Research Article

Depressive and Anxiety Symptoms in Patients with Fuchs Endothelial Corneal Dystrophy: A Cross-Sectional Study Psychological Burden in FECD Patients

Constantin Niederau MD[1,2], Philomena Alice Wawer-Matos Reimer, MD[1,2], Sina Jo Fischer[1], Johanna Wiedemann, MD[1], Michael Simon, MD[1,2], Katrin Löw, MD[1], Philip Zeyen, MD[3], Ludwig Heindl, MD, PhD[1,2,4], Alexander Rokohl, MD[1,2,4]

[1]Department of Ophthalmology, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany

[2]Center for Integrated Oncology (CIO), Aachen-Bonn-Cologne-Duesseldorf, Cologne, Germany

[3]Department of Psychiatry and Psychotherapy, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany

[4]Center for Anatomy and Cell Biology, Institute of Anatomy and Cell Biology-Salzburg, Paracelsus Medical University, Salzburg, Austria

*Corresponding Author: Constantin Niederau, Department of Ophthalmology, Faculty of Medicine and University Hospital Cologne, University of Cologne Kerpener Str. 62, 50937 Köln, Deutschland.

Abstract

Purpose: To investigate the psychological burden of patients with Fuchs endothelial corneal dystrophy (FECD) regarding depressive and anxiety symptoms using highly validated questionnaires, to identify associated factors, and reveal potential gaps in medical care. **Methods:** A total of 140 patients with FECD were assessed using the 9-item Patient Health Questionnaire (PHQ-9) and the 7-item Generalized Anxiety Disorder Scale (GAD-7). Scores were correlated with Hospital Anxiety and Depression Scale (HADS), Short Form 12 Health Survey (SF-12), and demographic and clinical factors. **Results:** Depressive symptoms were present in 41 patients (29.3%), and anxiety symptoms in 35 patients (25%), exceeding prevalences reported for the German population (20.76% and 18.5%, respectively). Higher PHQ-9 scores were associated with higher GAD-7 and HADS scores, lower SF-12 scores, younger age, and an increased number of FECD-specific risk factors ($p \leq 0.013$). Higher GAD-7 scores were similarly associated with higher PHQ-9 and HADS scores, lower SF-12 scores, and younger age ($p \leq 0.043$). Although epithelial transplantation improved best-corrected visual acuity, it had no detectable influence on psychological scores ($p > 0.05$). **Conclusions:** FECD patients exhibit a higher prevalence of depressive and anxiety symptoms than the general population, particularly younger patients and those with multiple risk factors, suggesting under diagnosis in routine clinical practice. Standardized psychological screening and interdisciplinary collaboration are therefore warranted, as psychological burden is neither sufficiently recognized nor reduced by vision-improving surgery alone.

Keywords: Depressive symptoms; Anxiety symptoms; Fuchs endothelial corneal dystrophy (FECD); psychological burden; FECD risk factors; Epithelial transplantation.

Introduction

Vision and visual acuity are crucial for everyday life. These are essential for maintaining mental well-being, and their impairment may lead to the onset of disorders like depression and anxiety [1-5]. Fuchs endothelial corneal dystrophy (FECD) is a genetic, bilateral corneal disease affecting approximately 7.33% of the global population [6-8]. With increasing age, the degeneration of corneal endothelial cells leads to their destruction. In a healthy state, these cells actively pump water out of the cornea, enabling light to pass through the transparent cornea almost unimpeded. However, if these cells are impaired, water accumulates in the cornea, causing stromal oedema and, over time, epithelial oedema and scarring. The progressive loss of endothelial cells in FECD thus leads to progressive visual impairment in affected patients. Keratoplasty with endothelial replacement (DMEK) is usually performed to restore or improve vision. In some cases, a gas bubble must be reintroduced into the anterior chamber of the eye within the first few days after surgery to re-adapt a dehiscent endothelial lamella. This process is known as rebubbling. Mental health conditions such as depression and anxiety disorders are becoming increasingly prevalent worldwide, representing a significant issue for affected individuals, their families, and society as a whole [9,10]

The lifetime prevalence of generalized anxiety disorder is estimated between 4.7% and 7.3% in different populations [11-14]. A recent German population-based revealed that 18.5% of the subjects presented with symptoms consistent with anxiety disorders, as indicated by elevated scores on the GAD-7 questionnaire [15]. Additionally, there is significant comorbidity with depression, which has a lifetime prevalence of approximately 15-18% in Germany [1, 9-11,16]. Anxiety disorders in particular are often undetected. Various studies have already described the association between reduced visual acuity in various eye diseases and the increased prevalence of depressive and anxiety symptoms [1,4,3,17]. However, to date, no study has focused on these psychological disorders specifically in the context of patients with FECD. It also remains unclear whether endothelial transplantation in one or both eyes results in a reduced prevalence of depressive and anxiety symptoms. To address this, we collected scores from validated questionnaires for depressive symptoms (PHQ-9 and HADS), anxiety symptoms (GAD-7 and HADS), and health-related quality of life (SF-12). Demographic and FECD-specific clinical data were also collected to investigate correlations within these parameters.

This prospective, validated questionnaire-based, cross-sectional study aims to evaluate the extent of depressive and anxiety symptoms in patients with FECD, and to compare these parameters in patients who have undergone surgery with those who have not. Furthermore, the study intends to identify specific factors associated with these psychological disorders and to uncover possible gaps in care for affected patients.

Patients and methods

Between August 2020 and February 2023, 155 patients were informed about the study during their consultation in our Cornea Department at Cologne University Hospital, immediately prior to their examination. The patients were given full information about the study and its possible consequences, and their written informed consent was obtained. This study was conducted by the Department of Ophthalmology at the University of Cologne in Germany. It was performed in accordance with the principles of the Declaration of Helsinki and was approved by the University of Cologne's Institutional Review Board (approval number 19-1665). This study was also performed independently of previous studies.

Inclusion and exclusion criteria

Inclusion criteria comprised an age of >18 years, sufficient proficiency in the German language, and a confirmed clinical diagnosis of FECD, irrespective of prior ocular surgery. Exclusion criteria included inability to provide informed consent and the presence of ocular comorbidities other than cataract, the latter being almost universally observed within the target cohort.

Demographic and Clinical variables

Researchers asked patients face-to-face questions using a standardized three-section questionnaire [18]:

Section 1 of the survey asked for general demographic data, e.g. age, gender, ethnicity, current relationship status, highest educational qualification, occupation, occupational disability and the urge to change or quit one's occupation due to FECD.

Section 2 requested potential pre-diagnosed depression or anxiety disorders, and whether they already had undergone psychotherapeutic or pharmacological treatment. Furthermore, risk factors associated with FECD were documented, including age over 40 years, female sex, familial history, and the presence of conditions such as hypertension, diabetes mellitus, and smoking [8]. In addition, data were collected regarding previously conducted endothelial transplants and the best corrected visual acuity (BCVA) before and after surgery.

Psychometric Questionnaires

Section 3 contained German versions of four standardized and established questionnaires, which were used to evaluate depressive and anxiety symptoms, and health-related quality of life. The Patient Health Questionnaire (PHQ-9) was used to screen for depressive disorders. This short, frequently validated questionnaire examines the nine criteria set out in the Diagnostic and Statistical Manual of Mental Disorders (DSM) in terms of their occurrence within the past two weeks [19,20]. Scores range from 0 ("not at all") to 3 ("nearly every day") and the total score corresponds to mild, moderate, moderately severe or severe depressive symptoms at 5, 10, 15 and 20 points, respectively [19,20]. The Generalized

Anxiety Disorder (GAD-7) questionnaire is a valid and efficient tool for assessing anxiety disorder symptoms [12,21]. Seven DSM criteria are queried with regard to their occurrence within the past two weeks, with scores ranging from 0 ("not at all") to 3 ("nearly every day") [12, 21]. The scores are added up and correspond to minimal, mild, moderate or severe anxiety disorder symptoms at 5, 10, 15 or 21 points, respectively [12,21].

In addition to the well-established PHQ-9 and GAD-7 instruments, this study also used the Hospital Anxiety and Depression Scale (HADS), which was specifically developed for the psychological screening of patients with somatic illnesses [22]. The HADS contains seven questions on the categories of anxiety and depression, respectively, with scores ranging from 0 to 3 points [22,23]. Adding the points separately results in separate scores for depressive and anxiety symptoms of 0-7 points ("normal"), 8-10 points ("borderline abnormal") and 11-21 points ("abnormal") [22,23]. In contrast to the PHQ-9 and GAD-7, somatic items such as sleep disorders or changes in appetite were deliberately omitted to avoid confounding with physical illnesses. This is useful for the study group surveyed, which consists predominantly of older people, most of whom have general illnesses, in order to ensure a differentiated assessment of psychological stress, independent of physical symptoms. The Short Form Health Survey (SF-12) is an abbreviated version of the SF-36. It uses twelve items to calculate a score that assesses the respondent's general physical and mental condition [24]. A higher physical composite score (PCS) or mental composite score (MCS) indicates a better health-related quality of life. The average value for the general population is 50, with a standard deviation of 10 points [25]. The SF-12 is significantly more efficient in clinical practice, while still reflecting the results of the SF-36 very accurately [24].

Statistical analyses

All statistical analyses were performed using commercial software (SPSS version 30.0 for Mac; SPSS, Inc., Chicago, IL). Kolmogorov–Smirnov and Shapiro–Wilk tests were performed to analyze the normal distribution of all scores graphically and statistically and showed that the distribution was not normal (p value < 0.001 for all instruments in both tests). Differences in best corrected visual acuity (BCVA) before and after surgery were calculated by using Wilcoxon test (p value < 0.001). To investigate factors related to PHQ-9 and GAD-7 scores,

Single linear regression models were performed, analyzing the following explanatory variables:

Depression and anxiety scoring without somatic context (HADS); physical (SF-12 PCS) and general mental health condition (SF-12 MCS); age; gender (male vs. female); highest educational degree; relationship status (single or not); body mass index (BMI); FECD-

specific risk factors; and transplantation status (whether surgery was performed, or not). All p values from the regression analysis < 0.05 were classified as statistically significant. Statistically significant explanatory variables (patients' age and FECD-specific risk factors) were examined in a further linear regression in relation to all completed questionnaires (PHQ-9, GAD-7, HADS, SF-12) at the same significance level. To compare the evaluated questionnaire scores according to whether surgery was performed on no eye, one eye, or both eyes, Mann-Whitney U tests were performed.

Results

Demographic and clinical data

Among the 155 patients diagnosed with FECD who participated in this study, 140 met the inclusion criteria and agreed to participate in the study. The average age of these patients was 67.82 years, with 42 men and 98 women taking part (Table 1).

Regarding ethnicity, 139 participants self-identified as European, while one participant self-identified as Asian. Overall, 73.5% were married or in a committed relationship; 19 patients were widowed and 18 are single. 59.3% of respondents had completed an apprenticeship, while nearly 22.9% had a university degree. Thirteen patients had a secondary school degree and three had either a high school degree or no degree. In line with the age group studied, most patients were retired (63.6%), while 39 were employed full-time or part-time, four were self-employed and one was in training. Two patients were unemployed and five did not provide information on this question. Five patients (3.5%) had changed jobs or become unable to work due to FECD. Of the 140 patients surveyed, 17 (12.1%) reported having been diagnosed with depression, while three (2.1%) reported having been diagnosed with an anxiety disorder. In terms of treatment, six people (4.2%) were receiving psychotherapy, six (4.2%) were taking medication, and a further six (4.2%) were receiving a combination of both. Only one person diagnosed with depression was not receiving pharmacological or psychological treatment.

Patients were grouped according to the surveyed risk factors for FECD, including age over 40 years, female sex, family history and conditions such as hypertension, diabetes mellitus and smoking. Fifty-four patients (38.6%) had one or two risk factors; more than half of all patients (56.4%) had three or four risk factors; and seven patients (5%) had five or six risk factors. The BCVA for diagnosed FECD with no previous transplantation was 0.48 ± 0.18 for the right eye and 0.47 ± 0.19 for the left eye. Following transplantation, regardless of whether DMEK or triple DMEK was performed, visual acuity improved significantly, reaching 0.76 ± 0.24 for the right eye (p value < 0.001, Wilcoxon test) and 0.79 ± 0.23 for the left eye (p value < 0.001).

Age, mean ± SD (range)	67.82 ± 8.88 (range 48 - 88)
Gender	
Male, *n* (%)	42 (30%)
Female, *n* (%)	98 (70%)
Ethnicity	
European, *n* (%)	139 (99.3%)
Asia, *n* (%)	1 (0.7%)
Current relationship status	
Married or in a comitted relationship, *n* (%)	103 (73.5%)
Widowed, *n* (%)	19 (13.6%)
Single, *n* (%)	18 (12.8%)
Highest educational degree	
No degree, *n* (%)	3 (2.1%)
Secondary school, *n* (%)	19 (13.6%)
High school, *n* (%)	3 (2.1%)
Apprenticeship, *n* (%)	83 (59.3%)
University degree, *n* (%)	32 (22.9%)
Job	
Self-employed, *n* (%)	4 (2.9%)
Employed full-time, *n* (%)	23 (16.4%)
Employed part-time, *n* (%)	16 (11.4%)
Retired, *n* (%)	89 (63.6%)
In training, *n* (%)	1 (0.7%)
No job, *n* (%)	2 (1.4%)
Not specified, *n* (%)	5 (3.5%)
Occupational disability or change due to FECD	
Yes, *n* (%)	5 (3.5%)
No, *n* (%)	135 (96.5%)
Diagnosed depression	
Yes, *n* (%)	17 (12.1%)
No, *n* (%)	125 (89.3%)
Diagnosed anxiety disorder	
Yes, *n* (%)	2 (1.4%)
No, *n* (%)	138 (98.6%)
Therapy	
Psychotherapy alone, *n* (%)	6 (4.2%)
Drug therapy, *n* (%)	6 (4.2%)

Both, drug and psychotherapy, *n* (%)	6 (4.2%)
Epithelial transplantation	
Yes, *n* (%)	104 (74.3%)
One eye, *n* (%)	47 (45.2%)
Two eyes, *n* (%)	57 (54.8%)
No eye, *n* (%)	36 (25.7%)
Risk factors for FECD	
Age > 40, *n* (%)	140 (100%)
Female sex, *n* (%)	98 (70%)
Positive family history, *n* (%)	22 (15.7%)
Hypertonus, *n* (%)	68 (48.6%)
Diabetes mellitus, *n* (%)	13 (9.3%)
Smoking history, *n* (%)	58 (41.4%)
Sum of risk factors for FECD	
1-2 items, *n* (%)	54 (38.6%)
3-4 items, *n* (%)	79 (56.4%)
5-6 items, *n* (%)	7 (5%)

Table 1: Demographics and clinical data of 140 patients with FECD.

Depressive and anxiety symptoms are elevated in FECD patients

The mean PHQ-9 and HADS depression scores for all FECD patients were within the normal range (PHQ-9: 3.39 ± 3.61; HADS: 2.82 ± 2.75) [20,22]. According to the PHQ-9, 99 patients (70.7%) had no depressive symptoms, while 29.3% showed symptoms (scoring 5-27). Of those patients, 30 (21.4%) had mild depressive symptoms, nine (6.4%) had moderate depressive symptoms, two (1.4%) had moderately to severe depressive symptoms, and none had severe depressive symptoms (Table 2).

The anxiety symptom scores for all FECD patients were also within the normal range for the GAD-7 (2.94 ± 3.39) [21] and HADS anxiety (3.76 ± 3.61) [22] scales. According to the GAD-7, 105 patients (75%) had no anxiety symptoms, while 25% showed anxiety symptoms (scoring 5-21). Of those patients, 28 (20%) had mild anxiety symptoms, five (3.6%) had moderate anxiety symptoms, and two (1.4%) had severe anxiety symptoms (Table 2).

The assessment of physical and mental condition, collected using the SF-12 questionnaire, was within the normal range at 47.09 ± 10.38 (PCS) and 52.78 ± 8.9 (MCS) [24,25].

(A)	All FECD patients (scores 0-27)	FECD patients without depression symptoms (0-4)	FECD patients with … symptoms				
			Depression (5-27)	mild depression (5-9)	moderate depression (10-14)	moderatly severe depression (15-19)	severe depression (20-27)
Patients, *n* (%)	140 (100%)	99 (70.7%)	41 (29.3%)	30 (21.4%)	9 (6.4%)	2 (1.4%)	0 (0%)
Patient Health Questionnaire (PHQ-9)	3.39 ± 3.61 (0 - 15)	1.46 ± 1.35 (0 - 4)	8.02 ± 3.12 (5 - 15)	6.37 ± 1.33 (5 - 9)	12.0 ± 1.41 (10 - 14)	15.0 ± 0.0 (15 - 15)	-
Hospital anxiety and depression scale (HADS)							
Anxiety score (HADS)	3.76 ± 3.61 (0 - 15)	2.51 ± 2.53 (0 - 12)	6.8 ± 4.01 (0 - 15)	6.07 ± 3.86 (0 - 15)	8.33 ± 4.12 (1 - 13)	11.0 ± 1.41 (10 - 12)	-
Depression score (HADS)	2.82 ± 2.75 (0 - 12)	1.78 ± 1.89 (0 - 10)	5.34 ± 2.89 (1 - 12)	4.4 ± 2.57 (1 - 12)	7.89 ± 2.26 (4 - 10)	8.0 ± 1.41 (7 - 9)	-
Generalized Anxiety Disorder (GAD-7)	2.94 ± 3.39 (0 - 18)	1.68 ± 1.86 (0 - 9)	6.0 ± 4.24 (0 - 18)	4.97 ± 3.47 (0 - 13)	9.0 ± 5.59 (1 - 18)	8.0 ± 0.0 (8 - 8)	-
Short Form Health Survey (SF-12)							
Physical composite score (PCS)	47.09 ± 10.38 (17.61 - 61.08)	48.75 ± 9.33 (17.61 - 61.08)	43.08 ± 11.74 (19.86 - 60.18)	44.63 ± 11.63 (24.61 - 60.18)	39.77 ± 11.67 (19.86 - 58.44)	34.71 ± 13.8 (24.95 - 44.47)	-
Mental composite score (MCS)	52.78 ± 8.9 (26.35 - 67.07)	55.55 ± 6.19 (30.62 - 67.07)	46.1 ± 10.81 (26.35 63.13)	47.67 ± 10.53 (26.35 - 63.13)	41.46 ± 12.09 (27.75 - 59.75)	43.43 ± 3.36 (41.06 - 45.81)	-

(B)	All FECD patients (scores 0-21)	FECD patients without anxiety symptoms (0-4)	FECD patients with … symptoms			
			anxiety (5-21)	mild anxiety (5-9)	moderate anxiety (10-14)	severe anxiety (15-21)
Patients, *n* (%)	140 (100%)	105 (75%)	35 (25%)	28 (20%)	5 (3.6%)	2 (1.4%)
Patient Health Questionnaire (PHQ-9)	3.39 ± 3.61 (0 - 15)	2.05 ± 2.12 (0 - 10)	7.4 ± 4.18 (1 - 15)	6.82 ± 4.25 (1 - 15)	8.4 ± 2.7 (6 - 13)	13.0 ± 0.0 (13 - 13)

Hospital anxiety and depression scale (HADS)						
Anxiety score (HADS)	3.76 ± 3.61 (0 - 15)	2.24 ± 2.1 (0 - 9)	8.34 ± 3.31 (3 - 15)	7.61 ± 3.12 (3 - 13)	10.8 ± 2.68 (8 - 15)	12.5 ± 0.71 (12 - 13)
Depression score (HADS)	2.82 ± 2.75 (0 - 12)	1.77 ± 1.8 (0 - 10)	5.97 ± 2.71 (2 - 12)	5.43 ± 2.56 (2 - 12)	8.0 ± 2.55 (5 - 11)	8.5 ± 2.12 (7 - 10)
Generalized Anxiety Disorder (GAD-7)	2.94 ± 3.39 (0 - 18)	1.37 ± 1.29 (0 - 4)	7.66 ± 3.39 (5 - 18)	6.25 ± 1.48 (5 - 9)	11.6 ± 0.89 (11 - 13)	17.5 ± 0.71 (17 - 18)
Short Form Health Survey (SF-12)						
Physical composite score (PCS)	47.09 ± 10.38 (17.61 - 61.08)	48.2 ± 9.78 (17.61 - 58.95)	43.77 ± 11.52 (19.86 - 61.08)	43.04 ± 12.11 (19.86 - 61.08)	50.17 ± 7.45 (38.47 - 57.76)	37.98 ± 6.44 (33.43 - 42.53)
Mental composite score (MCS)	52.78 ± 8.9 (26.35 - 67.07)	55.88 ± 5.5 (34.19 - 67.07)	43.47 ± 10.61 (26.35 - 58.5)	45.65 ± 10.37 (26.35 - 58.5)	37.2 ± 6.2 (26.8 - 42.4)	28.68 ± 1.32 (27.75 - 29.61)

Table 2: Questionnaire scores in 140 FECD patients without and with depression (A) or anxiety (B) symptoms (mean ± SD and range).

Age and clinical risk factors affect psychological symptoms in FECD patients

The linear regression models for explanatory variables in relation to PHQ-9 or GAD-7 scores demonstrated a highly significant association with the other questionnaires surveyed (p values < 0.001 in each case; linear regression, exception: PCS in relation to GAD-7, $p = 0.043$; Table 3). Among the other tested variables, age showed a significant negative correlation with a p value of 0.013 for the PHQ-9 and a p value of < 0.001 for the GAD-7. The same association was also identified in the linear regression model with regard to age for the HADS scores (depression score p value = 0.01, anxiety score p value = 0.013). Consequently, younger patients, irrespective of somatic comorbidities associated with psychological disorders, displayed a substantial increase in depressive and anxiety symptoms.

No statistically significant associations were identified with regard to gender, highest educational degree, single (or not), BMI, or transplantation status.

	association to PHQ-9		association to GAD-7	
Explanatory variable	**Beta coefficient**	**p value**	**Beta coefficient**	**p value**
Patient Health Questionnaire (PHQ-9)	-	-	0.701	< 0.001
Hospital anxiety and depression scale (HADS)				
Anxiety score (HADS)	0.646	< 0.001	0.836	< 0.001
Depression score (HADS)	0.714	< 0.001	0.69	< 0.001
Generalized Anxiety Disorder (GAD-7)	0.701	< 0.001	-	-
Short Form Health Survey (SF-12)				
Physical composite score (PCS)	-0,355	< 0.001	-0,171	0.043
Mental composite score (MCS)	-0,565	< 0.001	-0.697	< 0.001
Age	-0,21	0.013	-0.33	< 0.001
Gender (male vs. female)	0.105	0.218	0.077	0.369
Highest educational degree	-0.101	0.236	-0.16	0.06
Single (or not)	0.061	0.477	0.105	0.217

BMI	0.164	0.068	0.098	0.279
FECD-specific risk factors	0.307	< 0.001	0.145	0.088
Performed transplantation (or not)	0.058	0.492	0	0.997

Table 3: Linear regression of explanatory variables in relation to PHQ-9 and GAD-7.

Furthermore, a highly significant association was identified between FECD-specific risk factors and the PHQ-9 score (p value < 0.001), with a slight tendency observed in the GAD-7 score (p value = 0.088). Consequently, additional analyses were conducted using linear regression, with the risk factors for FECD serving as the dependent variable (Table 4).

	Beta coefficient	p value
Patient Health Questionnaire (PHQ-9)	0.307	< 0.001
Hospital anxiety and depression scale (HADS)		
Anxiety score (HADS)	0.171	0.043
Depression score (HADS)	0.242	0.004
Generalized Anxiety Disorder (GAD-7)	0.145	0.088
Short Form Health Survey (SF-12)		
Physical composite score (PCS)	-0.273	0.001
Mental composite score (MCS)	-0.149	0.079
Age	0.016	0.851

Table 4: Linear regression of psychological scores in terms of clinical risk factors for FECD.

A significant positive correlation was discovered among patients with depressive symptoms (PHQ-9, p value < 0.001 and HADS depression score, p value = 0.004) according to the presence of increasing risk factors. In patients exhibiting anxiety symptoms, this significant correlation was less prominent (GAD-7, p value = 0.088 and HADS anxiety score, p value = 0.043). Furthermore, with the increase of risk factors, which also include health-restricting items such as hypertension, diabetes mellitus, and smoking, there was a decrease in the physical and mental condition of the patients. A highly significant negative association was identified for the physical composite score (PCS) of the SF-12 (p = 0.001). A tendency towards significant negative association was observed for the mental composite score (MCS) of the SF-12 (p = 0.079). A notable finding was the absence of a correlation between the risk factors for FECD and the patients' age (p value = 0.851). Consequently, an increase in risk factors for FECD is associated with an increase in depressive and anxiety symptoms, as well as a decrease in physical and mental health. There is no statistically significant correlation between patients age and the number of risk factors.

Epithelial transplantation has no influence on psychological symptoms

To investigate the potential impact of epithelial transplantation on anxiety and depressive symptoms, patients were compared according to whether or not they had undergone transplantation after being diagnosed with FECD. The following three groups were formed: "transplantation of no eye"; "transplantation of one eye"; "transplantation of two eyes." When comparing the groups mentioned above, no significant influence on the scores collected to measure anxiety and depressive symptoms could be demonstrated (p value > 0.05 in each case, Table 5). Thus, a successful transplant, regardless of whether one or both eyes were operated, has no influence on the psychological setting of the patients. The transplantation of one or even both eyes also had no significant influence on the physical and mental condition of the patients (SF-12 score, p value > 0.05 in each case, Mann-Whitney-U test, Table 5).

	Transplantation of **no eye *vs* one eye** (p value) "no eye" n = 36; "one eye" n = 47	Transplantation of **one eye *vs* two eyes** (p value) "one eye" n = 47; "two eyes" n = 57	Transplantation of **no eye *vs* two eyes** (p value) "no eye" n = 36; "two eyes" n = 57
Patient Health Questionnaire (PHQ-9)	0,826	0,576	0,763
Hospital anxiety and depression scale (HADS)			
Anxiety score (HADS)	0,306	0,137	0,792
Depression score (HADS)	0,167	0,482	0,38
Generalized Anxiety Disorder (GAD-7)	0,37	0,549	0,685
Short Form Health Survey (SF-12)			
Physical composite score (PCS)	0,22	0,746	0,141
Mental composite score (MCS)	0,836	0,288	0,211

Table 5: Epithelial transplantation has no influence on psychological scores.

Discussion

This study provides significant results for the following four key statements regarding patients with FECD:

(1)   Depressive and anxiety symptoms are underdiagnosed in surveyed FECD patients. Therefore, these patients should undergo psychological screening in clinical practice to detect and treat relevant disorders early on.

(2)   Younger patients with FECD have an increased prevalence of depressive and anxiety symptoms. This patient group should be specifically targeted for appropriate psychological screening in clinical practice.

(3)   The more FECD-specific risk factors patients have, the more severe their depressive and anxiety symptoms are, and the more impaired their physical and mental health is. This highlights the need for interdisciplinary treatment of affected patients, who require not only good ophthalmological care, but also reliable general practitioners.

(4)   After guideline-based therapy using epithelial transplantation, BCVA increases significantly, while no influence on depressive and anxiety symptoms or on physical and mental condition could be demonstrated. Thus, in addition to ophthalmological rehabilitation through transplantation, the psychological setting of patients must be addressed and treated separately.

People with reduced vision face multiple challenges in life, including an increased risk of depression and anxiety disorders [1-3]. Working with those questionnaires it should be noted, that both PHQ-9 and GAD-7 evaluate and grade severity of depressive or anxiety symptoms and neither score provides any information about the genesis of the examined disorders or equals a medical diagnosis made by a psychiatrist [12,19-21]. Compared to the general German population, which has a rate of elevated depressive symptoms of 20.76%, our patient group had a significantly higher rate of depressive symptoms with 29.7% (41 patients) [1,9,10,11,16,26]. Although most patients (30 out of 41) have mild symptoms, nine have moderate symptoms, and two have moderate-to-severe symptoms. The study also revealed a discrepancy between the general German population and the study group with regard to anxiety disorder symptoms. As indicated by the elevated GAD-7 scores, 18.5% of the German population exhibited pronounced anxiety symptoms compared to 25% (35 patients) of the examined patients demonstrating significant elevations [11-15].

However, only 12.1% reported suffering from diagnosed depression and 1.4% suffering from diagnosed anxiety disorder, there seems to be a mismatch with significantly more patients affected by the disease specific symptoms.

In all statistical calculations, the PHQ-9 and the depression score of HADS as well as the GAD-7 and the anxiety score of HADS were aligned. A high burden on the surveyed patients due to somatic complaints would have led to differences here, allowing the focus to be placed on the psychological burden of the patients. The available data on patients with FECD even exceed the increased prevalence of depressive symptoms in visually impaired patients of up to 24% reported by *Schuster et al.* [4]. This substantial discrepancy between the prevalence in the general population and in cohorts with impaired visual function underscores the necessity of psychological screening in patients with FECD. Since depression and anxiety disorders and symptoms impose a significant psychological and socioeconomic burden, early screening and, if necessary, intervention, are advisable [27,28].

In addition to the increased risk of depressive and anxiety symptoms in general, we were also able to demonstrate a significant negative correlation with patients' age. Interestingly, we found that symptoms of depression and anxiety increased when patients were younger. However, other studies have shown that the highest lifetime prevalence of depression is among 60- to 69-year-olds, which roughly corresponds to the average age of our FECD patients and thus does not correspond to our younger patients [29-31]. Furthermore, other studies have described an increase in lifetime depression prevalence in older age groups in German cohorts [32,33,34].

This contrast could perhaps be explained by the circumstance that younger patients have had the disease for a shorter period of time and have therefore had less time to come to terms with and maybe accept it. Other studies have shown that the rate and severity of depression decrease with time since diagnosis [18,35]. Furthermore, younger patients may exhibit increased symptoms of psychological disorders due to impaired visual function if they are still working or planning to start a family [36,37]. As diagnoses of impaired visual function become more common with age, older people are maybe more familiar with reduced vision [5]. Younger people with a first diagnosis of FECD may have received their first diagnosis of a vision-threatening disease. Regardless of the possible causes, it is important for ophthalmologists to pay particular attention to symptoms of depression and anxiety in younger patients with FECD. For example, special attention should be paid to age in brief screenings to identify affected individuals early and refer them for targeted pharmacological, psychotherapeutic, or combined therapy.

In addition to the significant correlation between increased depressive and anxiety symptoms and FECD, a linear regression model demonstrated that psychological symptoms increase with an elevated number of FECD-specific risk factors, such as age over 40, female sex, family history, and the presence of hypertension,

diabetes mellitus, and smoking. The more risk factors a patient has, the more likely they are to be diagnosed with FECD [8] and experience symptoms of depression and anxiety. At the same time, physical and mental health decline as risk factors increase. Since the risk factors of being over 40 years old, being female, and having a positive family history cannot be influenced, the risk factors of having hypertension, diabetes mellitus, and being a smoker become more important. On one hand, ophthalmologists should ask about these risk factors and take them into account in psychological screenings. On the other hand, interdisciplinary cooperation with the general practitioner should be emphasized. Additionally, patients should be educated on the significant role of these risk factors in causing depression, anxiety disorders, and impaired visual function due to various disorders, including FECD. As multiple studies have shown, reducing the risk of FECD, depression, and anxiety disorders further leads to a reduction in individual morbidity and mortality [38,39].

Surgical treatment for FECD patients using epithelial transplantation significantly improves BCVA. Interestingly, successful transplantation did not result in a notable reduction in symptoms of depression or anxiety, regardless of whether one or both eyes were treated. Similarly, no influence on physical or mental condition could be demonstrated. These findings underscore the unique challenges faced by ophthalmologists treating FECD patients, as improving visual acuity alone is not sufficient for comprehensive patient care. Thus, the increased rate of depressive and anxiety symptoms in FECD patients appears to be less associated with visual function. It is possible that the general risk profile of hypertension, diabetes mellitus, and smoking is much more likely to be the cause, as these factors themself are strongly associated with an increased prevalence of depression and anxiety disorders [40-42]. This is also probable because, in comparison to patients with cataracts, who also exhibit elevated symptoms of anxiety and depression and an impaired BCVA, their psychological burden is demonstrably reduced after surgery [43,44,45]. In addition, individuals diagnosed with glaucoma or age-related macular degeneration (AMD) are also more prone to manifest depressive and anxiety symptoms to a greater extent than the general population, as shown by *Pan et al.* analyzing a total of 67 studies [46]. In such cases, the primary objective of treatment shifts from achieving substantial BCVA enhancement to preserving the existing BCVA. This approach contrasts with the treatment strategies employed in conditions such as FECD or cataracts. The findings imply that the elevated prevalence of depression and anxiety may be attributable to a combination of factors, beyond the scope of BCVA alone, as all these vision-impairing diseases have a significant impact on the psychological burden. It underscores the necessity to consider the patient comprehensively and to address comorbidities with a comparable level of emphasis, aiming to enhance their quality of life.

One limitation of this study is the lack of data on potential changes in the pre- and post-epithelial transplantation questionnaire scores. Surveying depression and anxiety scores before and after surgery

in the same patient could provide a more precise depiction of symptom dynamics. Additionally, the cross-sectional design of the study has led to a limitation in the derivation of causality of the presented data. The usage of screening questionnaires is highly validated, can easily be used by non-psychiatrists, and is timely effective. In the context of a large study group, as depicted in this paper, they serve as a highly advantageous instrument. However, it should be noted that these methods are inferior to diagnostic structured interviews, which are significantly more precise and capable of differentiating symptoms from diagnoses. In terms of visual function, subjective visual function would be an interesting parameter to consider in addition to objective BCVA. After all, each patient experiences their disease and visual impairment differently, so subjective perception could be useful when it comes to psychological disorders such as depression and anxiety. According to the available literature, this study is the first to assess the psychological burden experienced by patients with FECD. Further studies are necessary to thoroughly examine the psychological challenges confronting these patients.

In summary, the cohort of patients with FECD examined in this study showed significantly higher rates of depressive and anxiety symptoms than the general German population. This suggests an underdiagnosis of these conditions in clinical practice. This rate is even higher among younger patients and those with more FECD-specific risk factors. Therefore, it is recommended that a standardized psychological screening should be implemented in routine clinical care for these patients. Interdisciplinary collaboration with general practitioners is essential to address FECD- and morbidity- and mortality-specific risk factors. Close cooperation with psychiatrists and psychologists is also necessary, because FECD patients have an increased psychological burden that is not significantly improved by surgery.

Acknowledgements

Conflict of interest

Funding statement

Author contributions

LHM, ACR and CN contributed to the study conception and design. SJF collected the data. CN and PZ analyzed the data. CN wrote the article. PAWMR, SJF, JW, MS, PZ and ACR provided revisions. All authors approved the final manuscript.

Data Availability

Data generated during this study are available from the corresponding author on reasonable request.

References

1. Evans JR, Fletcher AE, Wormald RPL (2007) Depression and Anxiety in Visually Impaired Older People. Ophthalmology 114: 283-288.

2. Frank CR, Xiang X, Stagg BC, Ehrlich JR (2019) Longitudinal Associations of Self-reported Vision Impairment With Symptoms of Anxiety and Depression Among Older Adults in the United States. JAMA Ophthalmol 137: 793.

3. Li D, Chan VF, Virgili G, Piyasena P, Negash H, et al. (2022) Impact of Vision Impairment and Ocular Morbidity and Their Treatment on Depression and Anxiety in Children. Ophthalmology 129: 1152-1170.

4. Schuster AK, Tesarz J, Rezapour J, Beutel ME, Bertram B, et al. (2018) Visual Impairment Is Associated With Depressive Symptoms—Results From the Nationwide German DEGS1 Study. Front Psychiatry 9: 114.

5. Wahl HW (2013) The Psychological Challenge of Late-Life Vision Impairment: Concepts, Findings, and Practical Implications. J Ophthalmol 2013: 278135.

6. Aiello F, Gallo Afflitto G, Ceccarelli F, Cesareo M, Nucci C (2022) Global Prevalence of Fuchs Endothelial Corneal Dystrophy (FECD) in Adult Population: A Systematic Review and Meta-Analysis. J Ophthalmol 1-7.

7. Altamirano F, Ortiz-Morales G, O'Connor-Cordova MA, Sancén-Herrera JP, Zavala J, et al. (2024) Fuchs endothelial corneal dystrophy: An updated review. Int Ophthalmol 44: 61.

8. Ong Tone S, Kocaba V, Böhm M, Wylegala A, White TL, et al. (2021) Fuchs endothelial corneal dystrophy: The vicious cycle of Fuchs pathogenesis. Prog Retin Eye Res 80: 100863.

9. Malhi GS, Mann JJ (2018) Depression. The Lancet 392: 2299-2312.

10. Steffen A, Thom J, Jacobi F, Holstiege J, Bätzing J (2020) Trends in prevalence of depression in Germany between 2009 and 2017 based on nationwide ambulatory claims data. J Affect Disord 271: 239-247.

11. Beekman ATF, De Beurs E, Van Balkom AJLM, Deeg DJH, Van Dyck R, et al. (2000) Anxiety and Depression in Later Life: Co-Occurrence and Communality of Risk Factors. Am J Psychiatry 157: 89-95.

12. Hinz A, Klein AM, Brähler E, Glaesmer H, Luck T, et al. (2017) Psychometric evaluation of the Generalized Anxiety Disorder Screener GAD-7, based on a large German general population sample. J Affect Disord 210: 338-344.

13. Schoevers RA, Deeg DJH, Van Tilburg W, Beekman ATF (2005) Depression and Generalized Anxiety Disorder: Co-Occurrence and Longitudinal Patterns in Elderly Patients. Am J Geriatr Psychiatry 13: 31-39.

14. Somers JM, Goldner EM, Waraich P, Hsu L (2006) Prevalence and Incidence Studies of Anxiety Disorders: A Systematic Review of the Literature. Can J Psychiatry 51: 100-113.

15. Kliem S, Sachser C, Lohmann A, Baier D, Brähler E, et al. (2025) Psychometric evaluation and community norms of the GAD-7, based on a representative German sample. Front Psychol 16: 1526181.

16. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, et, al. (2003) The Epidemiology of Major Depressive Disorder: Results From the National Comorbidity Survey Replication (NCS-R). JAMA 289: 3095.

17. Rezapour J, Nickels S, Schuster AK, Michal M, Münzel T, et al. (2018) Prevalence of depression and anxiety among participants with glaucoma in a population-based cohort study: The Gutenberg Health Study. BMC Ophthalmol 18: 157.

18. Heindl LM, Trester M, Guo Y, Zwiener F, Sadat N, et al. (2021) Anxiety and depression in patients wearing prosthetic eyes. Graefes Arch Clin Exp Ophthalmol 259: 495-503.

19. Costantini L, Pasquarella C, Odone A, Colucci ME, Costanza A, et al. (2021) Screening for depression in primary care with Patient Health Questionnaire-9 (PHQ-9): A systematic review. J Affect Disord 279: 473-483.

20. Kroenke K, Spitzer RL, Williams JBW (2001) The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 16: 606-613.

21. Spitzer RL, Kroenke K, Williams JBW, Löwe B (2006) A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. Arch Intern Med 166: 1092-1097.

22. Zigmond AS, Snaith RP (1983) The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 67: 361-370.

23. Bjelland I, Dahl AA, Haug TT, Neckelmann D (2002) The validity of the Hospital Anxiety and Depression Scale. J Psychosom Res 52: 69-77.

24. Ware JE, Kosinski M, Keller SD (1996) A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. Med Care 34: 220-233.

25. Ware JE (2000) SF-36 Health Survey Update. Spine 25: 3130-3139.

26. Kliem S, Sachser C, Lohmann A, Baier D, Brähler E, et al. (2024) Psychometric evaluation and community norms of the PHQ-9, based on a representative German sample. Front Psychiatry 15: 1483782.

27. Arias D, Saxena S, Verguet S (2022) Quantifying the global burden of mental disorders and their economic value. eClinicalMedicine 54: 101675.

28. Kirkbride JB, Anglin DM, Colman I, Dykxhoorn J, Jones PB, et al. (2024) The social determinants of mental health and disorder: Evidence, prevention and recommendations. World Psychiatry 23: 58-90.

29. Busch MA, Maske UE, Ryl L, Schlack R, Hapke U (2013) Prävalenz von depressiver Symptomatik und diagnostizierter Depression bei Erwachsenen in Deutschland: Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1). Bundesgesundheitsblatt - Gesundheitsforschung ☐ Gesundheitsschutz 56: 733-739.

30. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, et al. (2005) Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62: 593-602.

31. Steffens DC, Fisher GG, Langa KM, Potter GG, Plassman BL (2009) Prevalence of depression among older Americans: The Aging, Demographics and Memory Study. Int Psychogeriatr 21: 879-888.

32. Kamtsiuris P, Lange M, Hoffmann R, Schaffrath Rosario A, Dahm S, et al. (2013) Die erste Welle der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1): Stichprobendesign, Response, Gewichtung und Repräsentativität. Bundesgesundheitsblatt - Gesundheitsforschung ☐ Gesundheitsschutz 56: 620-630.

33. Luppa M, Sikorski C, Luck T, Ehreke L, Konnopka A, et al. (2012) Age- and gender-specific prevalence of depression in latest-life – Systematic review and meta-analysis. J Affect Disord 136: 212-221.

34. Scheidt-Nave C, Kamtsiuris P, Gößwald A, Hölling H, Lange M, et al. (2012) German health interview and examination survey for adults (DEGS)☐Design, objectives and implementation of the first data collection wave. BMC Public Health 12: 730.

35. Amaro TAC, Yazigi L, Erwenne C (2009) Depression and quality of life during treatment of ocular bulb removal in individuals with uveal melanoma: Quality of life and uveal melanoma. Eur J Cancer Care 19: 476-481.

36. Boerner K, Wang SW (2010) How it Matters When it Happens: Life Changes Related to Functional Loss in Younger and Older Adults. Int J Aging Hum Dev 70: 163-179.

37. Goulia P, Papadimitriou I, Machado MO, Mantas C, Pappa C, et al. (2012) Does psychological distress vary between younger and older adults in health and disease? J Psychosom Res 72: 120-128.

38. Pan A, Wang Y, Talaei M, Hu FB (2015) Relation of Smoking With Total Mortality and Cardiovascular Events Among Patients With Diabetes Mellitus: A Meta-Analysis and Systematic Review. Circulation 132: 1795-1804.

39. Simons LA, Simons J, McCallum J, Friedlander Y (2005) Impact of smoking, diabetes and hypertension on survival time in the elderly: The Dubbo Study. Med J Aust 182: 219-222.

40. Basiri R, Seidu B, Rudich M (2023) Exploring the Interrelationships between Diabetes, Nutrition, Anxiety, and Depression: Implications for Treatment and Prevention Strategies. Nutrients 15: 4226.

41. Liu MY, Li N, Li WA, Khan H (2017) Association between psychosocial stress and hypertension: A systematic review and meta-analysis. Neurol Res 39: 573-580.

42. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, et al. (2014) Change in mental health after smoking cessation: Systematic review and meta-analysis. BMJ 348: 1151-1151.

43. Mitsonis CI, Dimopoulos NP, Andriotis NM, Mitropoulos PA, Mitsonis MI, et al. (2006) Anxiety and Depression in Cataract Surgery: A Pilot Study in the Elderly. Psychol Rep 99: 257-265.

44. Nijkamp MD, Kenens CA, Dijker AJM, Ruiter RAC, Hiddema F, et al. (2004). Determinants of surgery related anxiety in cataract patients. Br J Ophthalmol 88: 1310-1314.

45. Wang S, Du Z, Lai C, Seth I, Wang Y, et al. (2024) The association between cataract surgery and mental health in older adults: A review. Int J Surg 110: 2300-2312.

46. Dong X, Hu H, Ying Z, Chen D, Xie J, et al. (2025) Major sight☐threatening eye disorders and mental disorders. Acta Ophthalmol 103: 257-271.