitalization times (6.1 ± 6.5 vs 3.5 ± 4.5 , $p < 0.01$, Cohen's $d = 0.481$) than the normal HDL-C group. Low HDL-C group (normal HDL-C = 0, low HDL-C = 1) negatively associated with height. Demographic characteristics included age and cigarette use, and other disease characteristics included the antipsychotics dose did not differ significantly between the groups. There were no significant differences of hypolipidemic drugs use and diabetes mellitus between groups.

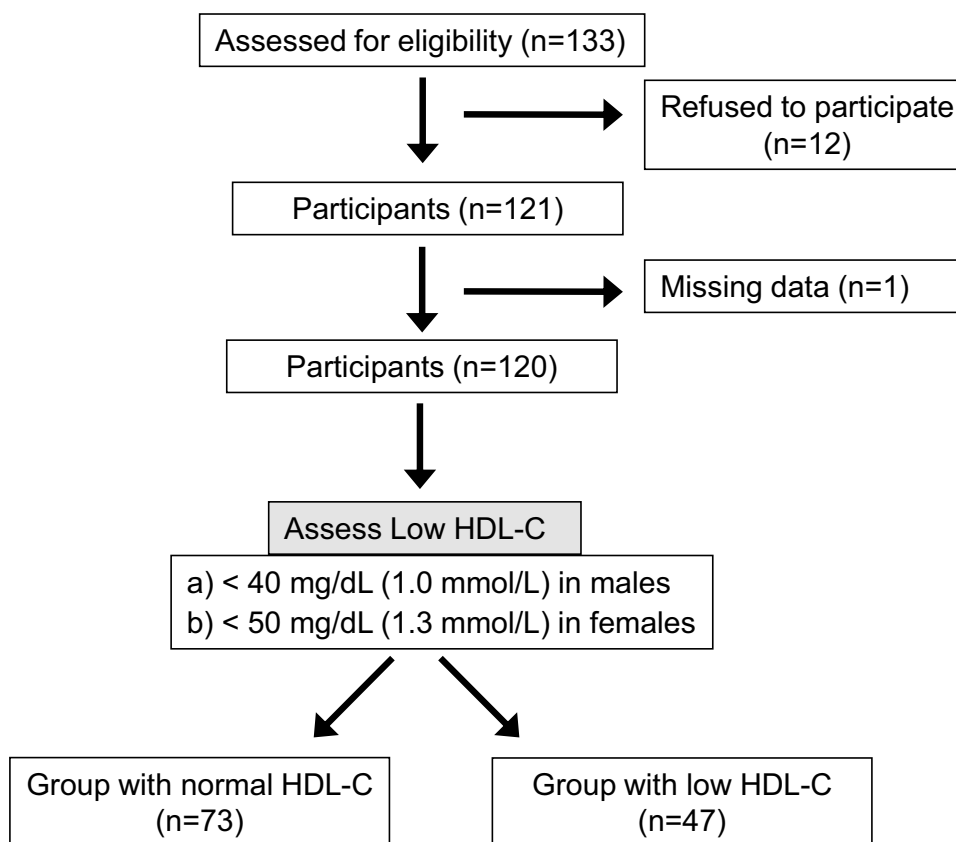


Figure 1 The participant flowchart of study design.

Table 1 Comparisons of Subject Characteristics Between Schizophrenia Patients with Normal HDL-C (n = 73) and Low HDL-C (n = 47)

	Normal HDL-C (n=73)	Low HDL-C (n=47)	Statistic Value	P-value
Demographic data				
Age	40.9 ± 8.8	42.2 ± 10.2	t = -0.740	0.461
Sex, female n (%)	33 (45.2)	36 (76.6)	$\chi^2 = 11.528$	<0.01**
Education, years	13.0 ± 2.2	13.9 ± 2.0	t = -2.102	0.039* [†]
Cigarette use, n (%)	9 (12.3)	8 (17.0)	$\chi^2 = 0.518$	0.472
Height, cm	164.9 ± 9.5	161.6 ± 7.2	t = 2.190	0.040*
Body weight, kg	70.9 ± 14.5	75.1 ± 17.6	t = -1.406	0.162
Body mass index, kg/m ²	26.2 ± 5.4	28.8 ± 6.0	t = -2.482	0.041*
Disease characteristics				
Age of onset, years	22.9 ± 5.9	24.9 ± 8.4	t = -1.564	0.224 [†]
Duration of illness, years	18.0 ± 8.8	17.1 ± 9.7	t = 0.530	0.597
Hospitalization times	3.5 ± 4.5	6.1 ± 6.5	t = -2.565	0.001** [†]
Total score of PANSS	75.5 ± 15.7	74.5 ± 13.1	t = 0.334	0.739
Positive symptoms score	15.4 ± 4.2	15.8 ± 4.3	t = -0.411	0.816 [†]
Negative symptoms score	20.6 ± 5.2	20.4 ± 4.2	t = 0.257	0.998 [†]
General symptoms score	39.5 ± 8.4	38.4 ± 6.7	t = 0.730	0.467
DDD of antipsychotics	1.0 ± 0.6	0.8 ± 0.6	t = 1.688	0.062 [†]
Groups of antipsychotics			$\chi^2 = 2.124$	0.346
Olanzapine or Clozapine, n (%)	32 (43.8)	27 (57.4)		
Aripiprazole or ziprasidone, n (%)	16 (21.9)	8 (17.0)		
Other antipsychotics, n (%)	25 (34.2)	12 (25.5)		
Hypolipidemic drugs use, n (%)	6 (8.2)	5 (10.6)	$\chi^2 = 1.201$	0.654
Diabetes Mellitus, n (%)	6 (8.2)	7 (14.9)	$\chi^2 = 1.319$	0.251

Note: [†] p value calculated by Mann Whitney *u*-test. **p*<0.05, ***p*<0.01.

Abbreviations: DDD, defined daily dose; HDL-C, high-density lipoprotein-cholesterol; PANSS, Positive and Negative Syndrome Scale.

Between-Group Differences of Metabolic Indices and AIP

Figure 2 shows that the group with low-HDL had higher TG values (156.7 ± 103.3 mg/dL vs 111.0 ± 75.8 mg/dL, *p* < 0.01, Cohen's *d* = 0.522) and higher AIP (0.5 ± 0.2 vs 0.2 ± 0.3 , *p* < 0.001, Cohen's *d* = 1.297) than the group with normal HDL-C, while there were no significant differences of TC (181.9 ± 32.6 mg/dL vs 189.4 ± 36.1 mg/dL, Cohen's *d* = 0.215) and LDL (107.1 ± 35.2 mg/dL vs 105.1 ± 29.8 mg/dL, Cohen's *d* = 0.063) between groups.

Between-Group Differences of 6MWT Distances

Figure 3 presents that the group of low HDL-C had shorter 6MWT distances (426.6 ± 93.0 m vs 470.4 ± 80.4 m, *p* < 0.01, Cohen's *d* = 0.511) than the group with normal HDL-C. By using the value of 366-meter as the cut-off point of the 6MWT distances, higher proportion of shorter 6MWT distances in the group of low HDL-C (19.1% vs 6.8%, *p* < 0.05) was statistically significant.

Logistic Regression Analysis for Examining the Most Correlation with Low HDL-C

Model 1 (AUC = 0.79, 95% CI = 0.716–0.864, accuracy/sensitivity/specificity = 0.73/0.60/0.81) revealed that female sex (B = 1.382, SE = 0.460, OR = 3.982, 95% CI = 1.617–9.808), hospitalization times (B = 0.080, SE = 0.040, OR = 1.083, 95% CI = 1.002–1.171), 6MWT distances (B = -0.005, SE = 0.003, OR = 0.995, 95% CI = 0.990–1.000) and TG (B = 0.007, SE = 0.003, OR = 1.008, 95% CI = 1.002–1.013) significantly correlated with low HDL-C after FDR correction (all *p* < 0.05). The above-mentioned predictors were significant correlation after controlling for covariates of education in Model 2 (AUC = 0.82, 95% CI = 0.740–0.883, accuracy/sensitivity/specificity = 0.75/0.66/0.81). Model 3 (AUC = 0.82, 95% CI = 0.742–0.892, accuracy/sensitivity/specificity = 0.76/0.64/0.84) controlled for education, height and BMI, and found that female sex (B = 1.382, SE = 0.648, OR = 3.983, 95% CI = 1.118–14.185), hospitalization times (B = 0.086,

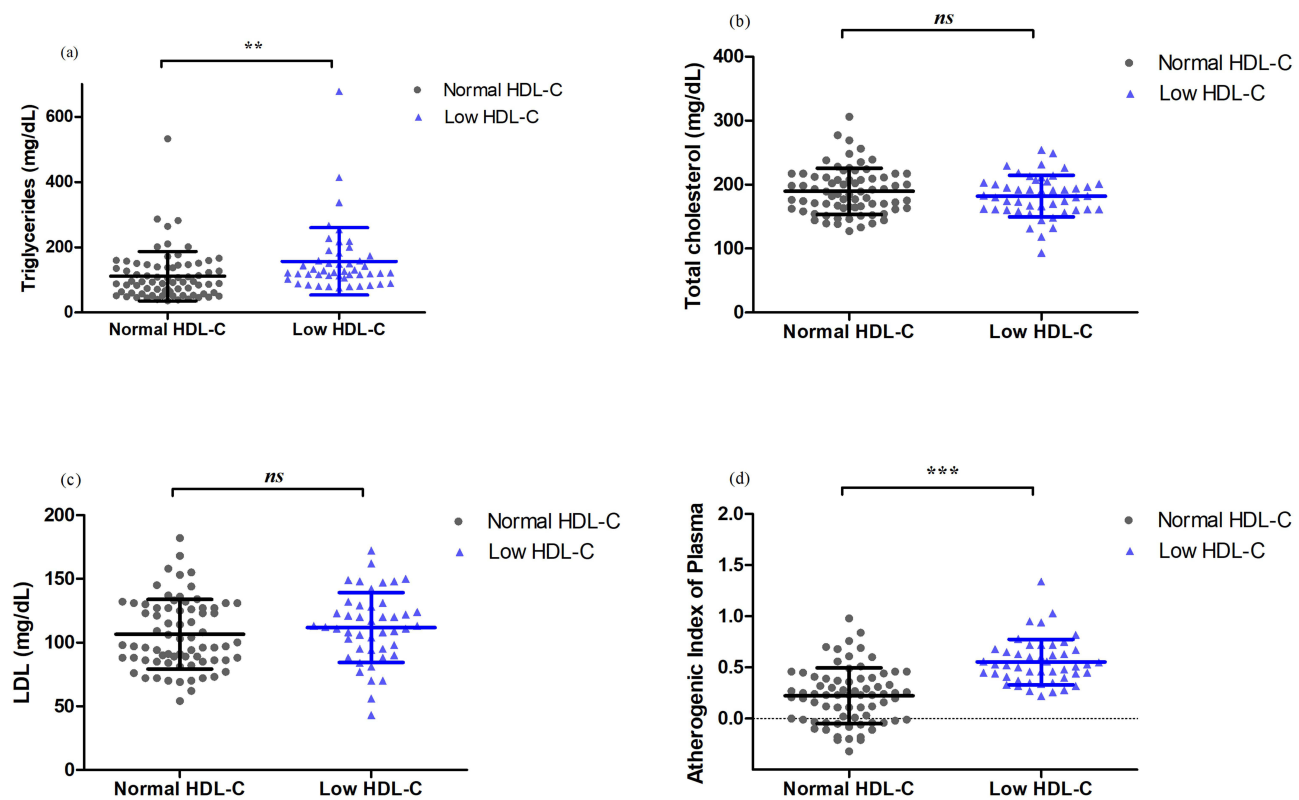


Figure 2 The differences of metabolic indices and the atherogenic index of plasma levels between the group with normal HDL-C (n=73) and the group with low HDL-C (n=47). (a) Triglycerides. (b) Total cholesterol. (c) Low-density lipoprotein cholesterol. (d) Atherogenic index of plasma. ** $p < 0.01$, *** $p < 0.001$; ns, nonsignificant.

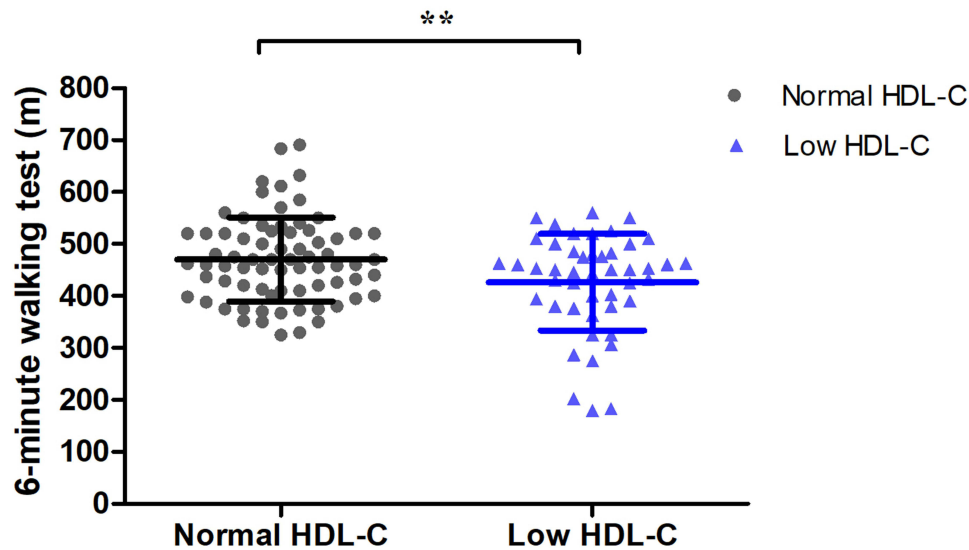


Figure 3 The differences of the 6-minute walk test distances between the group with normal HDL-C (n=73) and the group with low HDL-C (n=47). ** $p < 0.01$.

SE = 0.042, OR = 1.090, 95% CI = 1.003–1.184), 6MWT distances (B = -0.007, SE = 0.003, OR = 0.993, 95% CI = 0.987–0.999) and TG (B = 0.008, SE = 0.003, OR = 1.008, 95% CI = 1.002–1.014) (all $p < 0.05$) remained significant (Table 2). Both Model 2 and 3 had superior performance than Model 1, while Model 3 showed relatively optimal accuracy and specificity with similar performance of Model 2.

Table 2 Logistic Regression Models Predicting Low HDL-C Among All Participants (n = 120)

	Model 1				Model 2				Model 3			
	B SE	Odds Ratio	95% CI	P-value	B SE	Odds Ratio	95% CI	P-value	B SE	Odds Ratio	95% CI	P-value
Sex ^a	1.382 0.460	3.982	1.617–9.808	< 0.05*	1.276 0.477	3.583	1.408–9.119	< 0.05*	1.382 0.648	3.983	1.118–14.185	< 0.05*
Hospitalization times	0.080 0.040	1.083	1.002–1.171	< 0.05*	0.091 0.041	1.095	1.010–1.188	< 0.05*	0.086 0.042	1.090	1.003–1.184	< 0.05*
6-minute walk test, m	−0.005 0.003	0.995	0.990–1.000	< 0.05*	−0.007 0.003	0.993	0.987–0.998	< 0.05*	−0.007 0.003	0.993	0.987–0.999	< 0.05*
Triglycerides, mg/dL	0.007 0.003	1.008	1.002–1.013	< 0.05*	0.008 0.003	1.008	1.002–1.014	< 0.05*	0.008 0.003	1.008	1.002–1.014	< 0.05*

Note: The group was dummy coded “0” for normal HDL-C, and “1” for low HDL-C according to the sex-dependent HDL-C threshold. ^a Sex was dummy coded “0” for female, and “1” for male as category reference. Model 1 had no adjustment for covariates. Model 2 was adjusted for one covariate of education. Model 3 was adjusted for three covariates of education, height and body mass index. B: unstandardized coefficients; SE: standard errors; 95% CI: 95% confidence interval. * significant at < 0.05 Benjamini-Hochberg FDR level for multiple comparisons.

Discussion

To our knowledge, this is the first study to date to evaluate the predictors of low HDL-C in schizophrenia patients. The study provides the following insights in schizophrenia patients: (1) the low HDL-C group had higher female proportion, higher education years, shorter height, higher BMI, higher hospitalization times, higher TG values, higher AIP level and poorer physical capacity, (2) female sex, higher hospitalization times, poor physical capacity and high TG levels had increased risks of low HDL-C in all three models, in which Model 3 had superior accuracy and specificity, but with similar performance of Model 2.

The Association Between Sex and Low HDL-C

The results regarding the effect of sex on serum lipids remain inconsistent.²⁸ The prevalence of low HDL-C in this study was 39.2%, which is higher than that (25%) in the general population,²⁹ and lower than previous finding in treated patients (44.7%).³⁰ Our results show that female schizophrenia is predominant in higher risks of manifesting low HDL-C is supported by previous studies.^{29–31} The overall prevalence of metabolic syndrome is increasing worldwide, and the trend is higher in females than males, especially in younger age. Obesity is suggested to play an important role in this trend.²⁸ The difference in the distribution of metabolic syndrome components between male and female contributes to the different trend of metabolic syndrome.³¹ Lipids accumulation patterns differ between females and males. Although peripheral and central obesity could be found in both sex, females are more often to develop peripheral obesity, while males are more frequent to develop central obesity. After menopause, the lipid accumulation shifts from peripheral to central obesity.^{28–31} However, the studies focusing on investigating the effect of estrogen on the prevalence of metabolic syndrome components reveal mixed findings. Other sex-related disparities such as shorter height in females and various patterns of lifestyle activities and nutrition intake between males and females are also considered.^{29–33} In our study, we suggest that female is a significant predictor of low HDL-C in schizophrenia patients after controlling for height as well as education years and BMI. This finding gives an important hint to screen HDL-C levels in order to assess if the HDL-C meeting the diagnosis of low HDL-C in schizophrenia, especially in female patients.

The Association Between Hospitalization Times and Low HDL-C

Psychiatric hospitalizations is an important factor in the illness course in schizophrenia, which exerts an unfavorable effect on treatment outcomes and likelihood to recover from acute phase, especially re-hospitalizations.³⁴ However, other researchers found that deinstitutionalization may be associated with increasing cardiovascular mortality ratios for all causes of death.³⁵ Despite this, chronic schizophrenia with antipsychotics treatment has higher risk of cardiometabolic abnormalities than those in the first episode through lifestyle interventions.³⁰ In our study, we found that increased hospitalization times after psychosis relapsing is a significant predictor of low HDL-C in schizophrenia patients, who also

manifested higher cardiometabolic risk indexed by AIP levels. This exploratory result hints that the treatment to prevent relapses is essential for reducing cardiometabolic comorbidity in schizophrenia patients. More investigations are warranted to explore the underlying mechanisms regarding the relationship between hospitalization times and low HDL-C.

The Association Between Physical Capacity and Low HDL-C

Enhancing physical activity and reducing sedentary patterns are suggested as essential strategies in modifying lifestyle to prevent cardiovascular disease.³⁶ Some studies reported that physical activity has beneficial effect on improving HDL-C and lowering TG.^{37–39} On population cohort study observed that physical activity at different ages in adulthood has positive effect on HDL-C; though the association between physical activity and lipid profile became nonsignificant after controlling for lifestyle factors and BMI, except males with activity higher than moderate intensity.⁴⁰ On the contrary, one population cohort study found that, after controlling for confounding factors, physical activity correlated with increasing HDL-C level significantly in female, but not in male.⁴¹ Another study observed that physical activity has no significant correlation with HDL-C level in female.⁴² Previous study observed that schizophrenia patients with metabolic syndrome achieve shorter 6MWT distances than those without metabolic syndrome though there is no difference of HDL-C levels between groups.¹³ In our study, we observed that patients with shorter 6MWT distances showed significantly higher risks of low HDL-C than those with normal HDL-C. The result provides important information to fill the prior knowledge gap; if taking into account of sex-specific HDL-C threshold to assess the diagnosis of low HDL-C, the association between physical capacity and low HDL-C is significant.

The Association Between TG and Low HDL-C

HDL-C particles consist of various subgroups of proteins with abundant apolipoprotein A-I, cholesterol, and phospholipids and present various functions, including antioxidant, anti-inflammatory, and immunomodulatory effects.⁴³ HDL-C metabolism is closely linked with TG metabolism. During the HDL particle maturation process, the hydrolysis of TG is suggested to play an important role in transferring cholesterol and apolipoproteins to HDL particles as surface components.⁴⁴ Alterations in plasma TG levels may result in a significant change in HDL-C catabolic pathways.¹⁵ It has been suggested that high TG levels which contribute to TG-rich lipoproteins of HDL-C particles could increase the catabolism rate of HDL-C.^{15–45} Increased TG together with decreased HDL-C concentrations are associated with increased risk of atherosclerosis and the following cardiovascular disease.⁴⁶ In our study, the result that the group with low HDL-C had higher AIP level provides information that schizophrenia patients with low HDL-C have more severe inflammation and higher risks in manifesting atherosclerosis. On the other hand, we observed that higher TG level demonstrates an independent factor in correlation with low HDL-C, which is in agreement with the above-mentioned metabolism process of HDL-C and TG. The conclusion implies clinicians keep in mind the modifiable factors regarding elevated TG levels in schizophrenia patients to prevent low HDL-C and the following cardiovascular disease risks in schizophrenia.

Limitations

This study has some limitations that should be considered. First, this work suggests a cross-sectional correlation among the independent factors and low HDL-C in patients with schizophrenia and therefore does not provide information regarding the possible directionality of any associations. Second, this design did not control for the diet, adiposity distribution, medication effects, and menopausal status, which may be associated with lipid profiles. For example, high percentage of carbohydrate intake is associated with decreased HDL-C and increased TG levels and lower HDL levels.⁴⁷ Further research is warranted to include the variables for further clarification. Finally, the relatively small sample size may limit the interpretation of this study, and the results may not be generalized to all patients with schizophrenia.

Conclusion

In summary, the results provide an important clinical utility for physicians to assess low HDL-C, especially for female schizophrenia with higher hospitalization, shorter 6MWT distances or higher TG due to increased susceptibility to

cardiometabolic risks. Future prospective studies with larger samples are necessary to further clarify the causal relationship among the various metabolic indices and physical capacity and low HDL-C during their treatment with antipsychotics.

Abbreviations

6MWT, 6-minute walk test; AIP, Atherogenic index of plasma; BMI, body mass index; CI, confidence interval; DDD, defined daily dose; DSM-5, fifth edition of the Diagnostic and Statistical Manual of Mental Disorders; HDL-C, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein-cholesterol; MINI, Mini International Neuropsychiatric Interview; OR, Odds ratios; PANSS, Positive and Negative Syndrome Scale; SE, standard errors; TC, total cholesterol; TG, triglycerides.

Acknowledgments

The authors express their deepest gratitude to all participants enrolled in this study, and the Biostatistics Center, Kaohsiung Chung Gung Memorial Hospital for statistics work.

Funding

This study was supported by the Ministry of Science and Technology Research Project in Taiwan (MOST 110-2314-B-182A-038-MY3, MOST 110-2629-B-182A-001, NSTC 113-2629-B-182A-001). The funding sources had no involvement in the study design, collection, analysis and interpretation of data, writing of the report or the decision to submit the article for publication.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Lakhan SE. Schizophrenia proteomics: biomarkers on the path to laboratory medicine? *Diagn Pathol.* **2006**;1(1):11. doi:10.1186/1746-1596-1-11
2. Vancampfort D, Stubbs B, Mitchell AJ, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry.* **2015**;14(3):339–347. doi:10.1002/wps.20252
3. Vancampfort D, Correll CU, Gallinger B, et al. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. *World Psychiatry.* **2016**;15(2):166–174. doi:10.1002/wps.20309
4. Hoang U, Goldacre MJ, Stewart R. Avoidable mortality in people with schizophrenia or bipolar disorder in England. *Acta Psychiatr Scand.* **2013**;127(3):195–201. doi:10.1111/acps.12045
5. Hwang L-C, Bai C-H, Chen C-J, Chien K-L. Gender difference on the development of metabolic syndrome: a population-based study in Taiwan. *Eur J Epidemiol.* **2007**;22(12):899–906. doi:10.1007/s10654-007-9183-5
6. Vinik AI. The metabolic basis of atherogenic dyslipidemia. *Clin Cornerstone.* **2005**;7(2–3):27–35. doi:10.1016/S1098-3597(05)80065-1
7. Musunuru K. Atherogenic dyslipidemia: cardiovascular risk and dietary intervention. *Lipids.* **2010**;45(10):907–914. doi:10.1007/s11745-010-3408-1
8. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American heart association/national heart, lung, and blood institute scientific statement. *Circulation.* **2005**;112(17):2735–2752. doi:10.1161/CIRCULATIONAHA.105.169404
9. Lu Q, Tian G, Zhang Y, Lu M, Lin X, Ma A. Low HDL-C predicts risk and PCI outcomes in the Han Chinese population. *Atherosclerosis.* **2013**;226(1):193–197. doi:10.1016/j.atherosclerosis.2012.09.011
10. Kim SH, Cho YK, Kim YJ, et al. Association of the atherogenic index of plasma with cardiovascular risk beyond the traditional risk factors: a nationwide population-based cohort study. *Cardiovasc Diabetol.* **2022**;21(1):81. doi:10.1186/s12933-022-01522-8
11. Tien Y-T, Wang L-J, Lee Y, et al. Comparative predictive efficacy of atherogenic indices on metabolic syndrome in patients with schizophrenia. *Schizophr Res.* **2023**;262:95–101. doi:10.1016/j.schres.2023.10.023
12. Stubbs B, Chen L-J, Chung M-S, Ku P-W. Physical activity ameliorates the association between sedentary behavior and cardiometabolic risk among inpatients with schizophrenia: a comparison versus controls using accelerometry. *Compr Psychiatry.* **2017**;74:144–150. doi:10.1016/j.comppsy.2017.01.010
13. Vancampfort D, Sweers K, Probst M, et al. Association of the metabolic syndrome with physical activity performance in patients with schizophrenia. *Diabetes Metab.* **2011**;37(4):318–323. doi:10.1016/j.diabet.2010.12.007
14. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. *Circulation.* **2009**;120(16):1640–1645. doi:10.1161/CIRCULATIONAHA.109.192644
15. Lamarche B, Rashid S, Lewis GF. HDL metabolism in hypertriglyceridemic states: an overview. *Clin Chim Acta.* **1999**;286(1–2):145–161. doi:10.1016/S0009-8981(99)00098-4

16. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. VA United States: American Psychiatric Association; 2013.
17. Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean? *Schizophr Res*. 2005;79(2–3):231–238. doi:10.1016/j.schres.2005.04.008
18. American College of Sports Medicine. 2025. Available from: <https://www.acsm.org/education-resources/trending-topics-resources/physical-activity-guidelines>. Accessed January 13, 2026.
19. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59(Suppl 20):22–33;quiz34–57.
20. Chou FH-C, Chou P, Su TT-P, et al. Quality of life and related risk factors in a Taiwanese Village population 21 months after an earthquake. *Aust N Z J Psychiatry*. 2004;38(5):358–364. doi:10.1080/j.1440-1614.2004.01364.x
21. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276. doi:10.1093/schbul/13.2.261
22. Aringhieri S, Carli M, Kolachalam S, et al. Molecular targets of atypical antipsychotics: from mechanism of action to clinical differences. *Pharmacol Ther*. 2018;192:20–41. doi:10.1016/j.pharmthera.2018.06.012
23. WHO. Available from: http://www.whooc.no/atc_ddd_index/. Accessed January 13, 2026. 2025.
24. Bernard P, Romain AJ, Vancampfort D, Baillot A, Esseul E, Ninot G. Six minutes walk test for individuals with schizophrenia. *Disabil Rehabil*. 2015;37(11):921–927. doi:10.3109/09638288.2014.948136
25. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111–117. doi:10.1164/ajrcm.166.1.at1102
26. Gomes E, Bastos T, Probst M, Ribeiro JC, Silva G, Corredeira R. Reliability and validity of 6MWT for outpatients with schizophrenia: a preliminary study. *Psychiatry Res*. 2016;237:37–42. doi:10.1016/j.psychres.2016.01.066
27. Huang W-J, Pellegrini CA, Chen M-D, et al. The correlates and reference values for the 6-minute walk distance in Taiwanese adults with schizophrenia. *Disabil Rehabil*. 2023;45(21):3567–3572. doi:10.1080/09638288.2022.2125592
28. Regitz-Zagrosek V, Lehmkuhl E, Weickert MO. Gender differences in the metabolic syndrome and their role for cardiovascular disease. *Clin Res Cardiol*. 2006;95(3):136–147. doi:10.1007/s00392-006-0351-5
29. Yang Y-M, Shin B-C, Son C, Ha I-H. An analysis of the associations between gender and metabolic syndrome components in Korean adults: a national cross-sectional study. *BMC Endocr Disord*. 2019;19(1):67. doi:10.1186/s12902-019-0393-0
30. Mitchell AJ, Vancampfort D, De Herdt A, Yu W, De Hert M. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. *Schizophr Bull*. 2013;39(2):295–305. doi:10.1093/schbul/sbs082
31. Yousefzadeh G, Sheikvatan M. Age and gender differences in the clustering of metabolic syndrome combinations: a prospective cohort research from the Kerman coronary artery disease risk study (KERCADRS). *Diabetes Metab Syndr*. 2015;9(4):337–342. doi:10.1016/j.dsx.2013.02.023
32. Group EUCCS, Regitz-Zagrosek V, Oertelt-Prigione S, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur Heart J*. 2016;37(1):24–34.
33. Ogata T, Hattori A, Fukami M. *SHOX* and sex difference in height: a hypothesis. *Endocr J*. 2025;72(1):37–42. doi:10.1507/endocrj.EJ24-0249
34. Lieberman JA, Koren AR, Chakos M, et al. Factors influencing treatment response and outcome of first-episode schizophrenia: implications for understanding the pathophysiology of schizophrenia. *J Clin Psychiatry*. 1996;57 Suppl 9(Suppl 9):5–9.
35. Hansen V, Jacobsen BK, Arnesen E. Cause-specific mortality in psychiatric patients after deinstitutionalisation. *Br J Psychiatry*. 2001;179(5):438–443. doi:10.1192/bjp.179.5.438
36. Artinian NT, Fletcher GF, Mozaffarian D, et al. Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American heart association. *Circulation*. 2010;122(4):406–441. doi:10.1161/CIR.0b013e3181e8edf1
37. Aadahl M, von Huth Smith L, Pisinger C, et al. Five-year change in physical activity is associated with changes in cardiovascular disease risk factors: the Inter99 study. *Prev Med*. 2009;48(4):326–331. doi:10.1016/j.ypmed.2009.01.015
38. Monda KL, Ballantyne CM, North KE. Longitudinal impact of physical activity on lipid profiles in middle-aged adults: the atherosclerosis risk in communities study. *J Lipid Res*. 2009;50(8):1685–1691. doi:10.1194/jlr.P900029-JLR200
39. Thompson PD, Buchner D, Pina IL, et al. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the council on clinical cardiology (subcommittee on exercise, rehabilitation, and prevention) and the council on nutrition, physical activity, and metabolism (subcommittee on physical Activity). *Circulation*. 2003;107(24):3109–3116. doi:10.1161/01.CIR.0000075572.40158.77
40. Ki M, Poulouli T, Li L, Power C. Physical (in)activity over 20y in adulthood: associations with adult lipid levels in the 1958 British birth cohort. *Atherosclerosis*. 2011;219(1):361–367. doi:10.1016/j.atherosclerosis.2011.07.109
41. Skoumas J, Pitsavos C, Panagiotakos DB, et al. Physical activity, high density lipoprotein cholesterol and other lipids levels, in men and women from the ATTICA study. *Lipids Health Dis*. 2003;2(1):3. doi:10.1186/1476-511X-2-3
42. Ohmura S, Moji K, Aoyagi K, et al. Body mass index, physical activity, dietary intake, serum lipids and blood pressure of middle-aged Japanese women living in a community in the goto archipelago. *J Physiol Anthropol Appl Human Sci*. 2002;21(1):21–28. doi:10.2114/jpa.21.21
43. Mishra M, Muthuramu I, De Geest B. HDL dysfunction, function, and heart failure. *Aging*. 2019;11(2):293–294. Available from: <https://pubmed.ncbi.nlm.nih.gov/30654330/>
44. Murdoch SJ, Breckenridge WC. Influence of lipoprotein lipase and hepatic lipase on the transformation of VLDL and HDL during lipolysis of VLDL. *Atherosclerosis*. 1995;118(2):193–212. doi:10.1016/0021-9150(95)05606-8
45. Collins MW, Konig CS, Abbas A, Jewkes C, Jones AF, Ramachandran S. Association between triglyceride and high-density lipoprotein cholesterol change following fibrate therapy. *Diabetes Metab Syndr*. 2014;8(4):212–215. doi:10.1016/j.dsx.2014.09.004
46. Burchfiel CM, Laws A, Benfante R, et al. Combined effects of HDL cholesterol, triglyceride, and total cholesterol concentrations on 18-year risk of atherosclerotic disease. *Circulation*. 1995;92(6):1430–1436. doi:10.1161/01.CIR.92.6.1430
47. Jung C-H, Choi KM. Impact of high-carbohydrate diet on metabolic parameters in patients with type 2 diabetes. *Nutrients*. 2017;9(4):322. doi:10.3390/nu9040322

Neuropsychiatric Disease and Treatment**Dovepress**
Taylor & Francis Group**Publish your work in this journal**

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the 'PsycINFO' database and CAS, and is the official journal of The International Neuropsychiatric Association (INA). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>