



## RESEARCH ARTICLE

# Evaluation of resilience, quality of life, and depression in family members of alcohol or substance dependent patients

Guliz Senormanci<sup>1</sup>, Elif Esmen<sup>2</sup>, Cetin Turan<sup>1</sup>, Omer Senormanci<sup>1</sup>

<sup>1</sup>University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital, Department of Psychiatry, Bursa - Turkey

<sup>2</sup>University of Health Sciences Erenkoy Mental Health and Neurological Diseases Training and Research Hospital, Department of Psychiatry, Istanbul - Turkey

### ABSTRACT

**Objective:** The aim of this study was to compare resilience, quality of life, and depression levels in family members of patients suffering from dependence with a control group and to assess the relationship between resilience, quality of life, depression, and clinical features in family members.

**Method:** The sample consisted of 41 female participants who had a family member with a history of at least one year of alcohol or substance dependence with outpatient and/or inpatient treatment and 41 female participants with no history of psychiatric admission or treatment matched to the family members by age, length of education, and marital status. Written informed consent was obtained from all participants and a sociodemographic data form, the Resilience Scale for Adults (RSA), the Short Form-36 (SF-36), and the Beck Depression Inventory (BDI) were administered.

**Results:** Levels of resilience and quality of life were lower and levels of depression were higher in family members of alcohol or substance-dependent individuals compared to the control group. Depression scores were negatively correlated with resilience and quality of life scores. Resilience was positively correlated with all subscale scores for quality of life except general health. In family members, there were positive correlations between the duration of dependence and the scores on the family cohesion subscale and between the number of substance withdrawal periods and structured style subscale scores. With regard to family members' resilience and quality of life, levels in siblings were higher compared to those of mothers and spouses, whereas the depression levels were higher in mothers compared to siblings of alcohol or substance-dependent patients. There was no difference between the scores for the family cohesion dimension among family members.

**Conclusion:** Strengthening resilience is important for understanding, preventing, and treating psychiatric conditions. Resilience is a dynamic concept that can be learned and improved; therefore, resilience-enhancing programs may be beneficial in improving the quality of life and alleviating the level of depression in family members of dependent patients.

**Keywords:** Dependence, depression, quality of life, resilience

## INTRODUCTION

Dependence is a chronic disease progressing through episodes of relapse and recovery. Patients who give up

substance use may relapse into their habit especially during the first year of abstinence (1). Relapse rates of dependence and complications are similar to those in other chronic diseases like type 2 diabetes mellitus,

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**Correspondence:** Guliz Senormanci, University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital, 16240, Nilüfer, Bursa - Turkey

**Phone:** +90 224 800 21 00 **E-mail:** gulizsenormanci@yahoo.com

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hypertension, or asthma. Therapeutic approaches recommended for this type of chronic diseases, including continuous medical follow-up after recovery with regular screenings to notice relapses at an early stage have also been suggested for dependence (2). Family members play a central role in the lives of many persons suffering from dependency and over the years help filling the gaps in the healthcare system in assuring the continuity of treatment (3).

Due to the significant burden on their family, patients addicted to alcohol or substances have a negative impact on their family members' functionality (4). These family members have significantly more medical problems than comparable individuals with no addicted person in their family (5).

Psychological resilience has been defined as a person's ability to recover from difficult life experiences (6). This concept expresses the personal adaptation process when encountering stressful events, significant adversity, or traumas (7). It means being able to return to a level of functioning like that before the adverse experience (8) or to reach a relatively good adaptation despite risky experiences that might have caused more serious consequences (9). The individual can achieve adequate functioning with a balance in the relation between protective and risky or potentially detrimental factors (10). Resilience is a multidimensional concept, related not only with individual characteristics, abilities, and skills, but also with family support and other external support systems (11).

A number of issues such as material problems caused by the addiction, domestic violence, and disputes in the family expose the other family members to severe stress (12).

Masten (13) defined resilience as the capacity of a dynamic system to withstand or recover from significant challenges that threaten its stability, viability, or development. The resilience of the caregiver, apart from coping with the daily burden brought by the psychiatrically ill family member, is related with being a more flexible and healthy person (14). Data in the literature regarding the family members of addicted persons and resilience are very limited. A study with the wives of male alcohol addicts found that with increasing duration and severity of the dependence, resilience decreased (15). Another study with the wives of male alcohol addicts found anxiety or depressive disorder in most participants (16).

The quality of life of individuals with family members suffering from a chronic psychiatric disease tends to suffer due to the burden and stress they

experience (17). A correlation between an increase in resilience scale scores and a rise in quality of life scores has been found in psychiatric patients as well as in healthy volunteers (18). An increase in resilience is related with a reduction in depression level and a better quality of life (19).

Complications caused by addiction lead to distress in the family and affect family members psychologically. Studies in the literature mostly focus on the predictive power of the attitude of addicted patients' parents for the development of dependence in their children. There are relatively few studies looking at the mental state of family members (20). As far as we are aware, there are no studies examining the relation between resilience and quality of life and depression in the patients' family members.

Our study aimed at a comparison between female family members of alcohol or substance-dependent patients with a control group regarding resilience, quality of life, and depression levels and to research the relation of resilience, quality of life, and depression with clinical characteristics in the family member group.

## METHOD

This study was carried out at the Treatment Center for Alcohol and Substance Dependence of Bursa Advanced Specialist Training and Research Hospital of the Health Sciences University. The sample consisted of 41 female family members of in- or outpatients with a history of at least 1 year of alcohol or substance dependence and a control group of 41 women with no history of psychiatric presentations, matched to the group of patient relatives by age, education level, and civil status.

Inclusion criteria were voluntary participation, an age of 18 and above, having sufficient mental capacities to fill in the self-report scales used in the study, and providing written consent. Tests were administered in a single session in random order. The local ethics committee approved the study under protocol number KAEK-25 2018/10-17.

### Measures

**Sociodemographic data form:** Prepared by the researchers, this form included questions relating to the aim of the study.

**Resilience Scale for Adults (RSA):** This self-report scale was developed by Friberg et al. (21) and adapted to Turkish by Basim and Cetin (6). It is used to measure resilience-related protective factors in adults. The scale includes 33 items with 5 separate numbered boxes in a

Likert-like fashion. It consists of 6 subdimensions: "perception of self," "perception of future," "structured style," "social competence," "family cohesion," and "social resources." Perception of self includes a person's strengths, competences, and trust in self-sufficiency. The subdimension perception of future regards believes to be able to realize future plans and aims. Structured style assesses an individual's ability to plan and to maintain and organize daily tasks. The subdimension social competence consists of questions regarding a person's extroversion, sociability, and social adaptation. Family cohesion aims at assessing the support received from other family members and cohesion and shared values between family members. Social resources, finally, consists of questions related with the support a person receives from significant individuals outside the core family, such as relatives or friends (21).

**Short Form-36 (SF-36):** This form, developed by Ware and Sherbourne (22) mainly to assess the quality of life in patients with physical ailments, is the most commonly used instrument to measure this dimension. There is no total score for the scale; rather, total scores are calculated for the 8 subdimensions "physical function," "social function," "limitations in physical role," "limitations in emotional role," "mental health," "vitality," "bodily pain," and "general health perception." A validity and reliability study for the Turkish version of the scale has been carried out by Kocyigit et al. (23).

**Beck Depression Inventory (BDI):** This scale was developed by Beck et al. (24) to establish the depression risk and to measure the course of the level and severity of depression symptoms. A validity and reliability study for Turkey was performed by Hisli (25).

### Statistical Analysis

Study results were evaluated using SPSS version 18 for Windows. Continuous variables were tested for normal distribution using Shapiro-Wilk test. In comparing between groups, continuous variables conforming to the assumption of parametric tests were evaluated with Student's t test and one-way analysis of variance (ANOVA), while those not conforming to the parametric test assumption were assessed with Mann-Whitney U-test. For the groupwise comparison of categorical variables, Fisher's exact test was used. To establish correlations between scales, Pearson correlation analysis was used for continuous variables conforming to the parametric test assumption. Numeric values are presented as mean±standard deviation (SD) or median (min-max), categorical variables as number

of observations and percentage (n-%). In this study, a value for  $p < 0.05$  was considered statistically significant for the comparisons.

## RESULTS

The age at onset of dependence for the alcohol- or substance-dependent patients was  $30.6 \pm 11.1$  years. All of the dependent patients were consuming the respective substance orally or by inhaling. The duration of alcohol or substance use was  $6.3 \pm 5.0$  years, with  $1.9 \pm 2.3$  attempts at quitting and 1 episode (0-6) of hospitalization at AMATEM. Of the dependent patients, 23 (56.1%) used multiple substances, 10 (24.4%) methamphetamine, and 8 (19.5%) alcohol. Sixteen patients (39%) had experienced legal problems due to their substance use, while 25 patients (61%) had never encountered any legal issues. Ten patients (24.4%) had a history of attempted suicide, while 31 patients (75.6%) had no such history. Of the patient relatives, 15 (36.6%) were mothers, 12 (29.3%) spouses, and 14 (34.1%) siblings.

There was no statistically significant difference between the family members group and the control group regarding age, years of education, civil status, and employment status ( $p > 0.05$ ). The BDI score in the family members group was significantly higher than in the control group ( $p < 0.05$ ). The RSA total score and all subscale scores as well as SF-36 scores for all subscales in the control group were significantly higher than in the family members group ( $p < 0.05$ ). The comparison of sociodemographic data and BDI, RSA, and SF-36 scores between the groups is reported in Table 1.

For the family members, RSA total and subscale scores were generally positively related with the SF-36 subscale scores, while both scores were negatively related with the BDI. Correlations of BDI, RSA, and SF-36 scores in the family members group are shown in Table 2.

### Correlation of RSA, BDI, and SF-36 Scores with Clinical Variables in the Family Members Group

Correlations of the RSA, BDI, and SF-36 scores with clinical variables of the dependent patients have been statistically evaluated and those that were found to be significant are reported below.

A moderate level of negative correlations was found for the age at onset of dependence with RSA perception of self ( $r = -0.52$ ,  $p < 0.001$ ), RSA perception of future ( $r = -0.56$ ,  $p < 0.001$ ), RSA structured style ( $r = -0.53$ ,  $p < 0.001$ ), RSA social competence ( $r = -0.60$ ,  $p < 0.001$ ), RSA total

**Table 1: Comparison of sociodemographic data and BDI, RSA, and SF-36 scores between groups**

	FM-ASD (n=41)		HC (n=41)		t/z	df	p
	Mean/(Min-Max)/n	SD/Median (%)	Mean/(Min-Max)/n	SD/Median (%)			
<b>Age<sup>+</sup></b>	36.9	10.3	35.3	9.1	0.745	80	0.459
<b>Years of education<sup>**</sup></b>	8 (5-15)		8 (5-17)		-1.014	1	0.311
<b>Civil status<sup>***</sup></b>							
Married	32	78%	31	75.6%			0.999
Single	9	22%	10	24.4%			
<b>Employment status<sup>***</sup></b>							
Working	14	34.1%	17	41.5%			0.649
Not working	37	65.9%	24	58.5%			
<b>BDI<sup>+</sup></b>	25.2	15.1	6.8	5.0	7.372	48.859	<0.001
<b>RSA perception of self<sup>+</sup></b>	20.6	6.3	24.4	3.8	-3.271	66.071	0.002
<b>RSA perception of future<sup>+</sup></b>	12.6	5.1	16.2	3.3	-3.798	68.582	<0.001
<b>RSA structured style<sup>+</sup></b>	13.7	3.7	16.0	3.2	-2.985	80	0.004
<b>RSA social competence<sup>+</sup></b>	21.5	6.9	25.0	4.2	-2.682	65.891	0.009
<b>RSA family cohesion<sup>+</sup></b>	21.5	5.4	24.5	4.8	-2.661	80	0.009*
<b>RSA social resources<sup>+</sup></b>	26.1	7.7	30.4	3.6	-3.207	57.082	<0.001*
<b>RSA total<sup>+</sup></b>	116.3	30.3	136.8	16.4	-3.804	61.621	<0.001*
<b>SF-36 physical function<sup>+</sup></b>	68.6	37.4	91.2	12.2	-3.665	48.437	0.001*
<b>SF-36 role limitations (physical)<sup>+</sup></b>	59.1	43.2	79.2	26.1	-2.551	65.850	0.013*
<b>SF-36 bodily pain<sup>+</sup></b>	71.7	23.9	81.4	13.5	-2.246	63.222	0.028*
<b>SF-36 general health<sup>+</sup></b>	56.9	17.6	69.2	17.3	0.507	80	0.015*
<b>SF-36 role limitations (emotional)<sup>+</sup></b>	49.5	44.1	82.9	29.9	-4.000	70.331	0.013*
<b>SF-36 vitality (vitality)<sup>+</sup></b>	38.5	24.9	66.7	16.6	-6.026	69.696	<0.001*
<b>SF-36 mental health<sup>+</sup></b>	45.3	20.9	70.5	14.9	-6.268	80	<0.001*
<b>SF-36 social function<sup>+</sup></b>	58.7	23.6	78.5	19.9	-4.103	80	<0.001

<sup>+</sup>Student's t test, <sup>\*\*</sup>Mann-Whitney U test, <sup>\*\*\*</sup>Fisher's exact test, BDI: Beck Depression Inventory, RSA: Resilience Scale for Adults, SF-36: Short Form-36, FM-AS: Family members of alcohol- or substance-dependent patients, HC: Healthy controls

**Table 2: Correlations of BDI, RSA, and SF-36 scores in the group of family members**

	BDI	RSA PS	RSA PF	RSA SS	RSA SC	RSA FC	RSA SR	RSA total
<b>BDI</b>		-0.49*	-0.60*	-0.49*	-0.63*	-0.25	-0.54*	-0.59*
<b>SF-36 PF</b>	-0.73*	0.55*	0.50*	0.42*	0.58*	0.32*	0.61*	0.61*
<b>SF-36 RL (physical)</b>	-0.64*	0.53*	0.44*	0.41*	0.51*	0.23*	0.51*	0.53*
<b>SF-36 BP</b>	-0.64*	0.55*	0.44*	0.43*	0.51*	0.28*	0.55*	0.56*
<b>SF-36 GH</b>	-0.54*	0.33*	0.29*	0.03	-0.03	-0.14	-0.12	-0.06
<b>SF-36 RL (emotional)</b>	-0.73*	0.52*	0.52*	0.46*	0.55*	0.32*	0.58*	0.60*
<b>SF-36 V</b>	-0.73*	0.57*	0.67*	0.50*	0.54*	0.38*	0.57*	0.65*
<b>SF-36 MH</b>	-0.71*	0.51*	0.62*	0.47*	0.59*	0.35*	0.52*	0.61*
<b>SF-36 SF</b>	-0.55*	0.31*	0.28*	0.27*	0.31*	0.05	0.28*	0.30*

Pearson correlation analysis, \*p<0.05, BDI: Beck Depression Inventory, RSA PS: Resilience Scale for Adults perception of self, RSA PF: Resilience Scale for Adults perception of future, RSA SS: Resilience Scale for Adults structured style, RSA SC: Resilience Scale for Adults social competence, RSA FC: Resilience Scale for Adults family cohesion, RSA SR: Resilience Scale for Adults social resources, SF-36 PF: Short Form-36 physical function, SF-36 RL (physical): Short Form-36 role limitations (physical), SF-36 BP: Short Form-36 bodily pain, SF-36 GH: Short Form-36 general health, SF-36 RL (emotional): Short Form-36 role limitations (emotional), SF-36 V: Short Form-36 vitality, SF-36 MH: Short Form-36 mental health, SF-36 SF: Short Form-36 social function

**Table 3: Comparison of BDI, RSA, and SF-36 scores between mothers, spouses, and siblings**

	Mothers (n=15)		Spouses (n=12)		Siblings (n=14)		f	df	p
	Mean	SD	Mean	SD	Mean	SD			
<b>BDI</b>	35.2	12.5	24.3	14.1	15.2	12.0	8.733	2	0.001
<b>RSA perception of self</b>	17.3	7.0	21.4	5.5	23.5	4.7	4.172	2	0.023
<b>RSA perception of future</b>	9.2	5.5	12.5	3.8	16.3	2.6	9.983	2	<0.001
<b>RSA structured style</b>	11.4	3.4	14.2	3.7	15.7	2.8	6.204	2	0.005
<b>RSA total</b>	102.0	31.8	116.5	29.8	131.5	22.4	3.918	2	0.028
<b>SF-36 bodily pain</b>	53.0	21.5	78.7	17.6	85.8	18.1	11.597	2	<0.001
<b>SF-36 role limitations (emotional)</b>	22.2	32.5	50.0	43.8	78.5	38.3	7.936	2	0.001
<b>SF-36 vitality</b>	24.0	20.9	33.3	18.7	58.5	20.8	11.031	2	<0.001
<b>SF-36 mental health</b>	34.4	19.5	44.6	16.3	57.7	20.1	5.519	2	0.008

One-Way ANOVA test, BDI: Beck Depression Inventory, RSA: Resilience Scale for Adults, SF-36: Short Form-36

**Table 4: Pairwise group comparison of BDI, RSA, and SF-36 scores**

	Mother x spouse, p	Sibling x mother, p	Spouse x sibling, p
<b>BDI</b>	0.086	<0.001	0.189
<b>RSA perception of self</b>	0.189	0.019	0.627
<b>RSA perception of future</b>	0.125	<0.001	0.076
<b>RSA structured style</b>	0.094	0.004	0.481
<b>RSA total</b>	0.396	0.021	0.377
<b>SF-36 bodily pain</b>	0.004	<0.001	0.619
<b>SF-36 role limitations (emotional)</b>	0.157	0.001	0.150
<b>SF-36 vitality</b>	0.469	<0.001	0.009
<b>SF-36 mental health</b>	0.350	0.006	0.199

Tukey's test, BDI: Beck Depression Inventory, RSA: Resilience Scale for Adults, SF-36: Short Form-36

( $r=-0.54$ ,  $p<0.001$ ), SF-36 bodily pain ( $r=-0.58$ ,  $p<0.001$ ), and SF-36 role limitations (emotional) ( $r=-0.60$ ,  $p<0.001$ ). A low-to-moderate level of negative correlations was found for age at onset of dependence with RSA social resources ( $r=-0.46$ ,  $p=0.002$ ), SF-36 physical function ( $r=-0.46$ ,  $p=0.002$ ), SF-36 role limitations (physical) ( $r=-0.43$ ,  $p=0.004$ ), SF-36 vitality ( $r=-0.43$ ,  $p=0.005$ ), SF-36 social function ( $r=-0.44$ ,  $p=0.004$ ), and SF-36 mental health ( $r=-0.35$ ,  $p=0.021$ ). A moderate level of positive correlation was found for age at onset of dependence and BDI ( $r=0.50$ ,  $p=0.001$ ).

A low-to-moderate level of positive correlation was found between duration of substance use and RSA family cohesion ( $r=0.41$ ,  $p=0.007$ ) as well as for the number of attempts at quitting and RSA structured style ( $r=0.42$ ,  $p=0.006$ ).

When comparing depression, resilience, and quality of life of alcohol and substance-dependent patients' mothers, spouses, and siblings by ANOVA and Tukey's test, mothers' BDI scores were significantly higher than siblings' ( $p<0.05$ ); siblings' RSA perception of self, RSA

perception of future, RSA structured style, RSA total, SF-36 role limitations (emotional), and SF-36 mental health scores were significantly higher than mothers' ( $p<0.05$ ); SF-36 bodily pain scores in siblings were significantly higher than in mothers and spouses ( $p<0.05$ ), and SF-36 vitality scores in siblings were significantly higher than in mothers and in spouses ( $p<0.05$ ). Comparison of BDI, RSA, and SF-36 scores between mothers, spouses, and siblings is provided in Table 3 and pairwise group comparison of BDI, RSA, and SF-36 scores in Table 4.

Student's t test was used to compare family members' SF-36 role limitations (physical) score according to the presence of a history of suicide attempts in the alcohol- or substance-dependent patients, finding a significantly higher SF-36 role limitations (physical) score in family members of patients with no history of suicide attempts than in family members of patients who had attempted suicide ( $p=0.003$ ,  $t=-3.185$ ). Comparing family members' SF-36 bodily pain scores according to the presence of suicide

attempts in the patients by Student's *t* test, the score was significantly higher in relatives of patients with no history of suicide attempts ( $p=0.001$ ,  $t=-3.432$ ), as was the SF-36 social function score ( $p=0.007$ ,  $t=-2.831$ ).

## DISCUSSION

In our study, we found a significantly elevated level of depression in family members of patients compared to the control group. Individuals caring for chronic psychiatric patients are exposed to chronic stress, and a high depression level has been found in 40-70% (26,27). The patient groups examined in these studies showed chronic and destructive characteristics, and in contrast with our sample, relatives also had the role of caregiver. A study using a similar method to ours to assess family members of alcohol- or substance-dependent patients found an increase in depression scores both on BDI and on the Symptom Checklist (SCL-90-R) (20).

Our study found lower values for family members in resilience total and subscale scores and quality-of-life subscale scores compared to the control group. This difference may be generated by the burden and exhaustion caused by having an alcohol- or substance-dependent patient in the family. In our study, we found a negative correlation of resilience and quality-of-life scores with depression scores. In general, resilience and depression are found to be negatively correlated in persons giving care to patients with serious chronic diseases (28). A study with spouses of alcohol-dependent persons also found an inverse correlation between depression and resilience, which the authors established to be related with hopelessness and a negative development of the clinical course of dependence (15). Caregivers' quality-of-life scores, too, have been seen to be negatively correlated with depression scores (29).

In our study, with the exception of general health, which evaluates the perception of general health, family members' quality-of-life scores were positively related with resilience subscales and total scores. Resilient persons attempt active coping strategies when dealing with difficult conditions and use social and professional support and social activities more effectively (30). Studies with a variety of different samples also found similar positive relations between resilience and quality of life (18,19,31,32).

In our study, with increasing duration of substance use we found a rise in resilience family cohesion scores, which may indicate that family relations among relatives of alcohol- or substance-dependent patients

over time adapt to the new situation; in addition, resilience might develop as a protective factor in the coping process of the family dimension. A study evaluating the intercultural validity of the RSA found depression and anxiety symptom levels to be negatively correlated with all subscale scores except for family cohesion and with the resilience total score (33). A study in Turkey examining resilience in patients with depression found family cohesion and social resources in patients to be similar to healthy controls, in contrast to resilience total score and all other subscales (34). In our study, family cohesion scores in relatives of alcohol- or substance-dependent patients tended to be lower than in healthy controls, while they increased with the duration of substance use. In contrast with resilience total scores and all other resilience subscores, family cohesion scores have been found to be uncorrelated with depression scores and social function scores. Due to our cross-sectional approach, correlations between two variables cannot be interpreted as causal relations; however, given that resilience is a dynamic concept, comprising the possibility of improvement, that is not limited to personal skills or abilities but includes family support and other external support systems, it is likely that the family dimension of resilience over time develops in a way that increases resilience overall. Resilience differs from family to family and from culture to culture; it may even vary for the same person when being exposed to different stressors (35). RSA is related with protective factors in resilience (33).

Our study established a negative correlation between age at onset of dependence and all resilience subscales except for family cohesion and with the resilience total score. A study with spouses of persons with alcohol abuse or dependence, in contrast with our study, found no correlation between age at onset of dependence or age at first consumption of alcohol and spouses' resilience (36). Another study with spouses of alcohol- or heroin-dependent individuals also found no significant level of correlation between burden on the caregiver and age at onset (35).

The higher resilience structured style score according to the number of attempts at quitting substance use might be related with family members being more playful, thus encouraging the dependent patient to seek therapy, or learning to be more playful over time during the quitting and resumption process (11).

In siblings, resilience and quality-of-life scores were significantly higher than in spouses and mothers, while depression scores in mothers were significantly higher than in siblings, which might be related with the quality

of the relation with the dependent patient. In persons caring for alcohol- and substance-dependent patients, no difference was found in the resilience family cohesion scores, which are thought to be culture-specific. Whoever the carer may be, this situation, is related with family ties, relations, and being close (33).

In family members of alcohol- or substance-dependent patients who had attempted suicide, scores for quality of life limitations (physical), bodily pain, and social function were significantly lower than in those with no history of their relative's suicide attempt. Possibly, patients with suicide attempts may have had psychiatric comorbidities such as severe episodes of depression or a more serious level of dependence and life events secondary to dependence in the past. Due to physical and emotional problems, family members exposed to alcohol- or substance-dependent patients with a history of attempted suicide may have experienced problems at work or in other settings as a result of limitations in their social relations, complaints of bodily pain, and impaired physical health.

Our study has certain limitations: We used a cross-sectional approach, and the study was carried out at a single center and only with female family members. As the number of participants was relatively low, the number of persons per group in the statistical analysis is small. While the SF-36 is an instrument more geared towards measuring the quality of life of physically ill persons, it is also being used in studies with caregivers of patients with psychiatric and other medical conditions (37,38). Studies using other instruments to measure the quality of life with participants of both sexes and a larger sample would be desirable.

Understanding resilience is important for understanding, preventing, and treating psychiatric problems. Resilience is a concept that can be learned and developed; programs developing resilience can be useful in improving the quality of life and the level of depression (28,39).

Contribution Categories		Author Initials
Category 1	Concept/Design	G.S., O.S.
	Data acquisition	E.E., C.T.
	Data analysis/Interpretation	G.S., O.S.
Category 2	Drafting manuscript	G.S., C.T., O.S.
	Critical revision of manuscript	G.S., E.E., C.T., O.S.
Category 3	Final approval and accountability	G.S., E.E., C.T., O.S.
Other	Technical or material support	None
	Supervision	None

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**Informed Consent:** Written informed consent was obtained from the participants.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** All authors declare that they have no conflicts of interest.

**Financial Disclosure:** None declared.

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