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Chronotype Differences in Lipid Profile and Atherogenic Risk Indices Among Patients with Bipolar Disorder

Bipolar Bozukluğu Olan Hastalarda Lipid Profili ve Aterojenik Risk İndekslerinde Kronotip Farklılıkları

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Abstract

Objective: Bipolar disorder (BD) is associated with a high cardiometabolic burden, influenced by factors such as lifestyle, medication, and circadian disruption. The study aimed to investigate the association between chronotype and cardiometabolic parameters in patients with BD.
Materials and Methods: This cross-sectional study included 69 euthymic patients with BD I or II attending a community mental health center in Türkiye. Sociodemographic and clinical data were obtained alongside anthropometric measures, fasting blood samples, and psychometric assessments. Chronotype was determined using the Morningness–Eveningness Questionnaire, and patients were categorized into eveningness, intermediate, or morningness groups. Metabolic markers included body mass index, fasting glucose, triglycerides, total cholesterol, LDL-c, HDL-c, atherogenic coefficient, and Castelli risk indices.
Results: Chronotype distribution was 27.5% (n=19) eveningness, 47.8% (n=33) intermediate, and 24.6% (n=17) morningness. Eveningness was associated with significantly lower total cholesterol and LDL-cholesterol levels, as well as more favorable atherogenic coefficient and Castelli risk indices compared with intermediate and morningness types (all FDR-corrected p<0.05). In ANCOVA models, chronotype remained significantly associated with LDL-cholesterol and all atherogenic indices after adjustment for demographic variables, BMI, smoking, antipsychotic treatment, and valproate use (all p<0.05). Higher MEQ scores (greater morningness) were positively correlated with LDL-cholesterol and atherogenic indices.
Conclusion: Eveningness was linked to a healthier lipid profile in euthymic patients with bipolar disorder. This finding differs from most earlier studies and suggests that the effect of chronotype on metabolism may change depending on context. Considering chronotype could help personalize care and prevent metabolic problems in bipolar disorder.
Keywords: Atherogenic indices, bipolar disorder, cardiometabolic risk, chronotype, circadian rhythm

Öz

Amaç: Bipolar bozukluk (BB), yaşam tarzı, ilaç kullanımı ve sirkadiyen ritim bozukluğu gibi faktörlerden etkilenen yüksek bir kardiyometabolik yük ile ilişkilidir. Çalışmanın amacı, BB tanılı hastalarda kronotip ile kardiyometabolik parametreler arasındaki ilişkiyi araştırmaktır.
Materyal ve Metot: Bu kesitsel çalışmaya, Türkiye'de bir toplum ruh sağlığı merkezine başvuran 69 ötimik BB I veya II hastaları dahil edilmiştir. Sosyodemografik ve klinik veriler, antropometrik ölçümler, açlık kan örnekleri ve psikometrik değerlendirmelerle birlikte elde edilmiştir. Kronotip, Sabahçıl-Akşamcıl Anketi kullanılarak belirlenmiş ve hastalar akşamcı, ara form veya sabahçı gruplarına ayrılmıştır. Metabolik belirteçler arasında vücut kitle indeksi, açlık glukozu, trigliseritler, toplam kolesterol, LDL-kolesterol, HDL-kolesterol, aterojenik katsayı ve Castelli risk indeksleri yer almaktadır.
Bulgular: Kronotip dağılımı %27,5 (n=19) akşamcıl, %47,8 (n=33) ara form ve %24,6 (n=17) sabahçıl olarak bulunmuştur. Akşamcıl tip, ara form ve sabahçıl tiplere kıyasla anlamlı derecede daha düşük toplam kolesterol ve LDL-kolesterol seviyeleri ile daha olumlu aterojenik katsayı ve Castelli risk indeksleri ile ilişkiliydi (tüm FDR düzeltilmiş p<0,05). ANCOVA modellerinde, demografik değişkenler, VKİ, sigara kullanımı, antipsikotik tedavi ve valproat kullanımı için ayarlama yapıldıktan sonra bile kronotip, LDL-kolesterol ve tüm aterojenik indekslerle anlamlı derecede ilişkili kaldı (tüm p<0,05). Daha yüksek MEQ puanları (daha fazla sabahçıl), LDL-kolesterol ve aterojenik indekslerle pozitif korelasyon gösterdi.
Sonuç: Akşamcılık, bipolar bozukluğu olan ötimik hastalarda daha sağlıklı bir lipid profiliyle ilişkilendirilmiştir. Bu bulgu, önceki çalışmaların çoğundan farklıdır ve kronotipin metabolizma üzerindeki etkisinin bağlama göre değişebileceğini düşündürmektedir. Kronotipin dikkate alınması, bipolar bozuklukta bakımın kişiselleştirilmesine ve metabolik sorunların önlenmesine yardımcı olabilir.
Anahtar Kelimeler: Aterojenik indeksler, bipolar bozukluk, kardiyometabolik risk, kronotip, sirkadiyen ritim

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INTRODUCTION

Bipolar disorder (BD) is a chronic mood disorder and has recurrent episodes of mania, hypomania, and depression.[1] Overall, cardiometabolic disorders, such as dyslipidemia, obesity, insulin resistance, and cardiovascular disease, are major causes of illness and early mortality in BD.[2] These risks are linked to lifestyle factors, medication effects, and shared biological mechanisms.[3] Recently, circadian rhythms and chronotype have gained attention as modifiable factors that may influence metabolic health in BD.[4]

Chronotype is defined as preferences for activity and alertness at certain times of the day and is generally categorized into morningness, intermediate, and eveningness types.[5] Most studies investigating cardiometabolic health by chronotype have shown that morningness is associated with more favorable metabolic outcomes.[6] However, eveningness-type individuals often have irregular eating habits, consume more calories, and are less physically active, which can increase metabolic risk.[7,8] Eveningness has also been linked to higher triglycerides, LDL cholesterol, glucose, and inflammation, increasing the risk of metabolic syndrome and type 2 diabetes.[6] In contrast, recent findings suggest that these patterns may differ by age and population. For example, eveningness has been linked to a lower risk of metabolic syndrome in adults under 40,[9] and one study reported lower arterial pressures in eveningness types.[10] In Black adults, morningness has been associated with higher rates of hypertension, diabetes, anxiety, and sleep apnea.[11] These mixed findings indicate that the chronotype–metabolism relationship is complex and warrants further study.[6,7]

Individuals with BD show a higher prevalence of eveningness compared with the general population.[12] Eveningness, or a preference for later sleep and wakefulness, has been associated with mood disturbances and more severe depressive symptoms.[13,14] In recent years, researchers have examined chronotype as a potential link between circadian disruption and metabolic health in BD.[4] Bipolar disorder patients with an evening chronotype have shown higher triglycerides, cholesterol, body mass index, and atherogenic risk, as well as a greater likelihood of metabolic syndrome and cardiovascular risk.[15-17] In addition, beyond standard lipid measurements, atherogenic indices and lipid-based inflammation ratios are emerging as sensitive markers of cardiovascular risk in bipolar disorder, particularly during acute mood episodes.[18] Together, these studies suggest that chronotype may modulate cardiometabolic risk in BD and potentially identify a subgroup of patients at high risk.[15]

This study aimed to explore the association between chronotype and cardiometabolic parameters in patients with BD. We hypothesized that different chronotypes would show distinct metabolic profiles, particularly in cholesterol levels and atherogenic indices.

MATERIALS AND METHODS

Ethics Committee Approval: This study was approved by the Health Sciences Scientific Research Ethics Committee of Sakarya University (Date: 19.11.2024, decision no: 2024/129). All procedures adhered to the ethical standards of the Declaration of Helsinki (2013 revision), and written informed consent was obtained from all participants before enrollment.

Study Design: This investigation was designed as a cross-sectional study carried out at the regional community mental health center (CMHC) in Türkiye. Individuals diagnosed with BD according to DSM-5 criteria and regularly attending the CMHC were invited to participate. The study combined structured sociodemographic assessments, anthropometric measurements, fasting blood analyses, and standardized rating scales for psychiatric and functional evaluation.

Sample: Sixty-nine patients diagnosed with BD were included in this study. Participants were required to be 18 years or older with a primary clinical diagnosis of BD type I or II confirmed by expert psychiatrists. Clinical euthymia at study entry was required and defined as a Young Mania Rating Scale (YMRS) score <6 and a Beck Depression Inventory (BDI) score <10, assessed during routine follow-up visits at the community mental health center. Only patients meeting these criteria were invited to participate. Exclusion criteria included patients with schizophrenia spectrum or related disorders, BD secondary to substance use or medical conditions, pregnancy or the postpartum period, significant cognitive or language impairments interfering with assessment, major neurological disorders (including acute injury, intellectual disability, or major neurocognitive disorder), any lifetime diagnosis of cardiovascular disease, metabolic disease (including diabetes mellitus, hypertension, metabolic syndrome), or thyroid disease, and current use of lipid-lowering, antidiabetic, or antihypertensive medications, as these conditions and treatments may substantially influence lipid profiles and atherogenic indices. Patients unwilling or unable to provide written consent were also excluded.

Clinical and Laboratory Assessments: Sociodemographic data were collected during a semi-structured interview and included age, sex, education level, occupation, marital status, and living conditions. In addition, questions were asked about the age at disease onset, the number of hospitalizations, the number of manic and depressive episodes, the time of the last episode, family history, and history of suicide and substance use. Medical history was systematically screened to confirm the absence of lifetime cardiovascular, metabolic, and thyroid disorders, and medication records were reviewed to exclude lipid-lowering, antidiabetic, or antihypertensive agents. Antipsychotic doses were converted to risperidone equivalents based on previous studies.[19] Body weight (in kilograms) and height (in meters) were measured during the index visit, and body mass index (BMI; kg/m²) was calculated. Venous blood samples were drawn from the forearm between 8:30 and 9:30 a.m., coinciding with chronotype evaluation. All participants were instructed to fast for at least 12 h; those who had not fasted were rescheduled. Laboratory analyses included glucose (mg/dL), triglycerides (mg/dL), low-density lipoprotein (LDL; mg/dL), high-density lipoprotein (HDL; mg/dL) and total cholesterol (mg/dL) levels. In addition, Castelli risk index-I (total cholesterol/HDL cholesterol), Castelli risk index-II (LDL cholesterol/HDL cholesterol), and atherogenic coefficient ([total cholesterol–HDL cholesterol]/HDL cholesterol) were calculated.

Psychometric Tools

Morningness–Eveningness Questionnaire (MEQ): Chronotype was measured using the 19-item MEQ, which assesses preferred sleep–wake timing and daily activity patterns. Scores range from 16 to 86 and classify individuals as eveningness (16–41), intermediate (42–58), or morningness (59–86). The Turkish version is valid and reliable, and Cronbach's alpha values are above 0.80.[20]

Young Mania Rating Scale (YMRS)**:** The form assesses manic symptoms through 11 clinician-rated items covering mood, speech, activity, sleep, sexual interest, and disruptive behavior. Total scores range from 0 to 60, with established reliability (Cronbach's $\alpha = 0.70–0.85$). The Turkish version has demonstrated good psychometric validity.[21] For this study, a YMRS score < 6 indicated euthymia.

Beck Depression Inventory (BDI)**:** The form measures the cognitive, emotional, and somatic aspects of depressive symptoms with 21 items. Items are scored 0–3, with higher scores reflecting greater severity. The Turkish version shows good reliability (Cronbach's $\alpha = 0.80$) and convergent validity.[22] In this study, a BDI score below 10 indicated euthymia.

Statistical Analysis: All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA).[23] Descriptive statistics were presented as means and standard deviations (SD) for continuous variables and as frequencies and percentages for categorical variables. The distribution of continuous variables was assessed using the Shapiro–Wilk test and histogram inspection.

Group comparisons of categorical variables across chronotypes were performed using the chi-square test. For non-normally distributed continuous variables, the Kruskal–Wallis H test was applied, and results were expressed as medians and interquartile ranges (IQR). For normally distributed continuous variables, one-way analysis of variance (ANOVA) was applied, and post hoc pairwise comparisons were carried out using Tukey's honestly significant difference test. Given the number of metabolic parameters and derived atherogenic indices evaluated, we prespecified LDL-c and Castelli Risk Index-I as the primary outcomes based on their established clinical relevance for cardiovascular risk stratification in bipolar disorder. All other lipid variables and indices were considered secondary/exploratory outcomes. To control for multiple testing among the secondary outcomes, p-values were additionally adjusted using the Benjamini–Hochberg false discovery rate (FDR) procedure. Results are therefore reported as unadjusted and FDR-corrected p-values, and findings that remained significant after correction are interpreted as robust, whereas the others are considered exploratory. To examine whether chronotype-related differences in lipid parameters were independent of potential confounders, analysis of covariance (ANCOVA) models were conducted. Chronotype (eveningness, intermediate, morningness) was entered as a fixed factor, and age, sex, BMI, smoking status, presence of atypical antipsychotic treatment, and valproate use (coded as yes/no) were included as covariates. Separate models were run for LDL-cholesterol, atherogenic coefficient, Castelli Risk Index-I, and Castelli Risk Index-II. Adjusted group differences were evaluated using Bonferroni-corrected pairwise comparisons, and effect sizes were expressed as partial eta squared (η^2). Correlation analyses between MEQ scores and metabolic parameters were performed using Pearson's correlation coefficients, with corresponding 95% confidence intervals (CIs). A two-tailed *p*-value of < 0.05 was considered statistically significant for all analyses.

RESULTS

The study included 69 euthymic patients diagnosed with BD. The mean age of all patients was 36.52 ± 8.87 years. The sample consisted of 47.8% males and 52.2% females; 52.2% were single and 47.8% married. Educational levels were distributed as follows: 24.7% had elementary school education, 39.1% high school education, and 36.2% were university graduates. At the time of assessment, 44.9% were employed, 89.9% lived with their families, and 92.8% resided in city centers. The mean scores were 48.59 ± 9.98 for MEQ, 5.04 ± 3.22 for BDI, and 0.55 ± 1.29 for YMRS. Regarding chronotype, 27.5% of participants were classified as eveningness types, 47.8% as intermediate types, and 24.6% as morningness types. Sociodemographic information of patients with BD is in Table 1.

Table 1. Sociodemographic and clinical characteristics of patients with bipolar disorder.

Characteristics		**Descriptives (n = 69)**
Age, years, Mean ± SD		36.52 ± 8.87
Sex, n (%)	Male	33 (47.8)
	Female	36 (52.2)
Marital status, n (%)	Single	36 (52.2)
	Married	33 (47.8)
Education, n (%)	Elementary school	17 (24.7)
	High school	27 (39.1)
	University	25 (36.2)
Occupational status, n (%)	Present	31 (44.9)
	Absent	38 (55.1)
Living with, n (%)	Alone	7 (10.1)
	Family	62 (89.9)
Place of residence, n (%)	City center	64 (92.8)
	Rural area	5 (7.2)
BDI, Mean ± SD		5.04 ± 3.22
YMRS, Mean ± SD		0.55 ± 1.29
MEQ, Mean ± SD		48.59 ± 9.98
Chronotype, n (%)	Eveningness	19 (27.5)
	Intermediate	33 (47.8)
	Morningness	17 (24.6)

MEQ: Morningness–Eveningness Questionnaire; BDI: Beck Depression Inventory; YMRS: Young Mania Rating Scale; SD: Standard deviation.

No significant differences were observed among the groups with respect to family history of bipolar disorder or psychosis, history of suicide attempt, history of substance use, or smoking status (all $p > 0.05$). Likewise, key illness-related variables, including age at onset, number of hospitalizations, time since last episode, number of manic and depressive episodes, and antipsychotic equivalent dose, did not differ significantly between chronotype groups (all $p > 0.05$). Table 2 summarizes the comparison of sociodemographic and clinical characteristics across chronotype groups (eveningness, intermediate, and morningness).

Table 2. Comparison of clinical variables by chronotype in patients with bipolar disorder.

Variables	Eveningness (n = 19)	Intermediate (n = 33)	Morningness (n = 17)	Statistics[a]	p
Family history of bipolar disorder, n (%)	8 (42.1)	12 (36.4)	5 (29.4)	χ^2=0.626	0.731
Family history of psychosis, n (%)	5 (26.3)	6 (18.2)	3 (17.6)	χ^2=0.591	0.744
History of suicide attempt, n (%)	5 (26.3)	6 (18.2)	5 (29.4)	χ^2=0.938	0.626
History of substance use, n (%)	3 (15.8)	7 (21.2)	1 (5.9)	χ^2=1.968	0.374
Smoking, n (%)	11 (57.9)	19 (57.6)	7 (41.2)	χ^2=1.406	0.495
Age of disorder onset, year, Median (IQR)	20.0 (14.5)	23.0 (11.0)	26.0 (16.3)	*H*=3.7744	0.154
Number of hospitalizations, Median (IQR)	2.0 (2.0)	3.0 (2.0)	2.0 (2.8)	*H*=2.018	0.365
Time since last episode, Median (IQR)	1.0 (2.5)	2.0 (2.0)	2.0 (3.1)	*H*=0.024	0.988
Manic episodes, Median (IQR)	2.0 (1.5)	3.0 (3.0)	2.5 (3.0)	*H*=2.647	0.266
Depressive episodes, Median (IQR)	0.0 (1.5)	0.0 (1.0)	0.0 (0.8)	*H*=1.670	0.434
Antipsychotic equivalent dose[b], Median (IQR)	5.4 (6.9)	5.4 (7.1)	5.3 (6.6)	*H*=0.335	0.846

IQR: Interquartile range; [a]: Categorical variables were analyzed with the Chi-square test (χ^2) and continuous variables with the Kruskal-Wallis test (*H*); [b]: Risperidone equivalent dose (mg).

Table 3 presents the comparison of metabolic parameters across patients with eveningness (n = 19), intermediate (n = 33), and morningness (n = 17) chronotypes. No significant differences were found between chronotypes for height, weight, BMI, triglycerides, HDL-c, and glucose levels (all $p > 0.05$). For the predefined primary outcomes, LDL-c and Castelli Risk Index-I differed significantly across chronotype groups and remained significant after FDR correction. In addition, the atherogenic coefficient and Castelli Risk Index-II also showed significant group differences after correction and are therefore reported as robust secondary findings, whereas the remaining metabolic parameters are considered exploratory. Total cholesterol was lower in eveningness types compared to intermediate and morningness types (F = 4.079, p = 0.021). LDL-c levels also differed significantly across groups (F = 5.663, p = 0.005), with eveningness types showing lower values. Furthermore, atherogenic coefficient (F = 8.390, p < 0.001), Castelli risk index-I (F = 8.390, p < 0.001), and Castelli risk index-II (F = 7.868, p < 0.001) were all significantly higher in both intermediate and morningness types compared with eveningness types (all Tukey post hoc p values < 0.05).

Table 3. Metabolic parameters across chronotype groups in bipolar disorder.

Metabolic parameters	Eveningness (n = 19) Mean ± SD	Intermediate (n = 33) Mean ± SD	Morningness (n = 17) Mean ± SD	F	p	Post hoc[a]	p[b]
Height, cm	171.58 ± 10.42	167.74 ± 8.45	168.47 ± 8.28	1.042	0.359	-	-
Weight, kg	78.65 ± 17.18	81.06 ±19.74	82.63 ± 21.67	1.224	0.301	-	-
BMI	26.95 ± 1.21	28.84 ± 1.06	31.25 ± 1.93	2.108	0.141	-	-
Total cholesterol	164.47 ± 31.50	193.81 ± 35.25	183.47 ± 40.62	4.079	**0.021**	I > E	**0.048**
						I = M	0.597
						M = E	0.383
HDL-c	50.26 ± 11.88	47.03 ± 9.58	47.93 ±10.78	0.608	0.547	-	-
LDL-c	106.58 ± 24.69	132.00 ± 27.53	124.82 ± 25.63	5.663	**0.005**	I > E	**0.012**
						I = M	0.634
						M = E	0.155
Triglycerides	142.68 ± 81.27	175.03 ± 70.30	151.88 ± 86.02	1.190	0.311	-	-
Glucose	96.32 ±19.85	92.48 ± 13.18	100.65 ± 20.78	1.287	0.283	-	-
Atherogenic coefficient	2.36 ± 0.66	3.20 ± 0.80	2.99 ± 0.63	8.390	**<0.001**	I > E	**0.001**
						I = M	0.593
						M > E	**0.042**
Castelli risk index-I	3.36 ± 0.66	4.20 ± 0.80	3.99 ± 0.63	8.390	**<0.001**	I > E	**0.001**
						I = M	0.593
						M > E	**0.042**
Castelli risk index-II	2.18 ± 0.55	2.87 ± 0.66	2.74 ± 0.57	7.868	**<0.001**	I > E	**0.002**
						I = M	0.760
						M > E	**0.032**

SD: Standard deviation; BMI: Body mass index; HDL-c: High-density lipoprotein cholesterol; LDL-c: Low-density lipoprotein cholesterol; E: Eveningness; I: Intermediate; M: Morningness; [a];Tukey's HSD test; [b];False Discovery Rate (FDR) was checked using the Benjamini-Hochberg method; Primary endpoints: LDL-c and Castelli Risk Index-I; Other lipid parameters and indices are secondary/exploratory outcomes.

In ANCOVA models adjusting for age, sex, BMI, smoking status, atypical antipsychotic use, and valproate use, chronotype remained significantly associated with LDL-cholesterol ($F(2,60)=4.721$, $p=0.012$, partial $\eta^2=0.136$), atherogenic coefficient ($F(2,60)=7.583$, $p=0.001$, partial $\eta^2=0.202$), Castelli Risk Index-I ($F(2,60)=7.583$, $p=0.001$, partial $\eta^2=0.202$), and Castelli Risk Index-II ($F(2,60)=6.997$, $p=0.002$, partial $\eta^2=0.189$). Bonferroni-adjusted post-hoc comparisons indicated significantly higher adjusted values in the intermediate chronotype group compared with the eveningness group, whereas differences between morningness and eveningness did not remain significant after full adjustment. These findings indicate that the more favorable lipid and atherogenic profile observed in eveningness types is not explained by differences in BMI, basic demographics, smoking, or exposure to metabolically active psychotropic medications.

Table 4. ANCOVA results for lipid and atherogenic indices by chronotype.

Outcome	Chronotype effect (F, df)	Partial η^2	p	Key post-hoc (Bonferroni)
LDL-cholesterol (mg/dL)	F(2,60)=4.721	0.136	**0.012**	Intermediate > Evening (Δ=24.27, ***p*=0.010**)
Atherogenic Coefficient	F(2,60)=7.583	0.202	**0.001**	Intermediate > Evening (Δ=0.760, ***p*=0.001**)
Castelli Risk Index-I	F(2,60)=7.583	0.202	**0.001**	Intermediate > Evening (Δ=0.760, ***p*=0.001**)
Castelli Risk Index	F(2,60)=6.997	0.189	**0.002**	Intermediate > Evening (Δ=0.610, ***p*=0.001**)

Chronotype entered as fixed factor; age, sex, body mass index (BMI), smoking status (yes/no), presence of atypical antipsychotic treatment (yes/no), and valproate use (yes/no) were included as covariates; Effect sizes are expressed as partial eta squared (η^2); Post-hoc comparisons are Bonferroni-adjusted.

Correlation analyses revealed significant associations between chronotype and several metabolic risk indicators. Higher MEQ scores, indicating greater morningness, were positively correlated with Castelli Risk Index-II ($r = 0.38$, 95% CI [0.16, 0.57]), atherogenic coefficient ($r = 0.37$, 95% CI [0.15, 0.56]), and Castelli Risk Index-I ($r = 0.37$, 95% CI [0.15, 0.56]). In addition, MEQ scores were positively correlated with LDL-c levels ($r = 0.27$, 95% CI [0.03, 0.47]). The associations between MEQ scores and these metabolic parameters are illustrated in Figure 1.

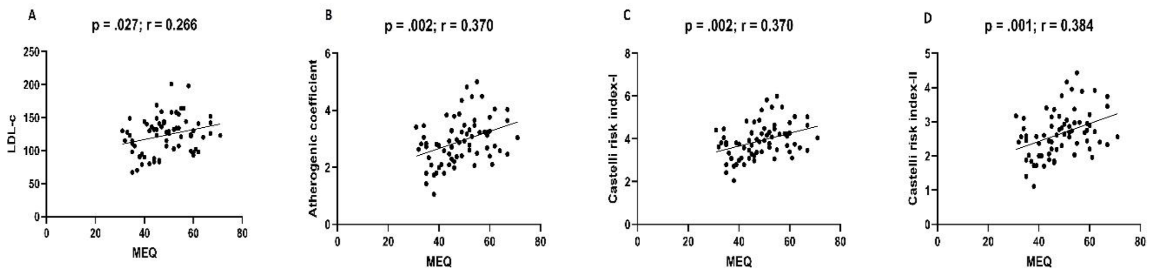

Figure 1. Scatter plots illustrating the correlations between chronotype (MEQ scores) and metabolic risk indicators in patients with bipolar disorder. Higher MEQ scores (greater morningness) were positively correlated with (A) LDL-c levels, (B) atherogenic coefficient, (C) Castelli Risk Index-I, and (D) Castelli Risk Index-II. Regression lines with 95% confidence intervals are displayed.

DISCUSSION AND CONCLUSION

The present findings unexpectedly showed an inverse association between chronotype and specific cardiometabolic markers in BD. Specifically, BD patients with an evening chronotype had significantly lower total cholesterol and LDL-c levels, along with more favorable atherogenic coefficients and Castelli risk indices, compared to those with intermediate or morning chronotypes. Importantly, the main findings for LDL-c and Castelli Risk Index-I (primary outcomes) remained significant after FDR correction, supporting the robustness of the observed chronotype-related differences, whereas interpretations of other lipid indices should be considered secondary. Moreover, these chronotype-related differences in LDL-cholesterol and atherogenic indices remained significant after adjustment for age, sex, BMI, smoking, antipsychotic use, and valproate treatment in ANCOVA models, indicating that the observed associations are not attributable solely to the higher mean BMI observed in the morningness group. This contrasts with the bulk of previous research, which has generally linked eveningness to higher cardiometabolic risk in BD.[16-18] Nevertheless, our findings also mirror the mixed and population-dependent results reported in recent chronotype research.[10,12]

We did not observe differences in chronotype for BMI, fasting glucose, HDL-c, or triglycerides. This partially aligns with earlier studies reporting inconsistent findings across metabolic parameters.[17,18] For example, in Aktürk et al.'s study, evening-type patients had lower HDL and higher blood pressure, but other metabolic parameters (e.g., triglycerides and glucose) did not differ significantly between chronotypes.[17] Godin et al. likewise reported mixed results, in which eveningness was linked to higher triglycerides and an elevated atherogenic index, but not necessarily to differences in BMI or total cholesterol.[18] Our results suggest that chronotype does not influence all metabolic markers in the same way and that lipid measures may be more sensitive to chronotype differences.

Several factors may explain why our findings differ from prior work. First, our sample consisted of clinically stable, euthymic outpatients. In contrast, some earlier studies examined inpatients or individuals with acute mood episodes, where illness severity, hospitalization, or recent medication changes could affect metabolic outcomes.[16] Second, age patterns may matter. Eveningness is more common in younger individuals, who may have fewer metabolic problems. Moreover, our sample consists of a younger population compared to previous studies.[16] Third, unmeasured factors, such as diet, physical activity, and daily routines, may have influenced lipid levels.[24] Lifestyle habits related to work schedules, meal timing, or physical activity could modify or even reverse expected chronotype risk patterns.

Medication effects are another important consideration. Atypical antipsychotics and some mood stabilizers can lead to weight gain and dyslipidemia, contributing to metabolic syndrome in BD.[25] Although antipsychotic dose equivalents did not differ among chronotype groups in this study, specific medication types or long-term treatment histories could still play a role. Future studies should examine these factors more closely.

Lifestyle and cultural habits may significantly influence the relationship between chronotype and metabolic health.[26] Eveningness types often have habits such as later meals, skipped breakfast, and less exercise, which can increase the risk of obesity and heart disease.[7,27] Conversely, morningness types typically follow more regular and healthier routines.[28] However, these trends are not inevitable. In our study, the expected risks might have been lessened or even reversed. For instance, some eveningness types may have avoided unhealthy late-night eating or maintained regular schedules, while some morningness types might have had poorer dietary habits. This suggests that sociocultural context, such as meal timing and daily routines, can shape an individual's health risks regardless of their chronotype. Future studies should collect detailed lifestyle data to examine how eveningness types can maintain healthy profiles under appropriate conditions.

Overall, our findings do not contradict the importance of chronotype in metabolic health but suggest that the relationship in BD is more complex than previously assumed. Chronotype likely interacts with age, lifestyle, treatment, and illness stage.[26,29] Larger and multi-center studies are needed to determine whether the protective pattern observed among eveningness types can be replicated. Longitudinal research will also help clarify how chronotype influences metabolic changes over time and whether shifts in chronotype modify risk.

The current research has important strengths. We used a clinical sample of patients who were all euthymic and had a confirmed diagnosis of BD. This minimizes the confounding effects of acute mood symptoms. The use of validated psychometric scales and a comprehensive panel of laboratory-validated metabolic markers, including calculated atherogenic indices, contributes to the robustness of our findings.

Some limitations also apply to our results. First, the cross-sectional method of the study precludes an explanation of causality; we can only report associations, not determine whether chronotype influences metabolic changes or vice versa. Second, our sample size was relatively modest, which may have limited our statistical power to detect smaller differences in other variables, such as BMI or triglycerides. Third, although patients with lifetime cardiovascular, metabolic, and thyroid disorders and those using lipid-lowering, antidiabetic, or antihypertensive medications were excluded, subclinical metabolic alterations and unmeasured lifestyle factors such as diet, physical activity, and meal timing were not assessed and may have contributed to the observed associations. Finally, for studies conducted in a single center, the generalizability of findings to other populations is limited.

In conclusion, this study offers a new and somewhat unexpected view of the chronotype–metabolism link in bipolar disorder. Past research has shown that eveningness is a risk factor for metabolic syndrome.[16,18] In contrast, our euthymic sample showed the opposite pattern for lipid measurements, and some recent studies support our findings.[10,12] This suggests that the impact of chronotype is not straightforward and may depend on factors such as age, treatment, lifestyle, and disease phase. The main message is that chronotype is relevant for understanding health in BD, but it must be interpreted within a personalized context. Considering chronotype could improve risk assessment and guide tailored management, including medication timing, lifestyle advice, and preventive monitoring. Incorporating circadian rhythm care, through psychoeducation, lifestyle adjustments, or chronotherapy, may support both mood stability and cardiometabolic health. Further research is needed to clarify when chronotype increases risk and when it may be neutral or even protective, so that more targeted interventions can be developed for patients with BD.

Ethics Committee Approval: This study was approved by the Health Sciences Scientific Research Ethics Committee of Sakarya University (Date: 19.11.2024, decision no: 2024/129). All procedures adhered to the ethical standards of the Declaration of Helsinki (2013 revision), and written informed consent was obtained from all participants before enrollment.
Conflict of Interest: No conflict of interest was declared by the authors.
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