Volume: 39, Number: 2, June 2026 ISSN 1018 - 8681

DUSUNEN ADAM

Journal of Psychiatry and Neurological Sciences

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Journal of Psychiatry and Neurological Sciences

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ISSN 1018 - 8681

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Journal of Psychiatry and Neurological Sciences

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Volume: 39, Number: 2, June 2026

This is a medical scientific journal, published quarterly in March, June, September, and December and distributed free.

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Owner
The Journal is owned by Mustafa Nuray Namli, Assoc. Prof., M.D., (Istanbul, Turkiye) on behalf of Bakirkoy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery

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Publishing Company
Kare Medya (Kare Media)
Goztepe Mahallesi, Fahrettin Kerim Gokay Caddesi,
No: 200, Daire: 2, Kadikoy, Istanbul - Turkiye
Phone / Telefon: +90 (216) 550 61 11 Fax / Faks: +90 (216) 550 61 12
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Printed in
Filmevi Grafik Renk Ayrımı Sistemleri San.
Tic. LTD. ŞTİ. Istanbul-Turkiye
Phone / Telefon: +90 (212) 429 29 03

Publication Type: Quarterly Periodical

This publication is printed on acid-free paper that meets the international standart ISO 9706: 1994 (Requirements for Permanence).

www.dusunenadamdergisi.org / ISSN: 1018-8681 (Print edition) / ISSN: 1309-5749 (Electronic edition)

Contents

DOI: 10.14744/DAJPNS.2026.00320
Dusunen Adam J Psychiatr Neurol Sci
2026;39:75-79

GUEST EDITORIAL

From peripheral blood neutrophils and monocytes to microglia in the brain: Converging evidence for innate immune activation in schizophrenia and major depression

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Major depressive disorder (MDD) and schizophrenia (SCZ) are traditionally treated as distinct diagnoses, yet converging evidence suggests that some pathophysiological mechanisms span the affective–psychosis spectrum (1). Innate immune activation has emerged as a potential link between peripheral myeloid alterations and microglia-related processes in the brain (1). This perspective provides a framework for integrating blood-based inflammatory findings with central nervous system dysfunction and supports stratified treatment approaches.

Genetic and epidemiological studies further link prenatal and lifetime infections, as well as autoimmune disease, to later risk of schizophrenia and mood disorders (2-4). In schizophrenia, the major histocompatibility complex locus on chromosome 6 represents one of the strongest common variant signals (4). Peripheral inflammatory proteins such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) are elevated in both disorders, although effect sizes, heterogeneity, and study designs vary (5).

This editorial integrates evidence from differential blood counts, positron emission tomography (PET) imaging, cerebrospinal fluid (CSF), and postmortem studies to examine whether a shared innate immune pathway links peripheral blood changes to microglia-related alterations in the brain. Proposed mechanisms include cytokine signaling, blood–brain barrier (BBB) dysfunction, complement-related pathways, and immune cell trafficking (Fig. 1). Peripheral cytokines (e.g., IL-1) can activate vagal afferents and the cholinergic anti-inflammatory reflex, enabling rapid immune-to-brain signaling. Complement components (C1q, C3, C4) may bridge peripheral innate immune activation and microglial synapse tagging in the central nervous system (CNS) (6). However, these data are largely cross-sectional and correlational and should be considered a working model rather than evidence of a causal sequence (1, 7-9).

PERIPHERAL INNATE IMMUNE ACTIVATION

Most psychiatric immunology research has focused on cytokines and mononuclear cells, but

How to cite this article: Dudeck L, Guest PC, Steiner J. From peripheral blood neutrophils and monocytes to microglia in the brain: Converging evidence for innate immune activation in schizophrenia and major depression. Dusunen Adam J Psychiatr Neurol Sci 2026;39:75-79.

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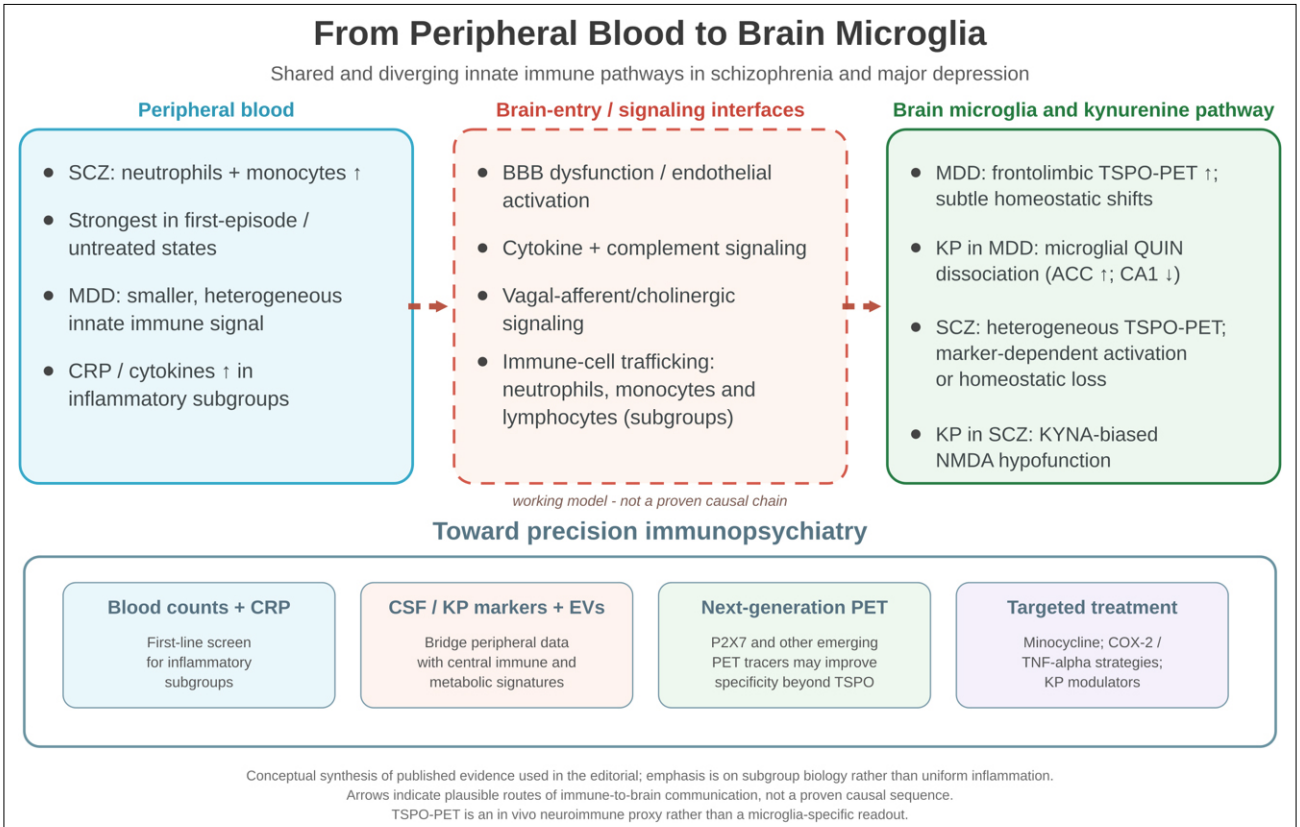

Figure 1. Conceptual bridge linking peripheral innate immune activation with central microglial and kynurenine pathway alterations in schizophrenia and major depression. Proposed routes of immune-to-brain communication include blood–brain barrier (BBB) dysfunction and endothelial activation, cytokine and complement signaling, vagal afferent/cholinergic anti-inflammatory pathways, and trafficking of peripheral innate immune cells (neutrophils and monocytes) and lymphocytes in selected subgroups. Downstream signatures appear to be partly disorder-specific. Major depressive disorder (MDD) is characterized by reproducible frontolimbic translocator protein positron emission tomography (TSPO-PET) elevations, subtle postmortem shifts in homeostatic microglial markers without a consistent classical activation pattern, and regionally dissociated microglial quinolinic acid (QUIN) signals (increased in anterior cingulate subregions and reduced in hippocampal cornu ammonis 1 [CA1]). Schizophrenia (SCZ) is associated with heterogeneous TSPO-PET findings, marker-dependent activation or homeostatic loss in postmortem studies, and a kynurenic acid (KYNA)-biased N-methyl-D-aspartate (NMDA)-hypofunction profile. TSPO-PET should be interpreted as an in vivo neuroimmune proxy rather than a microglia-specific readout. Arrows indicate plausible pathways within a conceptual working model rather than a uniform or established causal chain.

ACC: Anterior cingulate cortex; BBB: Blood–brain barrier; CA1: Cornu ammonis 1; COX-2: Cyclooxygenase-2; CRP: C-reactive protein; CSF: Cerebrospinal fluid; EVs: Extracellular vesicles; KP: Kynurenine pathway; KYNA: Kynurenic acid; MDD: Major depressive disorder; NMDA: N-methyl-D-aspartate; P2X7: Purinergic P2X7 receptor; PET: Positron emission tomography; QUIN: Quinolinic acid; SCZ: Schizophrenia; TNF-α: Tumor necrosis factor alpha; TSPO: Translocator protein.

granulocytes also deserve attention. In the largest meta-analysis to date, we found significantly elevated neutrophil and monocyte counts in schizophrenia, whereas other leukocyte populations were not consistently altered. This pattern suggests selective activation of innate immunity rather than generalized inflammation (9). The effects were strongest in first-episode and antipsychotic-naïve patients and attenuated with treatment (8, 9). Peripheral measures are also influenced by smoking, body mass index, acute stress, infection, and medication use (8).

In MDD, peripheral immune activation appears less specific and more heterogeneous. Meta-analyses demonstrate elevated neutrophil and monocyte counts, although lymphocyte findings are less consistent (10). In stage-sensitive clinical studies, we observed increased neutrophil counts and CRP levels during acute depressive episodes, with smaller effect sizes than those observed in schizophrenia (7).

Peripheral signals may also relate to brain alterations. In first-episode psychosis, higher neutrophil counts were associated with reduced gray matter volume and enlarged ventricles (11).

Mechanistically, neutrophils may transmigrate across a disrupted BBB into the brain parenchyma, contributing to neuroinflammation through chemokine-mediated pathways (12).

CENTRAL IMMUNE ACTIVATION: MICROGLIA

In addition to immune defense, microglia regulate synaptic pruning, neurotransmission, myelination, and BBB integrity. Our recent systematic review integrating translocator protein positron emission tomography (TSPO-PET) imaging, kynurenine pathway metabolism, and postmortem microglial markers across the affective–psychosis spectrum found that microglia-related alterations may map more closely onto symptom dimensions and biologically defined subgroups than onto conventional diagnostic categories (1).

In MDD, meta-analyses of TSPO-PET studies have reported increased binding, particularly in the hippocampus, cingulate, and prefrontal regions (13). In contrast, findings in schizophrenia are more heterogeneous and often non-significant, reflecting biological and cohort variability, as well as methodological differences (1, 14).

Postmortem findings further refine this distinction. In MDD, several studies suggest that microglia do not exhibit a classical pro-inflammatory phenotype. Instead, they demonstrate altered expression or compensatory shifts in homeostatic markers such as TMEM119, P2Y12/P2RY12, and CX3CR1 (15). We found increased quinolinic acid (QUIN)-positive microglia in subregions of the anterior cingulate cortex in patients with severe depression, indicating that region-specific and functionally relevant microglial alterations can occur in the absence of global classical activation (16).

In schizophrenia, one study reported increases in activation markers (17), whereas another found no overall increase in density but a reduction in mature microglial markers, suggesting impaired homeostatic identity rather than uniform classical activation (18). These findings may partly reflect infiltrating macrophages rather than resident microglia.

Findings in bipolar disorder are more limited but appear to place the disorder between the MDD and schizophrenia patterns, consistent with a dimensional rather than categorical interpretation (1). Overall, these findings suggest that microglial alterations vary according to brain region, disease stage, and biological subgroup.

THE KYNURENINE PATHWAY

The kynurenine pathway links immune signaling to glutamatergic neurotransmission. Inflammatory cytokines induce indoleamine 2,3-dioxygenase (IDO), diverting serotonin synthesis toward kynurenine metabolism (19, 20). Microglial kynurenine-3-monooxygenase (KMO) activity converts kynurenine into quinolinic acid, an N-methyl-D-aspartate (NMDA) receptor agonist with excitotoxic potential. Astrocytes lack KMO and instead metabolize kynurenine into kynurenic acid (KYNA), an NMDA receptor antagonist.

In MDD, evidence suggests region-specific increases in QUIN rather than global pathway activation. Elevated QUIN-positive microglia have been documented in anterior cingulate subregions, whereas reduced immunoreactivity has been observed in the hippocampus; CSF findings remain inconsistent (16, 21). This regional dissociation may reflect differential microglial KMO activity and local IDO-mediated kynurenine pathway activation within stress-sensitive circuits. In schizophrenia, the pattern shifts toward increased KYNA production (22), consistent with NMDA receptor hypofunction, a proposed feature of schizophrenia pathophysiology.

This distinction may have clinical relevance. MDD appears to involve regionally circumscribed, microglia-associated QUIN alterations within frontolimbic circuits, whereas schizophrenia is characterized more strongly by KYNA-related hypoglutamatergic signaling.

IMMUNE HETEROGENEITY AND BIOMARKER STRATIFICATION

A central finding across studies is heterogeneity. Only approximately 30% of patients with MDD exhibit elevated inflammatory markers or broader immune signatures (10). In schizophrenia, postmortem and transcriptomic studies have identified high-inflammation subgroups rather than a universal inflammatory phenotype, again in approximately one-third of cases (23). Consistent with these findings, increased densities of T and B lymphocytes have been observed in subsets of brains from patients with schizophrenia and mood disorders, suggesting that BBB dysfunction or immune cell trafficking occurs in some individuals (24). Analyses of such studies should carefully account for clinical variables including sex, illness phase, medication status, smoking, and metabolic factors, which may function more appropriately as stratifiers than as confounders.

This variability suggests that anti-inflammatory or microglia-targeted strategies are unlikely to benefit all patients. Adjunctive minocycline has shown some efficacy, particularly for negative symptoms in schizophrenia (25). Anti-inflammatory agents such as celecoxib and infliximab have demonstrated benefits in treatment-resistant depression among subgroups with elevated CRP levels (26, 27). Kynurenine pathway modulators are also attractive candidates because they directly target the immune-glutamate interface (20).

Future approaches should emphasize biomarker-guided stratification. Candidate biomarkers include differential blood counts, CRP, cytokines, CSF metabolites, microglia-derived extracellular vesicles, and next-generation PET tracers targeting microglial receptors (1). Integration with clinical phenotyping, dimensional symptom assessment, and computational clustering will also be essential for identifying biologically coherent subgroups.

OUTLOOK

Among currently available measures, differential blood counts represent the most pragmatic entry point for clinical application. In schizophrenia, elevated neutrophil and monocyte counts, particularly early in the disease course or before treatment, may serve as accessible markers of innate immune activation (9). In MDD, immune cell alterations appear more subtle and heterogeneous but may still support subgroup identification (7, 10).

The broader goal is the development of precision immunopsychiatry by linking peripheral profiles with BBB integrity, microglial phenotypes, and kynurenine pathway signatures to guide targeted interventions. Achieving this goal will require longitudinal studies, harmonized protocols, microglia-selective biomarkers, and biomarker-enriched clinical trials.

Future research should aim to identify which patients exhibit clinically relevant immune dysregulation. If successful, this approach could facilitate a transition from syndrome-based diagnosis toward mechanism-informed care in psychiatry.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: A generative AI tool (ChatGPT, OpenAI) was used only to assist with the graphical design and layout of Figure 1, the conceptual content of which was devised by the authors. AI was not used for manuscript text. The authors take full responsibility for all content.

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DOI: 10.14744/DAJPNS.2026.00321
Dusunen Adam J Psychiatr Neurol Sci
2026;39:80-89

RESEARCH ARTICLE

The relationship between phubbing behavior and social media addiction, emotion regulation difficulties, and social anxiety in adolescents

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ABSTRACT

Objective: Phubbing—defined as the act of ignoring people in one's physical environment in favor of engaging with a smartphone—has become increasingly prevalent among adolescents. While social media use is often central to this behavior, the psychological mechanisms underlying phubbing remain insufficiently explored. This study aimed to investigate the relationships between phubbing behavior, social media addiction, emotion regulation difficulties, and social anxiety in adolescents. It was hypothesized that social media addiction would predict phubbing both directly and indirectly through emotional and social factors.

Method: The sample consisted of 125 adolescents aged 12–17 years who attended a child and adolescent psychiatry outpatient clinic in Turkiye. Standardized self-report measures were used to assess phubbing behavior, social media addiction, emotion regulation difficulties, and social anxiety. Correlation and mediation analyses were conducted using SPSS and Hayes' PROCESS Macro (Models 4 and 6), with 5,000 bootstrap resamples applied to test indirect and serial effects.

Results: Social media addiction, emotion regulation difficulties, and social anxiety were all positively and significantly associated with phubbing behavior. Mediation analyses indicated that both social anxiety and emotion regulation difficulties partially mediated the relationship between social media addiction and phubbing. The serial mediation model further suggested that social media addiction may be linked to phubbing through increased social anxiety and subsequent emotion regulation difficulties.

Conclusion: These findings highlight a potential interplay between digital habits and emotional functioning in adolescents. Phubbing may be understood not only as a behavioral outcome of digital engagement but also as a maladaptive coping strategy shaped by emotional vulnerabilities. Preventive interventions targeting emotion regulation and social media use may help reduce phubbing-related social difficulties.

Keywords: Phubbing, social media addiction, emotion regulation difficulties, social anxiety, adolescents

INTRODUCTION

The development of smartphones has transformed the way individuals communicate, enabling constant and convenient interaction. These multifunctional devices provide seamless access to communication tools, allowing users to maintain contact with others regardless of time or location (1). Smartphone

How to cite this article: Aksoy Avunduk S, Avunduk S, Gavcar EG, Tulaci OD. The relationship between phubbing behavior and social media addiction, emotion regulation difficulties, and social anxiety in adolescents. Dusunen Adam J Psychiatr Neurol Sci 2026;39:80-89.

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Received: November 27, 2025; **Revised:** March 06, 2026; **Accepted:** May 03, 2026

ownership has increased substantially in recent years, with nearly 70% of the global population reported to be using these devices by 2023 (2). This trend is particularly pronounced among younger age groups; studies indicate that approximately one-third of 8-year-old children (3) and nearly all adolescents in the United States own a smartphone (4). However, concerns have been raised about the negative effects of smartphones on the mental and physical health of young people, as these devices provide not only communication but also access to entertainment and online gaming (5-7).

While smartphones facilitate social connection, they may also contribute to social disconnection during face-to-face interactions (8). A common manifestation of this is the diversion of attention from physically present individuals to a smartphone. This behavior, referred to as phubbing, has become increasingly normalized in everyday communication (9). Phubbing can negatively affect interpersonal relationships by reducing relationship satisfaction and overall well-being (10). It is a complex, multifaceted phenomenon influenced by various forms of digital dependency, including mobile phone use, text messaging, social media, internet use, and online gaming (11). Moderate associations have also been observed between phubbing and factors such as smartphone addiction, internet addiction, and fear of missing out (FoMO) (9).

Although research on the prevalence of phubbing remains limited, available evidence suggests that it is relatively widespread among young people. One study involving individuals aged 15 to 29 found that nearly half (49%) engaged in phubbing (12). In Spain, 17% of participants aged 12 to 21 reported being distracted by their phones during face-to-face interactions (13). Similarly, an Australian study demonstrated that younger individuals exhibit phubbing more frequently than older adults (14). Furthermore, a systematic meta-analysis examining predictors of phubbing identified a strong association with problematic smartphone use, as well as moderate links with psychopathology and the experience of being phubbed by others (15).

Social media use has become increasingly pervasive, with nearly half of the global population engaging in social networking; a substantial proportion of users are adolescents belonging to the digital generation (16). Although these platforms facilitate communication, excessive use has raised concerns regarding its impact on mental health (17). Despite the absence of formal diagnostic criteria, social media addiction has been conceptualized as a behavioral addiction characterized by compulsive engagement with social networking sites that interferes with daily functioning (18). Problematic social media use—marked by excessive preoccupation, compulsive engagement, and difficulty disengaging—can adversely affect mental health and overall well-being (19). For example, social media addiction has been associated with poorer academic performance (20).

Adolescents may use social media as a strategy to cope with difficulties in emotion regulation. Evidence suggests that individuals with social media addiction often exhibit poor self-control, which may further impair their capacity to regulate emotions (21). Moreover, studies have demonstrated significant associations between social media addiction and depressive symptoms among youth aged 12 to 23, (22) and excessive social media use has been linked to diminished self-perception and increased depressive symptoms (23).

Social media platforms may also provide socially anxious adolescents with a perceived safe space, allowing them to avoid face-to-face interactions. However, such avoidance may negatively affect real-life social relationships, potentially increasing dependence on online platforms, exacerbating social anxiety symptoms, and hindering emotional and social development (24). Adolescents are particularly sensitive to social media feedback, which activates dopaminergic reward systems and reinforces prolonged engagement. Individuals who frequently seek reassurance or engage in passive scrolling may rely on social media to manage anxiety; however, this strategy may paradoxically intensify feelings of loneliness, social disconnection, and persistent negative thought patterns (25-28).

Based on this framework, the present study aimed to examine the relationships among phubbing behavior, social anxiety, social media addiction, and difficulties in emotion regulation in adolescents. It was hypothesized that higher levels of social media addiction, social anxiety, and emotion regulation difficulties would each be positively associated with increased phubbing behavior. Furthermore, difficulties in emotion regulation were expected to mediate the relationship between social media addiction and phubbing. Similarly, social anxiety was anticipated to act as a mediator. A serial mediation model was also proposed, suggesting that social media addiction may be associated with phubbing behavior through a sequential pathway involving social anxiety and emotion regulation difficulties. At the same time,

alternative theoretical sequences are plausible, including models in which difficulties in emotion regulation may precede or interact with social anxiety. Accordingly, the proposed serial mediation model is examined as one theoretically informed pathway rather than a definitive causal ordering.

METHODS

Study Design and Participants

The study was conducted with individuals who presented to the Child and Adolescent Psychiatry Outpatient Clinic of Balikesir Ataturk City Hospital. Participants were excluded if they had a diagnosis of autism spectrum disorder, intellectual disability, or a psychotic disorder. All participants and their parents provided informed consent/assent, and participation was voluntary. Psychiatric evaluations were conducted by child and adolescent psychiatrists in accordance with the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Diagnoses were established through comprehensive clinical assessments performed during routine outpatient evaluations. Comorbid psychiatric conditions were not considered exclusion criteria unless they corresponded to the predefined exclusion diagnoses (i.e., autism spectrum disorder, intellectual disability, or psychotic disorder). In addition, participants receiving psychotropic medication were not excluded. This approach allowed for the inclusion of a clinically representative outpatient sample.

A power analysis conducted using the G*Power 3.1.9 indicated that a minimum of 82 participants would be required to detect a medium effect size, assuming a significance level of 0.05 and a statistical power of 0.80, for examining the relationships between phubbing behavior, social media addiction, and emotion regulation difficulties in adolescents. Accordingly, the study was designed to include at least 82 participants.

A total of 132 adolescents aged 12 to 17 years were initially recruited. However, seven participants were excluded due to incomplete responses on the administered scales. The final sample consisted of 125 adolescents and their families, all of whom provided written informed consent to participate in the study.

Ethical Considerations

Written and verbal informed consent was obtained from all participants and their legal guardians prior to participation. The study protocol was approved by the institutional review board of the participating hospitals at the meeting held on February 20, 2025 (approval number: E-30041352-514.19.99-269198443).

Data Collection

Data were collected using several standardized instruments. In addition to a sociodemographic data form, the following scales were administered:

Sociodemographic Data Form

Developed by the researchers, this form included questions regarding participants' age, gender, number of siblings, family structure, socioeconomic status, parental age and education level, peer relationships, family harmony, academic performance, and screen time.

General Phubbing Scale

Developed by Chotpitayasunondh and Douglas, (9) this 15-item scale uses a 7-point Likert format (1=never to 7=always) and comprises four subscales: nomophobia, interpersonal conflict, self-isolation, and problem acknowledgment. Higher scores indicate greater levels of phubbing behavior. The Turkish validity and reliability study for adolescents was conducted by Gavcar et al. (2023), (29) reporting a Cronbach's alpha coefficient of 0.94.

Social Media Addiction Scale for Adolescents

This 9-item scale was developed based on DSM-5 criteria for behavioral addiction and uses a 5-point Likert response format (1=never to 5=always). Total scores range from 9 to 45, with higher scores indicating greater levels of social media addiction. The reliability coefficient (Cronbach's alpha) was reported as 0.904 by Özgenel et al. (2019) (30).

Emotion Regulation Scale for Adolescents

This brief version assesses four subdimensions of emotion regulation using a 5-point Likert scale (1=never to 5=always). The scale has demonstrated good reliability (α=0.92) (31). Higher scores on each subdimension indicate more frequent use of that specific emotion regulation strategy (32). In the present study, the total score was used rather than individual subscale scores. Although the instrument assesses the frequency of emotion regulation strategies, higher total scores were interpreted as reflecting greater difficulties in emotion regulation.

Social Anxiety Scale for Adolescents

This 18-item scale, developed by La Greca and Lopez (33), includes three subscales: Fear of Negative Evaluation; Social Avoidance and Anxiety in General Situations; and

Social Avoidance and Anxiety in New Situations. Items are rated on a Likert scale, with total scores ranging from 18 to 90. Higher scores indicate greater social anxiety. The Turkish version has demonstrated good construct validity and internal consistency, with a Cronbach's alpha coefficient of 0.88 (34).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 26.0. Descriptive statistics were used to summarize demographic and clinical characteristics and are presented as mean±standard deviation (SD) for continuous variables and frequency (n) and percentage (%) for categorical variables.

Normality assumptions were assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. For comparisons between two independent groups, the Mann–Whitney U test was used when parametric assumptions were not met, and the independent samples t-test was applied when assumptions were satisfied. For comparisons involving more than two groups, the Kruskal–Wallis test or analysis of variance (ANOVA) was used, depending on the distribution of the data.

Correlations between continuous variables were examined using Pearson's correlation analysis when parametric assumptions were met and Spearman's correlation analysis otherwise. The level of statistical significance was set at $p<0.05$.

Mediation analyses were conducted using a bootstrapping approach, following the recommendations, models, and procedures outlined by Preacher and Hayes (2008) (35). All analyses were performed using the PROCESS Macro developed by Hayes. A bootstrap resampling procedure with 5,000 iterations was applied. A mediation effect was considered statistically significant if the 95% confidence interval (CI) did not include zero (36). PROCESS Macro Model 4 was used for simple mediation analyses, while Model 6 was employed for serial mediation analyses. Age, gender, and daily internet use duration were included as covariates in the mediation models.

RESULTS

Of the 125 adolescents included in the study, 53.6% were female. Regarding parental education, 48.8% of mothers and 64% of fathers had completed high school or higher education. A majority of participants (72.8%) reported having at least one social media account, and 59.2% indicated using the internet for more than three hours per day. The mean age of the participants was 14.20 years (SD=1.75), with a median age of 14.00 years (Table 1).

Table 1: Sociodemographic characteristics of the participants (n=125)

Variables	Category	n	%
Gender	Female	67	53.6
	Male	58	46.4
Family structure	Intact	99	79.2
	Non-intact	26	20.8
Mother's education	Below high school	64	51.2
	High school or above	61	48.8
Father's education	Below high school	45	36.0
	High school or above	80	64.0
Perceived economic status	Low	11	8.8
	Moderate	86	68.8
	High	28	22.4
Academic achievement	Low	24	19.2
	Moderate	67	53.6
	High	34	27.2

Percentages may not total 100 due to rounding.

Correlation Analysis

Spearman's correlation analysis revealed a strong and significant positive relationship between social anxiety and difficulties in emotion regulation ($r=0.561$, $p<0.001$), suggesting that higher levels of social anxiety are associated with greater difficulty in regulating emotions. Social anxiety was also positively correlated with phubbing behavior ($r=0.357$, $p<0.001$) and, to a lesser extent, with social media addiction ($r=0.229$, $p<0.05$).

Difficulties in emotion regulation showed moderate and significant correlations with both phubbing behavior ($r=0.534$, $p<0.001$) and social media addiction ($r=0.465$, $p<0.001$). The strongest correlation was observed between social media addiction and phubbing behavior ($r=0.744$, $p<0.001$), indicating that higher levels of social media addiction are closely associated with increased phubbing behavior (Table 2).

Mediation Analyses

Age, gender, and daily internet use duration were included as covariates in all mediation models. After controlling for these variables, both direct and indirect effects remained statistically significant, indicating that the findings were robust to the inclusion of covariates.

Table 2: Spearman correlations among study variables (n=125)

Variables	1. Social anxiety	2. Emotion regulation difficulties	3. Phubbing behavior	4. Social media addiction
1. Social anxiety	–			
2. Emotion regulation difficulties	0.561**	–		
3. Phubbing behavior	0.357**	0.534**	–	
4. Social media addiction	0.229*	0.465**	0.744**	–

*p<0.05; **p<0.01. Correlation coefficients are based on Spearman's rho.

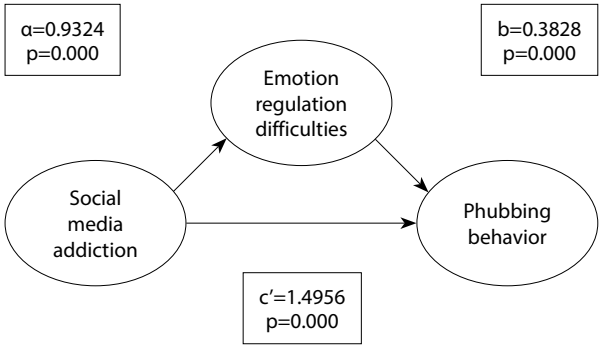

Figure 1. Mediation models of the relationship between social media addiction and phubbing behavior.

N=125. All effects were estimated using Hayes' PROCESS Macro (Model 4) with 5,000 bootstrap resamples. CI = 95% bias-corrected confidence interval. Total Effect (c) = 1.8525, 95% CI [1.5517-2.1533]; Direct Effect (c') = 1.4956, 95% CI [1.1708-1.8204]; Indirect Effect (a × b) = 0.3569, 95% CI [0.1880-0.5582].

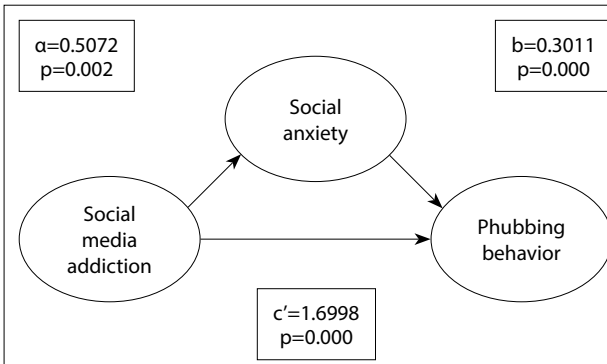

Figure 2. Mediating role of social anxiety in the relationship between social media addiction and phubbing behavior.

N=125. All effects were estimated using Hayes' PROCESS Macro (Model 4) with 5,000 bootstrap resamples. CI=95% bias-corrected confidence interval. Total effect (c)=1.8525, 95% CI [1.5517–2.1533]. Direct effect (c')=1.6998, 95% CI [1.4037–1.9959]. Indirect effect (a × b)=0.1527, 95% CI [0.0398–0.3189].

Model 1: Mediation Model of the Relationship Between Social Media Addiction and Phubbing Behavior

A mediation analysis using PROCESS Macro Model 4, with 5,000 bootstrap resamples and a 95% confidence interval, was conducted to examine whether difficulties in emotion regulation mediated the relationship between social media addiction and phubbing behavior. As the confidence interval did not include zero, the indirect effect was statistically significant (Indirect Effect=0.3569, 95% CI [0.1880–0.5582]). These findings suggest that the association between social media addiction and phubbing may be partially explained by increased difficulties in emotion regulation (Fig. 1).

Model 2: The Mediating Role of Social Anxiety in the Relationship Between Social Media Addiction and Phubbing Behavior

A second mediation model (PROCESS Model 4) tested the mediating role of social anxiety in the same relationship. The total effect of social media addiction on phubbing behavior remained significant (c=1.8525, 95% CI [1.5517–2.1533]), as did the direct effect (c'=1.6998, 95% CI [1.4037–1.9959]). The indirect effect through social anxiety was also statistically significant (Indirect Effect=0.1527, 95% CI [0.0398–0.3189]), indicating that social media addiction may be indirectly associated with phubbing behavior through increased levels of social anxiety (Fig. 2).

Model 3: Serial Mediation Model of the Relationship Between Social Media Addiction and Phubbing Behavior via Social Anxiety and Difficulties in Emotion Regulation

Finally, a serial mediation analysis (PROCESS Model 6) was conducted to examine the sequential mediating roles of social anxiety and emotion regulation difficulties in the relationship between social media addiction and phubbing behavior.

Social media addiction significantly predicted both social anxiety (a_1=0.5072, p=0.002) and difficulties in emotion regulation (a_2=0.7029, p<0.001). Social anxiety also significantly predicted difficulties in emotion regulation (d_{21}=0.4525, p<0.001).

Regarding the b paths, difficulties in emotion regulation significantly predicted phubbing behavior (b_2=0.2817, p=0.006), whereas social anxiety did not reach statistical significance (b_1=0.1737, p=0.055).

The direct effect of social media addiction on phubbing behavior remained significant after

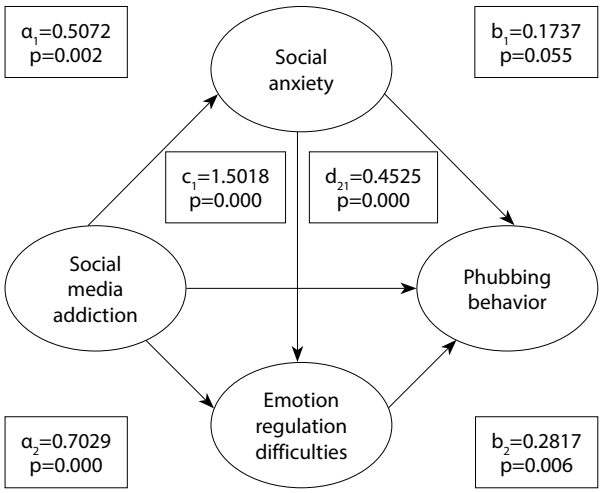

Figure 3. Serial mediation model of the relationship between social media addiction and phubbing behavior through social anxiety and difficulties in emotion regulation.

N=125. All effects were estimated using Hayes' PROCESS Macro (Model 6) with 5,000 bootstrap resamples. CI=95% bias-corrected confidence interval. Three indirect pathways were evaluated: Indirect Path 1 (Social Anxiety) (a_1b_1): IE [-0.0030-0.2316]– not significant. Indirect Path 2 (Emotion Regulation Difficulties) (a_2b_2): IE=[0.0658-0.3638]–significant. Indirect Path 3 (Serial Mediation through Social Anxiety → Emotion Regulation) ($a_1d_{21}b_2$): IE=[0.0150-0.1427] significant.

controlling for the mediators (c′=1.5018, p<0.001), indicating partial mediation.

Bootstrapping analyses showed that the indirect effect through social anxiety alone was not statistically significant (95% CI [-0.0030–0.2316]). In contrast, the indirect effect through difficulties in emotion regulation was significant (95% CI [0.0658–0.3638]). Importantly, the serial indirect pathway—from social media addiction to social anxiety, to difficulties in emotion regulation, and finally to phubbing behavior—was also statistically significant (95% CI [0.0150–0.1427]), as the confidence interval did not include zero (Fig. 3).

These findings indicate that social media addiction contributes to phubbing behavior both directly and indirectly through increased difficulties in emotion regulation, as well as through a sequential process in which elevated social anxiety leads to greater emotion regulation difficulties, which in turn increase phubbing behavior.

DISCUSSION

This study examined the relationships among phubbing behavior, social media addiction, difficulties in emotion regulation, and social anxiety in adolescents. The findings revealed several significant associations that enhance our understanding of how digital behaviors and emotional difficulties interact during this developmental period.

First, a strong positive correlation was observed between phubbing behavior and social media addiction. This finding supports previous research suggesting that phubbing may be a byproduct of excessive and compulsive smartphone and social media use (9). In the context of social media addiction—characterized by disruptions in social relationships and engagement in deceptive behaviors during platform use (37)—individuals may experience negative emotions such as irritability, sadness, or stress when access to social media is restricted (38). These adverse emotional experiences, combined with a preference for online interactions over face-to-face communication, may directly interfere with social participation and interpersonal functioning (39). Excessive focus on social media at the expense of real-life interactions has been associated with reduced social competence and impaired interpersonal relationships (40, 41). The decline in social skills observed in such individuals may be linked to phubbing, whereby individuals increasingly prioritize virtual interactions over in-person communication (42). Those who frequently engage in phubbing tend to divert their attention away from their immediate social environment toward their smartphones and social media platforms (43). This behavioral pattern is consistent with the findings of the present study, which demonstrate a strong association between phubbing behavior and social media use.

In addition, phubbing behavior was positively associated with both difficulties in emotion regulation and social anxiety. A 2022 meta-analysis demonstrating a strong association between emotion dysregulation and problematic smartphone use (44) supports our finding that phubbing is significantly related to difficulties in emotion regulation. Such difficulties may predispose individuals to maladaptive coping behaviors, including excessive smartphone use. Given that phubbing can be conceptualized as a specific form of problematic smartphone use, it may serve a functional role beyond merely signaling social disengagement, particularly among adolescents with elevated social anxiety. This behavior may reflect an attempt to cope with overwhelming emotional states. Supporting this interpretation, a study involving 1,401 Chinese undergraduate students (45) found that peer phubbing was positively associated with social networking site addiction, with social anxiety partially mediating this relationship. Recent findings from Turkiye

further support the link between problematic digital engagement and emotional processes in youth (46). A clinical study on school refusal reported that higher levels of social media disorder symptoms were associated with increased emotional distress and avoidance-related behaviors in children and adolescents. These findings suggest that excessive digital media use may co-occur with emotional vulnerability and avoidance tendencies, consistent with the pattern observed in the present study. In line with our results, phubbing may be associated with heightened social anxiety, particularly among adolescents who are sensitive to social evaluation. This may indicate that adolescents who struggle to regulate their emotions or experience increased social discomfort turn to their phones as a maladaptive coping strategy. While digital device use may provide temporary relief from social demands or negative emotions, it may also hinder the development of effective emotional and interpersonal skills.

Finally, the observed associations between social media addiction, emotion regulation difficulties, and social anxiety further support the notion that adolescents may use social media as a means of managing or avoiding emotional distress. Our findings are consistent with a meta-analysis indicating a strong and bidirectional relationship between social media use and anxiety (47), suggesting that increased engagement with social media may both contribute to and be exacerbated by anxiety symptoms. Given that adolescence is a developmental stage characterized by heightened vulnerability to low self-esteem, anxiety, and depression (48, 49), understanding the impact of social media use on these psychological factors is critically important. This behavioral pattern may contribute to increased phubbing, ultimately weakening real-life social connections. Excessive engagement with screen-based media has been associated with higher levels of social anxiety symptoms, particularly among developmentally vulnerable adolescents (50). Individuals who frequently seek reassurance or engage in passive scrolling on social media platforms may initially attempt to cope with anxiety; however, this pattern may exacerbate feelings of loneliness, social withdrawal, and repetitive negative thinking (25–28). The finding that difficulties in emotion regulation are associated with higher levels of social media addiction is consistent with existing literature. Previous research has shown that poor emotion regulation skills are linked to increased impulsive behaviors (51), and impulsivity has been identified as a significant risk factor in the development of various forms of addiction (52). In this context, our results support the view that individuals with difficulties in emotion regulation may be more vulnerable to problematic social media use due to heightened impulsivity, in line with prior theoretical and empirical findings.

Model 1 – Emotion Regulation Difficulties as a Mediator

The mediation analysis revealed that difficulties in emotion regulation significantly mediated the relationship between social media addiction and phubbing behavior. This finding suggests that adolescents who struggle to manage their emotional responses may turn to excessive smartphone use as a maladaptive coping strategy. Consistent with previous research, problematic social media use appears to be associated with increased emotion dysregulation, which in turn is linked to greater phubbing behavior (44, 53). Thus, difficulties in emotion regulation may serve as a key explanatory mechanism in the association between social media addiction and phubbing behavior.

Model 2 – Social Anxiety as a Mediator

The second mediation model demonstrated that social anxiety also mediates the relationship between social media addiction and phubbing behavior. This suggests that adolescents with higher levels of social anxiety may rely on their smartphones to avoid face-to-face interactions, thereby increasing their likelihood of engaging in phubbing. Although the indirect effect through social anxiety was smaller than that observed for emotion regulation difficulties, the finding nonetheless supports the notion that social anxiety may contribute to a preference for online interactions over in-person social engagement.

Serial Mediation Model – Social Anxiety and Emotion Regulation Difficulties as Sequential Mediators

The serial mediation analysis indicated a sequential pattern in which social media addiction was associated with higher levels of social anxiety, which in turn were linked to greater difficulties in emotion regulation and, ultimately, increased phubbing behavior. This pattern highlights how emotional and anxiety-related processes may co-occur and interact in adolescents' disengagement from their immediate social environment. The presence of indirect effects, including the serial pathway, suggests that these psychological mechanisms may operate jointly in shaping phubbing behavior. Consistent with prior research, these findings align with broader evidence indicating that internalizing symptoms and deficits in self-regulation are closely associated with maladaptive technology use during adolescence (54).

However, although the serial mediation findings are consistent with the proposed model, alternative pathways should also be considered. In particular, difficulties in emotion regulation may represent a pre-existing vulnerability that contributes to the development or maintenance of social anxiety, rather than solely arising as a downstream consequence. Given the cross-sectional design of the study, the temporal ordering of these variables cannot be established. Therefore, the observed pathways should be interpreted as theoretically informed associations rather than definitive causal relationships. Future longitudinal research is needed to test competing models and clarify the directionality of these associations.

Taken together, these findings suggest that phubbing is not merely a social habit but may reflect broader emotional and psychological challenges, particularly among emotionally vulnerable adolescents. Interventions targeting emotion regulation skills and social anxiety may therefore be beneficial in addressing problematic smartphone and social media use. However, as the sample was drawn from a child and adolescent psychiatry outpatient clinic, these implications should be interpreted with caution, and the findings may not be directly generalizable to adolescents in community settings.

Limitations

Despite the valuable insights provided by this study, certain limitations should be acknowledged. First, the cross-sectional design precludes causal inferences regarding the observed relationships. Second, the data were based on self-report measures, which may be subject to social desirability and recall biases. The exclusive reliance on self-report instruments also raises the possibility of shared method variance and construct overlap, particularly among conceptually related variables such as social anxiety, emotion regulation difficulties, and social media addiction. Future longitudinal or experimental studies employing multi-method assessment approaches are needed to better clarify the directionality and underlying mechanisms of these relationships.

CONCLUSION

The present study demonstrated that social media addiction significantly predicts phubbing behavior both directly and indirectly through difficulties in emotion regulation and social anxiety. Correlational analyses revealed strong associations among social media addiction, emotion regulation difficulties, social anxiety, and phubbing behavior. Mediation analyses further highlighted the central role of emotion regulation difficulties as a mediator, with additional evidence supporting a serial mediation pathway involving social anxiety. These findings suggest that interventions aimed at reducing phubbing behavior in adolescents should address not only patterns of social media use but also underlying emotional and psychological processes, particularly anxiety and emotion regulation skills.

Ethical Approval: The study was approved by the Ethics Committee of Balikesir Ataturk City Hospital. (Approval Number: E-30041352-514.19.99-269198443, Date: 20.02.2025).

Informed Consent: Written informed consent was obtained from all participating adolescents and their legal guardians prior to participation in the study.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: Not declared.

Contribution Categories		Author Initials
Category 1	Concept/Design	S.A.A., O.D.T.
	Data acquisition	S.A., O.D.T.
	Data analysis/Interpretation	E.G.G.
Category 2	Drafting manuscript	S.A.A., S.A., E.G.G., O.D.T.
	Critical revision of manuscript	S.A.A., S.A., E.G.G., O.D.T.
Category 3	Final approval and accountability	S.A.A., S.A., E.G.G., O.D.T.
Other	Technical or material support	S.A.
	Supervision	E.G.G.

Peer-review: Externally peer-reviewed.

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DOI: 10.14744/DAJPNS.2026.00322
Dusunen Adam J Psychiatr Neurol Sci
2026;39:90-100

RESEARCH ARTICLE

Distinct fatigue profiles and psychological mechanisms among breast cancer survivors: A latent profile and mediation analysis

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ABSTRACT

Objective: Cancer-related fatigue (CRF) is highly prevalent among breast cancer survivors. This study aimed to identify CRF subgroups in breast cancer survivors using latent profile analysis (LPA) and to examine the effects of rumination on CRF through anxiety, depression, and fear of cancer recurrence.

Method: A total of 201 women diagnosed with early-stage breast cancer completed standardized assessments of fear of cancer recurrence, rumination, anxiety, depression, and cancer-related fatigue. Latent profile analysis was conducted to identify distinct CRF profiles, and differences in psychological variables across groups were examined. Mediation analyses were performed using the PROCESS macro with bootstrapping (5,000 samples) to test indirect effects.

Results: LPA identified three distinct profiles: low (50.2%), moderate (37.3%), and high (12.4%). The model demonstrated excellent classification quality (entropy=0.80; average posterior probabilities=0.89–0.93). Participants in the high-CRF group reported significantly higher levels of rumination, anxiety, depression, and fear of recurrence than those in the other two groups (all $p<0.001$, $\eta^2=0.10–0.30$). Multinomial regression analysis showed that depression, anxiety, and fear of cancer recurrence significantly predicted membership in the high-CRF group. Mediation analyses indicated that rumination predicted CRF indirectly through depression (b=0.07, 95% confidence interval (CI) [0.01, 0.15]), anxiety (b=0.20, 95% CI [0.05, 0.34]), and fear of recurrence (b=0.17, 95% CI [0.04, 0.30]), jointly accounting for 32.6% of the total effect.

Conclusion: The findings suggest that fear of recurrence, anxiety, and depression may increase vulnerability to CRF. The results also underscore the importance of targeting transdiagnostic processes such as rumination in psychological interventions for breast cancer survivors.

Keywords: Breast cancer survivors, cancer-related fatigue, fear of recurrence, latent profile analysis, mediation, rumination

INTRODUCTION

Breast cancer is one of the most prevalent cancers among women worldwide, and advances in early detection and treatment have led to a growing population of long-term survivors (1). However, both survivors and patients undergoing treatment continue to face numerous physical and psychological

How to cite this article: Turkel NN, Turkel A, Ekmekci I, Dogan M. Distinct fatigue profiles and psychological mechanisms among breast cancer survivors: A latent profile and mediation analysis. Dusunen Adam J Psychiatr Neurol Sci 2026;39:90-100.

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Received: December 01, 2025; **Revised:** May 05, 2026; **Accepted:** May 06, 2026

challenges. Among these, cancer-related fatigue (CRF) is one of the most common and distressing symptoms. CRF often persists after treatment completion, and approximately 66% of breast cancer survivors experience fatigue to some degree (2). A meta-analysis including 84 studies reported an overall CRF prevalence of 52% across all cancer types. (3) CRF is broadly defined as a sense of physical, emotional, and cognitive exhaustion that impairs functioning and is disproportionate to recent activity (4). Numerous factors have been associated with CRF. In addition to physical factors such as chemoradiotherapy, female sex, pain, neurotic personality traits, sleep disorders, and depression have all been identified as potential risk factors (3). However, the mechanisms through which psychological factors contribute to fatigue severity remain incompletely understood.

One approach that may improve understanding of CRF heterogeneity is the use of person-centered statistical methods. CRF is a multidimensional phenomenon encompassing cognitive, emotional, and physical components, and patients may experience fatigue in qualitatively different ways. Latent profile analysis (LPA) is a person-centered statistical approach used to identify subgroups of individuals based on shared patterns of psychological characteristics (5). By identifying distinct fatigue profiles, LPA may provide clinically meaningful insights into symptom heterogeneity and help guide the development of more tailored supportive interventions.

In addition to symptom heterogeneity, cognitive processes may play an important role in the development and maintenance of cancer-related fatigue. Rumination, broadly defined as repetitive thinking about past losses and failures or anticipated future threats, has been identified as a transdiagnostic cognitive process associated with both depression and anxiety (6). In the context of cancer, intrusive rumination may emerge following diagnosis and treatment and has been associated with greater psychological distress and poorer adjustment among cancer survivors (7). Such repetitive cognitive processing may amplify emotional distress and heighten attention to bodily sensations, thereby contributing to the perception and persistence of fatigue.

The current study had two primary objectives. First, we aimed to identify distinct CRF profiles among early-stage breast cancer survivors using latent profile analysis. Second, we investigated whether rumination predicts CRF and whether anxiety, depression, and fear of cancer recurrence mediate or contribute to this relationship. By integrating person-centered and process-focused approaches, this study seeks to improve understanding of CRF and its underlying mechanisms and to inform the development of more tailored psycho-oncological interventions.

METHODS

Study Design and Participants

This cross-sectional study was conducted in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. A convenience sampling method was used to recruit patients with early-stage breast cancer, defined in this study as stage I–III non-metastatic disease in remission, who attended outpatient follow-up visits at the Medical Oncology Department of Dr. Abdurrahman Yurtaslan Ankara Oncology Research and Training Hospital between March and July 2024. Inclusion criteria were: (1) age 18 years or older; (2) sufficient Turkish literacy to complete self-report questionnaires; (3) diagnosis of early-stage breast cancer and remission status; and (4) absence of severe neurological or psychiatric disorders. Patients with stage IV breast cancer or those receiving active chemotherapy or radiotherapy at the time of the study were excluded. Eligible participants who provided written informed consent completed a set of standardized self-report questionnaires. Of the 210 patients invited to participate, 201 provided valid responses and were included in the final analysis, yielding a response rate of 95.7%.

Measures

Sociodemographic and Disease-Related Variables

Sociodemographic data were collected using a structured questionnaire developed by the researchers. Participants reported their age, marital status, educational level, employment status, family history of cancer, previous cancer diagnoses, and the presence of psychiatric or physical comorbidities. Clinical data, including time since diagnosis, cancer stage, and history of chemotherapy, radiotherapy, and hormone therapy, were obtained from hospital medical records.

Fear of Cancer Recurrence Inventory–Short Form (FCR-SF)

Fear of cancer recurrence (FCR) was assessed using the 9-item Fear of Cancer Recurrence Inventory–Short Form, a 5-point Likert-type scale that evaluates the severity of recurrence-related concerns among cancer

patients. The FCRI-SF is derived from the "Severity" subscale of the original 42-item multidimensional Fear of Cancer Recurrence Inventory (FCRI) developed by Simard et al. (8), which consists of seven subscales. Higher scores indicate greater fear of recurrence (8). The Turkish version of the scale has demonstrated good validity and reliability in cancer populations (9). In the present study, the Cronbach's alpha for the scale was 0.840.

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale, developed by Zigmond and Snaith, is a 14-item, 4-point Likert-type scale designed to assess symptoms and severity of anxiety and depression. Odd-numbered items assess anxiety, whereas even-numbered items assess depression (10). The Turkish validity and reliability study conducted by Aydemir et al. demonstrated that the scale is appropriate for use in medically ill populations (11). In the current study, Cronbach's alpha coefficients were 0.766 for the depression subscale and 0.799 for the anxiety subscale.

Cancer Fatigue Scale (CFS)

The Cancer Fatigue Scale was developed to assess fatigue in patients with cancer, particularly breast cancer patients. The scale evaluates three dimensions of fatigue: physical, affective, and cognitive. Each item is rated on a 5-point Likert scale (12). The Turkish validity and reliability study of the scale was conducted by Şahin et al. (13) In the present study, the Cronbach's alpha coefficient for the scale was 0.807.

Event-Related Rumination Inventory (ERRI)

The Event-Related Rumination Inventory, developed by Cann et al., assesses repetitive thoughts related to stressful events. The scale consists of 20 self-report items rated on a 4-point Likert scale and includes two subscales: intrusive/involuntary rumination and deliberate rumination. (14) The Turkish version of the ERRI has demonstrated adequate validity and reliability. Only the intrusive/involuntary rumination subscale was used in the present study (15). Cronbach's alpha for this subscale was 0.936.

Statistical Analysis

Descriptive statistical analyses were conducted using SPSS version 25.0. Frequencies and percentages were calculated for categorical sociodemographic and clinical variables, whereas means and standard deviations were calculated for continuous variables. LPA was performed to identify subgroups of early-stage breast cancer survivors based on levels of CRF. Model fit was evaluated using the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and entropy values. Lower AIC and BIC values and entropy values greater than 0.80 were considered indicative of better model fit. The Bootstrap Likelihood Ratio Test (BLRT) was also used to compare successive models (k vs. k−1 classes), consistent with the recommendations of Nylund et al. (16), who identified BLRT and BIC among the most reliable indicators for class enumeration. Four models were tested, and the optimal number of latent classes was determined based on a combination of statistical fit indices and theoretical interpretability. LPA was conducted using the "tidyLPA" package in R. After selecting the final model, chi-square tests and univariate analyses were conducted to compare demographic, clinical, and psychological variables across the identified latent profiles. A p-value <0.05 was considered statistically significant.

To further examine predictors of class membership, multinomial logistic regression analyses were conducted using the "nnet" package in R. Because multinomial logistic regression treats CRF as a categorical outcome, potential indirect effects among variables may not be fully captured. Therefore, complementary mediation analyses were conducted using PROCESS version 4.2, treating CRF as a continuous variable, to examine the mediating roles of depression, anxiety, and fear of cancer recurrence in the relationship between rumination and CRF.

RESULTS

Demographic and Clinical Characteristics

The study initially enrolled 210 female patients diagnosed with early-stage breast cancer. Of these, 201 provided valid responses and were included in the final analyses, resulting in a response rate of 95.7%. Most participants were married (78.1%), and 35.8% had completed a university education. All participants had undergone breast surgery, and 22.4% had been diagnosed with stage III breast cancer. The mean age of the sample was 51.88 years (standard deviation [SD]=9.40), and the mean time since diagnosis was 5.45 years (SD=4.75). Detailed demographic and clinical characteristics of the participants are presented in Table 1.

Latent Profile Analysis

Table 2 summarizes the fit indices for the models generated using the "tidyLPA" package based on

Table 1: Demographic and clinical characteristics of participants (n=201)

Variables	n	%	Variables	n	%
Age group (years)			Psychiatric comorbidity		
<45	56	27.9	Yes	13	6.5
45–65	130	64.7	No	188	93.5
>65	15	7.5	Physical comorbidity		
Marital status			Yes	37	18.4
Unmarried	44	21.9	No	164	81.6
Married	157	78.1	Cancer stage		
Educational level			Stage I	45	22.4
Secondary school	74	38.8	Stage II	111	55.2
High school	55	27.4	Stage III	45	22.4
University	72	35.8	Time since diagnosis		
Employment status			<5 years	134	66.7
Employed	51	25.4	5–10 years	39	19.4
Unemployed	108	53.7	>10 years	28	13.9
Retired	42	20.9	Chemotherapy history		
Family history of cancer			Yes	177	84.3
Yes	63	31.3	No	34	15.7
No	138	68.7	Radiotherapy history		
Previous cancer diagnosis			Yes	153	77.2
Yes	49	24.4	No	48	22.8
No	152	75.6	Hormone therapy history		
Time since diagnosis, mean (SD)	5.45 (4.75)		Yes	172	86.8
Age, mean (SD)	51.88 (9.40)		No	29	13.2

SD: Standard deviation.

Table 2: Fit indices for latent profile models

Variables	AIC	BIC	Entropy	BLRT	BLRT-p	Smallest Class %	Largest Class %
1-Class	1720.23	1740.05	NA	NA	NA	1	1
2-Class	1587.81	1620.84	0.79	140.43	0.001	0.29	0.71
3-Class	1534.66	1580.91	0.80	61.15	0.001	0.12	0.50
4-Class	1532.11	1591.57	0.78	10.55	0.10	0.05	0.53
5-Class	1516.08	1588.76	0.80	24.02	0.001	0.05	0.50
6-Class	1500.25	1586.14	0.81	23.83	0.001	0.05	0.43

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; BLRT: Bootstrap Likelihood Ratio Test; NA: Not applicable; Entropy: Classification accuracy index. Lower AIC and BIC values and higher entropy values (>0.80) indicate better model fit.

dimensions of the Cancer Fatigue Scale among early-stage breast cancer survivors. Model fit improved with the addition of each class, as reflected by decreasing AIC and BIC values. Entropy values remained high across models, indicating good classification quality. The three-class model demonstrated the best fit according to the Bayesian Information Criterion (BIC=1580.91) and showed satisfactory entropy value (0.80), indicating clear separation among latent groups. The Bootstrap Likelihood Ratio Test was significant (p=0.01) when comparing the three-class model with the two-class model, further supporting selection of the three-class solution as the optimal model. Models with four or more classes did not improve model fit and resulted in very small latent groups (n<5%).

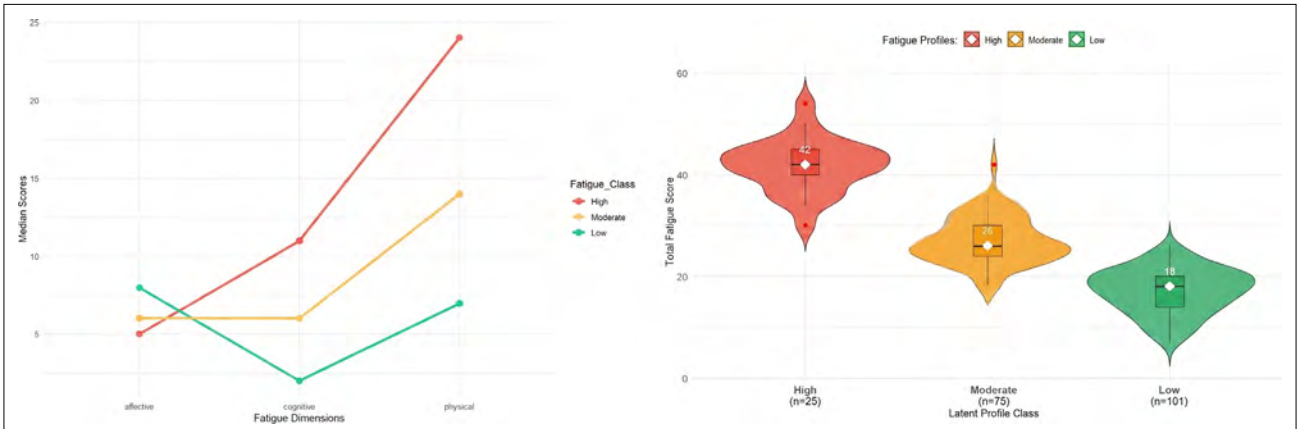

Figure 1. Mean item scores on the Cancer Fatigue Scale (CRF) across the three latent CRF profiles (low, moderate, and high CRF; left panel) and violin plots illustrating the distribution of total Fear of Cancer Recurrence (FCR) scores across profiles (right panel). Error bars represent 95% confidence intervals. Boxes within the violin plots indicate the interquartile range, and horizontal lines represent median values.

Classification quality was high (entropy=0.80). Class-specific average posterior probabilities (APPs) indicated adequate-to-excellent classification accuracy, with values of 0.94, 0.89, and 0.90 for the High, Moderate, and Low fatigue profiles, respectively. The overall classification correctness (OCC) was 0.91, further supporting the robustness of the class assignments.

The identified classes were labeled according to severity of cancer-related fatigue: High Fatigue (12.4%, n=25), Moderate Fatigue (37.3%, n=75), and Low Fatigue (50.2%, n=101). Mean Cancer Fatigue Scale scores across the profiles are presented in Figure 1, demonstrating a clear gradient in symptom severity among the three latent profiles.

Differences in Demographic and Clinical Characteristics Among the Latent Profiles

Table 3 presents comparisons of sociodemographic and clinical characteristics across the cancer-related fatigue profiles. χ^2 tests were used for categorical variables, whereas the Kruskal–Wallis test was used for continuous variables. No significant differences were observed among the profiles with respect to marital status, educational level, occupational status, disease stage, or the presence of additional psychiatric or physical illnesses. However, rank-based analysis of variance revealed significant between-profile differences in fear of cancer recurrence, rumination, anxiety, depression, and cancer-related fatigue scores. Post hoc analyses demonstrated that patients in the High-CRF group scored significantly higher than those in the Moderate- and Low-CRF groups across all measures. Effect sizes were moderate to large (η^2=0.10–0.30), indicating clinically meaningful differences between profiles. Given the exploratory nature of these analyses, p values were interpreted cautiously and were not adjusted for multiple comparisons.

Continuous variables are presented as median (Q1–Q3) values and were compared using the Kruskal–Wallis test followed by Dunn–Bonferroni post hoc analyses. Categorical variables were analyzed using chi-square tests, and Fisher's exact test was applied when expected cell counts were below five.

Multinomial Logistic Regression Analysis

Sociodemographic and clinical variables that differed significantly across latent profiles in the univariate analyses (Table 4) were included in the multinomial logistic regression model.

The final regression model demonstrated acceptable fit indices (AIC=314.06; McFadden's pseudo R^2=0.2481), indicating good overall model fit for multinomial logistic regression. The model correctly classified 63.2% of cases overall, with particularly high accuracy for the Low-Risk Group (80.2%), moderate accuracy for the High-Risk Group (44.0%), and lower accuracy for the Moderate-Risk Group (46.7%).

In the moderate- versus low-risk comparison, depression emerged as a significant independent predictor (odds ratio [OR]=1.159, 95% confidence interval [CI]: 11.032–1.302, p=0.013), indicating that each one-point increase in depression scores was associated with a 15.9% greater likelihood of belonging to the moderate-risk group.

Table 3: Differences in demographic and clinical characteristics across latent profiles (n=201)

Variables	High CFS n (%)	Moderate CFS n (%)	Low CFS n (%)	Test statistic	p
Marital status				2.5515	0.2792
Unmarried	7 (15.9)	12 (27.2)	25 (56.8)		
Married	18 (11.5)	63 (40.1)	76 (48.4)		
Educational level				6.975	0.1432
Secondary school	15 (20.3)	27 (36.5)	32 (43.2)		
High school	4 (7.27)	21 (38.2)	30 (54.5)		
University	6 (8.33)	27 (37.5)	39 (54.2)		
Family history of cancer				12.668	0.5278
Yes	9 (14.3)	20 (31.7)	34 (54.0)		
No	16 (11.6)	55 (39.9)	67 (48.6)		
Previous cancer diagnosis				4.8363	0.08167
Yes	7 (14.3)	24 (49.0)	18 (36.7)		
No	18 (11.8)	51 (33.6)	83 (54.6)		
Psychiatric comorbidity				4.3252	0.07292
Yes	3 (23.1)	7 (53.8)	3 (23.1)		
No	22 (11.7)	68 (36.2)	98 (52.2)		
Physical comorbidity				1.7562	0.45551
Yes	3 (8.11)	17 (45.9)	17 (45.9)		
No	22 (13.4)	58 (35.4)	84 (51.2)		
Cancer stage				5.7944	0.1926
Stage I	7 (16.7)	10 (23.8)	25 (59.5)		
Stage II	12 (10.5)	44 (38.6)	58 (50.9)		
Stage III	6 (13.3)	21 (46.7)	18 (40.0)		
Age, M (Q_1, Q_3)	52 (45–57)	49 (44–56)	52 (46–60)	5.66	0.059
Time since diagnosis, M (Q_1, Q_3)	5 (3–8)	4 (2–6)	5 (2–8)	1.59	0.451
Cognitive fatigue, M (Q_1, Q_3)	11 (9–14)	6 (4–8)	2 (1–4)	119.0	**<0.001**
Emotional fatigue, M (Q_1, Q_3)	5 (4–8)	6 (5–8)	8 (6–10)	26.7	**<0.001**
Physical fatigue, M (Q_1, Q_3)	24 (23–28)	14 (12–16)	7 (4–8)	153.0	**<0.001**
FCR, M (Q_1, Q_3)	24 (21–28)	17 (13.5–22)	15 (9–22)	36.9	**<0.001**
Anxiety, M (Q_1, Q_3)	14 (10–16)	8 (6–10)	5 (2–8)	61.4	**<0.001**
Depression, M (Q_1, Q_3)	10 (7–11)	6 (4–9)	3 (1–5)	49.5	**<0.001**
Rumination, M (Q_1, Q_3)	22 (16–28)	17 (10–20)	12 (6–19)	21.2	**<0.001**

CFS: Cancer Fatigue Scale; FCR: Fear of Cancer Recurrence.

In the high- versus low-risk comparison, anxiety demonstrated the strongest predictive value (OR=1.538, 95% CI: 1.231–1.922, p<0.001), indicating that each one-point increase in anxiety scores was associated with a 53.8% greater likelihood of membership in the high-risk group. FCR also emerged as a significant predictor (OR=1.196, 95% CI: 1.040–1.372, p=0.010), with each unit increase associated with a 19.6% greater likelihood of high-risk classification.

Mediation Analysis

Because multinomial logistic regression treats CRF as a categorical outcome, this approach may obscure the continuous nature of fatigue severity. To address this limitation and further examine potential indirect pathways, a mediation analysis (PROCESS Model 4) was conducted treating CRF as a continuous variable. Rumination was entered as the independent variable (X), anxiety, depression,

Table 4: Predictors of latent profile membership

Predictor	β	SE	Wald	p	OR	95% CI
Moderate CRF vs. Low CRF						
Intercept	-2.188	0.493	19.68	<0.001	0.112	0.043–0.295
Anxiety	0.119	0.069	3.07	0.086	1.126	0.983–1.290
Depression	0.148	0.059	6.20	0.013	1.159	1.032–1.302
FCR	0.018	0.034	0.30	0.587	1.126	0.983–2.090
Rumination	0.005	0.030	0.03	0.867	1.005	0.948–1.065
High CRF vs. Low CRF						
Intercept	-9.809	1.691	33.63	<0.001	0.000	0.000–0.002
Anxiety	0.430	0.114	14.25	<0.001	1.538	1.231–1.922
Depression	0.141	0.099	2.03	0.154	1.152	0.948–1.399
FCR	0.170	0.070	6.58	0.010	1.196	1.040–1.372
Rumination	-0.004	0.056	0.00	0.946	0.996	0.893–1.111

Reference category=Low-CRF group; SE: Standard error; OR: Odds ratio; CI: Confidence interval; CRF: Cancer-related fatigue; FCR: Fear of cancer recurrence.

Table 5: Parallel mediation model regression coefficients predicting cancer-related fatigue scale (CFS)

Dependent variable	Independent variable	β	SE	t	p	R^2
Anxiety	Rumination	0.29	0.03	8.63	<0.001	0.27
Depression	Rumination	0.18	0.04	5.22	<0.001	0.12
FCR	Rumination	0.59	0.05	12.20	<0.001	0.43
CFS	Rumination	-0.05	0.10	-0.56	0.58	
CFS	Anxiety	0.69	0.20	3.38	<0.001	
CFS	Depression	0.39	0.18	2.12	0.03	
CFS	FCR	0.29	0.11	2.60	0.01	

SE: Standard error; FCR: Fear of cancer recurrence.

and fear of cancer recurrence as parallel mediators (M_1, M_2, M_3), and total CRF score as the dependent variable (Y) (Table 5).

The direct effect of rumination on fatigue was not statistically significant (b=–0.05, p=0.58). Therefore, indirect pathways through depression, anxiety, and fear of cancer recurrence were examined.

The total indirect effect was significant (b=0.44, 95% CI [0.26, 0.61]). Each mediator contributed a significant indirect effect:

- Through depression: b=0.07, 95% CI [0.01, 0.15];
- Through anxiety: b=0.20, 95% CI [0.05, 0.34];
- Through fear of cancer recurrence: b=0.17, 95% CI [0.04, 0.30].

Together, the mediators explained 32.6% of the variance in fatigue severity.

These findings suggest that higher levels of rumination are associated with greater depression, anxiety, and fear of cancer recurrence, which in turn contribute to increased fatigue severity. Among the mediators, anxiety exerted the strongest indirect effect, followed by FCR and depression.

DISCUSSION

This study highlights the heterogeneous nature of cancer-related fatigue among patients with early-stage breast cancer in remission by identifying distinct fatigue subgroups—low, moderate, and high CRF—and examining differences between these profiles. Additionally, CRF was conceptualized as a continuous construct to investigate its relationship with rumination and the potential mediating roles of depression, anxiety, and fear of cancer recurrence.

Latent profile analysis revealed that 50.2% of participants belonged to the low-CRF group, 37.3% to the moderate-CRF group, and 12.4% to the high-CRF group. As expected, the high-CRF profile demonstrated the highest CFS scores, whereas the low-CRF profile showed the lowest scores. These proportions are comparable to findings from previous studies. In a study of colorectal cancer survivors, Thong et al. (17) identified three distinct CRF classes: a no fatigue/no distress group (n=644, 56%), a low fatigue/moderate distress group (n=256, 22%), and a high fatigue/moderate distress

group (n=256, 22%). Similarly, Li et al. (18) identified three CRF profiles among patients with hepatocellular carcinoma: "Physical balance–Low fatigue" (20.1%), "Physical imbalance–Moderate fatigue" (69.6%), and "Physical prominent–High fatigue" (10.2%). In the present study, the combined prevalence of moderate and high CRF was 49.7%, consistent with the findings of a systematic review by Ruiz-Casado et al. (19). Collectively, these findings support previous literature indicating that CRF remains a highly prevalent and clinically significant concern among breast cancer survivors.

Progression from minimal to severe CRF was significantly associated with several baseline clinical characteristics. Although previous studies have suggested that younger breast cancer survivors tend to experience higher fatigue levels, findings regarding age remain inconsistent (19). In the present study, age did not significantly differentiate fatigue profiles. One possible explanation is that the sample consisted predominantly of middle-aged participants with relatively homogeneous age distributions, limiting variability across groups. Furthermore, fatigue in breast cancer survivors may be influenced more strongly by psychological and behavioral factors than by demographic variables alone. Consistent with previous research, no significant association was found between cancer stage and CRF severity (19). This finding may reflect the possibility that fatigue is more strongly influenced by long-term treatment effects and psychological adjustment processes than by disease severity itself. Similarly, although social support has been identified as a protective factor against CRF and married individuals are often reported to experience lower fatigue levels, marital status was not associated with fatigue profiles in the present study (20). A possible explanation is that marital status alone may not adequately reflect the quality or availability of social support, which may be a more relevant factor influencing fatigue experiences.

Rank-based analysis of variance (Kruskal–Wallis ANOVA) indicated that individuals with high CRF exhibited elevated levels of fear of cancer recurrence, depression, rumination, and anxiety. Multinomial logistic regression analyses identified depression as the sole significant predictor of transition from the low-CRF group to the moderate-CRF group (OR=1.16, 95% CI: 1.03–1.30, p=0.013). These findings are consistent with recent evidence from a large sample of breast cancer survivors demonstrating that individuals reporting both depression and fatigue experience greater fatigue severity than those reporting fatigue alone (21). Moreover, studies investigating predictors of fatigue have consistently shown that higher fatigue levels are associated with depression (22, 23) Depression and fatigue are strongly correlated, and each symptom may function both as a cause and a consequence of the other (24). Additionally, both conditions may arise through shared pathophysiological mechanisms, or fatigue may develop as a secondary response to the adaptive demands of CRF or post-treatment stress (25, 26). These shared mechanisms include elevated pro-inflammatory cytokines and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (27, 28). Increased inflammatory activity has been associated with fatigue, insomnia, and depression among breast cancer survivors (29). In recent years, depression has increasingly been conceptualized as a maladaptive response to impaired interoception (30). From this perspective, individuals with depression may engage in dysfunctional bodily self-focus, potentially interpreting somatic sensations in ways that amplify perceptions of fatigue. Consequently, depression may not only intensify the subjective experience of fatigue but also impair physiological energy regulation, thereby contributing to the persistence of cancer-related fatigue.

A markedly different pattern emerged for the transition to the high-CFR profile, in which FCR (OR=1.20, 95% CI: 1.04–1.37, p=0.010) and anxiety (OR=1.54, 95% CI: 1.23–1.92, p<0.001) emerged as significant predictors, whereas depression was no longer significant. A recent meta-analysis including 34 studies reported significant associations between fear of cancer recurrence and cancer-related fatigue (31). Although FCR and CRF are both prevalent concerns among cancer survivors, their relationship is multifaceted. Pre-treatment anxiety, which is strongly associated with FCR, has been shown to predict CRF both before and after treatment (32). Furthermore, individuals with high levels of FCR often demonstrate heightened anxiety sensitivity and catastrophizing tendencies, which may contribute to the misinterpretation of bodily sensations and thereby intensify fatigue experiences (3, 33). Supporting this interpretation, a meta-analysis of mindfulness-based interventions in cancer patients demonstrated that improvements in mindfulness skills were associated with reductions in both CRF and FCR (34). Conversely, physical symptoms may be misinterpreted as signs of cancer recurrence, while cancer-related fatigue itself may contribute to more negative illness perceptions and intensify concerns that cancer will not be cured, thereby perpetuating FCR (35, 36). Consistent with this interpretation, findings from a recent longitudinal study demonstrated that higher CRF levels significantly predicted increases in FCR over time (36).

Contrary to our hypotheses, intrusive rumination did not significantly predict fatigue transitions in the multivariate model. One possible explanation is that the effects of rumination are fully mediated through depression and anxiety, leaving no remaining unique predictive variance once these variables are statistically controlled. Indeed, when CRF was modeled as a continuous variable, mediation analyses demonstrated that depression, anxiety, and cancer-related fatigue fully mediated the relationship between rumination and CRF. In the parallel mediation model, rumination exerted only indirect effects on CRF, whereas the direct effect remained non-significant.

The cancer diagnosis and treatment process constitutes a highly challenging and potentially traumatic experience that may give rise to intrusive rumination. (37) Previous research has indicated that rumination may exacerbate anxiety and depression by interfering with effective problem-solving and reducing engagement in mood-enhancing or distracting activities (6, 38). From a Bayesian perspective, repetitive thoughts about the self and past experiences may increase expectations of future threat (39). Although FCR is conceptually distinct from anxiety and depression, it is particularly closely associated with anxiety-related processes (40, 41). Dugas et al. proposed that rumination represents a cognitive response to uncertainty and the inability to control ambiguous life situations. (42) In this context, and consistent with Leventhal's Common-Sense Model and Mishel's Uncertainty in Illness Theory, the unpredictable nature of cancer may increase sensitivity to somatic experiences such as fatigue. The present findings are consistent with previous research demonstrating associations between intrusive rumination and cancer-related fatigue among cancer survivors (7).

Our findings support a multidimensional threshold model of cancer-related fatigue development. Rather than representing a simple continuum in which the same factors operate across all severity levels, different psychological mechanisms appear to govern progression through distinct fatigue stages. This perspective challenges linear conceptualizations of fatigue and supports the view that fatigue profiles may represent qualitatively distinct syndromes with different etiological pathways.

The non-overlapping predictive patterns observed for depression versus FCR/anxiety further suggest that these factors may operate through distinct mechanisms. Depression's association with moderate fatigue may reflect its established links with motivational systems and neuroimmune pathways, whereas the specific relationship between FCR/anxiety and severe fatigue may involve heightened threat perception and sustained cognitive-emotional arousal (36, 43). Regarding rumination, our findings suggest that it functions as a transdiagnostic process that operates across fatigue levels but exerts its effects indirectly through other psychological mechanisms. Rather than serving as a direct predictor of specific fatigue transitions, rumination may create a cognitive vulnerability that amplifies both depressive symptoms (relevant to moderate fatigue) and anxiety/FCR (relevant to severe fatigue). This pattern aligns with the conceptualization of rumination as a cognitive style that cuts across diagnostic categories and exacerbates multiple forms of psychological distress.

This study has several limitations. First, the cross-sectional design precludes conclusions regarding the temporal progression of cancer-related fatigue among breast cancer survivors. Future studies should employ longitudinal designs to better capture the dynamic nature of CRF and its psychological correlates over time. Second, the study was conducted in a single tertiary care center in Turkiye, which may limit the generalizability of the findings to other healthcare settings or cultural contexts. Third, all data were derived from self-report measures, which may be influenced by recall bias and social desirability effects. Additionally, the relatively small size of the high-CRF group (n=25) may have limited statistical power for subgroup comparisons. Future studies should incorporate clinician-rated assessments and objective clinical indicators to improve validity.

CONCLUSION

This study provides evidence for distinct fatigue profiles among breast cancer survivors, with differential psychological predictors. The finding that depression predicts moderate fatigue, whereas FCR and anxiety predict severe fatigue, represents a significant advance in understanding the heterogeneous nature of cancer-related fatigue. These results have important implications for both theoretical models of fatigue development and clinical approaches to fatigue management.

The identification of profile-specific risk factors supports moving beyond one-size-fits-all approaches toward personalized interventions targeting the specific psychological mechanisms underlying different fatigue presentations. Clinically, these findings support the implementation of stratified assessment protocols and tailored interventions addressing depression in moderate fatigue and FCR/anxiety in severe fatigue. From a research perspective, these findings underscore the importance of considering fatigue heterogeneity in future study design and analysis.

Ethical Approval: The Gazi University Research Ethics Committee granted approval for this study (date: 13.02.2024, number: 2024–248/03).

Informed Consent: All participants confirmed their understanding of the study procedures by signing an informed consent form.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

Contribution Categories		Author Initials
Category 1	Concept/Design	N.N.T.
	Data acquisition	A.T.
	Data analysis/Interpretation	N.N.T.
Category 2	Drafting manuscript	N.N.T.
	Critical revision of manuscript	I.E.
Category 3	Final approval and accountability	I.E., M.D.
Other	Supervision	M.D.

Peer-review: Externally peer-reviewed.

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DOI: 10.14744/DAJPNS.2026.00323
Dusunen Adam J Psychiatr Neurol Sci
2026;39:101-111

RESEARCH ARTICLE

Comparative assessment of demographic and clinical characteristics among applicants for firearm possession and carrying licenses: A community hospital sample from Turkiye

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ABSTRACT

Objective: This study aimed to compare individuals applying to the health board for firearm possession and carrying licenses in terms of various sociodemographic and clinical parameters and to examine whether effective symptom profiling could be achieved in this specific population using self-report rating scales.

Method: The study included 170 consecutive first-time applicants (155 men and 15 women) aged 21–68 years. Applicants for firearm possession and carrying licenses were divided into two groups and underwent a detailed psychiatric interview, including psychiatric history and mental status examination. Past medical records were reviewed through the national "e-Nabız" health database. Eligibility was restricted to individuals without a documented psychiatric diagnosis within the previous five years or psychotropic medication use within the previous six months. Participants also completed a case report form and a screening battery consisting of the Beck Depression Inventory, Beck Anxiety Inventory, State–Trait Anger Expression Inventory, and Barratt Impulsiveness Scale to evaluate symptom profiles.

Results: The difference in gender distribution between the two groups was statistically significant (p=0.029). A statistically significant difference was also found between the possession and carrying license groups regarding reasons for firearm acquisition (p<0.001). The most common reason in the possession group was inheritance or transfer from a relative or friend (31.8%), whereas in the carrying group the most common reason was employment in occupations perceived to endanger personal safety (32.9%). In both groups, no participant scored above the established cut-off values for depression, anxiety, impulsivity, or trait anger.

Conclusion: The findings indicate clear differences in firearm acquisition motives between applicants for possession and carrying licenses. In high-stakes licensing contexts, applicants may present socially acceptable justifications for firearm acquisition, thereby limiting the interpretive value of self-reported statements. Self-report screening instruments alone may not reliably identify clinically meaningful symptom profiles in this legally and clinically sensitive setting. Conclusions based solely on applicant declarations may therefore lack sufficient scientific validity, and corroboration through official documentation may assist clinicians in contextualizing evaluations.

Keywords: Firearm carrying license, firearm possession license, health board report, homicide, suicide

How to cite this article: Akbas I, Sahin S. Comparative assessment of demographic and clinical characteristics among applicants for firearm possession and carrying licenses: A community hospital sample from Turkiye. Dusunen Adam J Psychiatr Neurol Sci 2026;39:101-111.

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Received: January 05, 2026; **Revised:** February 24, 2026; **Accepted:** May 13, 2026

INTRODUCTION

In Turkiye, firearm possession and carrying licenses are regulated primarily by Law No. 6136, Law No. 2521, and their associated implementation regulations. Firearm acquisition is considered a conditional privilege rather than an individual right and therefore requires fulfillment of specific criteria (1-3). Carrying licenses, which inherently include possession rights, are restricted to certain professional groups (4) or individuals considered to face serious threats to personal safety (5). By contrast, possession licenses may be obtained by citizens older than 21 years of age who have no criminal record and who receive a medical board report confirming eligibility. These licenses permit firearms to be stored at home or in the workplace but do not authorize carrying them in public. Both license types must be renewed every five years (1-3). A medical board report confirming eligibility is mandatory, and psychiatric evaluation constitutes a central component of the assessment process. However, the relevant legislation defines psychiatric disqualification in broad and non-operational terms, such as the presence of "psychological, neurological, or mental disorders," without specifying standardized diagnostic thresholds, structured assessment tools, or evidence-based risk indicators (1-3). Consequently, eligibility decisions rely heavily on individual clinical judgment rather than validated assessment frameworks.

In contrast, firearm access in the United States is shaped by a constitutional framework in which the Second Amendment recognizes an individual right to keep and bear arms, and no general federal licensing requirement exists for private individuals exercising this right (6). Regulatory oversight primarily targets manufacturers, importers, dealers, and collectors under the Gun Control Act of 1968, which defines prohibited categories—including unlawful substance users and individuals adjudicated as mentally defective or committed to a mental institution—through legal and adjudicative mechanisms rather than routine psychiatric certification (7, 8). Accordingly, psychiatrists do not function as routine gatekeepers in firearm acquisition, and their involvement is generally limited to court-based determinations or mandated reporting pathways, with relevant information transmitted to state systems and the National Instant Criminal Background Check System when applicable (9-12). Even in states that historically required carrying permits, these systems generally did not depend on prospective psychiatric evaluations, and subsequent Supreme Court decisions have further limited discretionary permitting practices (6).

Across the United Kingdom and the European Union, firearm acquisition is similarly treated as a conditional privilege regulated through administrative authorization rather than routine psychiatric certification (13). In the United Kingdom, licensing decisions are made by local chief officers of police based on "good reason" and public safety considerations and include background investigations, interviews, and secure storage inspections. Mental illness is not considered an automatic disqualifier, and prior detention under mental health legislation does not constitute a permanent prohibition, although it may be considered in evaluating current fitness and risk (14). At the European Union level, Directive (EU) 2021/555 establishes harmonized standards for firearm categorization, authorization, traceability, and secure storage while leaving carrying regulations and additional safeguards to individual member states. Notably, the directive does not mandate psychiatric assessment or explicitly refer to psychiatrist involvement as a supranational requirement (15).

This uniquely structured Turkish framework places psychiatrists in a central gatekeeping role with substantial legal and public safety implications while providing limited guidance regarding how risk should be evaluated, particularly among applicants without a documented psychiatric history. In routine practice, eligibility decisions therefore rely largely on self-report, clinical impression, and available health records, despite the absence of assessment tools specifically validated for firearm licensing contexts. Given the large number of applications processed annually in Turkiye (16), this represents a significant yet underexamined area of routine psychiatric practice.

Firearm-related violence remains a major public health concern worldwide, encompassing suicide, homicide, and accidental injury (17-20), and has been associated with multiple clinical, social, and demographic factors (21-24). Although most firearm-related violence involves unlicensed weapons, licensed firearms are also implicated in suicide and homicide in Turkiye and elsewhere, underscoring the importance of accurate psychiatric assessment during the licensing process (25-29). Nevertheless, no Turkish study has yet proposed evidence-based methods for objectively identifying psychiatric risk profiles in this population, likely in part because self-report instruments are particularly vulnerable to dissimulation and socially desirable responding in evaluations associated with legal benefit (30-32). Against this background, the present study aimed to compare applicants for firearm possession and carrying

licenses in terms of sociodemographic characteristics, clinical markers, and firearm acquisition motives and to examine whether self-report screening instruments can identify clinically meaningful symptom profiles in this legally and clinically sensitive context.

METHODS

Study Design and Setting

Individuals who met the inclusion criteria and consecutively presented to the outpatient psychiatry clinic of Istinye State Hospital between May 2021 and December 2022 for medical board assessment were included in the study. Applicants seeking a medical board report for the first-time acquisition of either a firearm carrying license or a firearm possession license were eligible for inclusion. The study was approved by the Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee on May 20, 2021 (approval number: 560).

Participants and Eligibility Criteria

The study included literate male and female participants who were able to complete the assessment instruments used in the study. To determine the required sample size for the independent samples t-test, an a priori power analysis was conducted using G*Power version 3.1. Assuming a large effect size ($f=0.40$), a significance level of $p<0.05$ ($\alpha=0.05$), and a statistical power of 80% ($1-\beta=0.80$), the analysis indicated that a total sample of 156 participants would be sufficient, with 78 participants required in each group. To account for potential attrition or incomplete data, the target sample size was increased to 170 participants. All participants received verbal and written information regarding the study and provided written informed consent prior to participation. The study specifically targeted first-time firearm license applicants. Individuals applying for license renewal or those who had previously obtained a firearm license and were applying for an additional license for a newly purchased or intended firearm were excluded.

Psychiatric Interview Procedure

All psychiatric evaluations were conducted as part of the standard medical board procedure for firearm license applications. Two board-certified psychiatrists participated in the assessment process. Evaluations were performed using a semi-structured clinical interview format consistent with routine psychiatric practice. This approach allowed for a natural reciprocal interview flow while ensuring systematic assessment of relevant domains, including psychiatric history, medical history, substance use history, forensic history, and comprehensive mental status examination. No fully structured diagnostic instrument was used because the evaluations were conducted within the framework of routine administrative assessments rather than research-oriented diagnostic interviews. Inter-rater reliability was not formally assessed. However, both psychiatrists completed their residency training at the same institution and adhered to the same institutional clinical evaluation standards throughout their training.

Recruitment and Procedure

Individuals who had been prescribed psychotropic medication within the previous six months, had a history of regular psychiatric follow-up, had received a disability report within the previous five years due to a psychiatric diagnosis other than schizophrenia spectrum or bipolar disorder spectrum disorders, or had been prescribed psychotropic medication at any point in their lives due to a schizophrenia spectrum or bipolar disorder spectrum diagnosis were individually interviewed prior to application following verification of e-Nabız records. These individuals were informed about the relevant legislation and the general evaluation framework. Following the preliminary interview, none proceeded with the application process, assuming that their request would be rejected under the applicable regulations; therefore, they were not included in the study. Consequently, all individuals included in the study sample had no documented psychiatric diagnosis or treatment history recorded in the official nationwide personal health database (e-Nabız) within the previous five years.

Because the relevant legislation contains vague definitions, the six-month and five-year exclusion periods described above were determined according to the clinical judgment and experience of the evaluating psychiatrists. The Regulation on the Implementation of Law No. 6136 on Firearms, Knives, and Other Instruments does not provide explicit temporal criteria, thereby increasing the importance of clinician discretion in establishing a practical evaluative framework.

During the study period, 178 individuals consecutively presented for firearm license medical board evaluation. All applicants were screened for eligibility. Six individuals were excluded following the preliminary psychiatric interview because of documented psychiatric history or recent psychotropic medication use according to the study exclusion criteria. No applicants were excluded because of illiteracy, and

no eligible individuals declined participation. The remaining 170 applicants met the psychiatric eligibility criteria and were included in the study. Accordingly, all participants included in the analysis were considered psychiatrically eligible for firearm licensure.

Psychometric Instruments

Participants completed a detailed case report form including demographic information and various clinical variables. Data were reviewed for completeness prior to analysis. Psychometric scale data and primary demographic variables were complete for all included participants. Occupational information, however, contained substantial missing and non-standardized responses and was therefore excluded from statistical analyses through listwise deletion for that variable. All remaining analyses were conducted using complete-case data. Both groups—applicants for firearm possession licenses and applicants for firearm carrying licenses—completed a screening battery consisting of self-administered clinical assessment scales. Collected data were compared with respect to demographic variables, clinical characteristics, and screening battery results.

Scales Included in the Screening Battery Beck Depression Inventory (BDI)

The Beck Depression Inventory was developed by Beck et al. (1961) to assess the severity of depressive symptoms. It consists of 21 items, each scored from 0 to 3. The Turkish validity and reliability study was conducted by Hisli (1988) (33, 34).

Beck Anxiety Inventory (BAI)

The Beck Anxiety Inventory was developed by Beck et al. (1988) to assess anxiety severity. It consists of 21 items, each scored from 0 to 3. The Turkish validity and reliability study was conducted by Ulusoy et al. (1998) (35, 36).

State–Trait Anger Expression Inventory

The State–Trait Anger Expression Inventory was developed by Spielberger et al. (1983) to assess anger levels and anger expression styles. The scale includes four subscales: Trait Anger, Anger-In, Anger-Out, and Anger Control. The Turkish validity and reliability study was conducted by Özer (1994) (37, 38).

Barratt Impulsiveness Scale–11 Short Form (BIS-11)

The Barratt Impulsiveness Scale was originally developed by Barratt (1959) to assess impulsivity and was later revised by Patton, Stanford, and Barratt (1995). The Turkish validity and reliability study was conducted by Güleç et al. (2008) (39-41).

Statistical Analysis

Descriptive statistical measures, including mean, standard deviation, percentage, minimum, and maximum values, were used to evaluate the demographic and clinical characteristics of applicants for firearm carrying and possession licenses. For both groups, the normality assumptions of the Beck Depression Inventory, Beck Anxiety Inventory, State–Trait Anger Expression Inventory subscales (Trait Anger, Anger Control, Anger-Out, and Anger-In), and Barratt Impulsiveness Scale scores were evaluated by examining whether skewness and kurtosis values fell within the range of ±2 (42). Formal normality tests such as the Shapiro–Wilk or Kolmogorov–Smirnov tests were not performed because skewness and kurtosis criteria are considered acceptable indicators of distributional normality in samples of this size.

Because the Beck Depression Inventory, Beck Anxiety Inventory, Anger Control subscale, and Barratt Impulsiveness Scale scores did not meet normality assumptions, group comparisons for these variables were performed using the Mann–Whitney U test. Since Trait Anger, Anger-Out, and Anger-In subscale scores demonstrated normal distribution, comparisons between groups for these variables were conducted using the independent samples t-test.

Chi-square analysis and Fisher's exact test (when expected cell frequencies were below 5) were used to compare categorical variables between groups. Because the psychological measures represented conceptually related constructs and the analyses were exploratory in nature, no correction for multiple comparisons was applied. Statistical significance was defined as $p<0.05$ for all analyses. Data analyses were performed using JAMOVI version 2.6.45.0.

RESULTS

The demographic and clinical characteristics of the sample according to license type are presented in Table 1. The difference in gender distribution between the two groups was statistically significant and demonstrated a small effect size ($p=0.029$, Cramer's $V=0.176$).

Individuals evaluated for both firearm possession and firearm carrying licenses reported no current emotional or psychiatric complaints, no history of suicide attempts, no prior psychiatric hospitalization, and no current illicit substance use. Among applicants for firearm possession licenses, only one individual (1.1%) reported a forensic history, whereas two individuals (2.4%) in the firearm carrying license group

Table 1: Demographic characteristics of applicants for firearm possession and carrying licenses

	Possession		Carrying		p	Effect size
	n	%	n	%		
Gender						
Male	76	86.4	79	96.3	**0.029***	**0.176[a]**
Female	12	13.6	3	3.7		
Marital status						
Married	63	71.6	54	65.9	0.713*	0.076[a]
Single	22	25.0	23	28.0		
Divorced	3	3.4	4	4.9		
Educational level						
No formal education	1	1.1	0	0	0.706*	0.138[a]
Primary school	11	12.5	9	11		
Middle school	13	14.8	8	9.8		
High school	23	26.1	26	31.7		
University degree	34	38.6	30	36.5		
Postgraduate degree	6	6.8	9	11		
Occupational status						
Employed	73	83.0	76	92.7	0.127*	0.156[a]
Unemployed	10	11.4	3	3.7		
Retired	5	5.7	3	3.7		
Living arrangement						
Living with family	83	94.3	69	84.1	0.095*	0.171[a]
Living alone	4	4.5	10	12.2		
Living with a friend or relative	0	0	1	1.2		
Dormitory residence	1	1.1	2	2.4		
Age	**Mean±SD**	**Median**	**Minimum**	**Maximum**		
Possession	35.6±8.87	34.0	21.0	62.0	0.195**	-0.200[b,c]
Carrying	37.4±9.29	26.0	18.0	68.0		

SD: Standard deviation; *: Chi-square test; **: Independent samples t-test; a: Cramer's V; b: Cohen's d; c: H_0: possession ≠ carrying.

reported such a history. Regarding alcohol use, two individuals (2.3%) in the firearm possession group and one individual (1.2%) in the firearm carrying group reported current alcohol consumption.

Reasons for firearm acquisition and the presence of a specific adverse event associated with firearm license applications according to license type are presented in Table 2. Applicants in the possession license group most commonly sought licensure for inheritance or transfer of firearm ownership from a relative or acquaintance, whereas applicants in the carrying license group most frequently cited employment in occupations perceived to pose risks to personal safety. The difference in firearm acquisition motives between the two groups was statistically significant and demonstrated a medium-to-large effect size ($p<0.001$, Cramer's V=0.498) (Table 2, Fig. 1, 2).

Comparisons of mean scores for anxiety, depression, anger control, impulsivity, trait anger, anger-out, and anger-in are presented in Table 3.

In both groups, none of the individuals evaluated for firearm possession or carrying licenses scored 10 or above on the Beck Depression Inventory, 8 or above on the Beck Anxiety Inventory, 20 or above on the Trait Anger subscale, or 30 or above on the Barratt Impulsiveness Scale. Among applicants for firearm possession licenses, only 11.4% scored 23 or below on the Anger Control subscale, 2.3% scored 16 or above on the Anger-Out subscale, and 6.8% scored 16 or above on the Anger-In subscale. Among applicants for firearm carrying licenses, 4.6% scored 23 or below on the Anger Control subscale, 3.7% scored 16 or above on the Anger-Out subscale, and 4.9% scored 16 or above on the Anger-In subscale (Fig. 2).

Table 2: Clinical characteristics of applicants for firearm possession and carrying licenses

	Possession		Carrying		p*	Effect size
	n	%	n	%		
Firearm acquisition motive						
"I have experienced an incident that threatened my personal safety or I am currently receiving threats."	1	1.1	5	6.1	**<0.001**	**0.498[a]**
"I work in an occupation that may place my personal safety at risk."	7	8.0	27	32.9		
"There are occasions when I need to carry or store large amounts of cash on my person or in my office."	17	19.3	26	31.7		
"I am applying for reasons related to curiosity, hobby, target shooting, hunting, or similar activities."	22	25.0	16	19.5		
"I have received or will receive a firearm through transfer or inheritance from a relative."	28	31.8	2	2.4		
Other reasons	13	14.8	6	7.3		
History of a specific incident leading to the firearm license application						
Yes	2	2.2	3	3.6	0.673	0.041[a]
No	86	97.8	79	96.4		

*: Chi-square test; a: Cramer's V.

DISCUSSION

In this study, significant differences were identified between applicants for firearm possession and firearm carrying licenses regarding their stated reasons for firearm acquisition. Inheritance or transfer from a relative or acquaintance was the predominant motive among applicants for firearm possession licenses, whereas employment in occupations perceived to endanger personal safety was the most common motive among applicants for firearm carrying licenses. Previous Turkish studies have generally examined firearm license applicants as a single group (43-49) without distinguishing between license categories. The observed pattern is consistent with the administrative and legal criteria governing eligibility for each type of license. Although the difference in firearm acquisition motives demonstrated a medium effect size, suggesting a more structurally meaningful distinction between possession and carrying license applicants, this difference most likely reflects regulatory framework differences rather than clinically meaningful variation.

The gender distribution of the sample was heavily skewed toward male applicants. This finding appears consistent with evidence suggesting that firearm ownership may be associated with norms related to masculinity, honor, family protection, and self-reliance (50, 51). In cultural settings where emotional restraint and self-control are socially valued masculine traits, applicants may be inclined to emphasize psychological stability while minimizing vulnerability (52). The predominance of male applicants in the present sample further reflects the gendered nature of firearm licensure in this context. A culturally sensitive perspective may therefore facilitate interpretation of both self-report data and clinical impressions.

Contrary to the study hypothesis, none of the participants in either group scored above established cut-off values for depression, anxiety, impulsivity, or trait anger. This uniformly low symptom burden is unlikely to reflect the true absence of subclinical distress or risk-relevant traits and instead may reflect positive self-presentation tendencies inherent to firearm licensing evaluations. Unlike therapeutic settings, in which individuals seek help for subjective distress, applicants undergoing firearm license assessments are motivated to demonstrate psychological fitness and the absence of potentially disqualifying characteristics (30-32).

Previous research has shown that self-report psychiatric scales may substantially underestimate symptom severity in non-therapeutic, high-stakes contexts, particularly when evaluations are linked to legal or administrative outcomes (53, 54). In such settings, impression management—whether conscious or unconscious—may compromise the validity of self-reported data. The present findings are consistent with this literature and suggest that commonly used self-report instruments, when administered in isolation, have limited utility for symptom profiling in firearm licensing contexts.

Importantly, the uniformly low scale scores observed in this study should not be interpreted as evidence that applicants are free from psychiatric risk. Rather, these

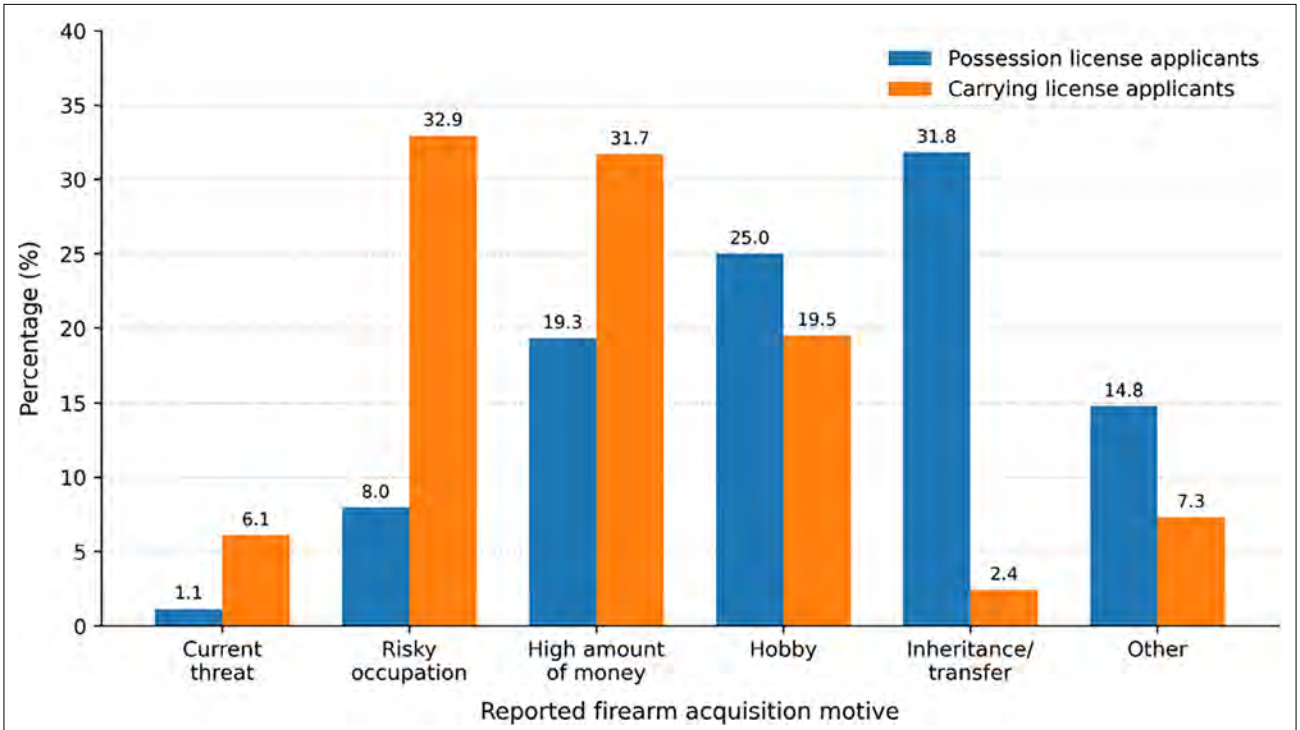

Figure 1. Distribution of reported firearm acquisition motives (%) among applicants for firearm possession and carrying licenses.

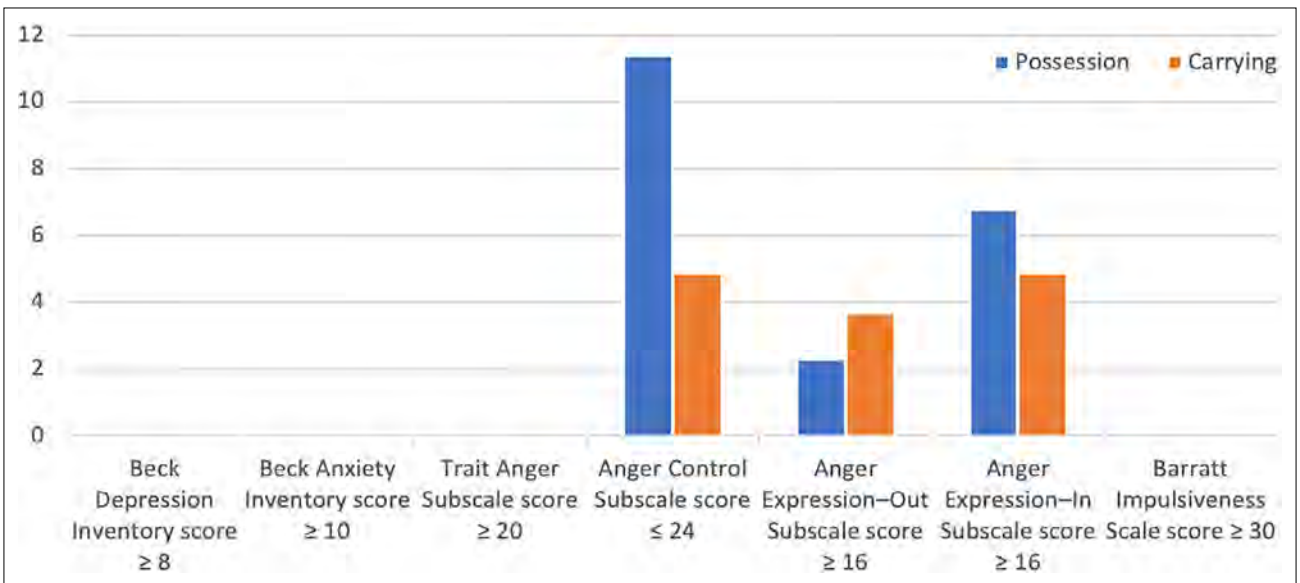

Figure 2. Distribution (%) of applicants for firearm possession and carrying licenses according to screening battery cut-off score status.

findings highlight the structural limitations of self-report measures in evaluations involving secondary gain and underscore the need for more objective, context-appropriate assessment strategies (30-32).

A critical methodological consideration in interpreting these findings is the exclusion of individuals with documented psychiatric diagnoses or recent psychiatric treatment. Although this selection may appear to limit the generalizability of symptom-based findings, it reflects the real-world structure of firearm licensing procedures in Turkiye rather than an unintended sampling bias. Individuals with known psychiatric treatment histories are often either legally ineligible or self-select out of the application process because of the anticipated likelihood of rejection under current regulations.

Table 3: Mean scores on the Beck Depression Inventory, Beck Anxiety Inventory, Barratt Impulsiveness Scale, and the Trait Anger, Anger Control, Anger Expression–Out, and Anger Expression–In subscales among firearm possession and carrying license applicants

	n	Mean	Median	SD	SE	Statistics	df	p	Effect size
Beck depression inventory									
Possession	88	0.659	0.0	1.10	0.118	-1.1806[a] 3464	168	0.601[x]	0.039[a]
Carrying	82	0.902	0.0	1.56	0.172				
Beck anxiety inventory									
Possession	88	0.591	0.0	1.20	0.128	0.8862 3435	168	0.486[x]	0.048[a]
Carrying	82	0.439	0.0	1.02	0.113				
Trait anger subscale									
Possession	88	11.648	11.0	2.06	0.219	0.4071 3578	168	0.684[y]	0.062[b]
Carrying	82	11.524	11.0	1.88	0.208				
Anger Control Subscale									
Possession	88	28.864	31.0	4.63	0.494	-1.4155[a] 3476	168	0.667[x]	0.036[a]
Carrying	82	29.707	31.0	2.87	0.316				
Anger expression-out subscale									
Possession	88	11.182	11.0	2.20	0.235	1.0747 3181	168	0.284[y]	0.164[b]
Carrying	82	10.817	11.0	2.22	0.245				
Anger expression-in subscale									
Possession	88	11.352	11.0	2.66	0.284	-0.2517 3466	168	0.802[y]	-0.038[b,c]
Carrying	82	11.451	11.0	2.45	0.271				
Barratt impulsiveness scale									
Possession	88	17.705	17.0	2.53	0.270	-0.0406 3499	168	0.732[x]	0.030[a]
Carrying	82	17.720	17.0	2.25	0.249				

SD: Standard deviation; SE: Standard error; df: Degrees of freedom; x: Mann–Whitney U test; y: Student's t-test; a: Rank-biserial correlation; b: Cohen's d; c: H_0: possession ≠ carrying.

Consequently, psychiatrists conducting firearm license evaluations are predominantly tasked with assessing individuals without documented psychiatric histories and must rely largely on self-report, clinical impression, and available administrative records (55). From this perspective, the principal clinical challenge in firearm licensing evaluations lies not only in identifying overt psychiatric disorders, but also in assessing potential risk among applicants without documented psychiatric morbidity.

The availability of national electronic health records (e-Nabız) (56) and official criminal record systems may reduce overt dissimulation by enabling cross-verification of applicant declarations. However, such systems do not capture subthreshold symptoms, personality traits, acute stressors, or contextual risk factors and therefore cannot fully compensate for the limitations of self-report instruments and brief clinical interviews.

Within the current Turkish firearm licensing system, psychiatrists occupy a decisive gatekeeping role with significant legal and public safety implications despite the absence of standardized, evidence-based frameworks for assessing risk among applicants without overt psychiatric illness. The present findings suggest that approaches relying primarily on subjective declarations and self-report scales are insufficient for this purpose. If self-report instruments are vulnerable to positive self-presentation in high-stakes administrative contexts, simply increasing the degree of interview structuring may not adequately resolve the underlying validity problem. Structured or semi-structured interview formats primarily improve procedural consistency, whereas deliberate impression management reflects a response-validity issue that may persist regardless of interview format. Similarly, although some personality inventories include defensiveness or validity indices,

the ethical and legal implications of denying firearm licensure solely on the basis of elevated impression management indicators remain unclear, particularly in the absence of validated predictive models linking such findings to adverse outcomes. More intensive approaches, such as performance-based or behavioral assessments, may be impractical, disproportionate, and financially burdensome within routine licensing procedures. At present, the most plausible alternative may involve incorporating formal collateral information, such as structured social circumstance reports prepared by social workers, alongside systematic cross-checking of administrative and forensic databases.

An additional issue warranting consideration is that firearm licensing procedures focus exclusively on the individual applicant, despite evidence that firearms stored in the home may be accessible to other household members and may contribute to domestic violence and lethal outcomes (25, 57, 58). Incorporating broader contextual or household-level considerations, where legally and ethically appropriate, may therefore enhance risk assessment, as is already practiced in other evaluative contexts such as adoption or foster care assessments.

Addressing these limitations will require large-scale retrospective and prospective studies linking firearm licensing data with real-world outcomes such as suicide, homicide, domestic violence, and forensic involvement. Multicenter collaborations integrating health records, judicial data, and forensic findings are essential for developing and validating structured, licensing-specific assessment models. Although actuarial tools such as OxRISK (59) were developed for forensic populations and are not designed specifically for firearm licensing contexts, they nevertheless illustrate the potential value of structured, data-integrated approaches when ethically adapted and rigorously validated.

Limitations

First, the measures of depression, anxiety, anger, and impulsivity used in this study were based on self-report instruments. In evaluative contexts such as firearm license applications, where personal stakes are substantial, participants may engage in positive self-presentation or symptom minimization, potentially resulting in artificially low scores that do not fully reflect underlying clinical status.

Second, the study was conducted at a single state hospital and included a relatively modest sample size (n=170). These factors limit the generalizability of the findings. Future multicenter studies incorporating diverse geographic regions and socioeconomic contexts would improve external validity and permit more robust comparisons across populations.

Third, several behavioral and environmental risk factors relevant to violence risk—including family dynamics, social support, psychosocial stressors, trauma exposure, and conditions of firearm access—were not systematically assessed. The absence of these variables limits the study's ability to contextualize psychological symptom scores within broader risk frameworks.

Fourth, the gender distribution of the sample was heavily skewed toward male applicants (approximately 91%). Although this likely reflects the real-world demographic characteristics of firearm license applicants in Turkiye, the predominance of male participants limits the generalizability of the findings to female applicants. Future studies including larger numbers of female applicants would help clarify whether similar patterns are observed across genders.

Finally, the cross-sectional design precluded longitudinal evaluation of firearm-related behaviors, including patterns of firearm use, the emergence of violent outcomes, or whether hypothesized risks subsequently materialized. Although the Turkish framework reflects a precautionary public safety orientation, whether such proactive psychiatric screening meaningfully enhances public safety, or instead places clinicians in a role with limited predictive capacity, remains an empirical question requiring longitudinal, outcome-based investigation.

Ethical Approval: The Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee granted approval for this study (date: 20.05.2021, number: 560).

Informed Consent: All participants received verbal and written information regarding the study and provided written informed consent prior to participation.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: Not declared.

Contribution Categories		Author Initials
Category 1	Concept/Design	I.A., S.S.
	Data acquisition	I.A., S.S.
	Data analysis/Interpretation	I.A.
Category 2	Drafting manuscript	I.A.
	Critical revision of manuscript	S.S.
Category 3	Final approval and accountability	I.A., S.S.
Other	Technical or material support	I.A.
	Supervision	I.A., S.S.

Peer-review: Externally peer-reviewed.

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DOI: 10.14744/DAJPNS.2026.00324
Dusunen Adam J Psychiatr Neurol Sci
2026;39:112-123

RESEARCH ARTICLE

Unipolar mania as a distinct clinical presentation: Differences in illness course and psychosocial functioning compared with bipolar I disorder

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ABSTRACT

Objective: Growing evidence suggests that unipolar mania (UM) may represent a distinct clinical condition rather than a subtype of bipolar disorder (BD). The present study aimed to compare the sociodemographic characteristics, clinical features, and psychosocial functioning of euthymic patients with UM or bipolar I disorder (BD-I) and healthy control subjects.

Method: This cross-sectional study included euthymic patients with UM (n=58), BD-I (n=58), and healthy control subjects (n=58). Diagnoses were established according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and euthymia was confirmed using the Young Mania Rating Scale, Beck Depression Inventory, and Positive and Negative Syndrome Scale. Psychosocial functioning was assessed using the Functioning Assessment Short Test (FAST) in all groups and the Bipolar Disorder Functioning Scale (BDFS) in the UM and BD-I groups. Sociodemographic and clinical data were collected using a structured form. Group comparisons were conducted using appropriate parametric and nonparametric statistical analyses.

Results: Both patient groups demonstrated significantly impaired psychosocial functioning compared with healthy controls across all FAST subdomains ($p<0.05$). On the BDFS, patients with UM showed better emotional functioning and less social withdrawal than patients with BD-I ($p<0.05$); however, total functioning scores did not differ significantly between groups ($p>0.05$). Clinically, UM was characterized by manic-predominant onset, higher rates of mood-congruent psychotic symptoms, longer episode duration, and more frequent hospitalizations. Suicidal behavior and total number of mood episodes were higher among patients with BD-I ($p<0.05$). In the final logistic regression model, mood-congruent psychotic symptoms during the first episode were independently associated with UM relative to BD-I, whereas a history of suicide attempts was associated with lower odds of UM ($p<0.05$).

Conclusion: Although both groups exhibited functional impairment, patients with UM demonstrated relatively better emotional and social functioning than those with BD-I. These findings suggest that UM may be associated with a distinct functional profile, with potential implications for prognosis and treatment planning. Incorporating functional outcomes into the clinical assessment of UM may help optimize therapeutic strategies and improve long-term psychosocial outcomes.

Keywords: Bipolar disorder, euthymia, functional outcome, psychosocial functioning, unipolar mania

How to cite this article: Izmir Soygenc E, Sahmelikoglu Onur O. Unipolar mania as a distinct clinical presentation: Differences in illness course and psychosocial functioning compared with bipolar I disorder. Dusunen Adam J Psychiatr Neurol Sci 2026;39:112-123.

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Received: February 02, 2026; **Revised:** May 12, 2026; **Accepted:** May 13, 2026

INTRODUCTION

Bipolar disorder (BD) is a chronic psychiatric illness associated with substantial impairments in psychosocial functioning and quality of life. Despite periods of euthymia, only approximately 40% of patients with BD return to their premorbid level of functioning following a mood episode (1). Functional outcomes in BD are influenced by multiple factors, including age, illness-course characteristics (e.g., number of episodes, mixed features, and chronicity), insight, residual depressive symptoms, substance use, and psychiatric or medical comorbidities (2). Most studies examining psychosocial functioning in BD have focused on comparisons between depressive and manic episodes, consistently showing that depressive episodes exert a more detrimental effect on functioning than manic episodes (2).

Growing evidence suggests that unipolar mania (UM) may constitute a distinct clinical profile rather than simply a subtype of BD. UM and BD differ across epidemiological, biochemical, clinical, and treatment-related domains (3). Clinically, patients with UM have been reported to exhibit a higher prevalence of psychotic symptoms than patients with BD (4). Notably, the first episode in UM is more likely to be psychotic and characterized predominantly by mood-congruent symptoms. In addition, hyperthymic temperament appears to be more prevalent in UM (5). Conversely, rapid cycling, suicide risk, and comorbid anxiety disorders have been reported less frequently in UM than in BD (5).

Beyond its diagnostic implications, distinguishing UM from BD is clinically important because differences in illness course, suicidality, and treatment response may translate into distinct functional outcomes and management strategies. A clearer understanding of psychosocial functioning in UM may therefore contribute to more individualized treatment planning and improved long-term outcomes. Nevertheless, studies employing comprehensive diagnostic criteria to compare UM and BD while simultaneously examining the relationship between clinical characteristics and functional outcomes are limited. Therefore, the present study aimed to compare the sociodemographic characteristics, clinical features, and psychosocial functioning of euthymic patients with UM or bipolar I disorder (BD-I) and healthy control subjects, thereby contributing to the limited literature on this underexplored topic. Based on previously reported distinctions, we hypothesized that euthymic patients with UM and BD-I would differ in psychosocial functioning, with patients with UM exhibiting distinct profiles, particularly in occupational, emotional, and social domains.

METHODS

This study was approved by the Ethics Committee of Bakirkoy Prof. Dr. Mazhar Osman Research & Training Hospital for Psychiatry, Neurology and Neurosurgery in 06.09.2022 (Protocol No. 345), with additional approval obtained from the Clinical Research Ethics Committee of Bakirkoy Dr. Sadi Konuk Research & Training Hospital on January 9, 2023 (Decision No. 2023-01-22; Protocol No. 2023/21). All procedures were conducted in accordance with the Declaration of Helsinki, and written and verbal informed consent was obtained from all participants prior to enrollment. The study sample consisted of euthymic patients with BD-I who were followed in outpatient clinics and Community Mental Health Centers affiliated with Bakirkoy Prof. Dr. Mazhar Osman Research & Training Hospital, euthymic patients with UM, and healthy control subjects. Due to coronavirus disease 2019 (COVID-19) restrictions, the local ethics committee was not convening; therefore, ethical approval was obtained from an alternative institutional ethics committee, consistent with procedures used in other studies conducted during the same period. Participants who met the inclusion criteria and provided informed consent were included in the study. Psychiatric diagnoses were established through comprehensive clinical interviews conducted by experienced psychiatrists, as the Structured Clinical Interview for DSM-5 Clinical Version (SCID-5-CV) does not include UM. Patients in the BD-I group met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria for BD-I, had a documented history of at least one manic episode and one depressive episode, and were euthymic at the time of assessment. Euthymia was defined as a Young Mania Rating Scale (YMRS) score <8 and a Beck Depression Inventory (BDI) score <10. The UM group was defined according to previously proposed criteria, including the absence of any lifetime depressive episode, a minimum illness duration of four years, a history of at least four manic or hypomanic episodes (including at least one manic episode), and a euthymic period of at least six months prior to assessment (3). Healthy control participants had no current or lifetime psychiatric diagnoses according to DSM-5 criteria. Exclusion criteria for all

groups included intellectual disability, neurological disorders, history of brain injury or head trauma, alcohol or substance use disorder, pregnancy, and significant medical comorbidities (e.g., autoimmune diseases, acute infections, malignancies, dementia, neurodegenerative disorders, or cerebrovascular diseases). Additional exclusion criteria for the patient groups included a history of mixed episodes, bipolar II disorder, electroconvulsive therapy within the previous six months, and comorbid psychiatric disorders other than specific phobia. Participants in the UM group were further excluded if they had a lifetime history of major depressive episodes or any history of antidepressant use. Participants who did not meet remission criteria based on the YMRS, BDI, and Positive and Negative Syndrome Scale (PANSS; all subscale scores ≤3) were also excluded. A total of 180 individuals who had read the study information form, provided written informed consent, and agreed to participate were initially interviewed. In the BD group, one patient was excluded because of largely incomplete scale data, and another was excluded because of communication difficulties related to language barriers. In the UM group, two patients were excluded due to alcohol/substance use disorder. In the healthy control group, two participants were excluded because they failed to complete a substantial portion of the scales. Consequently, the final sample consisted of 174 participants: 58 patients with BD, 58 patients with UM, and 58 healthy controls. Psychosocial functioning in both patient groups and healthy controls was assessed using the Functioning Assessment Short Test (FAST). In addition, functional differences between the UM and BD-I groups were further evaluated using the Bipolar Disorder Functioning Scale (BDFS).

Instruments

Sociodemographic Data Form

A structured form developed by the researchers was used to assess eligibility criteria and collect sociodemographic and clinical data, including age, sex, education level, marital status, occupation, socioeconomic status, age at illness onset, number of manic and depressive episodes, total number of episodes, illness duration, number of hospitalizations, history of suicide attempts, alcohol and substance use, family history of BD, comorbid medical conditions, and current medications and dosages. In the UM group, "manic onset" specifically referred to a first episode of full mania, excluding hypomanic episodes.

Young Mania Rating Scale (YMRS)

The YMRS is an 11-item clinician-administered scale developed by Young et al. (6) in 1978 to assess the severity of manic symptoms. The scale evaluates elevated mood, increased motor activity and energy, sexual interest, sleep, irritability, rate and amount of speech, thought disorder, thought content, disruptive or aggressive behavior, appearance, and insight. The validity and reliability study of the Turkish version was conducted by Karadağ et al. (7).

Beck Depression Inventory (BDI)

The BDI is a 21-item self-report scale developed by Beck et al. (8) in 1961 to assess somatic, emotional, and cognitive symptoms of depression. Higher total scores indicate greater severity of depressive symptoms. The validity and reliability study of the Turkish version was conducted by Hisli (9).

Positive and Negative Syndrome Scale (PANSS)

The PANSS is a 30-item clinician-rated scale developed by Kay et al. (10) in 1987 and consists of positive, negative, and general psychopathology subscales. The validity and reliability study of the Turkish version was conducted by Kostakoğlu et al. (11). The PANSS was administered to assess and exclude residual psychotic symptoms, given that psychotic negative symptoms may occur in BD even outside acute episodes.

Beck Anxiety Inventory (BAI)

The BAI is a 21-item self-report scale developed by Beck et al. (12) to assess anxiety symptoms, with higher scores indicating greater anxiety severity. The validity and reliability study of the Turkish version was conducted by Ulusoy et al. (13).

Bipolar Disorder Functioning Scale (BDFS)

The BDFS was developed by the Scientific Working Group on Mood Disorders of the Turkish Psychiatric Association (14). It consists of 52 items across 11 subscales assessing emotional, cognitive, sexual, and social functioning domains. Higher scores indicate better functioning.

Functioning Assessment Short Test (FAST)

The FAST was developed by Rosa et al. (15) in 2007, and the Turkish version was validated by Aydemir and Uykur in 2012 (16). It consists of 24 items assessing functioning over the previous 15 days across six domains: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure activities. Higher scores indicate worse functioning.

Statistical Analysis

All analyses were performed using Stata version 19.0 (StataCorp, College Station, TX, USA). Normality of continuous variables was assessed using graphical methods, skewness and kurtosis values, and formal normality tests. Descriptive statistics were presented as median (Q1–Q3) for continuous variables and frequency (%) for categorical variables. Continuous variables were compared using the Mann–Whitney U test or Kruskal–Wallis test, whereas categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. For PANSS scores, distributions were interpreted in relation to the theoretical minimum values and the presence of floor effects. As a sensitivity analysis, PANSS comparisons were additionally reassessed using one-way analysis of variance (ANOVA). When overall three-group comparisons were significant, post hoc pairwise comparisons were conducted using Bonferroni correction.

Multivariable linear regression models were used to examine psychosocial functioning (FAST total and subscale scores) across groups, with healthy controls serving as the reference category. Covariates included age, sex, education, employment status (employed vs. unemployed), and BDI score. Heteroskedasticity-robust standard errors were applied. Omnibus tests were used to assess overall group effects, and Šidák adjustments were applied to account for multiple comparisons. Additional regression models restricted to the UM and BD-I groups evaluated BDFS total score, emotional functioning, and social withdrawal while controlling for age, sex, education, employment status, BDI score, and treatment-related variables (current valproate or lamotrigine use and treatment duration).

To identify clinical correlates of UM relative to BD-I, univariable logistic regression analyses were first conducted within the patient groups. Variables associated with UM at $p<0.20$ in the univariable analyses were entered into the multivariable logistic regression model. Current treatment variables and functioning subscale scores were not included in the primary logistic regression model because they may reflect treatment decisions or consequences of illness course rather than independent baseline or illness-course correlates. Multicollinearity was assessed using variance inflation factors (VIFs), with VIF values <4 considered indicative of no substantial multicollinearity. Results are reported as regression coefficients or odds ratios (ORs) with 95% confidence intervals (CIs). All statistical tests were two-tailed, and $p<0.05$ was considered statistically significant.

RESULTS

Sociodemographic characteristics of the UM, BD-I, and healthy control groups are presented in Table 1. No significant differences were observed among the groups with respect to sex ($p>0.05$). Marital status also did not differ significantly across the groups ($p=0.085$ and $p=0.164$, respectively). In contrast, years of education differed significantly between groups ($p<0.001$), with the control group demonstrating higher educational attainment than both the UM group ($p<0.001$) and the BD-I group ($p<0.001$), whereas no significant difference was found between the UM and BD-I groups ($p=0.231$). Employment status also differed significantly among the groups. The proportion of participants who were actively employed was significantly higher in the control group than in both the UM and BD-I groups (both $p<0.001$), whereas no significant difference was observed between the two patient groups ($p=0.990$). Similarly, the overall five-category employment distribution differed significantly across groups ($p<0.001$). Post hoc analyses indicated that this difference was driven by comparisons between each patient group and the control group (both $p<0.001$), with no significant difference between the UM and BD-I groups ($p=0.507$).

Clinical characteristics of the UM and BD groups are summarized in Table 2. The type of first mood episode differed significantly between groups: euphoric mania predominated in the UM group, whereas depressive episodes were more common at illness onset in the BD group ($p<0.05$). Psychotic symptoms during the first episode were significantly more frequent in the UM group than in the BD group ($p<0.05$). Valproate use was significantly more common in the UM group, whereas lamotrigine use was more frequent in the BD group ($p<0.05$). The use of lithium and carbamazepine did not differ between the patient groups. The BD group had a higher total number of mood episodes, whereas manic episodes were more frequent in the UM group ($p<0.05$). Mean episode duration and number of hospitalizations were both significantly greater in the UM group ($p<0.05$). A history of suicide attempts was significantly more common in the BD group ($p<0.05$).

Symptom severity and psychosocial functioning scores are presented in Table 3. No significant differences were observed among the groups in YMRS, BDI, PANSS positive, PANSS negative, PANSS general psychopathology, PANSS total, or BAI scores

Table 1: Comparison of sociodemographic characteristics among the UM, BD-I, and healthy control groups

	UM (n=58)	BD-I (n=58)	Control (n=58)	p	UM vs. BD-I*	UM vs. control*	BD-I vs. control*
Age, years (median [Q1–Q3])	40.50 (35.00–49.00)	45.50 (40.00–52.00)	41.50 (35.00–48.00)	**0.027**[K]	0.077	1.000	**0.047**
Sex, n (%)							
Female	28 (48.3)	37 (63.8)	39 (67.2)	0.085[χ^2]	–	–	–
Male	30 (51.7)	21 (36.2)	19 (32.8)				
Education duration, years (median [Q1–Q3])	12.00 (5.00–12.00)	8.00 (5.00–12.00)	14.00 (12.00–16.00)	**<0.001**[K]	0.231	**<0.001**	**<0.001**
Employment: Currently employed	23 (39.7)	16 (27.6)	47 (81.0)	**<0.001**[a]	0.990[a]	**<0.001**[a]	**<0.001**[a]
Employment: Not currently employed, n (%)							
Unemployed	18 (31.0)	21 (36.2)	0 (0.0)	**<0.001**[b]	0.507[b]	**<0.001**[b]	**<0.001**[b]
Retired	5 (8.6)	5 (8.62)	4 (6.9)				
Housewife	10 (17.2)	16 (27.59)	5 (8.6)				
Student	2 (3.5)	0 (0.0)	2 (3.5)				
Marital status, n (%)							
Married	30 (51.7)	35 (60.3)	39 (67.2)	0.164[χ^2]	–	–	–
Single	20 (34.5)	10 (17.2)	15 (25.9)				
Widowed	0 (0.0)	2 (3.4)	0 (0.0)				
Divorced	7 (12.1)	10 (17.2)	4 (6.9)				
Separated	1 (1.7)	1 (1.7)	0 (0.0)				

K: Kruskal–Wallis (Mann–Whitney U test); *: Bonferroni-adjusted p-values for pairwise comparisons; a: p values for "working status" were calculated using a dichotomized employment variable (currently employed vs. not currently employed). The overall p value was obtained using Pearson's chi-square test, and pairwise p values represent Bonferroni-adjusted comparisons between UM vs. BD-I, UM vs. Controls, and BD-I vs. Controls; b: p values for "employment status" were calculated using the full five-category employment variable (employed, unemployed, retired, housewife, and student). The overall p value was calculated using Pearson's chi-square test, whereas pairwise comparisons were conducted using Fisher's exact test with Bonferroni adjustment for multiple comparisons (UM vs. BD-I, UM vs. Control, and BD-I vs. Control). UM: Unipolar mania; BD-I: Bipolar I disorder; C: Healthy control group. Bold p-values indicate statistical significance.

(all p>0.05), indicating that the patient groups were assessed during euthymia. In contrast, all FAST subscale scores and the FAST total score differed significantly across the three groups (all overall p<0.001). Post hoc pairwise comparisons demonstrated that both the UM and BD-I groups exhibited significantly greater impairment than healthy controls in autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, leisure activities, and total FAST score (all p<0.001 for both UM vs. controls and BD-I vs. controls). However, no statistically significant differences were found between the UM and BD-I groups in any FAST domain after Bonferroni correction. Although the BD-I group demonstrated numerically greater impairment in occupational functioning than the UM group, this difference did not reach statistical significance (p=0.057). Similarly, no significant differences were observed between the two patient groups in autonomy (p=1.000), cognitive functioning (p=0.566), financial issues (p=1.000), interpersonal relationships (p=0.473), leisure activities (p=0.605), or FAST total score (p=0.266).

Comparisons based on the BDFS are presented in Table 4. The UM group demonstrated significantly higher scores on the emotional functioning and social withdrawal subscales than the BD group (p<0.05). No other subscale or total score differences were observed between the groups (p>0.05).

After adjustment for years of education, employment status, age, sex, and BDI score, the overall group effect remained significant for the FAST total score (p<0.001). Both the UM group (B=11.52, 95% CI: 8.52–14.52; adjusted p<0.001) and the BD-I group (B=14.00, 95% CI: 10.03–17.96; adjusted p<0.001) showed greater impairment than healthy controls, whereas no significant difference was

Table 2: Comparison of clinical characteristics between the UM and BD-I groups

	UM		BD-I		p
	n	%	n	%	
Type of first episode					
Mania	53	91.4	27	46.6	**<0.001**$^{X^2}$
Hypomania	5	8.6	0	0.0	**0.022**$^{X^2}$
Depression	0	0.0	31	53.4	**<0.001**$^{X^2}$
Psychotic symptoms during first episode					
Absent	6	10.3	20	34.5	**0.002**$^{X^2}$
Present	52	89.7	38	65.5	
Current mood stabilizer treatment					
Valproate	38	65.5	18	31.0	**0.003**$^{X^2}$
Lithium	24	41.4	29	50.0	0.062$^{X^2}$
Carbamazepine	1	1.7	2	3.4	0.591$^{X^2}$
Lamotrigine	0	0.0	6	10.3	**0.006**$^{X^2}$
Seasonality					
Absent	16	28.6	26	44.8	0.072$^{X^2}$
Present	40	71.4	32	55.2	
Unknown	2	3.5	0	0.0	
History of suicide attempts					
Present	5	8.6	17	29.3	**0.004**$^{X^2}$
Absent	53	91.4	41	70.7	
Number of suicide attempts					
0	53	91.4	41	70.7	**0.013**$^{X^2}$
1	5	8.6	13	22.4	
2	0	0.0	2	3.4	
≥3	0	0.0	2	3.4	
Family history of psychiatric disorders					
Present	27	46.6	29	50.0	0.710$^{X^2}$
Absent	31	53.4	29	50.0	
Age at onset of first episode, median (Q1–Q3)	23.50 (20.00–27.00)		23.50 (20.00–32.00)		0.778^{m}
Age at initiation of psychiatric treatment, median (Q1–Q3)	23.50 (20.00–28.00)		24.00 (20.00–32.00)		0.680^{m}
Total number of episodes, median (Q1–Q3)	6.00 (5.00–9.00)		9.00 (5.00–13.00)		**0.036**^{m}
Number of manic episodes, median (Q1–Q3)	5.00 (4.00–7.00)		3.00 (2.00–5.00)		**<0.001**^{m}
Number of hypomanic episodes, median (Q1–Q3)	0.00 (0.00–3.00)		2.00 (0.00–3.00)		0.365^{m}
Number of depressive episodes, median (Q1–Q3)	0.00 (0.00–0.00)		3.00 (2.00–5.00)		**<0.001**^{m}
Mean duration of episodes, median (Q1–Q3)	30.00 (20.00–30.00)		22.00 (20.00–30.00)		**0.003**^{m}
Total number of psychiatric hospitalizations, median (Q1–Q3)	4.00 (3.00–6.00)		3.00 (2.00–5.00)		**0.002**^{m}

m: Mann–Whitney U test; X^2: Chi-square test (Fisher's exact test). UM: Unipolar mania; BD-I: Bipolar I disorder. Bold p-values indicate statistical significance.

observed between the two patient groups (B=2.48, 95% CI: -1.88–6.84; adjusted p=0.997). A similar pattern was observed across FAST subdomains, including autonomy, occupational functioning, cognitive functioning, interpersonal relationships, and leisure activities: both patient groups demonstrated significantly greater impairment than healthy controls, whereas no differences emerged between the UM and BD-I groups. In contrast, the financial issues domain was not significant in the adjusted model (p=0.091) (Table 5).

In treatment-adjusted analyses restricted to the patient groups, no significant difference was observed between UM and BD-I in BDFS total score (B=-3.62,

Table 3: Comparison of YMRS, BDI, PANSS, BAI, and FAST scores among the study groups

	UM median (Q1–Q3)	BD-I median (Q1–Q3)	Controls median (Q1–Q3)	p^K	UM vs. BD-I*	UM vs. controls*	BD-I vs. controls*
Young Mania Rating Scale	2.00 (1.00–3.00)	1.00 (1.00–2.00)	1.00 (1.00–1.00)	0.057	–	–	–
Beck Depression Inventory	3.00 (2.00–4.00)	3.00 (2.00–5.00)	3.00 (3.00–5.00)	0.146	–	–	–
PANSS Positive Symptoms[1]	7.00 (7.00–7.00)	7.00 (7.00–7.00)	7.00 (7.00–7.00)	0.231	–	–	–
PANSS Negative Symptoms[1]	7.00 (7.00–7.00)	7.00 (7.00–8.00)	7.00 (7.00–7.00)	0.312	–	–	–
PANSS General Psychopathology[1]	16.00 (16.00–16.00)	16.00 (16.00–17.00)	16.00 (16.00–16.00)	0.325	–	–	–
PANSS Total Score[1]	30.00 (30.00–31.00)	30.00 (30.00–31.00)	30.00 (30.00–31.00)	0.237	–	–	–
Beck Anxiety Inventory (BAI)	3.00 (2.00–3.00)	3.00 (2.00–5.00)	3.00 (1.00–4.00)	0.078	–	–	–
Functioning Assessment Short Test (FAST)							
Autonomy	2.00 (0.00–3.00)	1.00 (0.00–4.00)	0.00 (0.00–1.00)	**<0.001**	1.000	**<0.001**	**<0.001**
Occupational functioning	8.00 (2.00–11.00)	11.00 (6.00–14.00)	0.00 (0.00–0.00)	**<0.001**	0.057	**<0.001**	**<0.001**
Cognitive functioning	1.00 (0.00–4.00)	2.00 (1.00–4.00)	0.00 (0.00–0.00)	**<0.001**	0.566	**<0.001**	**<0.001**
Financial issues	0.00 (0.00–1.00)	0.00 (0.00–2.00)	0.00 (0.00–0.00)	**<0.001**	1.000	**<0.001**	**<0.001**
Interpersonal relationships	4.00 (3.00–7.00)	6.00 (3.00–8.00)	3.00 (2.00–4.00)	**<0.001**	0.473	**<0.001**	**<0.001**
Leisure activities	5.00 (4.00–6.00)	4.00 (3.00–6.00)	2.00 (1.00–3.00)	**<0.001**	0.605	**<0.001**	**<0.001**
FAST total score	22.00 (14.00–27.00)	25.00 (14.00–34.00)	6.00 (4.00–8.00)	**<0.001**	0.266	**<0.001**	**<0.001**

K: Kruskal–Wallis test for overall p-values; 1: PANSS scores were additionally reassessed using one-way analysis of variance (ANOVA) because of clustering near the theoretical minimum values. The pattern of statistical significance was consistent with the Kruskal–Wallis analyses (all p>0.05 with one-way ANOVA). *: Bonferroni-adjusted p values for pairwise comparisons. PANSS: Positive and Negative Syndrome Scale; FAST: Functioning Assessment Short Test; YMRS: Young Mania Rating Scale; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; UM: Unipolar mania; BD-I: Bipolar I disorder; C: Healthy control group. Bold p-values indicate statistical significance.

95% CI: -8.66 to 1.41; p=0.156). However, the BD-I group demonstrated lower emotional functioning than the UM group (B=-0.54, 95% CI: -0.90 to -0.18; p=0.004), whereas the difference in social withdrawal was attenuated and remained borderline significant (B=-0.38, 95% CI: -0.76 to -0.00; p=0.047). Among treatment-related variables, current lamotrigine use was associated with lower BDFS total scores (B=-12.57, 95% CI: -24.33 to -0.81; p=0.036), whereas valproate use and treatment duration were not significantly associated with functioning outcomes. BDI score was not independently associated with BDFS outcomes in the fully adjusted models (Table 6).

In the univariable logistic regression analyses, age (OR=0.96, 95% CI: 0.92–1.00; p=0.044), presence of psychotic symptoms during the first episode, history of suicide attempts (OR=0.23, 95% CI: 0.08–0.67; p=0.007), total number of episodes (OR=0.92, 95% CI: 0.86–0.99; p=0.023), and mean episode duration (OR=1.08, 95% CI: 1.03–1.14; p=0.003) were significantly associated with unipolar mania. Regarding characteristics of the first episode, both mood-congruent psychotic symptoms (OR=5.06, 95% CI: 1.79–14.29; p=0.002) and the coexistence of mood-congruent and mood-incongruent psychotic symptoms (OR=5.00, 95% CI: 1.25–19.96; p=0.023) were associated with higher odds of UM. Male sex, years of education, employment status, and seasonality met the predefined inclusion threshold (p<0.20) and were therefore entered into the multivariable model. The type of first episode could not be analyzed because of perfect separation. In the multivariable logistic regression model, mood-congruent psychotic symptoms during the first episode remained independently associated with higher odds of UM relative to BD-I (adjusted OR=4.72, 95% CI: 1.48–15.05; p=0.009). Conversely, a history of suicide attempts was independently associated with lower odds of UM (adjusted OR=0.27, 95% CI: 0.08–0.89; p=0.032). Mean episode duration showed a borderline association with UM (adjusted OR=1.06, 95% CI: 1.00–1.12; p=0.064). Age, sex, education, employment status, seasonality, total number of episodes, and other categories of psychotic symptoms were not significantly associated with UM (all p>0.05) (Table 7).

Table 4: Comparison of bipolar disorder functioning scale scores between the UM and BD-I groups

	UM median (Q1–Q3)	BD-I median (Q1–Q3)	p	
Emotional functioning	9.00 (9.00–9.00)	9.00 (8.00–9.00)	**0.001**	m
Intellectual functioning	12.00 (11.00–12.00)	12.00 (10.00–12.00)	0.304	m
Sexual functioning	10.00 (8.00–12.00)	8.00 (7.00–12.00)	0.058	m
Perceived stigma	10.00 (9.00–12.00)	10.00 (8.00–12.00)	0.869	m
Social withdrawal	9.00 (8.00–9.00)	8.00 (7.00–9.00)	**0.008**	m
Household relationships	16.00 (15.00–18.00)	16.00 (14.00–18.00)	0.472	m
Relationships with friends	13.00 (12.00–15.00)	12.50 (11.00–15.00)	0.708	m
Participation in social activities	13.00 (11.00–15.00)	12.00 (10.00–14.00)	0.291	m
Daily activities/hobbies	11.00 (10.00–13.00)	12.00 (10.00–13.00)	0.883	m
Ability to take initiative	6.00 (4.00–8.00)	5.00 (4.00–7.00)	0.655	m
Work functioning	11.00 (9.00–12.00)	11.00 (9.00–12.00)	0.742	m
Total Bipolar Disorder Functioning Score	118.00 (110.00–126.00)	116.00 (104.00–125.00)	0.115	t

t: t-test; m: Mann–Whitney U test; UM: Unipolar mania; BD-I: Bipolar I disorder.

DISCUSSION

In this study, we compared the sociodemographic, clinical, and functional characteristics of individuals with UM, BD-I, and healthy controls. Both patient groups demonstrated lower educational attainment and employment rates than healthy controls despite being comparable on other sociodemographic variables. Clinically, the UM group was characterized by manic and psychotic first episodes, whereas higher rates of suicide attempts were more prominent in the BD-I group, suggesting that early illness characteristics and suicidality may differentiate the clinical trajectories of the two conditions. Although symptom severity was comparable across groups during euthymia, both UM and BD-I patients exhibited significantly greater psychosocial impairment than healthy controls, with no overall functional differences between the patient groups. Nevertheless, patients with UM demonstrated better emotional functioning and less social withdrawal, suggesting selective areas of relative functional preservation. These findings remained significant after adjustment for potential confounders, supporting the view that UM and BD-I share a substantial functional burden while differing in specific clinical and functional domains. Overall, the final logistic regression model indicated that, relative to BD-I, UM was independently associated with mood-congruent psychotic symptoms during the first episode, whereas a history of suicide attempts was independently associated with lower odds of UM.

Sociodemographic findings indicated that healthy controls had higher educational attainment and employment rates than both patient groups, whereas no significant differences were observed between the UM and BD groups. Although data regarding educational and occupational outcomes in mood disorders are limited, previous studies have suggested better academic functioning among individuals with a manic-predominant course (17). This pattern was not observed in the present sample, which may be attributable to methodological factors such as the relatively small sample size, the cross-sectional design, or recruitment from a tertiary care setting, potentially limiting the detection of subtle group differences.

A family history of psychiatric disorders was more common in both patient groups than in healthy controls, with no significant difference between the UM and BD groups. Previous studies investigating familial aggregation in UM have yielded inconsistent findings, with some reporting lower familial loading (18) and others reporting no differences relative to BD (19). In a Turkish sample, Yazıcı et al. (3) reported lower rates of major depression and suicide history among relatives of patients with UM, although these differences did not reach statistical significance. Variability in the diagnostic criteria used to define UM across studies may partly explain these inconsistencies and complicates direct comparisons.

Several differences in clinical characteristics were observed between the UM and BD groups. Patients with UM more frequently presented with euphoric manic onset and mood-congruent psychotic symptoms during the first episode, whereas depressive onset and a greater total number of mood episodes were more common in BD. These findings are consistent with previous report describing a manic-predominant and psychotic-onset profile in UM (18, 20). In line with most

Table 5: Multivariable linear regression models for FAST scores

Predictor	FAST Total score		FAST Autonomy		FAST Occupational functioning		FAST Cognitive functioning	
	Coeff. (95% CI)	p (adj. p*)	Coeff. (95% CI)	p (adj. p*)	Coeff. (95% CI)	p (adj. p*)	Coeff. (95% CI)	p (adj. p*)
Overall group effect		**<0.001**		**<0.001**		**<0.001**	—	**<0.001**
UM vs. Control	11.52 (8.52 to 14.52)	**<0.001 (<0.001)**	1.08 (0.46 to 1.70)	**0.001 (0.002)**	4.06 (2.78 to 5.33)	**<0.001 (<0.001)**	2.11 (1.13 to 3.08)	**<0.001 (<0.001)**
BD-I vs. Control	14.00 (10.03 to 17.96)	**<0.001 (<0.001)**	1.41 (0.57 to 2.25)	**0.001 (0.003)**	5.33 (3.80 to 6.85)	**<0.001 (<0.001)**	2.42 (1.27 to 3.58)	**<0.001 (<0.001)**
BD-I vs. UM	2.48 (-1.88 to 6.84)	0.172 (0.997)	0.33 (0.64 to 1.30)	0.413 (1.000)	1.27 (-0.43 to 2.97)	0.073 (0.514)	0.32 (-0.88 to 1.51)	0.520 (1.000)
Age	-0.12 (-0.27 to 0.02)	0.090	-0.05 (0.09 to -0.01)	**0.008**	-0.04 (-0.10 to 0.02)	0.200	0.02 (-0.02 to 0.06)	0.333
Male sex	0.96 (-1.75 to 3.66)	0.486	0.50 (-0.11 to 1.10)	0.106	0.45 (-0.60 to 1.50)	0.400	-0.81 (-1.57 to -0.04)	**0.038**
Education duration	-0.35 (-0.75 to 0.04)	0.081	-0.03 (-0.11 to 0.05)	0.436	-0.17 (-0.32 to -0.02)	**0.028**	-0.04 (-0.15 to 0.08)	0.529
Employment status	-6.45 (-9.23 to -3.67)	**<0.001**	-0.88 (-1.52 to -0.24)	**0.007**	-5.74 (-6.97 to -4.51)	**<0.001**	0.09 (-0.73 to 0.92)	0.824
Beck Depression Inventory score	1.44 (0.67 to 2.22)	**<0.001**	0.11 (-0.08 to 0.31)	0.253	0.30 (0.02 to 0.59)	**0.036**	0.35 (0.07 to 0.62)	**0.013**

Linear regression models were adjusted for age, sex, education duration, employment status, and Beck Depression Inventory score. *: Pairwise adjusted p values for group contrasts were corrected using the Šidák method within each outcome. FAST: Functioning Assessment Short Test; Coeff: Coefficient; CI: Confidence interval; UM: Unipolar mania; BD-I: Bipolar I disorder.

previous studies (21), age at illness onset did not differ between the patient groups, although some studies have reported an earlier onset mania in UM (22).

Evaluation of illness course indicated that manic episodes predominated in the UM group, whereas depressive episodes were more frequent in the BD group. Although some studies have reported shorter episode durations in UM, patients with UM in the present study exhibited longer mean episode durations and higher hospitalization rates (23). This finding may reflect characteristics of the study setting, as participants were recruited from a tertiary referral center where patients with more severe or treatment-resistant illness are more likely to receive treatment. Consistent with previous literature, suicidality was significantly more prevalent in BD, likely reflecting the greater burden of depressive episodes in this group (3, 24, 25).

Differences in pharmacological treatment profiles were also observed between the two patient groups. Valproate use was more frequent in the UM group, whereas lamotrigine use was more common in the BD group. In contrast, the use of lithium and carbamazepine did not differ between the groups. Previous studies have suggested a reduced prophylactic response to lithium in UM and comparable responses to valproate in UM and BD, which may partly account for these findings (3). However, given the inconsistencies in the literature and the cross-sectional design of the present study, treatment-related findings should be interpreted cautiously and require further investigation in prospective studies (26).

Psychosocial functioning was significantly impaired in both patient groups compared with healthy controls, even during euthymic periods, as assessed by the FAST. These findings are consistent with previous literature demonstrating that functional impairment often persists beyond symptomatic remission in BD (27). No significant differences were observed between the UM and BD groups across FAST subdomains. However, further evaluation using the BDFS revealed that patients with UM demonstrated better emotional

Table 6: Clinical and treatment-adjusted predictors of BDFS total score, emotional functioning, and social withdrawal

Predictor	BDFS Total score		BDFS Emotional functioning		BDFS Social withdrawal	
	Coeff. (95% CI)	p	Coeff. (95% CI)	p	Coeff. (95% CI)	p
BD-I vs. UM	-3.62 (-8.66–1.41)	0.156	-0.54 (-0.90– -0.18)	**0.004**	-0.38 (-0.76– -0.00)	**0.047**
Age	0.08 (-0.29–0.44)	0.685	0.01 (-0.01–0.04)	0.309	0.01 (-0.02–0.03)	0.589
Male sex	0.90 (-3.56–5.37)	0.689	0.05 (-0.30–0.40)	0.787	0.08 (-0.27–0.43)	0.647
Education duration	0.11 (-0.51–0.73)	0.728	-0.02 (-0.07–0.02)	0.343	-0.01 (-0.05–0.03)	0.548
Employment status	1.47 (-3.57–6.52)	0.563	-0.15 (-0.59–0.28)	0.492	0.17 (-0.20–0.55)	0.360
Beck Depression Inventory score	0.67 (-1.12–2.46)	0.457	-0.06 (-0.20–0.08)	0.375	-0.02 (-0.13–0.09)	0.687
Current valproate use	-3.38 (-8.34–1.58)	0.179	0.04 (-0.31–0.40)	0.811	-0.05 (-0.40–0.30)	0.764
Current lamotrigine use	-12.57 (-24.33– -0.81)	0.036	-0.12 (-1.24–1.00)	0.831	-0.65 (-1.47–0.17)	0.117
Treatment duration	0.00 (-0.33–0.33)	0.984	-0.00 (-0.03–0.02)	0.892	0.00 (-0.02–0.03)	0.683

Linear regression models were adjusted for age, sex, education duration, employment status, Beck Depression Inventory score, current valproate use, current lamotrigine use, and treatment duration. BDFS: Bipolar Disorder Functioning Scale; Coeff: Coefficient; CI: Confidence interval; UM: Unipolar mania; BD-I: Bipolar I disorder.

Table 7: Univariable and multivariable logistic regression analyses of baseline and illness-course clinical correlates of UM relative to BD-I

Predictor	Univariable model		Multivariable model*	
	OR (95% CI)	p	Adjusted OR (95% CI)	p
Age	0.96 (0.92–1.00)	**0.044**	0.98 (0.93–1.03)	0.433
Male sex	1.89 (0.90–3.98)	0.095	1.37 (0.52–3.61)	0.522
Education duration	1.08 (0.98–1.18)	0.109	0.99 (0.88–1.12)	0.902
Type of first episode	N/A**	–	–	–
Psychotic symptoms during the first episode (reference category: absent)				
Mood-congruent psychotic symptoms	5.06 (1.79–14.29)	**0.002**	4.72 (1.48–15.05)	**0.009**
Mood-incongruent psychotic symptoms	1.33 (0.20–8.78)	0.765	1.35 (0.17–10.51)	0.774
Both mood-congruent and mood-incongruent psychotic symptoms	5.00 (1.25–19.96)	**0.023**	2.20 (0.44–10.95)	0.336
Seasonality (present vs. absent)	2.03 (0.93–4.43)	0.075	2.22 (0.85–5.82)	0.105
History of suicide attempts (present vs. absent)	0.23 (0.08–0.67)	**0.007**	0.27 (0.08–0.89)	**0.032**
Total number of episodes	0.92 (0.86–0.99)	**0.023**	0.95 (0.87–1.05)	0.306
Mean duration of episodes	1.08 (1.03–1.14)	**0.003**	1.06 (1.00–1.12)	0.064
Total number of psychiatric hospitalizations	1.10 (0.95–1.27)	0.222	–	–
Employment status (currently employed vs. not employed)†	1.73 (0.79–3.78)	0.173	1.24 (0.48–3.16)	0.658

*: Variables with p<0.20 in the univariable analyses were considered for inclusion in the multivariable model; **: Not estimable because of perfect prediction;
†: Because of sparse employment subgroups, a binary employment variable was used as a parsimonious indicator in the logistic regression analyses. OR: Odds ratio; CI: Confidence interval; ref: Reference category.

functioning and lower social withdrawal than patients with BD, whereas total functioning scores did not differ between the groups. These findings may be explained by the absence of depressive episodes, fewer total mood episodes, and lower suicidality in UM. Previous studies have consistently shown that depressive symptom burden, including subthreshold symptoms, is strongly associated with functional impairment (28,

29), and that recurrent episodes and hospitalizations contribute to poorer long-term outcomes (30). In this context, the relatively better emotional and social functioning observed in UM may reflect a lower cumulative illness burden.

The present study is notable for its comprehensive assessment of sociodemographic, clinical, and functional characteristics using validated and reliable instruments. Nevertheless, several limitations should be acknowledged. First, the relatively small sample size and cross-sectional design limit causal inferences. In addition, no a priori power analysis was conducted to determine whether the sample size was sufficient to detect meaningful between-group differences, which may have reduced the statistical power of the study. An important limitation concerns the operational definition of UM. The use of a four-year depression-free period is not based on a universally accepted temporal criterion, and depressive episodes in BD-1 may emerge later in the illness course. Therefore, some patients classified as having UM may eventually transition to a BD-1 phenotype, and the findings should be interpreted cautiously. Furthermore, although psychosocial functioning was assessed using the FAST and BDFS, both instruments rely primarily on patient-reported outcomes. The inclusion of clinician-rated instruments, such as the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) or the Hamilton Depression Rating Scale (HAM-D) could have strengthened the methodological rigor of the study. Specific phobias were not excluded because they are generally circumscribed and unlikely to substantially influence study outcomes. Nevertheless, several potential confounding variables were not controlled for in the analyses. In addition, reliance on patient- and caregiver-reported information may have introduced recall bias. The inclusion of only patients with BD-I and recruitment from a tertiary care center treating relatively severe cases further limit the generalizability of the findings. Despite these limitations, the assessment of patients during euthymia and the comprehensive evaluation of both clinical and functional characteristics represent important strengths of the study. Future longitudinal studies with longer follow-up periods and more objective functional measures are needed to clarify the validity of UM as a distinct clinical entity.

CONCLUSION

The present study provides evidence that UM differs from BD-I not only in clinical course but also in specific domains of psychosocial functioning during euthymia. Although overall functional impairment was comparable between the groups, patients with UM demonstrated relatively better emotional functioning and less social withdrawal. These findings suggest that depressive episode burden may play a critical role in shaping functional outcomes across mood disorder subtypes.

Clinically, the findings support consideration of UM as a distinct and clinically meaningful presentation, with potential implications for functional assessment, rehabilitation strategies, and individualized treatment planning. Future longitudinal studies with larger and diagnostically well-characterized samples are needed to determine the persistence of these functional differences over time and their relevance for long-term prognosis and treatment response.

Ethical Approval: This study was approved by the Ethics Committee of Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery Clinical Research (date: 06.09.2022, number: 345) with additional approval obtained from the Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research (date: 09.01.2023, number: 2023-01-22).

Informed Consent: Written informed consent was obtained from all participants prior to participation in the study.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: Not declared.

Contribution Categories		Author Initials
Category 1	Concept/Design	O.S.O.
	Data acquisition	E.I.S.
	Data analysis/Interpretation	O.S.O., E.I.S.
Category 2	Drafting manuscript	E.I.S.
	Critical revision of manuscript	O.S.O.
Category 3	Final approval and accountability	O.S.O., E.I.S.
Other	Technical or material support	E.I.S., O.S.O.
	Supervision	O.S.O.

Peer-review: Externally peer-reviewed.

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DOI: 10.14744/DAJPNS.2026.00325
Dusunen Adam J Psychiatr Neurol Sci
2026;39:124-135

RESEARCH ARTICLE

Associations of alexithymia, psychological problems, and emotion regulation difficulties with disordered eating behaviors in adolescents with type 1 diabetes

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ABSTRACT

Objective: This study aimed to compare levels of alexithymia, psychological problems, emotion regulation difficulties, and disordered eating behaviors between adolescents with type 1 diabetes mellitus (T1D) and healthy controls and to examine the relationship among these factors.

Method: The study was conducted at Ankara Bilkent City Hospital and included 115 adolescents aged 12–18 years, comprising 64 adolescents with T1D and 51 healthy controls. All participants completed the Alexithymia Questionnaire for Children (AQC), Difficulties in Emotion Regulation Scale (DERS), Strengths and Difficulties Questionnaire (SDQ), and Eating Disorder Examination Questionnaire (EDE-Q). Adolescents with diabetes were additionally assessed using the Diabetes Eating Problem Survey–Revised (DEPS-R), and their hemoglobin A1c (HbA1c) levels from the previous six months were recorded.

Results: No differences were found between adolescents with T1D and healthy controls in total scores on the AQC, DERS, SDQ, and EDE-Q. Female participants and adolescents with psychiatric disorders had higher DEPS-R score. DEPS-R scores were positively correlated with total SDQ, DERS, and AQC scores, as well as body mass index (BMI), and negatively correlated with maternal education level. Multiple linear regression analysis revealed that SDQ total difficulties scores and BMI were associated with higher DEPS-R scores.

Conclusion: These findings suggest that disordered eating behaviors in adolescents with T1D may be associated with psychological difficulties and higher BMI. Addressing these factors is important in the clinical management of adolescents with diabetes.

Keywords: Adolescent, alexithymia, diabetes mellitus, disordered eating behaviors, emotion regulation

How to cite this article: Onat M, Gurbuz F, Boyraz M, Akin Soyupek YO, Avci H, Konuksever D, Yigit M, Goren R, Senses Dinc G, Cop E. Associations of alexithymia, psychological problems, and emotion regulation difficulties with disordered eating behaviors in adolescents with type 1 diabetes. Dusunen Adam J Psychiatr Neurol Sci 2026;39:124-135.

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Received: December 09, 2025; **Revised:** May 20, 2026; **Accepted:** May 25, 2026

INTRODUCTION

Type 1 diabetes mellitus (T1D) is a chronic disease with peak incidence during early adolescence and may lead to cardiovascular and microvascular complications (1). Adolescents with T1D are more likely to develop eating disorders and disordered eating behaviors (DEBs), including subthreshold symptoms, than their healthy peers (2). In addition to dietary restriction, binge eating, purging, and excessive exercise for weight control, adolescents with T1D may intentionally restrict insulin doses to induce glucosuria and promote weight loss (3). Eating disorders and DEBs in individuals with T1D often emerge during adolescence, may persist into adulthood, and, if left untreated, can increase the risk of morbidity and mortality (4).

Previous studies have examined factors associated with DEBs in adolescents with T1D, including age, sex, body mass index (BMI), family-related factors, and mood disturbances (5, 6). Emotional problems, particularly anxiety and depressive symptoms, are common among adolescents with T1D and have been associated with DEBs (7). Although studies have linked emotional problems to DEBs in adolescents with T1D, these problems do not invariably lead to DEBs, suggesting that other factors may contribute to this relationship (8).

Alexithymia is one such factor that has been linked to DEBs but remains relatively understudied in adolescents with T1D (9, 10). Alexithymia is characterized by difficulties in identifying and distinguishing emotional experiences from bodily sensations (11). It has been associated with both psychiatric and medical conditions, including anxiety, depression, hypertension, and gastrointestinal disorders, and may occur more frequently in individuals with T1D than in healthy controls (12-14). Studies have also shown that alexithymia adversely affects diabetes self-management and glycemic control in both adolescents and adults (15, 16). Furthermore, alexithymia may be conceptualized as a stress-related response to chronic conditions such as diabetes, contributing to negative emotional states including anxiety and depression (13, 17).

Emotion dysregulation, which is closely related to alexithymia, is another psychological factor associated with DEBs and poor glycemic control in individuals with T1D (18-22). Emotion regulation refers to the processes through which individuals influence the initiation, intensity, frequency, and duration of emotional experiences (23). Adolescents with T1D face ongoing challenges related to treatment adherence, dietary restrictions, and disease management, all of which require effective emotion regulation. Individuals who have difficulty regulating their emotions may respond maladaptively to negative emotional experiences, potentially compromising their well-being (24). For example, DEBs may represent maladaptive coping strategies used to manage negative affect among adolescents with T1D (25).

Although several studies have investigated the roles of alexithymia, psychological problems, and emotion dysregulation in DEBs, most have focused on adults or general populations rather than adolescents with T1D. The present study aimed to examine the relationships among psychological problems, alexithymia, emotion regulation difficulties, DEBs, and glycemic control in adolescents with T1D and to compare psychological characteristics and DEBs between adolescents with T1D and healthy controls. Based on the existing literature, we proposed the following hypotheses:

1. Psychological problems, alexithymia, emotion regulation difficulties, and DEBs are more prevalent among adolescents with T1D than among healthy controls.
2. Psychological problems, alexithymia, and emotion regulation difficulties are associated with DEBs and glycemic control in adolescents with T1D.

To our knowledge, no previous study has simultaneously examined alexithymia, emotion regulation difficulties, psychological problems, and DEBs in adolescents with T1D. This study aims to contribute to the literature by clarifying the relationships among these psychological factors, DEBs, and metabolic control in this population.

METHODS

Participants

Between May and October 2023, 71 of 80 adolescents aged 12–18 years who had been diagnosed with T1D and attended the Pediatric Endocrinology Outpatient Clinic at Ankara Bilkent City Hospital volunteered to participate in the study. The remaining nine adolescents declined participation. Inclusion criteria for the T1D group were: (1) age between 12 and 18 years; (2) diagnosis of T1D for at least one year; (3) availability of a hemoglobin A1c (HbA1c) measurement obtained within the previous six months during routine pediatric endocrinology follow-up; (4) clinically normal intellectual functioning; and (5) provision of written informed consent by both

the participant and their parent(s). Exclusion criteria for the T1D group included a diagnosis of intellectual disability, autism spectrum disorder, psychotic disorder, or bipolar disorder, as these conditions were considered likely to interfere with study assessments. Intellectual disability was determined based on clinical evaluation and psychiatric history obtained during the clinical interview. Four adolescents with T1D were excluded because of coexisting intellectual disability, and three additional participants were excluded because of incomplete data. Psychiatric evaluations were conducted by the same child and adolescent psychiatrist using clinical interviews based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association). The inclusion criteria for the healthy control group were: age between 12 and 18 years; (2) no current or past psychiatric disorder according to DSM-5 criteria based on clinical evaluation; (3) clinically normal intellectual functioning; and (4) absence of any chronic medical condition. Participants and their parents were also required to provide informed consent. Healthy controls were recruited from adolescents aged 12–18 years attending the general pediatric outpatient clinic at the same hospital. Although no structured diagnostic interview was conducted, all participants in the control group underwent clinical evaluation by a child and adolescent psychiatrist. Adolescents with a history of psychiatric disorders, psychotropic medication use, or ongoing psychiatric follow-up were excluded. The control group was comparable to the T1D group in terms of sociodemographic characteristics, including age, sex, and socioeconomic status. The final sample consisted of 115 adolescents: 64 with T1D and 51 healthy controls.

Participants' sociodemographic characteristics, including age, sex, family characteristics, and socioeconomic status, were recorded using a researcher-developed sociodemographic data form. All participants completed the Alexithymia Questionnaire for Children (AQC), Difficulties in Emotion Regulation Scale (DERS), Strengths and Difficulties Questionnaire (SDQ) Youth Self-Report, and Eating Disorder Examination Questionnaire (EDE-Q) to assess alexithymia, emotion regulation difficulties, psychological problems, and DEBs, respectively. Adolescents with T1D additionally completed the Diabetes Eating Problem Survey–Revised (DEPS-R) and their HbA1c values measured within the previous six months were obtained from medical records to assess diabetes-specific DEBs and glycemic control.

Written informed consent was obtained from all participants and their parents. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Ankara Bilkent City Hospital (Date: 25.04.2023/No: E2-23-3957).

Data Collection Tools

Sociodemographic Data Form

The sociodemographic data form was developed by the researchers to collect information on participants' age, sex, family characteristics, and socioeconomic status.

Alexithymia Questionnaire for Children (AQC)

The AQC is based on the Toronto Alexithymia Scale-20 developed by Bagby et al. (11) for assessing alexithymia in adults. Rieffe et al. (26) developed the AQC as a 20-item, three-point Likert-type scale consisting of three subdimensions: Externally Oriented Thinking, Difficulty Identifying Feelings, and Difficulty Describing Feelings. Each item is scored from 0 to 2. Kocak et al. (27) conducted the Turkish adaptation study and confirmed that the original three-factor structure of the AQC was preserved in the Turkish version.

Difficulties in Emotion Regulation Scale (DERS)

The DERS is a 36-item, five-point Likert-type scale developed by Gratz and Roemer (28). It consists of six dimensions: Awareness, Clarity, Nonacceptance, Strategies, Impulse, and Goals. Higher scores indicate greater difficulties in emotion regulation. The Turkish validity and reliability study was conducted by Rugancı and Gencoz (29). A study conducted in Türkiye demonstrated that the DERS is a valid instrument for assessing emotion regulation difficulties in Turkish adolescents (30).

Diabetes Eating Problem Survey–Revised (DEPS-R)

The original Diabetes Eating Problem Survey (DEPS) is a 28-item scale developed to assess DEBs in adults. Markowitz et al. (31) revised the instrument into a 16-item version suitable for children and adolescents. The DEPS-R includes items related to weight concerns, eating behaviors, weight-control practices such as vomiting or insulin omission, and diabetes management. Items are scored on a scale from 0 to 5, and total scores ≥20 indicate risk for diabetes-related eating problems. Atik Altinok et al. (32) adapted the scale into Turkish and demonstrated its validity and reliability.

Eating Disorder Examination Questionnaire (EDE-Q)

The EDE-Q is a self-report version of the Eating Disorder Examination semi-structured interview. It consists of 33 items and includes five subscales that assess the severity of eating disorder psychopathology: Restraint, Binge Eating, Shape Concern, Eating Concern, and Weight Concern. Subscale and total scores range from 0 to 6, with higher scores indicating greater eating disorder psychopathology. The Turkish validity and reliability study for adolescents was conducted by Yucel et al. (33).

Strengths and Difficulties Questionnaire (SDQ)

The SDQ was developed by Goodman as a screening instrument for emotional and behavioral problems in children and adolescents and was later adapted into Turkish by Guvenir et al. (34, 35). The questionnaire includes parent-report, teacher-report, and self-report versions and comprises 25 items across five subscales: Emotional Symptoms, Conduct Problems, Hyperactivity/Inattention, Peer Problems, and Prosocial Behavior. Although each subscale is evaluated separately, the sum of the first four subscales yields the total difficulties score. Responses are scored from 0 to 2 (35). In the present study, only the adolescent self-report version was administered.

Hemoglobin A1c (HbA1c)

HbA1c levels were measured using capillary electrophoresis method (Capillarys Tera 3, Sebia, Lisses, France).

Post Hoc Power Analysis

A post hoc power analysis for the multiple linear regression model (F-test; fixed model, R^2 deviation from zero) was conducted using $\alpha=0.05$, a sample size of 64, and seven predictors. The model explained 62.3% of the variance ($R^2=0.623$). Cohen's effect size was calculated as $f^2=R^2/(1-R^2)$, indicating a very large effect size. Based on these parameters, the achieved statistical power was $1-\beta=1.00$, suggesting that the study had very high power to detect a significant overall regression model at the observed effect size.

Statistical Analysis

Analyses were conducted using the free and open-source software R version 4.4.1 (https://cran.r-project.org) and SPSS for Windows, version 23.0 (Chicago, IL), with the assistance of an academic biostatistician. Data normality was assessed using the Shapiro–Wilk test, and homogeneity of variance was evaluated using Levene's test. Descriptive statistics are presented as n (%) for categorical variables. Continuous variables are expressed as mean ± standard deviation when normally distributed and as median and interquartile range (IQR) when non-normally distributed. Pearson's chi-square test was used to compare categorical variables between groups. For continuous variables, between-group differences were assessed using the Mann–Whitney U test, the Kruskal–Wallis test or Student's t-test, depending on distributional assumptions. Appropriate effect sizes were calculated for hypothesis testing. A sensitivity analysis was also performed after excluding participants with psychiatric disorders from the T1D group. Within the T1D group, relationships between numerical variables were examined using Spearman's rank correlation coefficient. The Hmisc (36), GGally (37), and corrplot (38) packages were used to generate the correlation matrix plot. Univariate analyses and multiple linear regression analysis using the Enter method were performed to identify factors associated with the DEPS-R total score in adolescents with T1D. Because the DEPS-R assesses diabetes-specific DEBs, these analyses were conducted only in the T1D group. Variables with $p<0.20$ in univariate analyses were included in the multiple linear regression model (39, 40). Multicollinearity was assessed using variance inflation factor (VIF) values. Because the residuals were normally distributed, a multiple linear regression model was established. The ggplot (41) and qqnorm (42) functions were used to generate residual plots and Q-Q plots, respectively. A p-value <5% was considered statistically significant.

RESULTS

A total of 115 adolescents participated in the study: 64 diagnosed with T1D and 51 healthy controls. In the T1D group, 50% (n=32) were female and 50% (n=32) were male. In the control group, 47.1% (n=24) were female and 52.9% (n=27) were male. The median age was 13.5 years (IQR=4) in the T1D group and 15 years (IQR=3) in the control group. No significant differences were found between the groups in age, sex, BMI, or family characteristics ($p>0.05$). According to psychiatric assessment, 26.6% (n=17) of adolescents in the T1D group had at least one psychiatric disorder. The most common diagnoses were anxiety disorder (7.8%, n=5) and attention-deficit/hyperactivity disorder (7.8%, n=5), followed by specific learning disorder (6.3%, n=4), major depressive disorder (4.7%, n=3), and adjustment disorder (4.7%, n=3). No participant in

Table 1: Comparison of sociodemographic characteristics between adolescents with type 1 diabetes mellitus and healthy controls

Variables	HC (n=51)	T1D (n=64)	p	Effect size
Sex			0.754[a]	-0.029
Male	27 (52.9%)	32 (50%)		
Female	24 (47.1%)	32 (50%)		
Age	15 (3)	13.50 (4)	0.147[b]	0.136
BMI	19.60 (4.21)	20.54 (5.26)	0.263[b]	0.106
Number of siblings			0.732[a]	0.075
Only child	4 (8%)	7 (11.5%)		
One	19 (38%)	25 (41%)		
Two or more	27 (54%)	29 (47.5%)		
Birth order			0.956[a]	0.028
First	19 (38%)	23 (37.7%)		
Second	21 (42%)	27 (44.3%)		
Third or later	10 (20%)	11 (18%)		
Maternal age	41 (9)	40 (9)	0.156[b]	0.138
Maternal education (years)	12 (11)	8 (7)	0.102[b]	0.154
Paternal age	45 (8.50)	45 (9)	0.704[b]	0.038
Paternal education (years)	12 (8)	12 (4)	0.072[b]	0.170
Household income (TL)	20,000 (16,000)	17,000 (13,000)	0.070[b]	0.180

Data are presented as median (interquartile range) or n (%). BMI: Body mass index; HC: Healthy control; T1D: Type 1 diabetes mellitus; TL: Turkish Lira; a: Pearson Chi-Square Test; b: Mann–Whitney U test.

the T1D group met diagnostic criteria for any eating disorder. In addition, 7.8% (n=5) of adolescents in the T1D group were receiving psychotropic medication. Among adolescents with T1D, 40.6% (n=26) used a blood glucose sensor, and 12.5% (n=8) used an insulin pump. Table 1 presents the demographic characteristics of the study participants.

No significant differences were found between adolescents with T1D and healthy controls in AQC, SDQ, or EDE-Q scores (p>0.05). However, DERS Nonacceptance subscale scores were higher in healthy controls than in adolescents with T1D (p=0.020) (Table 2). A supplementary sensitivity analysis was conducted after excluding adolescents with psychiatric disorders (n=17) from the T1D group. Most primary findings remained consistent. However, the statistical significance of SDQ Internalizing Problems, SDQ Total Difficulties Score (SDQ-TDS), and DERS Strategies scores changed in the sensitivity analysis. Detailed results are presented in Supplementary Table 1.

Spearman correlation analysis was conducted in the T1D group to examine relationships among age, BMI, total daily insulin dose (units/kg/day), duration of T1D, HbA1c, maternal and paternal education levels, and total scores on the DEPS-R, SDQ, DERS, AQC, and EDE-Q. No significant correlations were found between the DEPS-R total score and age, total daily insulin dose, or HbA1c levels. However, a weak positive correlation was found between the DEPS-R total score and BMI (r=0.386, p=0.002). A weak negative correlation was also found between maternal education level and the DEPS-R total score (r=-0.280, p=0.029). Moderate positive correlations were found between the DEPS-R total score and SDQ Internalizing Problems and SDQ Externalizing Problems scores (r=0.667 and r=0.688, respectively; both p<0.001). A strong positive correlation was found between the DEPS-R total score and SDQ-TDS (r=0.731, p<0.001). Additionally, statistically significant moderate positive correlations were observed between the DEPS-R total score and the total scores of the DERS, AQC, and EDE-Q (r=0.671, r=0.599, and r=0.701, respectively; all p<0.001).

A significant negative correlation was found between HbA1c and total scores on the AQC and DERS (Fig. 1). In our study, HbA1c values were lower among adolescents using blood glucose sensors and insulin pumps (p<0.001 and p=0.043, respectively). Because sensor and insulin pump use were associated with HbA1c, Spearman correlation analyses were also performed among adolescents who did not use these

Table 2: Comparison of clinical characteristics between adolescents with type 1 diabetes mellitus and healthy controls

Variables	HC (n=51)	T1D (n=64)	p	Effect size
SDQ				
Emotional symptoms	4 (4)	3 (4.50)	0.204[a]	0.119
Conduct problems	2 (4)	2 (3)	0.586[a]	0.051
Hyperactivity/inattention	4.20±1.70	4.84±2.32	0.468[b]	0.137
Peer problems	3 (4)	2.50 (3)	0.406[a]	0.078
Prosocial behavior	7 (3.25)	8 (3)	0.593[a]	0.050
Externalizing problems	7 (6)	7 (6)	0.794[a]	0.024
Internalizing problems	7 (5.25)	6 (5.75)	0.154[a]	0.134
Total difficulties score	13.50 (10.25)	13 (10)	0.229[a]	0.113
EDE-Q				
Restraint	0.40 (1.40)	0.60 (2.20)	0.797[a]	0.024
Shape concern	0.75 (2.22)	0.87 (2.50)	0.951[a]	0.006
Eating concern	0.40 (1.45)	0.60 (1.75)	0.140[a]	0.138
Weight concern	1 (1.90)	0.80 (2.15)	0.662[a]	0.041
Global score	0.82 (1.60)	0.86 (1.51)	0.554[a]	0.056
DERS				
Awareness	17 (7.25)	17 (8)	0.510[a]	0.062
Clarity	14 (5.25)	13.50 (4)	0.911[a]	0.010
Nonacceptance	11 (9)	9.50 (6)	0.020[a]	0.219
Strategies	18.50 (12.75)	14 (13)	0.181[a]	0.126
Impulse	14 (9.75)	13.50 (13.50)	0.614[a]	0.048
Goals	17 (9.50)	14 (8)	0.364[a]	0.085
Total score	98 (37)	85 (41.13)	0.306[a]	0.097
AQC				
Difficulty identifying feelings	5 (7)	4 (6)	0.415[a]	0.077
Difficulty describing feelings	4 (4)	3.50 (4)	0.875[a]	0.015
Externally oriented thinking	7 (3)	7 (4)	0.597[a]	0.050
Total score	16.33±6.69	15.85±6.09	0.700[b]	0.075

Data are presented as mean±standard deviation (SD) or median (interquartile range). AQC: Alexithymia Questionnaire for Children; DERS: Difficulties in Emotion Regulation Scale; EDE-Q: Eating Disorder Examination Questionnaire; HC: Healthy control; SDQ: Strengths and Difficulties Questionnaire; T1D: Type 1 diabetes mellitus; a: Mann–Whitney U test; b: Student's t Test.

devices. The significant negative correlations between DERS and AQC scores and HbA1c remained among adolescents who did not use insulin pumps (r=-0.409, p<0.01; r=-0.313, p<0.05, respectively). Similarly, the significant negative correlations between DERS and AQC scores and HbA1c remained among adolescents who did not use blood glucose sensors (r=-0.464, p<0.01; r=-0.365, p<0.05, respectively). In addition, AQC total scores were positively correlated with the Restraint, Shape Concern, Eating Concern, Weight Concern, and Global scores of the EDE-Q (r=0.352, p=0.004; r=0.595, p<0.001; r=0.510, p<0.001; r=0.489, p<0.001; and r=0.603, p<0.001, respectively). DERS total scores were also positively correlated with the Restraint, Shape Concern, Eating Concern, Weight Concern, and Global scores of the EDE-Q (r=0.492, r=0.581, r=0.533, r=0.502, and r=0.633, respectively; all p<0.001).

Differences in DEPS-R total scores according to sex, presence of a psychiatric disorder, number of siblings, and birth order were analyzed using the Mann–Whitney U test or Kruskal–Wallis test. DEPS-R total scores were significantly higher in girls than in boys and in adolescents with psychiatric disorders than in those without psychiatric disorders (p=0.025 and p=0.008, respectively). Number of siblings and birth order had no significant effect on DEPS-R total scores (Table 3). Based on the univariate analysis of DEPS-R

Table 3: Comparison of DEPS-R total scores according to demographic characteristics

Variables	DEPS-R (n=64)	p	Effect size
Sex		0.025[a]	0.284
Male	16 (17)		
Female	20 (19)		
Psychiatric disorder		0.008[a]	0.337
Absent	14.75 (16.25)		
Present	27.25 (17)		
Number of siblings		0.289[b]	0.042
Only child	20 (18)		
One	13.50 (21)		
Two or more	19.75 (16.88)		
Birth order		0.425[b]	0.029
First	18 (17)		
Second	16.50 (16)		
Third or later	27 (19)		

Data are presented as median (interquartile range). DEPS-R: Diabetes Eating Problem Survey–Revised; a: Mann–Whitney U test; b: Kruskal–Wallis test.

total scores, variables with p<0.20 were identified as candidate variables for the multiple linear regression model. Accordingly, both sex and the presence of a psychiatric disorder were included in the model, and no multicollinearity or autocorrelation was detected in the data.

The model was considered adequate because the scatter plot of studentized deleted residuals against predicted values showed a random distribution around zero. According to the Kolmogorov–Smirnov test, the studentized deleted residuals were normally distributed (z=0.077, p=0.200) (Supplementary Fig. 1, 2). Multiple linear regression analysis was used to identify factors associated with DEBs. The analysis of variance (ANOVA) test showed that the model was statistically significant (F=12.065, p<0.001). SDQ-TDS and BMI were significantly associated with the DEPS-R total score (p=0.006 and p=0.036, respectively). The coefficient of determination for the multiple linear regression model predicting the DEPS-R total score was R^2=0.623. Based on the beta coefficients from the multiple linear regression model, the SDQ-TDS score made the largest contribution to the DEPS-R total score. Specifically, a one-standard-deviation increase in SDQ-TDS was associated with a 0.421-standard-deviation increase in the DEPS-R total score, whereas a one-standard-deviation increase in BMI was associated with a 0.205-standard-deviation increase in the DEPS-R total score (Table 4).

DISCUSSION

To the best of our knowledge, this is the first study to examine the roles of alexithymia, psychological problems, and emotion regulation difficulties in DEBs among adolescents diagnosed with T1D. In our study, psychological problems, alexithymia, emotional dysregulation, higher BMI, female sex, and lower maternal education level were associated with DEBs in adolescents with T1D. However, no relationship was found between DEBs and glycemic control.

In our study, alexithymia levels did not differ between adolescents with T1D and their healthy peers. Previous studies have reported high levels of alexithymia in both adults and adolescents with T1D (14, 43). However, Friedman et al. (44) suggested that alexithymia was low in patients with T1D. Our findings suggest that elevated alexithymia may not characterize all adolescents with T1D, but rather a subgroup of young patients. The finding that alexithymia was correlated with DEBs in adolescents with T1D is difficult to compare with previous work, as no prior study has directly examined this association in this population. However, DEBs have been associated with alexithymia in various other samples (45, 46). Surprisingly, alexithymia was associated with lower HbA1c levels in our study. The literature reports conflicting findings, with some studies linking alexithymia to poor glycemic control in T1D (47, 48) and others reporting no association (13, 45). Given these inconsistencies and the cross-sectional design of the present study, this finding should be interpreted cautiously. Overall, our findings suggest that alexithymia may be a relevant psychological factor to consider when DEBs are suspected in adolescents with T1D.

In our study, emotional dysregulation levels in adolescents with T1D were comparable to those of healthy controls. Similarly, a Turkish study found no difference between youth with T1D and healthy controls in emotion regulation difficulties (49). Contrary to our expectations, however, a group difference was observed specifically in the DERS Nonacceptance subscale, with adolescents with T1D reporting lower Nonacceptance scores than healthy controls. This finding may reflect differences in how emotional experiences are perceived or reported across groups. It should also be interpreted with caution because, although the control group was considered healthy based on clinical evaluation, the presence of subclinical emotional difficulties cannot

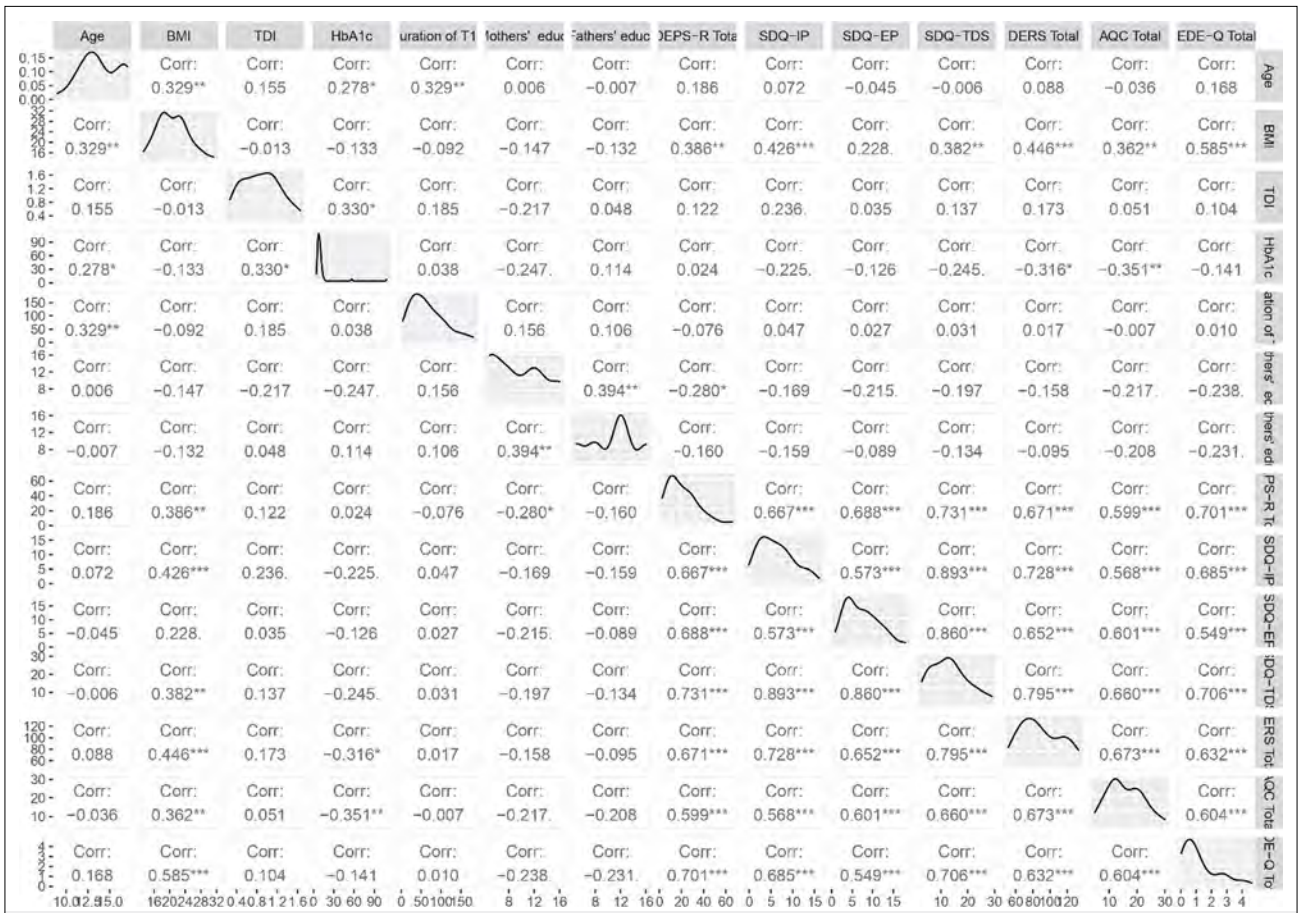

Figure 1. Correlation matrix showing the relationships between DEPS-R scores and sociodemographic and clinical variables.

*p<0.05; **p<0.01; ***p<0.001; AQC: Alexithymia Questionnaire for Children; BMI: Body mass index; DEPS-R: Diabetes Eating Problem Survey–Revised; DERS: Difficulties in Emotion Regulation Scale; EDE-Q: Eating Disorder Examination Questionnaire; HbA1c: Hemoglobin A1c; SDQ-EP: Strengths and Difficulties Questionnaire–Externalizing Problems; SDQ-IP: Strengths and Difficulties Questionnaire–Internalizing Problems; SDQ-TDS: Strengths and Difficulties Questionnaire Total Difficulties Score; TDI: Total daily insulin dose (units/kg/day); T1D: Type 1 diabetes mellitus.

be entirely excluded. Consistent with previous studies, emotion dysregulation was correlated with DEBs in adolescents with T1D (50, 51). However, contrary to expectations, an inverse relationship was observed between emotional dysregulation and HbA1c. Although previous studies (22, 52) have reported associations between emotion dysregulation and elevated HbA1c in adolescents and adults with T1D, a recent adolescent study (53) did not confirm this association. Considering the variability of previous findings and the cross-sectional design of our study, this association should be interpreted cautiously.

Psychological problem levels among adolescents with T1D were similar to those of healthy controls. Although youth with T1D are generally considered at increased risk for psychological difficulties (54, 55), a large-sample study (56) also found comparable levels between youth with T1D and the general population. Among the variables examined in our study, psychological problems were identified as the strongest factor associated with increased DEBs in adolescents with T1D. Previous studies support the association between DEBs and psychological problems in adolescents with T1D (50, 53). A recent systematic review also highlighted robust associations between psychological distress and DEBs in young people with T1D, suggesting that broader psychological difficulties may contribute to the development and maintenance of maladaptive eating patterns in this population (57). The association between psychological problems and DEBs may be explained by emotion regulation difficulties, whereby eating becomes a coping strategy for managing psychological distress (58, 59). These findings highlight the importance of screening for DEBs in adolescents with T1D, particularly when psychological problems are present.

Although DEBs have been reported more frequently in adolescents and adults with T1D (60,

Table 4: Multiple linear regression analysis of factors associated with DEPS-R total scores in adolescents with type 1 diabetes mellitus

	Unstandardized coefficients		Standardized coefficients	t	p	95% CI	VIF
	B	SE	β				
Constant	-8.809	7.749		-1.137	0.261	-24.377 to 6.748	
Sex	-2.702	2.430	-0.104	-1.112	0.271	-7.581 to 2.177	1.176
Presence of a psychiatric disorder	0.934	2.791	0.031	0.335	0.739	-4.670 to 6.537	1.179
Maternal education level	-0.356	0.288	-0.110	-1.239	0.221	-0.933 to 0.221	1.070
DERS Total Score	0.020	0.090	0.035	0.226	0.822	-0.160 to 0.201	3.178
SDQ-TDS	0.822	0.287	0.421	2.867	0.006	0.247 to 1.398	2.920
AQC total score	0.525	0.268	0.230	1.954	0.056	-0.014 to 1.064	1.870
BMI	0.789	0.366	0.205	2.159	0.036	0.055 to 1.523	1.219
$R=0.790$; $R^2=0.623$; $F=12.065$; $p<0.001$.							

Dependent variable: DEPS-R score. Abbreviations: AQC: Alexithymia Questionnaire for Children; BMI: Body mass index; CI: Confidence interval; DEPS-R: Diabetes Eating Problem Survey–Revised; DERS: Difficulties in Emotion Regulation Scale; SDQ-TDS: Strengths and Difficulties Questionnaire–Total Difficulties Score; SE: Standard error; T1D: Type 1 diabetes mellitus; VIF: Variance inflation factor.

61), no group differences were observed in our study. This may be because the study sample was closely monitored in a pediatric endocrinology outpatient clinic for diabetes management and eating attitudes. No relationship was found between DEBs and HbA1c. Similarly, Colton et al. (62) reported no association between DEBs and metabolic control, as assessed by HbA1c, in adolescent girls with T1D. The absence of a relationship between DEBs and glycemic control in our study may reflect the fact that some DEPS-R items assessing eating attitudes also capture general adolescent weight-loss behaviors.

Disordered eating behaviors in adolescents with T1D were associated with individual factors, including BMI, female sex, and lower maternal education level. Previous studies have shown that adolescents with T1D and higher BMI values may engage in more DEBs (50, 63). Consistent with our findings, other studies have reported that DEBs in adolescents with T1D are more common in girls than in boys (61, 64). Similarly, studies have shown that adolescents whose parents have lower educational levels are more likely to develop DEBs (65, 66). Thus, our findings are consistent with the literature.

A supplementary sensitivity analysis excluding adolescents with psychiatric disorders from the T1D group showed that most primary findings remained unchanged. Although the statistical significance of some psychological subscale comparisons differed, the associated effect sizes were small. Therefore, these findings should be interpreted cautiously, as psychiatric comorbidity may have influenced psychological scale scores.

This study has several limitations. One limitation of this study is that alexithymia, emotion regulation difficulties, and DEBs were assessed using self-report measures. Another limitation of this study is the absence of a structured diagnostic interview for the assessment of the adolescents included in the study. In the control group, psychiatric exclusion criteria were based on clinical evaluation rather than standardized diagnostic interviews. Consequently, undetected subclinical psychiatric symptoms or emotional difficulties may have been present in some participants and could have influenced comparisons involving psychological measures. Another important limitation is that adolescents with psychiatric disorders were included in the T1D group, whereas such individuals were excluded from the healthy control group. Although a supplementary sensitivity analysis was conducted, psychiatric comorbidity may still have influenced psychological scale scores and should be considered when interpreting the findings. Additionally, the cross-sectional design of the study precludes conclusions regarding causal relationships among the variables examined. As this was a single-center study, the generalizability of the findings may also be limited. Furthermore, the sample size was not determined using a power analysis. Although the post hoc analysis indicated high statistical power for the observed effect size, future studies with prospectively determined sample sizes would strengthen methodological rigor. Additionally, although psychotropic medication use was recorded, only a small proportion of participants were receiving such treatment. Because of the substantial imbalance between medication users and

non-users, medication status was not included in the statistical analyses. Therefore, the potential influence of medication use on DEBs cannot be entirely excluded. Finally, although the presence of a psychiatric disorder was included as a variable in the regression model, the absence of structured diagnostic interviews and the heterogeneity of comorbid conditions may still have resulted in residual confounding.

CONCLUSION

The findings of this study suggest that alexithymia, emotional dysregulation, and psychological problems may be associated with DEBs in adolescents with T1D. Additionally, DEBs in this population may also be associated with higher BMI, female sex, and lower maternal education level.

Online Supplementary Digital Appendix File: https://dusunenadamdergisi.org/storage/upload/files/1780929756-appendix-en.pdf

Ethical Approval: Ethics committee approval dated 25.04.2023 and numbered E2-23-3957 was obtained from the Ankara Bilkent City Hospital Ethics Committee for the research.

Informed Consent: Written informed consent was obtained from all participants.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

Contribution Categories		Author Initials
Category 1	Concept/Design	M.O., F.G., M.B., G.S.D., E.C.
	Data acquisition	Y.O.A.S., DK, M.Y., R.G.
	Data analysis/Interpretation	H.A.
Category 2	Drafting manuscript	M.O., Y.O.A.S., H.A., D.K., M.Y., R.G.
	Critical revision of manuscript	F.G., M.B., G.S.D., E.C.
Category 3	Final approval and accountability	M.O., F.G., M.B., Y.O.A.S., H.A., D.K., M.Y., R.G., G.S.D. E.C.

Peer-review: Externally peer-reviewed.

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DOI: 10.14744/DAJPNS.2026.00326
Dusunen Adam J Psychiatr Neurol Sci
2026;39:136-141

RESEARCH ARTICLE

Longer cumulative flight time is associated with an increased likelihood of surgical treatment for cervical and lumbar disc herniation in civil aviation personnel

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ABSTRACT

Objective: The aim of this study was to evaluate the occupational characteristics of civil aviation cabin crew and pilots who received medical or surgical treatment for lumbar or cervical disc herniation and to compare these characteristics with those of healthy controls, with a particular emphasis on age, sex, and cumulative flight time.

Method: In this retrospective study, civil aviation cabin crew members and pilots presenting with low back and/or neck pain were compared with healthy controls matched for age and sex. Sociodemographic characteristics (age and sex), occupational characteristics (years of service, cumulative flight time, and type of flight duty), treatments modalities, and magnetic resonance imaging (MRI) findings were recorded and analyzed.

Results: The mean age of affected personnel was 42.37±10.3 years (pilots: n=8, cabin crew: n=11), with the highest proportion of cases occurring in the 40–55-year age group. Males accounted for 73.7% of the surgical treatment group compared with 28.8% of the non-surgical treatment group. The rate of surgical treatment was significantly higher among personnel with cumulative flight times exceeding 15,000 hours, particularly among male pilots. Regression analyses demonstrated that male sex, age greater than 45 years, and cumulative flight time exceeding 15,000 hours were independently associated with an increased likelihood of requiring surgical intervention.

Conclusion: Our findings indicate that male sex, advancing age (particularly >45 years), and longer cumulative flight time are the primary risk factors associated with surgical treatment for lumbar and cervical disc herniation among civil aviation personnel. These results highlight the importance of early monitoring and preventive strategies for individuals at increased risk.

Keywords: Intervertebral disc displacement, vibration, aviation, flight hours

INTRODUCTION

Spinal disc herniation is an important public health problem that may lead to various neurological sequelae, including motor deficits and urinary incontinence, if not appropriately treated. Lumbar and cervical herniations can substantially impair quality of life, cause physical disability, and limit daily activities. They have been reported to represent the second leading cause of healthcare expenditure and loss of

How to cite this article: Dedei M, Sertbas I. Longer cumulative flight time is associated with an increased likelihood of surgical treatment for cervical and lumbar disc herniation in civil aviation personnel. Dusunen Adam J Psychiatr Neurol Sci 2026;39:136-141.

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Received: September 19, 2025; **Revised:** March 08, 2026; **Accepted:** June 04, 2026

workforce productivity after cancer-related pain (1). Common clinical manifestations include radicular pain, restricted mobility, paresthesia, and muscle weakness (2). Spinal disc herniations most commonly affect middle-aged men and occur predominantly in the lumbar (90%) and cervical (10%) regions, whereas thoracic herniations are relatively rare (3–5). Cervical disc herniations most frequently occur at the C5–C6 level (approximately 55%), while lumbar disc herniations are most commonly observed at the L4–L5 and L5–S1 levels (3, 4). The choice between conservative and surgical treatment depends primarily on the degree of neural compression and the severity of symptoms.

Personal risk factors associated with spinal disc herniation include advanced age, male sex, White race, genetic predisposition, obesity, greater height, poor posture, limited spinal range of motion, muscle weakness, and poor physical fitness or low exercise capacity. Occupational risk factors include heavy lifting, repetitive pushing or twisting movements, prolonged sitting, poor working posture, exposure to vibration, and extended working hours (6–8). Previous studies involving aviation personnel exposed to multiple risk factors for spinal disorders have shown that whole-body vibration contributes to back and neck pain associated with degenerative spinal conditions (9–11). Several studies have reported an increased risk of cervical lordosis abnormalities, pain, lumbar disc herniation, and degenerative cervical spine changes among helicopter and military aircraft pilots. Furthermore, surgical treatment rates for lumbar disc herniation have been reported to be elevated in these populations (12–15). However, no studies have specifically investigated cervical and lumbar disc herniation among fixed-wing commercial airline pilots and cabin crew members. Therefore, evaluating the occurrence and treatment of these conditions in civil aviation personnel is of considerable clinical and occupational importance.

The aim of this study was to evaluate cervical and lumbar disc herniation and the associated medical and surgical treatment outcomes among pilots and cabin crew members employed in commercial aviation.

METHODS

Study Population

This retrospective study included civil aviation flight personnel who presented to the Flight Health Center in Istanbul, Turkiye, between January 2014 and December 2018. All data were obtained from institutional medical records. The study population consisted of individuals diagnosed with cervical or lumbar disc herniation based on clinical evaluation and radiological imaging, including magnetic resonance imaging (MRI) and/or computed tomography (CT). A total of 85 patients were identified and categorized into two groups according to treatment modality: a conservative treatment group (n=66) and a surgical treatment group (n=19). In addition, a control group consisting of 83 healthy airline personnel was included. Ethical approval was obtained from the institutional ethics committee.

Inclusion Criteria

- Civil aviation flight personnel (e.g., pilots and cabin crew members) presenting to the Flight Health Center during the study period.
- Age between 18 and 65 years.
- Diagnosis of cervical or lumbar disc herniation confirmed by MRI or CT findings with corresponding clinical symptoms.
- For the control group, healthy airline personnel with no history of spinal pathology, matched for age and sex.

Exclusion Criteria

- Previous cervical or lumbar spinal surgery.
- Presence of other spinal disorders or systemic diseases that could explain the symptoms, including but not limited to spinal tumors, infections, inflammatory diseases, fractures, or congenital abnormalities.
- Neurological disorders unrelated to disc herniation.
- Incomplete medical records or missing imaging data.
- Refusal to participate or withdrawal from the study.

Treatment Modalities

Surgical treatment was performed in patients with motor deficits or persistent symptoms despite conservative management and physical therapy. Patients who did not meet these criteria received conservative treatment, including nonsteroidal anti-inflammatory drugs, opioids, muscle relaxants, and physical therapy.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows (version 20.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated for all variables and are presented as percentages and means ± standard deviations. Comparisons of normally

Table 1: Baseline characteristics of patients treated conservatively or surgically and healthy controls

	Conservative treatment (n=66)	Surgical treatment (n=19)	Healthy controls (n=83)	Total (n=168)	p
Age	32.5 (24.0–59.0)	40.0 (25.0–65.0)	34.0 (25.0–64.0)	34.0 (24.0–65.0)	**<0.01**[a]
Sex					**<0.01**[b]
Male	19 (28.8)	14 (73.7)	33 (39.8)	66 (39.3)	
Female	47 (71.2)	5 (26.3)	50 (60.2)	102 (60.7)	
Occupation					**<0.01**[b]
Cabin crew	60 (90.9)	11 (57.9)	69 (83.1)	140 (83.3)	
Pilot	6 (9.1)	8 (42.1)	14 (16.9)	28 (16.7)	
Duration of employment (years)	8.0 (1.0–30.0)	16.0 (2.0–36.0)	9.0 (1.0–35.0)	9.0 (1.0–36.0)	**<0.01**[a]
Cumulative flight time (hours)					**<0.01**[b]
<15,000	54 (81.8)	7 (36.8)	62 (74.7)	123 (73.2)	
≥15,000	12 (18.2)	12 (63.2)	21 (25.3)	45 (26.8)	
Cumulative flight time (×1,000 h)	9.6 (0.8–30)	16.8 (2.6–31.2)	10.4 (0.8–26.6)	10.6 (0.8–31.6)	**<0.01**[a]

a: Values are presented as median (minimum–maximum). Group comparisons were performed using the Kruskal–Wallis test. b: Values are presented as n (%). Group comparisons were performed using Pearson's Chi-Square test. Bold values indicate statistical significance (p<0.05).

Table 2: Distribution of treatment modalities according to disc herniation type

	Conservative treatment (n=66)	Surgical treatment (n=19)	Total (n=85)	p
Herniation type				0.23[a]
Lumbar	44 (66.7)	15 (78.9)	59 (69.4)	
Cervical	13 (19.7)	4 (21.1)	17 (20.0)	
Cervical + lumbar	9 (13.6)	0 (0.0)	9 (10.6)	

a: Values are presented as n (%). Group comparisons were performed using Pearson's Chi-Square test.

distributed continuous variables were performed using the independent-samples t-test. When the assumption of normality was not met, group comparisons were conducted using the Kruskal–Wallis test. Correlations between normally distributed variables were evaluated using Pearson's correlation coefficient. No adjustments were made for multiple comparisons and p-value <0.05 was considered statistically significant.

RESULTS

A total of 168 individuals were included in the study: 66 (39.3%) males and 102 (60.7%) females. The mean age of the study population was 35.4±8.4 years.

The median age (p=0.002) and duration of employment (p=0.002) were significantly higher in patients who underwent surgical treatment than in those who received conservative treatment and healthy controls. The sex distribution was similar between the conservative treatment and control groups. However, the proportion of males was significantly higher in the surgical treatment group than in the other two groups (p<0.01). Similarly, the distribution of occupational roles was comparable between the conservative treatment and control groups, whereas the proportion of pilots was significantly higher in the surgical treatment group (p<0.01). In addition, the proportion of personnel with cumulative flight times ≥15,000 hours was significantly greater in the surgical treatment group than in the conservative treatment and control groups. The distributions of cumulative flight time were similar between the conservative treatment and control groups (Table 1).

Among patients with disc herniation, 66.7% had lumbar disc herniation, 19.7% had cervical disc herniation, and 13.6% had combined cervical and lumbar disc herniation. Overall, 22.4% of patients required surgical treatment. No statistically significant association was found between herniation type and treatment modality (p=0.23) (Table 2).

Univariate logistic regression analysis identified increasing age (p<0.01), male sex (p=0.01), being a pilot (p<0.01), cumulative flight time ≥15,000 hours (p<0.01), and longer duration of employment

Table 3: Logistic regression analysis of factors associated with surgical treatment

	B	SE	Wald	Exp (B)	p
Male sex	1.983	0.651	9.283	7.267	**<0.01**
Cumulative flight time ≥15,000 h	2.091	0.638	10.757	8.093	**<0.01**
Constant	-3.083	0.622	24.58	0.046	

SE: Standard error. Bold values indicate statistical significance (p<0.05).

(p<0.01) as factors associated with surgical treatment. In the multivariable logistic regression model, sex and cumulative flight time remained significant independent predictors of surgical treatment. Males had a 7.267-fold higher likelihood of undergoing surgical treatment than females (p<0.01). Personnel with cumulative flight times ≥15,000 hours had an 8.903-fold higher likelihood of surgical treatment compared with those with fewer flight hours (p<0.01) (Table 3). Other variables included in the model, including being a pilot (p=0.58), age (p=0.71), and duration of employment (p=0.23), were not associated with surgical treatment.

DISCUSSION

Intervertebral disc herniation has been reported more frequently among aviation personnel operating helicopters and military aircraft than in the general population (2–4). In the present study, we evaluated the occupational characteristics and treatment outcomes of airline personnel diagnosed with lumbar and/or cervical disc herniation. Our findings demonstrated that personnel with cumulative flight times of 15,000 hours or more were significantly more likely to require surgical treatment.

Consistent with our findings, Ahsan et al. (16) reported an increased risk of lumbar disc herniation in occupations involving prolonged standing and heavy lifting. The authors suggested that poor posture, prolonged standing, heavy lifting, and physically demanding working conditions contributed to this increased risk. Several occupational factors associated with spinal disc herniation in other professions are also relevant to aviation personnel. For cabin crew members, prolonged standing and working in a constantly moving environment may contribute to spinal strain, whereas prolonged sitting and suboptimal posture may increase risk among pilots. In recent years, numerous studies have demonstrated a higher prevalence of low back and neck pain among aviation personnel compared with the general population. In a cross-sectional study of military pilots, 50% reported spinal pain during or after flights (17). Personnel working in airborne early warning and control systems have also been shown to be at increased risk of cervical pain and cervical lordotic abnormalities (15). Similarly, low back pain has been identified as a major occupational health problem among helicopter pilots (18).

Although these studies demonstrate an increased prevalence of neck and back pain among aviation personnel, the underlying pathological causes have not always been clearly defined. Neck and back pain may arise from various conditions, including disc herniation, spondylolisthesis, and muscular strain. Previous research has suggested that degenerative spinal changes typically associated with aging may develop earlier in military high-performance aircraft pilots (14). Furthermore, helicopter pilots have been reported to have a significantly increased risk of lumbar disc herniation compared with non-pilots (12). In a study of military pilots, it was reported that 7.4% of helicopter pilots with lumbar disc herniation were unable to continue flying duties because of complications related to their condition (13).

The increased risk of spinal pathology in aviation personnel has been attributed to poor posture and prolonged exposure to whole-body vibration (18, 19). Bongers et al. (20) reported that chronic back pain in helicopter pilots was associated with both vibration exposure and cumulative flight time. Similarly, Byeon et al. (9) demonstrated an association between increased flight time and degenerative changes in the cervical and lumbar spine among helicopter pilots. Aircraft generate whole-body vibration (WBV), which affects both crew members and passengers. WBV refers to low-frequency vibrations transmitted through contact surfaces, such as vehicle seats or workplace floors, to the entire body. Exposure to WBV has been associated with adverse effects on health, well-being, and occupational performance among pilots (21). Consistent with these findings, we observed that the likelihood of surgical treatment for disc herniation increased with cumulative flight time. No previous study in the literature has identified a specific flight-time threshold associated with a higher risk of surgically treated disc herniation. In the present

study, cumulative flight time was analyzed both as a continuous variable and using a threshold of 15,000 hours. In both analyses, as well as in the multivariable model, increased flight time was significantly associated with surgical treatment. Because of the retrospective nature of the study, we were unable to directly assess vibration exposure. One possible explanation for this finding is that increased flight time among airline personnel results in greater cumulative exposure to vibration, which may contribute to disease progression and more severe clinical manifestations.

In the present study, lumbar disc herniation accounted for 66.7% of cases, cervical disc herniation for 19.7%, and combined cervical-lumbar disc herniation for 13.6%. No association was observed between herniation type and the need for surgical treatment. Similarly, Mason et al. (13) reported that 74.2% of cases involved lumbar herniation and 25.8% involved cervical herniation, with no significant relationship between herniation type and surgical intervention. However, the rate of surgical treatment observed in our study (22.4%) was lower than the 66.6% reported by Mason et al. (13). Regression analysis further demonstrated that male sex was associated with surgical treatment for disc herniation. In contrast, Kelley et al. (11) found no sex-related differences in the prevalence of back pain among helicopter crew members.

One of the main limitations of this study is its retrospective design, which limited the availability of comprehensive data. In addition, long-term follow-up information was unavailable, preventing assessment of treatment outcomes and symptom resolution. Consequently, we were unable to determine the effectiveness of different treatment approaches. Several potential confounding factors associated with spinal disc herniation, including body mass index (BMI), genetic predisposition, height, postural characteristics, spinal range of motion, muscle strength, physical fitness, and exercise capacity, could not be evaluated. These variables may have influenced the observed associations. Another limitation is that cervical and lumbar disc herniations were analyzed together rather than as separate disease entities. Future studies examining these conditions independently may provide more clinically meaningful findings. Despite these limitations, to the best of our knowledge, this is the first study to provide detailed data on cervical and lumbar disc herniation and their treatment among fixed-wing commercial airline pilots and cabin crew members.

CONCLUSION

In conclusion, male sex and cumulative flight time exceeding 15,000 hours were the principal factors associated with surgical treatment for cervical and/or lumbar disc herniation among civil aviation personnel. Improved understanding of the mechanisms underlying spinal disc herniation in aviation personnel may facilitate the development of preventive strategies and assist in identifying individuals at increased risk of requiring surgical intervention. Nevertheless, the relatively small sample size of the present study should be considered when interpreting the results. Further studies with larger cohorts are needed to confirm and extend these findings.

Ethical Approval: The Ethics Committee for Science, Social Sciences and Non-Interventional Health Sciences Research at Istanbul Yeni Yuzyıl University granted approval for this study (Date: 07.01.2020, number: 2020/01).

Informed Consent: Written informed consent was obtained from all participants.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

Contribution Categories		Author Initials
Category 1	Concept/Design	M.D.
	Data acquisition	I.S.
	Data analysis/Interpretation	I.S.
Category 2	Drafting manuscript	M.D.
	Critical revision of manuscript	M.D., I.S.
Category 3	Final approval and accountability	M.D., I.S.
Other	Technical or material support	M.D.
	Supervision	I.S.

Peer-review: Externally peer-reviewed.

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DOI: 10.14744/DAJPNS.2026.00327
Dusunen Adam J Psychiatr Neurol Sci
2026;39:142-152

RESEARCH ARTICLE

Psychiatric and medical profiles of children receiving health protection measures in a tertiary care facility: A five-year analysis

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ABSTRACT

Objective: This study examined the psychiatric and medical characteristics of children and adolescents receiving health protection measures and explored their associations with maltreatment types, self-injurious behaviors, and suicide attempts.

Method: Medical records of 331 children and adolescents followed under health protection measures at a single tertiary care hospital were retrospectively reviewed. Data were collected using a standardized file review form that included sociodemographic variables, psychiatric diagnoses, child protection characteristics, and risk factors. Psychiatric diagnoses were established according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. Statistical analyses compared diagnostic distributions across maltreatment subgroups and examined associations with self-injurious behavior and suicide attempts.

Results: Of the 331 included cases, 235 children (71.0%) underwent psychiatric evaluation. Diagnostic distributions were analyzed within this subgroup. Among children exposed to neglect (n=161), intellectual disability (29.8%), attention-deficit/hyperactivity disorder (28.6%), and conduct disorder (24.2%) were the most prevalent diagnoses. Major depressive disorder was significantly more common among children exposed to physical abuse (50.0%; $p<0.001$), whereas major depressive disorder (37.5%; $p=0.008$) and social anxiety disorder (18.8%; $p=0.003$) were more frequent in the extrafamilial sexual abuse group. Self-injurious behaviors and suicide attempts were observed across maltreatment groups, with significant associations between self-injury and intrafamilial sexual abuse and between suicide attempts and physical and emotional abuse. Girls exhibited higher rates of both self-injurious behavior and suicide attempts than boys ($p<0.01$). Neurological (26.0%) and endocrine (8.5%) disorders were the most common non-psychiatric medical conditions.

Conclusion: Children referred to a tertiary care facility under health protection measures demonstrated a high burden of psychiatric morbidity. Diagnostic patterns varied according to maltreatment type, highlighting the need for trauma-informed, multidisciplinary care.

Keywords: Psychiatric profiles, child protection, health measures, psychiatric diagnoses, protective measures

How to cite this article: Kinay Ermis D, Guney O, Kasar N. Psychiatric and medical profiles of children receiving health protection measures in a tertiary care facility: A five-year analysis. Dusunen Adam J Psychiatr Neurol Sci 2026;39:142-152.

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Received: December 22, 2025; **Revised:** April 12, 2026; **Accepted:** June 04, 2026

INTRODUCTION

Childhood is a period of heightened vulnerability to adverse experiences. Exposure to neglect, abuse, poverty, and other traumatic events has been consistently shown to impair cognitive, emotional, and social development, making childhood adversity a major public health concern (1). Such experiences are strongly associated with a range of lifelong psychiatric disorders, including anxiety, depression, behavioral disorders, and substance use disorders, as well as physical health conditions such as asthma, obesity, cardiovascular disease, and premature mortality (2-4). Adverse childhood experiences may also have lasting effects on brain development, resulting in deficits in learning, attention, executive functioning, and language. Nevertheless, the high neuroplasticity of the developing brain suggests that timely interventions can reverse or mitigate these effects, underscoring the importance of early, evidence-based, and multidisciplinary preventive strategies (5, 6).

Given these risks, child protection systems worldwide play a central role in safeguarding children's health and development. In Turkiye, the child protection system is governed by Child Protection Law No. 5395, which defines five protective and supportive measures: counseling, education, health, care, and shelter. These judicially mandated interventions are designed to protect children's well-being and may be implemented individually or in combination, depending on the child's needs. In practice, however, their effectiveness depends not only on the judicial decision itself but also on continuity of follow-up and coordination among health, social service, educational, and judicial institutions (7). Among these measures, health protection measures are particularly important because they facilitate access to medical and psychiatric assessment and treatment for children at risk of neglect, abuse, delinquency, substance use, or family dysfunction (8, 9). Despite their critical role, research has identified significant challenges in implementation. Continuity of follow-up is often poor; for example, one study reported that 63.3% of children failed to attend regular follow-up appointments after the initial evaluation (10). Furthermore, some children are referred exclusively to non-psychiatric services or remain outside systematic multidisciplinary monitoring, highlighting structural limitations within the child protection system (3, 11). These limitations raise an important question: What are the actual psychiatric and medical needs of children receiving health protection measures, and to what extent are these needs being addressed? Previous studies from both Turkiye and other countries have consistently documented high rates of psychiatric morbidity and substantial service gaps, providing the rationale for the present study.

Studies conducted in Turkiye have reported that 60%–80% of children receiving health protection measures are diagnosed with at least one psychiatric disorder, most commonly post-traumatic stress disorder (PTSD), attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD), anxiety disorders, and depression (3, 8, 12). These children frequently come from socioeconomically disadvantaged backgrounds and are more likely to have parents with psychiatric disorders and disrupted family structures. Additional risk factors include migration status, delinquency, and being an unaccompanied minor (12, 13). Importantly, despite the high prevalence of psychiatric disorders, treatment adherence and regular follow-up remain suboptimal, and health protection measures are often implemented in a short-term or procedural manner (3, 8). Similarly, international studies suggest that psychiatric assessment alone is insufficient; children receiving health protection measures require comprehensive, sustainable, and trauma-focused interventions (14, 15). However, multidisciplinary approaches and long-term follow-up programs remain limited, and systematic evaluations of both the effectiveness of health protection measures and the clinical and psychosocial characteristics of affected children are scarce (10, 12).

This study aimed to evaluate children and adolescents referred to a tertiary city hospital under health protection measures between April 2020 and April 2025. Specifically, it examined their sociodemographic characteristics, psychiatric diagnoses, risk indicators such as self-injurious behavior and suicide attempts, and the types and reasons for concurrent protective and supportive measures. By analyzing clinical psychiatric assessments and case records, this study sought to provide a more comprehensive understanding of the clinical profiles of these high-risk children and the challenges associated with implementing health protection measures in a tertiary care setting.

METHODS

Participants

This study included children and adolescents referred to Basaksehir Cam and Sakura City Hospital under a health protection measure between April 2020

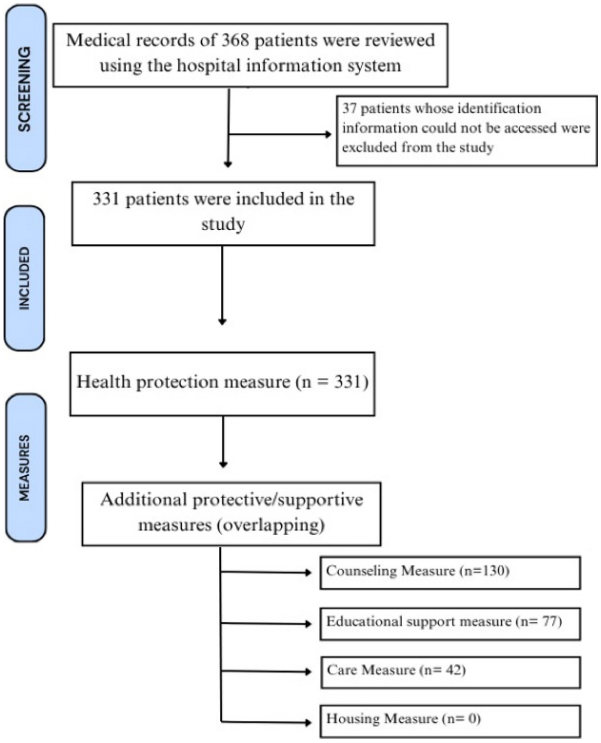

Figure 1. Flowchart of participant inclusion and the distribution of protective and supportive measures.

and April 2025. A total of 368 patient records were identified through the hospital information system and reviewed. Thirty-seven cases were excluded because identifying information was inaccessible, resulting in a final sample of 331 children and adolescents (Fig. 1). Outpatient records and social investigation reports were retrospectively reviewed. All 331 participants were receiving a health protection measure; however, not all underwent evaluation in the Child and Adolescent Psychiatry Department. Of the included cases, 235 received a face-to-face psychiatric assessment conducted by a child and adolescent psychiatry specialist. Psychiatric diagnoses were established according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria based on these clinical evaluations (16). The remaining cases were followed in other hospital departments according to their clinical needs and did not have a documented psychiatric evaluation during the available retrospective review period. Under Turkish Child Protection Law No. 5395, protective and supportive measures include counseling, education, health, care, and shelter. In the present study, all participants were receiving a health protection measure, a judicially mandated intervention intended to ensure access to medical and psychiatric assessment, treatment, and follow-up for children whose well-being is considered to be at risk. These measures may be implemented individually or concurrently according to the child's needs, and their effectiveness depends not only on the legal decision itself but also on continuity of follow-up and coordination among health, social service, educational, and judicial institutions. Accordingly, analyses involving psychiatric diagnoses were restricted to the subgroup that underwent psychiatric evaluation. Information on suicidal risk and self-injurious behavior was obtained from psychiatric interviews when such evaluations were available. Sociodemographic characteristics, clinical features, and treatment information were extracted from medical records. Data regarding the reasons for the health protection measure, concurrent protective and supportive measures (e.g., counseling, education, and care), and family and sociodemographic characteristics not available in the medical records were obtained from social investigation reports.

All data were extracted using a researcher-developed standardized data collection form. The study was approved by the Institutional Ethics Committee (Approval No. KAEK/14.05.2025.127). Written informed consent had been obtained from participants and their parents at the time of clinical evaluation. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection

Data were collected using a standardized file review form developed by the researchers to ensure systematic and comprehensive extraction of information from medical records, social service reports, and legal documents. The collected variables were grouped into five domains.

1. Sociodemographic Characteristics

Information on sex, age, and nationality was recorded. Educational information was also reviewed; however, because these data were incomplete and inconsistently documented across retrospective records, they were not included in the final analyses.

2. Health Protection Measure Process

Variables related to the health protection measure process included the date of the judicial decision, the date of the first psychiatric evaluation, the interval between the decision and initiation of follow-up (days), and follow-up regularity. Regular follow-up was defined as sustained adherence to the recommended

monitoring schedule. Cases that did not attend scheduled follow-up appointments consistently and for whom continuity of care could not be maintained were classified as not receiving regular follow-up. Information regarding psychiatric assessment and treatment was also recorded.

3. Clinical Characteristics

Current psychiatric diagnoses were coded according to DSM-5 diagnostic criteria and included disorders such as PTSD, ADHD, and major depressive disorder (MDD). Treatment-related variables included receipt of psychiatric treatment, treatment intensity (monotherapy, dual-drug therapy, or treatment with three or more psychotropic medications), and treatment modality (pharmacological, psychotherapeutic, or combined). Medication classes were derived from free-text treatment records and categorized accordingly.

4. Child Protection System Variables

Information on concurrent protective and supportive measures (e.g., counseling, education, care, and shelter) was collected, together with data regarding visitation orders, parental divorce or custody disputes, and whether the child had been abandoned or found.

5. Risk Factors

The selected risk factors were chosen because they could be identified relatively consistently and reliably within retrospective records and were considered clinically and legally relevant within the child protection context. They were not intended to represent an exhaustive list of psychosocial risk factors but rather predefined indicators that could be captured in a standardized manner within the available record system. The following risk factors were assessed and coded:

- History of delinquency
- Unaccompanied foreign minor status
- History of substance use
- Terrorism-related background.

Because these variables were either absent or observed at very low frequencies within the study sample, they are presented in the Supplementary Material rather than analyzed as primary variables in the main Results section (Supplementary Table 2).

Self-injurious behavior was defined as any intentional act of self-inflicted bodily harm without suicidal intent, including behaviors such as cutting, burning, hitting oneself, or head banging. Cases were coded as "present" when such behaviors were documented and "absent" otherwise.

A suicide attempt was defined as any self-directed behavior accompanied by evidence of intent to die, regardless of outcome. Examples included medication overdose, hanging, jumping from a height, and self-inflicted injury with suicidal intent. Cases were coded as "present" when at least one suicide attempt was documented and "absent" otherwise.

All variables were extracted from hospital medical records, social service reports, and relevant legal documents and subsequently entered into the study database for statistical analysis.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). All eligible cases identified during the study period were included in the analyses. Continuous variables are presented as mean±standard deviation (SD), whereas categorical variables are presented as frequencies and percentages (%). The normality of continuous variables was assessed using skewness and kurtosis values. Age, which demonstrated a normal distribution, was compared between groups using the independent-samples t test. Associations between categorical variables were examined using Pearson's chi-square test, and Fisher's exact test was used when expected cell frequencies were less than five. All statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant. Given the limited sample sizes in several maltreatment subgroups, comparative analyses should be considered exploratory and interpreted with caution. Furthermore, owing to the descriptive and exploratory design of the study, the findings should not be interpreted as indicating causal relationships.

RESULTS

Sample and Clinical Characteristics

Of the 368 medical records initially screened, 37 were excluded because of missing identification data, resulting in a final sample of 331 children and adolescents (Fig. 1). Of the included participants, 152 (45.9%) were female and 179 (54.1%) were male, with a mean age of 11.37±4.86 years. Most participants were Turkish nationals (76.7%), followed by Syrian nationals (19.3%) and individuals of other nationalities (3.9%) (Table 1). Of the 331 included cases, 210 children (63.4%) received regular follow-up. A total of 235

Table 1: Sociodemographic, clinical, and treatment characteristics of the study sample

Characteristic	n	%
Sex		
Female	152	45.9
Male	179	54.1
Age (mean±SD)	11.37±4.86	
Time from decision to first evaluation (months), median (IQR)	3.27 (1.33–11.03)	
Regular follow-up	210	63.4
Psychiatric evaluation	235	71.0
Psychiatric treatment initiated	123	37.2
Monotherapy	60	48.8
Dual-drug treatment	45	36.6
Three or more psychotropic medications	18	14.6
Medication class		
Antipsychotics	90	73.2
SSRI	54	43.9
Stimulants/methylphenidate	32	26.0
Atomoxetine	10	8.1
Other medications*	10	8.1
Non-psychiatric specialty evaluations		
Pediatric neurology	86	26.0
Pediatric endocrinology	28	8.5
Physical therapy and rehabilitation	20	6.0
Pediatric gastroenterology	19	5.7
Ophthalmology	18	5.4
Otolaryngology (ENT)	17	5.1
Pediatric nephrology	16	4.8
Orthopedics	14	4.2
Pediatric metabolism	14	4.2
General pediatrics	13	3.9
Hematology–oncology	12	3.6
Other specialties**	37	11.2
Nationality		
Turkish	254	76.7
Syrian	64	19.3
Other (Afghan, Chinese, Turkmen, Palestinian, Algerian, Azerbaijani)	13	3.9

*: Other medications included biperiden, melatonin, antiepileptic agents, and guanfacine; **: Other specialties included Genetics (n=8), Pulmonology (n=8), Pediatric Surgery (n=10), Urology (n=6), Allergy (n=4), Neurosurgery (n=4), Immunology (n=2), and Dermatology (n=2). Percentages for monotherapy, dual-drug treatment, treatment with three or more psychotropic medications, and medication classes were calculated among children who received psychiatric treatment (n=123). Medication classes were derived from free-text treatment records and were not mutually exclusive; therefore, individual children could be represented in more than one medication category.

children (71.0%) underwent face-to-face psychiatric evaluation in the Child and Adolescent Psychiatry Department, whereas the remaining children were followed in other hospital departments according to their clinical needs under the health protection measure. Among those who underwent psychiatric evaluation, psychiatric treatment was initiated in 123 children; in the remaining cases, psychiatric treatment was not considered clinically indicated at the time of assessment. In addition to psychiatric care, referrals to non-psychiatric specialties were common. The most frequent specialties involved were pediatric neurology (26.0%), pediatric endocrinology (8.5%), and physical therapy and rehabilitation (6.0%). Lower frequencies were observed for pediatric gastroenterology, ophthalmology, otolaryngology, nephrology, orthopedics, and other specialties. The non-psychiatric specialties presented in Table 1 were based on the entire sample of 331 cases and did not exclusively represent referrals following psychiatric assessment. Some children were followed directly by other specialties according to their medical conditions and clinical needs under the health protection measure. More than one specialty evaluation could be recorded for a single case. Low-frequency child protection system variables and predefined risk factors are summarized in Supplementary Table 2.

Psychiatric Diagnoses According to Maltreatment Type

The distribution of psychiatric diagnoses differed across the maltreatment subgroups (Table 2). Analyses in this section were restricted to children who underwent psychiatric evaluation.

Among children exposed to neglect (n=161), the most prevalent diagnoses were intellectual disability (29.8%), attention-deficit/hyperactivity disorder (28.6%), and conduct disorder (24.2%). ADHD showed a significant variation across maltreatment groups (p=0.003).

Among children exposed to physical abuse (n=28), major depressive disorder was the most frequent diagnosis (50.0%; p<0.001). Generalized anxiety disorder (25.0%; p=0.007) and oppositional defiant disorder (21.4%; p=0.013) were also significantly more common in this group.

In the emotional abuse group (n=9), major depressive disorder was the most prevalent diagnosis (55.6%; p=0.002), and ADHD was also frequently observed (33.3%).

Internalizing disorders were particularly prominent among children exposed to sexual abuse. Social anxiety

Table 2: Distribution of psychiatric diagnoses according to maltreatment type

Psychiatric diagnosis	Neglect (n=161) n (%)	Physical abuse (n=28) n (%)	Emotional abuse (n=9) n (%)	Intrafamilial sexual abuse (n=11) n (%)	Extrafamilial sexual abuse (n=16) n (%)
ADHD	46 (28.6)**	6 (21.4)	3 (33.3)	0	4 (25.0)
MDD	26 (16.1)	14 (50.0)***	5 (55.6)**	4 (36.3)*	6 (37.5)**
CD	39 (24.2)	8 (28.6)	1 (11.1)	2 (18.2)	5 (31.3)
ID	48 (29.8)	2 (7.1)	1 (11.1)	2 (18.2)	1 (6.3)
GAD	22 (13.7)	7 (25.0)**	2 (22.2)	2 (18.2)	3 (18.8)
SpLD	27 (13.7)	1 (3.6)	1 (11.1)	0	1 (6.3)
ODD	18 (11.2)	6 (21.4)*	2 (22.2)	0	3 (18.8)
SLD	18 (11.2)	2 (7.1)	1 (11.1)	1 (9.1)	2 (12.5)
ASD	22 (13.7)	1 (3.6)	0	0	0
SAD	4 (2.5)	0	0	2 (18.2)*	3 (18.8)**
PanD	4 (2.5)	1 (3.6)	0	0	1 (6.3)
OCD	2 (1.2)	1 (3.6)	1 (11.1)	0	1 (6.3)
Mania/hypomania	1 (0.6)	1 (3.6)	0	0	0
Eating disorder	1 (0.6)	1 (3.6)	0	0	0
PsyD	1 (0.6)	0	0	0	0
Other disorders*	–	–	–	–	–

*Disorders occurring fewer than three times across all maltreatment subgroups (e.g., agoraphobia, tic disorders, impulse-control disorders, etc.) are not shown for clarity. Statistically significant subgroup associations are indicated as follows: p<0.05 (*), p<0.01 (**), p<0.001 (***). ADHD: Attention-deficit/hyperactivity disorder; ASD: Autism spectrum disorder; CD: Conduct disorder; CSA: Child sexual abuse; Dx: Diagnosis; ED: Eating disorders; GAD: Generalized anxiety disorder; ID: Intellectual disability; M/H: Mania/hypomania; MDD: Major depressive disorder; OCD: Obsessive-compulsive disorder; ODD: Oppositional defiant disorder; PanD: Panic disorder; PsyD: Psychotic disorder; SAD: Social anxiety disorder; SLD: Specific learning disorder; SpLD: Speech/language disorder. Values are presented as n (%). Diagnoses are ordered according to their overall frequency across maltreatment subgroups.

Table 3: Association between maltreatment types and clinical variables

Variables	Neglect (n=161) n (%)	Physical abuse (n=28) n (%)	Emotional abuse (n=9) n (%)	Intrafamilial CSA (n=11) n (%)	Extrafamilial CSA (n=16) n (%)
Self-injurious behavior	25 (15.5)	6 (21.4)	0 (0.0)	4 (36.4)*	3 (18.8)
Suicide attempt	16 (9.9)	6 (21.4)*	3 (33.3)*	3 (27.3)	1 (6.3)

Values are presented as n (% within maltreatment subgroup). Maltreatment categories were not mutually exclusive, and not all psychiatrically evaluated children could be classified into the maltreatment categories shown. Therefore, column totals do not necessarily correspond to the overall number of children with self-injurious behavior or suicide attempts. Statistically significant subgroup associations are indicated as follows: p<0.05 (*), p<0.01 (**), p<0.001 (***). CSA: Child sexual abuse.

disorder was significantly more common in both the intrafamilial sexual abuse group (18.2%; p=0.02) and the extrafamilial sexual abuse group (18.8%; p=0.003). Major depressive disorder was also more prevalent among children exposed to extrafamilial sexual abuse (37.5%; p=0.008).

Self-Injurious Behavior and Suicide Attempts

Among the 235 children who underwent psychiatric evaluation, self-injurious behavior was identified in 36 (15.3%), and suicide attempts were documented in 28 (11.9%) (Table 3). Both self-injurious behavior and suicide attempts were more common among girls than boys (self-injury: 15.8% vs. 6.7%; suicide attempts: 16.4% vs. 1.7%, respectively).

When examined according to maltreatment type, self-injurious behavior occurred most frequently among neglected children in absolute numbers; however, a statistically significant association was observed only for intrafamilial sexual abuse (36.4%; p=0.023). Regarding suicide attempts, significantly higher rates were observed among children exposed to physical abuse (21.4%; p=0.02) and emotional abuse (33.3%; p=0.03). Although suicide attempts were also reported among neglected and sexually abused children, these associations did not reach statistical significance.

Health Protection Measures

Among the additional protective and supportive measures implemented, counseling measures were

Table 4: Categories of non-psychiatric medical conditions and representative diagnoses identified in the available records

Category	Representative diagnoses	Number of distinct diagnoses (n)
Neurological	Cerebral palsy (CP), epilepsy, hydrocephalus, congenital hypotonia, West syndrome, spinal muscular atrophy (SMA), spina bifida, migraine, medulloblastoma, craniopharyngioma	34
Developmental/genetic	Down syndrome, Angelman syndrome, neurofibromatosis type 1 (NF1), osteogenesis imperfecta, thalassemia, autism spectrum disorder (ASD), sacral agenesis, Wilms tumor, acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML)	18
Endocrine/metabolic	Type 1 diabetes mellitus, congenital hypothyroidism, adrenal insufficiency, glycogen storage disease, hypopituitarism	7
Hematological/oncological	Anemia, aplastic anemia, immune thrombocytopenia (ITP), AML, ALL, beta-thalassemia	5
Renal/cardiovascular	Chronic kidney disease (CKD), nephrotic syndrome, vesicoureteral reflux (VUR), posterior urethral valve (PUV), congenital heart disease, cardiac murmur, hydronephrosis	9
Respiratory/allergic	Asthma, rhinitis, bronchiolitis, allergic rhinitis	4
Gastrointestinal/nutritional	Protein-energy malnutrition (PEM), malnutrition, gastroesophageal reflux disease (GERD), colostomy/ileus, hypopituitarism with PEM	5
Other medical conditions	Strabismus, hearing loss, atopic dermatitis, psoriasis, juvenile idiopathic arthritis, spastic paraplegia, pilonidal cyst, acute tonsillitis, femur fracture, burn injury, etc.	49

Representative diagnoses are provided as illustrative examples within each category. The numbers in the final column represent the number of distinct diagnoses identified within each category, not the number of affected children.

the most common (39.3%), followed by educational measures (23.3%) and care measures (12.7%) (Fig. 1). Because all participants were receiving a health protection measure by definition, health measures constituted the baseline condition of the study sample rather than an additional intervention. Protective and supportive measures were not mutually exclusive, and individual children could receive multiple measures concurrently. No shelter measures were identified in the dataset.

Non-Psychiatric Diagnoses

A broad spectrum of non-psychiatric medical conditions was identified (Table 4). Neurological disorders were the most common, followed by developmental/genetic disorders, endocrine/metabolic disorders, and hematological/oncological conditions. Additional cardiological, renal, respiratory, and gastroenterological disorders were also observed, highlighting the multidimensional health needs of children receiving health protection measures. A substantial proportion of children presented with both psychiatric and non-psychiatric conditions. Specifically, 143 children (43.2% of the total sample) underwent both psychiatric and non-psychiatric evaluations (Supplementary Fig. 1, Supplementary Table 1).

DISCUSSION

In this study, psychiatric disorders were highly prevalent among children and adolescents receiving health protection measures, and diagnostic patterns varied according to the type of maltreatment experienced. Both externalizing and internalizing psychopathologies were common, underscoring the substantial mental health burden among children involved in the child protection system.

Consistent with previous research, high rates of externalizing disorders, such as ADHD and conduct disorder, as well as internalizing disorders, including anxiety and depressive disorders, were observed in this population (14, 17). These rates are substantially higher than the estimated prevalence of psychiatric disorders in the general pediatric population, which ranges from approximately 12% to 15% (18, 19). Studies conducted in Turkiye have similarly reported psychiatric diagnosis rates of 60%–80% among children receiving health protection measures (3). Taken together, these findings indicate high rates of both externalizing disorders, such as ADHD and conduct disorder, and internalizing disorders, including anxiety and depressive disorders, among children who underwent psychiatric evaluation (14, 17).

Self-Injurious Behaviors and Suicide Attempts

Self-injurious behavior and suicide attempts were identified in 15.3% and 11.9% of the psychiatrically evaluated group, respectively. Although the highest absolute numbers were observed among neglected children, statistically significant associations varied by maltreatment type. Self-injurious behavior was significantly associated with intrafamilial sexual abuse, whereas suicide attempts were significantly more frequent among children exposed to physical and emotional abuse. These findings suggest that patterns of self-injurious behavior and suicidality may differ across maltreatment categories; however, subgroup-specific findings should be interpreted cautiously because of the limited sample sizes in some abuse groups.

Previous meta-analyses have demonstrated that childhood physical, emotional, and sexual abuse are strong risk factors for both non-suicidal self-injury and suicide attempts, with reported odds ratios ranging from 2.5 to 4.9 (20-22). Emotional abuse and neglect have been identified as particularly potent predictors in some studies (21). Our findings extend this literature by suggesting that specific forms of maltreatment may be associated with distinct patterns of self-harm and suicide-related behaviors within clinically referred child protection populations.

When sex differences were examined, both self-injurious behavior and suicide attempts were markedly more common among girls than boys. This finding is consistent with previous research indicating that girls, particularly those exposed to emotional or sexual abuse, may be more vulnerable to self-harm and suicidal behavior (23, 24). Proposed mechanisms include emotional deprivation, impaired emotion regulation, depressive symptoms, and hopelessness. Furthermore, deficits in mentalization and personality functioning have been proposed as mediators linking childhood maltreatment to self-harm and suicidal behaviors (25).

Diagnostic Distributions by Maltreatment Type

Distinct diagnostic profiles were observed across maltreatment groups. Among children exposed to neglect, intellectual disability, ADHD, and conduct disorder were particularly prevalent. Previous research has demonstrated that insufficient caregiving and reduced environmental stimulation during critical developmental periods are associated with adverse cognitive outcomes, including lower intellectual functioning, language delays, and deficits in executive functioning (26-28). Neurobiological studies further suggest that early deprivation may disrupt synaptic pruning and myelination, resulting in alterations in cortical thickness and white matter integrity that contribute to long-term cognitive and behavioral difficulties (27, 29). These mechanisms may help explain the elevated prevalence of neurodevelopmental and externalizing disorders observed among neglected children.

In contrast, internalizing disorders were more prominent among children exposed to sexual abuse. Depression and social anxiety disorder were particularly common, likely reflecting trauma-related processes such as shame, guilt, fear, and interpersonal mistrust, which contribute to internalizing psychopathology (14, 15). The relatively high prevalence of depressive disorders in the emotional abuse group may be associated with chronic parental rejection, criticism, and emotional invalidation; however, this finding should be interpreted cautiously given the small subgroup size (30). Similarly, the prominence of depressive symptoms in the physical abuse group may reflect the effects of early exposure to violence on affect regulation and emotional functioning, although the relatively small sample size limits definitive conclusions (6, 31).

Multidisciplinary Health Needs

In addition to psychiatric morbidity, a substantial proportion of children required evaluation by non-psychiatric medical specialties, most commonly pediatric neurology, followed by endocrinology and physical therapy and rehabilitation. The high frequency of neurology involvement may reflect the impact of early adversity and neglect on neurodevelopment. Previous studies have shown that maltreated children experience impairments in learning, memory, language, and executive functioning, accompanied by structural and functional alterations in the prefrontal cortex, amygdala, hippocampus, and corpus callosum (27, 32).

Referrals to endocrinology were also notable. Chronic stress and trauma have been associated with long-term dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, contributing to endocrine and metabolic disturbances. Childhood maltreatment has been linked to blunted cortisol responses, flattened diurnal rhythms, and reduced physiological flexibility (33). These alterations, together with structural changes in the amygdala, hippocampus, and prefrontal cortex, may increase vulnerability to depression, anxiety, behavioral disorders, and chronic endocrine dysregulation (34). The presence of additional hematological, cardiological, renal, and respiratory conditions further emphasizes the complex and multidimensional health needs of children receiving health protection measures.

Our findings suggest that children receiving health protection measures carry substantial psychiatric and medical burdens, underscoring the need for comprehensive and sustained interventions. In Turkiye, current practices often remain limited to single assessments or short-term interventions, with inadequate coordination among psychiatry, pediatrics, and social services (10, 35). Such fragmented approaches may fail to address the multidimensional needs of these children and compromise continuity of care. International models have demonstrated the effectiveness of multidisciplinary teams that integrate psychiatric, pediatric, social, and legal services in improving both mental and physical health outcomes (14, 36). Accordingly, the establishment of multidisciplinary follow-up centers, systematic risk assessment procedures, and trauma-informed interventions is essential. Although multiple protective and supportive measures may be implemented concurrently, the potential combined effects of these interventions on outcomes such as self-injurious behavior and suicide attempts were not examined separately in the present study. Furthermore, the co-occurrence of psychiatric and non-psychiatric conditions in a substantial proportion of the sample underscores the complex and multidimensional clinical needs of children receiving health protection measures.

Limitations

This study has several limitations. First, it was conducted at a single center, which may limit the generalizability of the findings. Second, the available data were restricted to medical records, social service reports, and legal documents; consequently, incomplete or non-standardized documentation may have resulted in information loss. Third, although psychiatric diagnoses were originally established through face-to-face clinical assessments based on DSM-5 criteria, their validity could not be reassessed retrospectively. In addition, standardized and validated measures of suicidality and self-injurious behavior were not consistently available across records; therefore, these variables could only be analyzed as binary outcomes (present/absent). Furthermore, some family-related and legal variables obtained from social service reports may have reflected subjective evaluations. Variables such as maltreatment severity, duration of exposure, age at onset, time elapsed between maltreatment and clinical evaluation, and previous psychiatric treatment history were not available in a sufficiently standardized manner and therefore could not be included in the analyses. Sample sizes were relatively small in some maltreatment subgroups, particularly the physical abuse and emotional abuse groups, which may have reduced statistical power and limited the interpretation of subgroup comparisons. Accordingly, subgroup-specific findings should be interpreted with caution. Information regarding follow-up duration and the interval between the judicial decision and the initiation of follow-up was not available in a sufficiently standardized and reliable form across all cases. Consequently, these variables could not be evaluated as potential protective or risk-modifying factors. Additionally, variability in follow-up continuity precluded firm conclusions regarding long-term psychiatric and medical outcomes. Given the descriptive and exploratory nature of the study, the findings should not be interpreted as evidence of causal relationships. Despite these limitations, this study represents one of the larger single-center investigations of children and adolescents receiving health protection measures and highlights both their complex clinical needs and the systemic challenges associated with service delivery.

CONCLUSION

Children receiving health protection measures exhibit high rates of psychiatric and medical morbidity, with diagnostic profiles varying according to maltreatment type. Neglect appears to be more strongly associated with neurodevelopmental and externalizing disorders, whereas abuse-related subgroups demonstrate higher rates of internalizing psychopathology. Patterns of self-injurious behavior and suicide attempts also vary across maltreatment categories, emphasizing the importance of tailored risk assessment. These findings underscore the urgent need for systematic, trauma-informed, multidisciplinary models of care. Strengthening intersectoral collaboration and establishing specialized monitoring and follow-up centers may improve outcomes for this highly vulnerable population.

Online Supplementary Digital Appendix File: https://dusunenadamdergisi.org/storage/upload/files/1781269427-appendix-en.pdf

Ethical Approval: This study was approved by The Basaksehir Cam ve Sakura City Hospital Clinical Research Ethics Committee (Date: 03.06.2025 Decision no: KAEK/14.05.2025.127).

Informed Consent: Written informed consent was obtained from all participants and their parents at the time of clinical evaluation.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

Contribution Categories		Author Initials
Category 1	Concept/Design	D.K.E., O.G.
	Data acquisition	D.K.E., O.G., N.K.
	Data analysis/Interpretation	D.K.E.
Category 2	Drafting manuscript	D.K.E.
	Critical revision of manuscript	D.K.E., O.G., N.K.
Category 3	Final approval and accountability	D.K.E., O.G., N.K.
Other	Supervision	O.G.

Peer-review: Externally peer-reviewed.

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DOI: 10.14744/DAJPNS.2026.00328
Dusunen Adam J Psychiatr Neurol Sci
2026;39:153-155

LETTER TO THE EDITOR

Neuropsychiatric manifestations in hyperekplexia: A case with a novel *SLC6A5* variant

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Dear Editor,

Hyperekplexia is a rare neurodevelopmental disorder characterized by exaggerated startle responses to tactile or auditory stimuli and neonatal hypertonia, most commonly inherited in an autosomal recessive pattern (1). It results from dysfunction of the glycinergic inhibitory system and is frequently linked to mutations in the *GLRA1, GLRB*, and *SLC6A5* genes. *SLC6A5* encodes the presynaptic glycine transporter 2 (GlyT2), and mutations in this gene are associated with more severe phenotypes, including life-threatening apnea (2). Importantly, beyond its motor manifestations, hyperekplexia has also been reported to be associated with a range of neuropsychiatric features, including global developmental delay (GDD), intellectual disability (ID), learning difficulties, and speech and language impairments (3). These findings highlight the need for a multidisciplinary approach and underscore the importance of child psychiatric evaluation in the comprehensive assessment and long-term management of affected patients (4).

A 19-month-old girl was referred to child psychiatry due to delayed speech and developmental concerns. She had no major dysmorphic features aside from a flat nasal bridge. Notable findings included exaggerated startle responses to tactile and auditory stimuli, babbling without meaningful speech, inability to follow simple commands, delayed motor milestones, and limited social interaction. Developmental assessment using the Ankara Developmental Screening Inventory (ADSI) revealed significant delays across all domains, with performance falling below the 30th percentile. The specific developmental ages and domain scores of the ADSI are presented in Figure 1. A subsequent Denver II Developmental Screening Test also confirmed significant delays across all assessed domains, including personal-social, fine motor, language, and gross motor skills.

She was born at term via cesarean section to consanguineous parents, with a birth weight of 3600 grams. There was no known family history of neurological or genetic disorders. From the neonatal period onward, she exhibited startle-like muscle contractions. Electroencephalography (EEG), magnetic resonance imaging (MRI), and biochemical test results were unremarkable. Following psychiatric and developmental evaluation, the patient was assessed in collaboration with the pediatric neurology department. Based on this joint evaluation, the neurology team referred her for genetic testing, which identified a novel homozygous c.629G>T p.(Gly210Val) variant in the *SLC6A5* gene, thereby confirming the diagnosis of hyperekplexia. Initial treatment with phenobarbital and levetiracetam was replaced with clonazepam after diagnostic confirmation, resulting in a reduction of startle episodes. Further evaluations revealed bilateral partial hearing loss and a hemodynamically insignificant secundum atrial septal defect.

How to cite this article: Teke H, Tuter Mavi H. Neuropsychiatric manifestations in hyperekplexia: A case with a novel *SLC6A5* variant. Dusunen Adam J Psychiatr Neurol Sci 2026;39:153-155.

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Received: June 04, 2025; **Revised:** August 18, 2025; **Accepted:** September 27, 2025

Figure 1. Developmental ages based on the Ankara Developmental Screening Inventory (ADSI) results compared to the child's chronological age (19 months).

At the time of psychiatric evaluation, the patient was diagnosed with GDD. Although she exhibited speech delay and limited social interaction, she did not meet the diagnostic criteria for autism spectrum disorder (ASD) at that stage. A multidisciplinary early intervention plan was initiated, including individualized special education, speech-language therapy, and parental psychoeducation. The parents were advised on activities to stimulate the child's development at home, promote social play, and reduce screen time. Regular psychiatric follow-up was arranged for developmental surveillance and to monitor for the possible emergence of ASD, attention-deficit/hyperactivity disorder (ADHD), ID, or other psychiatric disorders.

This case involves a previously unreported *SLC6A5* variant associated with prominent developmental delays. Although the exact pathogenicity of this variant is uncertain, the breadth of neurodevelopmental impairment suggests an effect extending beyond motor circuits to cognitive and psychiatric domains. The co-occurrence of hearing loss and an atrial septal defect may further complicate developmental outcomes. GDD and ID are among the most prevalent neurodevelopmental disorders in childhood and are associated with substantial long-term morbidity. Approximately half of GDD/ID cases are linked to genetic etiologies (5). Compared to other hyperekplexia-related genes, *SLC6A5* and *GLRB* mutations have been more frequently associated with GDD/ID, learning difficulties, and speech impairments (2, 4, 6). These associations are summarized in Table 1, which compares the impact of different hyperekplexia-related gene mutations on GDD/ID, speech delay, and learning difficulties. Such manifestations likely arise from early and diffuse disruptions in neurodevelopmental pathways (6). In particular, mutations in *SLC6A5*, which encodes the presynaptic GlyT2, disrupt glycinergic inhibitory neurotransmission. This impaired inhibition not only explains the exaggerated motor startle responses but may also affect broader neural circuits involved

Table 1: Comparison of the effects of hyperekplexia-related gene mutations on global developmental delay (GDD), intellectual disability (ID), speech delay, and learning difficulties

Gene mutation	GDD/ID	Speech delay	Learning difficulties
GLRA1	Less common	Less common	Moderate
GLRB	Common	Very common (92%)	Common
SLC6A5	Common	Common	Common

in cognition, learning, and social behavior, thereby contributing to developmental delay and psychiatric manifestations.

Although hyperekplexia is pharmacologically manageable, associated cognitive and behavioral impairments often persist (7). This underscores the critical role of child psychiatrists in both diagnostic assessment and long-term follow-up. Early multidisciplinary intervention—particularly with active family engagement—has been shown to improve prognosis (8). In this case, early referral to child psychiatry enabled timely developmental evaluation and the initiation of a tailored support program, including special education, speech-language therapy, and parental guidance. Given the high prevalence of psychiatric comorbidities such as ASD and ADHD in genetic neurodevelopmental conditions, ongoing psychiatric surveillance remains essential (9, 10).

In conclusion, this case highlights the broader neurodevelopmental implications of SLC6A5-related hyperekplexia and underscores the importance of psychiatric and developmental evaluation in genetic disorders of this kind. Comprehensive management, including early diagnosis, individualized therapies, and longitudinal follow-up, is essential to optimize developmental outcomes. Written informed consent was obtained from the patient's parents for the publication of this case report and the accompanying images.

Informed Consent: Written informed consent was obtained from the patient's parents for the publication of this case report and the accompanying images.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: Not declared.

Acknowledgments: The authors would like to thank the child development specialists for their assistance in administering the developmental assessments. We also extend our gratitude to the Department of Medical Genetics for their contributions to the molecular diagnosis and genetic counseling. Additionally, we sincerely acknowledge the pediatric neurology team for their clinical follow-up and support in the early identification and management of the patient.

Peer-review: Externally peer-reviewed.

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DOI: 10.14744/DAJPNS.2026.00329
Dusunen Adam J Psychiatr Neurol Sci
2026;39:156-158

LETTER TO THE EDITOR

Sertraline use in mitochondrial cytopathy-associated depression: A case report

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Dear Editor,

Mitochondrial cytopathies are a heterogeneous group of inherited metabolic disorders caused by defects in mitochondrial DNA or nuclear genes encoding mitochondrial proteins, leading to impaired oxidative phosphorylation and multisystem involvement (1). These disorders are increasingly recognized as contributors to neuropsychiatric conditions, including major depressive disorder. Indeed, the lifetime prevalence of depression has been reported to reach approximately 50% in adult patients with primary mitochondrial cytopathies (2). To date, reliable epidemiological data specific to adolescents with mitochondrial cytopathy are lacking. Moreover, evidence-based guidance for managing such psychiatric comorbidities remains scarce. Here, we report the case of a 16-year-old boy with a diagnosed mitochondrial cytopathy and co-occurring moderate intellectual disability. Written informed consent was obtained from the patient and his parents for publication of this case. Over the course of one year, he developed a persistent depressive syndrome characterized by low mood, anhedonia, social withdrawal, irritability, decreased verbal communication, loss of interest in recreational activities, and sleep disturbance, as reported primarily by his caregivers. Importantly, no psychotic features, such as hallucinations, delusions, or thought disorganization, were observed at any point during evaluation or follow-up, thereby ruling out a prodromal psychotic phase. Given his neurodevelopmental profile, self-report measures were not feasible. Instead, the evaluation relied on the parent-rated Revised Child Anxiety and Depression Scale (RCADS-P) depression subscale and clinician-administered Clinical Global Impression scales (CGI-Severity and CGI-Improvement) (3-6).

Prior to initiating treatment, a comprehensive medical work-up was conducted to rule out other potential contributors to depression—including thyroid dysfunction, anemia, infection, and metabolic disturbances—all of which were within normal limits on laboratory screening. There was no evidence of substance use or exposure to other medications. Establishing this baseline also allowed for monitoring of tolerability: importantly, no clinically significant laboratory abnormalities emerged during therapy. No mitochondrial disease-specific biomarkers (such as serum lactate or pyruvate) were systematically monitored during psychiatric follow-up. Treatment was initiated with low-dose sertraline at 12.5 mg/day and titrated to 25 mg/day after two weeks. Between months 2 and 5 (weeks 8–20), the patient experienced a mild and transient partial re-emergence of symptoms—chiefly anhedonia, irritability, and social withdrawal—with occasional early-morning awakening. Appetite and psychomotor activity remained unchanged. There were no psychotic features and no global clinical deterioration; school

How to cite this article: Durak M, Ozlem Ates B. Sertraline use in mitochondrial cytopathy-associated depression: A case report. Dusunen Adam J Psychiatr Neurol Sci 2026;39:156-158.

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Received: July 20, 2025; **Revised:** September 08, 2025; **Accepted:** September 27, 2025

attendance remained regular, although participation in social and recreational activities transiently declined. Adherence was confirmed through caregiver-reported pill counts (≥95% of doses taken) and pharmacy refill records. No medical or etiological trigger was identified: there were no intercurrent infections or changes in medications or supplements, and repeat laboratory tests at month 5 (complete blood count, comprehensive metabolic panel, thyroid function tests) were within reference ranges. In addition, throughout the two-year follow-up period, the patient underwent periodic electrocardiogram (ECG) evaluations, all of which were normal. Weight and body mass index (BMI) were monitored regularly and remained stable without clinically significant changes. Sleep patterns, as reported by caregivers, were not adversely affected during treatment. The sertraline dose was subsequently increased to 50 mg/day at month 5, after which symptoms resolved within two weeks and remained stable thereafter.

At baseline, the patient's RCADS-P Major Depression Subscale score was in the severe clinical range, with a CGI-S score of 6. Symptoms improved to the moderate range by week 4 and to the mild range by week 6, corresponding to a CGI-S score of 3 and a CGI-I score of 2 (much improved). A transient worsening occurred at month 5 (moderate range; CGI-S score of 4). Thereafter, progressive recovery was observed, with scores reaching the remission range (RCADS-P score of 10; CGI-S score of 2) at the two-year evaluation, while the CGI-I was consistently rated as 1 (very much improved). Functionally, the patient's school attendance, which had been irregular prior to treatment, normalized. He demonstrated increased classroom engagement and renewed participation in social and recreational activities, reflecting sustained improvement in daily functioning alongside symptom reduction.

Sertraline was selected as the initial antidepressant in this case due to its well-established safety and tolerability profile in adolescents, as well as its pharmacological properties. Its low inhibition of CYP2D6 and minimal pharmacokinetic interaction risk allow for safer combination with other medications (7). Its relatively low sedative potential is advantageous for patients already experiencing fatigue and low energy. Furthermore, its putative antioxidant effects, which may mitigate oxidative stress associated with mitochondrial cytopathy (8, 9), provide an additional therapeutic rationale. Nevertheless, some reports have raised concerns regarding potential adverse effects of selective serotonin reuptake inhibitors (SSRIs) in the context of mitochondrial cytopathies. Recent studies suggest that SSRIs may impair mitochondrial function (10), and sertraline-associated lipid storage myopathy with mitochondrial respiratory chain deficiencies has also been documented (11). These findings underscore the importance of cautious monitoring when prescribing SSRIs to patients with mitochondrial disorders. Taken together, these considerations suggest that sertraline represents a rational and safe treatment option for depression associated with mitochondrial cytopathy. However, larger clinical studies are needed to confirm its superiority over other SSRIs.

Our report adds to the limited literature on the management of depression in the context of mitochondrial disease. Previous case reports indicate that standard antidepressants can be used in this population. For example, an adolescent with MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) demonstrated clinical recovery from a depressive episode following escitalopram therapy, and an adult with MELAS showed a similarly positive response to the serotonin–norepinephrine reuptake inhibitor (SNRI) duloxetine (12, 13). These observations support the feasibility of using SSRIs and SNRIs in patients with mitochondrial disorders. To the best of our knowledge, this is the first report of an adolescent with mitochondrial cytopathy and comorbid depression who was successfully treated with sertraline for more than one year. We acknowledge the inherent limitations of literature searches and recognize that other relevant reports may exist but were not identified. Nevertheless, the present case is distinctive in that it combines adolescent age, the coexistence of mitochondrial cytopathy and depression, and a two-year follow-up demonstrating sustained remission, thereby contributing a unique perspective to the literature.

Optimal management of psychiatric comorbidities in rare metabolic conditions requires an individualized and collaborative approach. In our case, close coordination among psychiatry, neurology, and metabolic specialists was essential. We emphasize slow titration, regular monitoring of psychiatric status and somatic health, and active caregiver engagement as key elements of care. Importantly, there are currently no definitive treatment guidelines for depression associated with mitochondrial disease; management is largely informed by case reports and clinical judgment (12-14). Existing therapies for mitochondrial disorders remain primarily supportive, focusing on symptomatic relief (e.g., coenzyme Q10 and vitamin

supplementation) rather than disease modification (15). Although this single-case observation has inherent limitations, it illustrates that an SSRI, when selected thoughtfully and monitored carefully, can lead to significant and sustained improvement in a patient with mitochondrial dysfunction. Systematic research and controlled trials are needed to establish safe, evidence-based treatment strategies for psychiatric manifestations in mitochondrial disease.

Informed Consent: Written informed consent was obtained from the patient's legal guardian for publication of this case.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: Not declared.
Peer-review: Externally peer-reviewed.

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DOI: 10.14744/DAJPNS.2026.00330
Dusunen Adam J Psychiatr Neurol Sci
2026;39:159-161

LETTER TO THE EDITOR

Halitosis as a rare adverse effect of atomoxetine in a child with attention-deficit/hyperactivity disorder

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Dear Editor,

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in childhood that often requires pharmacological treatment (1). Atomoxetine, a selective norepinephrine reuptake inhibitor, is widely used as a non-stimulant medication for ADHD, particularly in patients who cannot tolerate stimulants or have contraindications (1, 2). Although atomoxetine's safety profile is generally well established, rare and atypical adverse effects may go unrecognized, especially in pediatric populations (3). This report presents a case of halitosis as a rare adverse effect occurring during atomoxetine treatment in a child with ADHD, highlighting an uncommon but clinically relevant side effect that may affect treatment adherence and quality of life.

A 6-year-old boy was referred to a child psychiatry clinic due to hyperactivity and poor school adjustment. His prenatal, perinatal, and postnatal histories were unremarkable, and his developmental milestones were age appropriate. He had no prior medical or psychiatric diagnoses. During the evaluation, he was constantly moving, had difficulty remaining seated, was easily distracted during structured activities, and demonstrated a tendency to interrupt others or act impulsively. Based on clinical interviews, teacher feedback, and parent and teacher ratings on the Turgay DSM-IV–Based Disruptive Behavior Disorders Rating Scale, he was diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.

Pharmacological treatment was initiated with atomoxetine at 0.5 mg/kg/day and gradually titrated up to 1.2 mg/kg/day. Two weeks after reaching the target dose, his parents reported the emergence of persistent halitosis, which had not been present previously and was subsequently confirmed by the clinician during follow-up. The halitosis significantly interfered with the child's functioning, limiting daily social participation, including peer interactions and involvement in classroom activities.

To rule out organic causes, the patient underwent comprehensive dental and pediatric evaluations. The dental examination revealed no pathological findings. Moreover, other potential contributors—including dietary habits, hydration status, and oral hygiene factors—were considered and deemed unlikely. Physical examination and laboratory investigations, including a metabolic panel, were unremarkable. In the absence of an identifiable organic cause and given the clear temporal relationship between atomoxetine initiation and dose escalation, the medication was discontinued. The halitosis resolved within a few days of discontinuation. Given the therapeutic importance of atomoxetine and the need to confirm causality, a cautious re-challenge was performed under close clinical supervision with informed parental consent.

How to cite this article: Erarkadas M, Ozmeral Erarkadas K. Halitosis as a rare adverse effect of atomoxetine in a child with attention-deficit/hyperactivity disorder. Dusunen Adam J Psychiatr Neurol Sci 2026;39:159-161.

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Received: September 09, 2025; **Revised:** October 31, 2025; **Accepted:** November 24, 2025

Upon reinitiation of atomoxetine at the same dose, the halitosis promptly recurred. The medication was then permanently discontinued, and the symptom again resolved completely within days. This re-challenge strongly supports a causal association between atomoxetine and halitosis. Informed consent for publication was obtained from the patient's parents.

Following this clinical observation, a comprehensive literature search was conducted in the PubMed, Scopus, and Google Scholar databases using the keywords "atomoxetine," "halitosis," "oral malodor," "bad breath," "adverse effect," and "side effect," without time restrictions. No previous reports of atomoxetine-induced halitosis were identified in either pediatric or adult populations. To the best of our knowledge, this is the first documented case of atomoxetine-associated halitosis.

The Naranjo Adverse Drug Reaction Probability Scale yielded a score of 8, indicating a probable adverse drug reaction (4). Although halitosis is not listed among the known side effects of atomoxetine, this case suggests that it may represent a rare but clinically significant adverse effect. Because halitosis is not an immediately observable side effect and typically develops gradually after treatment initiation, it may be recognized some time after onset rather than during initial clinical observation. Such delayed recognition is consistent with the clinical course of the symptom and does not weaken the causal inference when temporal consistency is evident. In this case, the clinician directly observed the symptom during follow-up, and its prompt recurrence upon re-challenge further strengthened the causal association. Given the social and functional impact of halitosis in a child, as well as the importance of treatment adherence in long-term ADHD management, clinicians should remain alert to such atypical adverse events. Early recognition may prevent unnecessary investigations, facilitate timely intervention, and support individualized treatment decisions.

Atomoxetine was the first non-stimulant medication approved for the treatment of ADHD and remains an important option for patients who cannot tolerate stimulants, have contraindications, or are at risk of misuse (2). Although atomoxetine is widely used for ADHD and generally well tolerated, awareness of rare side effects such as halitosis is essential to maintain adherence and avoid unnecessary diagnostic procedures. Heightened recognition of atypical but clinically relevant adverse effects may enhance pharmacovigilance and assist clinicians in evaluating new-onset symptoms in children treated with psychotropic medications. Atomoxetine should be considered a potential cause of new-onset halitosis during treatment, particularly when no dental or metabolic abnormalities are identified and the symptom emerges shortly after treatment initiation.

Halitosis has previously been reported as a side effect of various medications. Among psychotropic agents, it has been described with imipramine and duloxetine (5). Both cases were reported in adult patients, and no additional contributing factors were identified. Interestingly, atomoxetine, imipramine, and duloxetine share two notable pharmacological properties. Firstly, they all function as norepinephrine reuptake inhibitors. Noradrenergic stimulation may contribute to halitosis by reducing salivary flow through increased sympathetic tone, altering salivary composition, inducing mucosal vasoconstriction, or affecting gastrointestinal motility. Moreover, xerostomia—a relatively common side effect of atomoxetine—may serve as an intermediary mechanism contributing to halitosis through reduced salivary secretion and oral dryness. However, in the present case, neither subjective complaints nor clinical signs of xerostomia were reported or observed during follow-up, suggesting that halitosis may occur independently of dry mouth. Secondly, all three medications are metabolized via cytochrome P450 2D6 (CYP2D6). In individuals with reduced CYP2D6 metabolic activity, accumulation of the drug or its metabolites may alter salivary composition, impair mucosal hydration, or affect gastrointestinal function—factors known to contribute to oral malodor (6,7). Given that duloxetine and imipramine—sometimes prescribed when ADHD is accompanied by comorbid mood or anxiety disorders—share pharmacodynamic and pharmacokinetic properties with atomoxetine, clinicians should remain alert to the possibility of similar adverse effects, such as halitosis, when prescribing these agents (2, 8).

This case highlights the importance of recognizing atypical adverse effects, such as halitosis, in children treated with atomoxetine for ADHD. Although rare, such reactions may negatively affect social functioning and treatment adherence, underscoring the need for careful pharmacovigilance in pediatric psychopharmacology. Clinicians should remain vigilant for unusual symptoms and consider drug-induced etiologies even in the absence of well-established side effect profiles. Further research is warranted to determine the prevalence and underlying mechanisms of this association.

Informed Consent: Written informed consent was obtained from the patient's parent.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: Not declared.

Peer-review: Externally peer-reviewed.

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DOI: 10.14744/DAJPNS.2026.00331
Dusunen Adam J Psychiatr Neurol Sci
2026;39:162-164

LETTER TO THE EDITOR

Brain zaps after antidepressant discontinuation: Heterogeneous responses across paroxetine, venlafaxine, and duloxetine—a three-case letter

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Dear Editor,

Antidepressant discontinuation syndrome encompasses a constellation of symptoms that may occur following the abrupt cessation or rapid dose reduction of serotonergic reuptake inhibitors, including selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) (1). Among these, "brain zaps" are particularly distinctive sensory phenomena, described by patients as sudden, electric shock-like sensations in the head, often triggered by head movements and capable of significantly impairing daily functioning (2). Prevalence estimates vary; recent meta-analyses suggest that approximately 15% of users experience general discontinuation symptoms (3). However, reliance on randomized controlled trial (RCT) samples may limit real-world generalizability and potentially underestimate prevalence in clinical settings (4). Key risk factors include the use of short half-life medications, such as paroxetine and venlafaxine, whereas fluoxetine is associated with a lower risk due to its prolonged elimination profile (5).

The first case involves a 35-year-old male with generalized anxiety disorder who had been treated with venlafaxine 150 mg/day for three years. This was his first attempt to taper the medication. The dose was gradually reduced over three months (150 mg/day to 112.5 mg/day, then to 75 mg/day). Two days after the final reduction to 37.5 mg/day in the third month, he developed electric shock-like sensations triggered by head movements, which he described as "an electrical cable snapping." These episodes lasted 1–3 seconds, occurred 25–30 times daily, and were accompanied by mild imbalance and nausea. Neurological examination revealed no focal deficits. An initial trial of fluoxetine 20 mg/day for four weeks yielded no improvement. Subsequently, short-term diazepam 5 mg/day was added, resulting in a marked reduction in symptoms within one week. Venlafaxine was discontinued in the second week, fluoxetine in the third, and diazepam in the fourth, with no recurrence at two-month follow-up. The Naranjo score was 4 (possible), and the presentation was consistent with acute withdrawal according to Chouinard's classification.

The second case is a 40-year-old female with major depressive disorder and comorbid anxiety who had received paroxetine 30 mg/day for five years. She had no prior discontinuation attempts. The dose was tapered from 30 mg/day to 20 mg/day in the first month. Upon reduction to 10 mg/day in the second month, she experienced electric sensations triggered by head movements, described as "lightning striking in my brain." These episodes lasted 1–2 seconds, occurred 15–20 times daily, and were accompanied by mild imbalance and transient

How to cite this article: Ileri Akdogan T. Brain zaps after antidepressant discontinuation: Heterogeneous responses across paroxetine, venlafaxine, and duloxetine—a three-case letter. Dusunen Adam J Psychiatr Neurol Sci 2026;39:162-164.

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Received: November 13, 2025; **Revised:** February 3, 2026; **Accepted:** February 21, 2026

Table 1: Total Naranjo Adverse Drug Reaction Probability Scale scores

Case	Drug	Naranjo score	Probability classification
Case 1	Venlafaxine	4	Possible
Case 2	Paroxetine	7	Probable
Case 3	Duloxetine	6	Probable

Adapted from Naranjo et al., Clin Pharmacol Ther. 1981;30(2):239–245 (8).

visual blurring. Neurological examination was unremarkable. Following complete discontinuation of paroxetine, fluoxetine 20 mg/day was initiated. She demonstrated significant improvement by the second week and achieved complete resolution by the fifth week. Fluoxetine was then gradually tapered and discontinued, with no recurrence at three-month follow-up. The Naranjo score was 7 (probable), and the presentation was consistent with acute withdrawal.

The third case concerns a 50-year-old male with generalized anxiety disorder who had been treated with duloxetine for 10 years (60 mg/day for the last five years). A previous tapering attempt two years earlier had failed due to electric shock sensations. Following clinical improvement, a dose reduction from 60 mg/day to 30 mg/day was attempted in the first month. On the second day, he developed electric shock-like sensations triggered by head movements, described as "an electrical current flowing through my brain." These episodes lasted 2–3 seconds, occurred 20–25 times daily, and were accompanied by mild imbalance. Neurological examination was normal. After one week of persistent symptoms, fluoxetine 20 mg/day was initiated. Symptoms persisted for another week before gradually resolving by the third week. Duloxetine was discontinued in the second week, and fluoxetine was continued for an additional two weeks before tapering. One-month follow-up revealed no recurrence. The Naranjo score was 6 (probable), consistent with acute withdrawal.

This three-case series demonstrates heterogeneous treatment responses across different antidepressants. Paroxetine showed a favorable response to fluoxetine bridging, venlafaxine was resistant to fluoxetine but responded to short-term diazepam, and duloxetine exhibited a delayed yet complete response to fluoxetine. These findings suggest that individualized treatment approaches may be necessary. Short-term benzodiazepines may be considered in selected resistant cases, with careful monitoring for risks such as dependence, sedation, and cognitive impairment. The observed variability in treatment response may reflect differences in pharmacodynamic profiles beyond pharmacokinetic properties. Paroxetine's selective serotonergic action responds predictably to serotonergic substitution, whereas venlafaxine's dual serotonergic-noradrenergic effects may render purely serotonergic substitution insufficient (6). For SNRIs, serotonergic substitution alone may inadequately address noradrenergic withdrawal components, potentially necessitating longer bridging periods, as observed with duloxetine (7). The limitations of this series include its small sample size, absence of placebo controls or rechallenge protocols, lack of biomarkers, and Naranjo scores within the "possible" to "probable" range (Table 1). Although the Naranjo scale is designed for adverse drug reactions, it was applied here in the absence of specific discontinuation assessment tools, warranting cautious interpretation. Furthermore, the absence of data on individual metabolic or genetic differences limits the generalizability of these findings. Future research should focus on larger, controlled studies to establish optimal management strategies for this clinically challenging phenomenon.

Informed Consent: Written informed consent for publication was obtained from all patients.

Conflict of Interest: The author declares that there is no conflict of interest.

Financial Disclosure: The author declared that this study has received no financial support.

Use of AI for Writing Assistance: AI-assisted language editing (ChatGPT, OpenAI) was used for linguistic refinement. All content was reviewed and verified by the author.

Peer-review: Externally peer-reviewed.

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DOI: 10.14744/DAJPNS.2026.00332
Dusunen Adam J Psychiatr Neurol Sci
2026;39:165-168

LETTER TO THE EDITOR

Secondary parkinsonism associated with tetrabenazine: A case report

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Dear Editor,

Tardive dyskinesia is a hyperkinetic movement disorder that usually emerges as a late complication of chronic dopamine D2 receptor antagonism. It typically presents with repetitive orofacial movements and is a common late-onset adverse effect of antipsychotic medications. Its pathophysiology involves postsynaptic dopamine receptor supersensitivity and dopaminergic imbalance (1).

Tetrabenazine, a vesicular monoamine transporter 2 (VMAT2) inhibitor, reduces synaptic dopamine release and is commonly used in the management of tardive dyskinesia. However, it may also induce depression, anxiety, or secondary parkinsonism, particularly in elderly or psychiatrically vulnerable individuals (2).

Here, we describe a rare case of tetrabenazine-induced secondary parkinsonism in an elderly woman with prior short-term antipsychotic exposure.

CASE REPORT

A 71-year-old woman was referred from the psychiatry outpatient clinic to the neurology outpatient clinic because of involuntary perioral movements, including jaw clenching and lip pursing, which worsened during speech. According to the available history, the symptoms emerged approximately two months after initiation of low-dose olanzapine (2.5 mg/day), risperidone (1 mg/day), and alprazolam (2.5 mg/day), prescribed in an outpatient psychiatric setting for bereavement-related anxiety and behavioral symptoms. A formal diagnosis of complicated grief was not established. Antipsychotics were prescribed empirically at low doses and introduced sequentially over a short period before referral. These medications were subsequently discontinued, and the patient was referred for neurological evaluation.

Her medical history included type 2 diabetes mellitus and hypertension. Current medications included insulin, sitagliptin/metformin, gliclazide, verapamil, and acetylsalicylic acid. She had no prior history of chronic psychiatric illness, long-term antipsychotic use, or exposure to other dopamine receptor-blocking agents such as metoclopramide. The recent two-month course of antipsychotic therapy represented her first exposure to antipsychotic medication. There was no history of extrapyramidal symptoms or tardive dyskinesia.

At the initial neurological examination, no bradykinesia, rigidity, or postural instability was detected, and the phenomenology of the movement disorder had not yet been fully characterized. Although the clinical picture was dominated by perioral hyperkinetic movements, an early

How to cite this article: Simar AS, Samanci MY, Zirh A, Helvaci Yilmaz N. Secondary parkinsonism associated with tetrabenazine: A case report. Dusunen Adam J Psychiatr Neurol Sci 2026;39:165-168.

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Received: October 31, 2025; **Revised:** May 07, 2026; **Accepted:** May 14, 2026

extrapyramidal syndrome related to recent dopamine receptor-blocking agent exposure was considered in the differential diagnosis. In this context, biperiden (2 mg twice daily) was initiated empirically. However, as the movements were subsequently recognized to be predominantly hyperkinetic and consistent with a tardive-type orofacial dyskinesia, and because no clinical benefit was observed, biperiden was discontinued after three weeks.

Approximately one month after the initial neurology evaluation, tetrabenazine was initiated at 25 mg twice daily for persistent involuntary movements. Partial symptomatic improvement was observed; however, depressive symptoms subsequently emerged, prompting the addition of sertraline (50 mg/day). Several weeks later, the tetrabenazine dose was reduced to 12.5 mg twice daily because of adverse effects. Lorazepam (1 mg/day) was introduced for accompanying anxiety symptoms.

Following the later emergence of generalized bradykinesia and jaw tremor, tetrabenazine was gradually reduced to 6.25 mg three times daily. Levodopa/benserazide (100/25 mg three times daily) was initiated as both a diagnostic and symptomatic trial to differentiate drug-induced parkinsonism from an underlying neurodegenerative parkinsonian disorder. The patient demonstrated minimal clinical improvement in parkinsonian features with levodopa. Treatment was continued temporarily during ongoing clinical evaluation and medication adjustments. Tetrabenazine was not immediately discontinued because of persistent hyperkinetic symptoms.

Cranial magnetic resonance imaging (MRI) was unremarkable. Dopamine transporter imaging (DaTSCAN) demonstrated normal presynaptic dopaminergic transporter activity, supporting a diagnosis of drug-induced secondary parkinsonism.

Several months later, tetrabenazine was discontinued because of supply limitations, while levodopa/benserazide was continued. During follow-up, psychiatric treatment adjustments were made by the psychiatry team in response to persistent and evolving depressive and anxiety symptoms. Treatment decisions, including initiation of sertraline and lorazepam, were based on clinical psychiatric assessment rather than standardized rating scales. At one stage, the regimen included clomipramine (25 mg three times daily), sertraline (50 mg/day), venlafaxine (225 mg/day), and alprazolam (1 mg/day), which were introduced sequentially rather than as part of a single planned combination. Given the patient's advanced age and cardiovascular comorbidities, such regimens required careful monitoring because of potential safety concerns and drug interactions.

During later follow-up, tetrabenazine was reinitiated at 25 mg/day.

At the most recent follow-up, involuntary movements had mildly worsened, whereas neuropsychiatric status remained stable. She continued treatment with tetrabenazine (6.25 mg three times daily), sertraline, and lorazepam, with doses adjusted as clinically indicated.

DISCUSSION

This case provides several clinically relevant insights. First, it highlights that even short-term, low-dose exposure to dopamine receptor-blocking agents in elderly patients may predispose to the development of tardive-type orofacial dyskinesia or related hyperkinetic syndromes. Second, it demonstrates the potential for sequential and overlapping drug-induced movement disorders, with initial hyperkinetic symptoms followed by hypokinetic features during VMAT2 inhibitor therapy. Third, it underscores the vulnerability of elderly patients to neuropsychiatric and motor adverse effects in the context of psychotropic polypharmacy. Finally, this case emphasizes the importance of individualized treatment strategies and close interdisciplinary collaboration in managing complex movement disorders accompanied by comorbid psychiatric symptoms.

Tardive dyskinesia is a well-recognized adverse effect of chronic dopamine D2 blockade. Its pathophysiology involves postsynaptic receptor upregulation and hypersensitivity, leading to involuntary orofacial movements (1). Tetrabenazine, a reversible VMAT2 inhibitor, depletes presynaptic dopamine by inhibiting vesicular uptake, thereby reducing hyperkinetic symptoms. However, because of its relatively short half-life (4-8 h), abrupt discontinuation or inadequate titration may result in fluctuating dopaminergic activity and symptom recurrence. In our patient, symptom recurrence following drug discontinuation may reflect a pharmacodynamic rebound phenomenon; however, this interpretation should be made cautiously, as concurrent medication changes and the absence of standardized objective measures limit causal inference. Additionally, VMAT2 inhibition may affect other monoamines, including serotonin and gamma-aminobutyric acid (GABA), contributing to neuropsychiatric adverse effects such as depression and anxiety (3). This underscores the importance of concurrent psychiatric monitoring and the potential

need for adjunctive treatment with selective serotonin reuptake inhibitors or benzodiazepines, as demonstrated in this case.

Secondary parkinsonism resulting from pharmacological dopamine depletion must be distinguished from idiopathic Parkinson's disease. In this case, the limited clinical response to levodopa, together with normal DaTSCAN findings and the temporal association with tetrabenazine exposure, supported a diagnosis of drug-induced secondary parkinsonism. In a cohort of 526 patients, Jankovic et al. (4) reported that 28.5% of patients with hyperkinetic disorders developed parkinsonism during tetrabenazine treatment. Reported risk factors include advanced age, prior dopamine antagonist exposure, and individual susceptibility (5).

Newer VMAT2 inhibitors such as deutetrabenazine and valbenazine offer improved pharmacokinetic profiles. Deutetrabenazine, through deuterium substitution, exhibits a prolonged half-life and reduced peak-to-trough fluctuations, while valbenazine offers once-daily dosing with selective VMAT2 inhibition and minimal off-target receptor binding. These pharmacological advantages may reduce the risk of neuropsychiatric side effects and drug-induced parkinsonism, particularly in elderly populations. In this context, the adverse effects observed in our patient during tetrabenazine therapy might have been mitigated through the use of newer VMAT2 inhibitors (6-9).

Differentiating tardive dyskinesia from drug-induced parkinsonism is clinically important, as these conditions differ in pathophysiology, phenomenology, and management. Tardive dyskinesia typically presents with hyperkinetic, non-rhythmic choreiform, athetoid, or stereotyped movements, particularly in the orofacial region, whereas drug-induced parkinsonism manifests with hypokinetic features such as bradykinesia, rigidity, and rhythmic tremor. In this case, the initial presentation of isolated orofacial hyperkinetic movements without parkinsonian signs suggested a tardive-type process, whereas the later emergence of generalized bradykinesia and jaw tremor during tetrabenazine therapy supported secondary drug-induced parkinsonism (10).

The diagnosis of tardive dyskinesia in this case should be interpreted cautiously, given the relatively short duration and low dose of antipsychotic exposure. Alternative drug-induced movement disorders were considered in the differential diagnosis, including acute drug-induced dyskinesia and withdrawal-emergent dyskinesia (11). Acute dyskinesias typically occur shortly after drug initiation and are often transient, whereas withdrawal-emergent dyskinesia usually develops following dose reduction or discontinuation and tends to resolve within weeks. In contrast, the movements in our patient were predominantly stereotyped and orofacial in distribution and persisted beyond discontinuation of dopamine receptor-blocking agents, favoring a tardive-type process. Therefore, a cautious interpretation as a probable or early tardive syndrome appears most appropriate.

An important limitation of this case is the presence of extensive psychotropic polypharmacy. The concurrent use of multiple agents may have influenced both motor and neuropsychiatric symptoms through complex dopaminergic and non-dopaminergic interactions. Consequently, clinical changes cannot be attributed with certainty to a single agent. Additionally, the absence of standardized psychiatric rating scales represents a limitation, as symptom severity and treatment response were assessed primarily on the basis of clinical judgment.

In conclusion, tetrabenazine is an effective treatment for hyperkinetic movement disorders but may induce reversible secondary parkinsonism, particularly in elderly patients with prior dopamine antagonist exposure. This case highlights the importance of careful medication selection, close monitoring, and individualized management strategies. It also underscores the need to consider diagnostic complexity and potential confounding factors in patients receiving multiple psychotropic medications.

Informed Consent: Written informed consent was obtained from the patient.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

Peer-review: Externally peer-reviewed.

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Tables should present information concisely and effectively, allowing data to be displayed with clarity and precision. Presenting data in tables rather than in the text often reduces the overall manuscript length. Each table must appear on a separate page with a descriptive title. Column or row headings should be short and specific, and any explanatory notes should be placed as footnotes—not within the heading. All nonstandard abbreviations and statistical measures of variation (e.g., standard deviation, standard error) should be defined in footnotes. Line spacing for tables should be double-spaced, and the maximum allowable size is 120 characters in width and 70 lines in length.

When materials such as tables, figures, or images are reproduced from another source, written permission from the copyright holder must be obtained, and the source must be appropriately cited in the text. Legends must be provided for all figures. Figure legends should be concise yet specific and must be listed together on a separate page at the end of the main manuscript text.

All figures should be submitted as separate high-quality digital files in JPEG format through the online submission system, in addition to being included at the end of the main document with their corresponding legends. Electronic images (e.g., photographs, radiographs, CT scans) must have a minimum resolution of 300 dpi to ensure print quality.

4.3.4. Author Contribution Form

This form must clearly specify the individual contributions of each author according to the ICMJE criteria. Each author should have participated in the conception, design, data acquisition, analysis, and/or interpretation, as well as in drafting or revising the manuscript and approving its final version. Authors who do not meet all authorship criteria should be listed in the acknowledgments section.

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This form confirms that the submitted manuscript is original, unpublished, and not under consideration elsewhere. It also verifies that all authors approve the submission and agree to transfer the copyright to Dusunen Adam Journal of Psychiatry and Neurological Sciences under the CC BY-NC 4.0 license. The form must be signed by all authors before publication.

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All authors must disclose any financial, institutional, or personal relationships that could be perceived as influencing the research. If no conflicts exist, this must be explicitly stated. The form also includes a section for declaring financial support or grants related to the study.

4.4. Manuscript Types

Dusunen Adam Journal of Psychiatry and Neurological Sciences accepts various types of submissions, including research articles, brief reports, systematic reviews and meta-analyses, and letters to the editor. Guest editorials are accepted by invitation only. Authors are encouraged to select the manuscript type that best represents the scope, design, and contribution of their study. The specific structure, length, and formatting requirements for each manuscript type are detailed below.

4.4.1. Research Articles

Research articles present substantial and original scientific findings within the scope of the journal. Each research article should contain an abstract, keywords, introduction, methods, results, discussion, conclusion, references, and tables or figures. The abstract and main text must follow the structured format described above. Ethics committee approval and informed consent information must be obtained and clearly stated in the manuscript.

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Brief reports follow the same general format and guidelines as research articles but focus on small-scale studies or research in early stages of development. They may include preliminary investigations with simple research designs or small sample sizes that provide initial findings and pilot data suggesting the need for further research. Ethics committee approval and informed consent information should also be obtained and clearly stated in the manuscript.

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Table: Manuscript types and corresponding word, abstract, reference, and table/figure

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table/ figure limit (total)
Research article	3500	250 (*structured*)	50	6
Systematic reviews and meta-analyses	4000	250	No limit	10
Brief report	1500	250 (*structured*)	15	2
Letter to the editor	750	No abstract	10	1
Guest editorial	1200	No abstract	20	2

Information For Reviewers

1. GENERAL INFORMATION

Dusunen Adam Journal of Psychiatry and Neurological Sciences publishes high-quality research and scholarly work in psychiatry, neurology, clinical psychology, and neuroscience. The journal promotes interdisciplinary perspectives on mental health and brain sciences and prioritizes studies offering novel insights with clear relevance to clinical practice.

The journal accepts submissions in the following categories:

- Research articles
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- Systematic reviews and meta-analyses
- Letters to the editor
- Guest editorials (invited, not peer-reviewed)

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- Clearly identify major and minor issues, suggesting ways to strengthen the study.
- Conclude with a clear recommendation: accept, revise, or reject.
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Before submitting your review, ensure that you have considered:

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Journal of Psychiatry and Neurological Sciences

Volume: 39, Number: 2, June 2026

GUEST EDITORIAL

RESEARCH ARTICLES

LETTERS TO THE EDITORS