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Investigation of sexual life and sleep quality in patients with hereditary angioedema

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Abstract

Background: Hereditary angioedema (HAE) is a genetic disorder characterized by recurrent, spontaneous, and sometimes life-threatening episodes of swelling. Attacks of angioedema that negatively impact quality of life can occur anywhere in the body. The chronic and unpredictable course of the disease can also affect mental health, sleep quality, and sexual life.

Objective: This study aimed to investigate sexual function, sleep quality, and related factors in HAE patients.

Material and Methods: In all, 40 patients diagnosed with type 1 and type 2 HAE were followed up in the Immunology and Allergy Clinic, and 40 healthy controls were included in the study. Participants completed the Arizona Sexual Experience Scale (ASEX), Pittsburgh Sleep Quality Index (PSQI), and Hospital Anxiety and Depression Scale (HADS).

Results: The patient group had significantly higher ASEX and PSQI scores compared to the healthy control group. In the patient group, ASEX scores showed a significant positive correlation with HADS-Depression (HADS-D) and HADS-Anxiety (HADS-A) scores. It was shown that as frequency of monthly attacks in patients increased, both HADS-D and HADS-A scores increased, and with increase in HADS-D scores, sleep efficiency decreased. Furthermore, a strong positive correlation was shown between HADS-A scores and PSQI scores. Longer disease duration, history of genital attacks, and decreased sleep quality were found to be significantly correlated with sexual dysfunction.

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Conclusion: The results supported our hypothesis that sexual life and sleep quality are more affected in this patient group than known previously. It is expected that evaluating sexual life, sleep quality, and general well-being in the routine follow-up of these patients may contribute to disease control.

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Introduction

Hereditary angioedema (HAE) is a rare autosomal-dominant disease that has affected approximately 1 in 50,000 individuals globally and is characterized by unpredictable, recurrent episodes of cutaneous or submucosal edema.¹ These episodes predominantly involve the skin, gastrointestinal tract, and upper airway, rendering it a potentially life-threatening, chronic, and debilitating condition.^{1,2}

Hereditary angioedema encompasses a heterogeneous group of disorders that, in spite of differing underlying genetic mechanisms, exhibit similar clinical phenotypes. It is classified into two main subtypes: HAE associated with deficiency of C1-esterase inhibitor (C1-INH), a crucial blood protein, and HAE with normal levels of C1-INH. Type 1, accounting for approximately 85% of HAE-C1-INH patients, is characterized by reduced C1-INH levels and functioning, whereas in type 2, levels are normal or elevated but functioning is impaired.² Although these distinctions are well established through extensive biochemical research, the broader psychosocial effects of the disease have long been overlooked.

Recent studies have indicated that HAE is not solely a physical condition but one with substantial psychosocial impacts as well. Patients frequently report anxiety, disease-related uncertainty, depressive symptoms, sleep disturbances, and a marked decline in quality of life.³⁻⁵ Sexual health remains an under-addressed topic in most clinical encounters, with patients often reluctant to disclose their sexual concerns.⁶⁻⁸ In particular, HAE attacks involving the genital region may lead to sexual avoidance and impaired body image.^{1,9}

Association between sleep disturbances and sexual function is an increasingly prominent research area in chronic diseases. Sleep insufficiency can intensify the severity of anxiety and depression; similarly, elevated psychological burden can adversely impact both sleep regulation and sexual function.^{6,10-13} This multifaceted interaction may become even more complex in HAE, as the disease's unpredictable course and anxiety regarding attacks affect both daily life behaviors and psychological resilience.^{10,14} Accordingly, the scarcity of studies on sexual dysfunction and sleep quality in HAE represents a significant knowledge gap.

This study aims to systematically assess sexual dysfunction, sleep quality, anxiety, and depression levels in HAE patients and to elucidate their association with clinical characteristics and complementary biomarkers. Based on the literature, it is hypothesized that poorer sleep quality and impaired sexual function are associated with higher psychological distress, increased disease burden, more frequent angioedema attacks, and alterations in specific complement markers in HAE patients.

Materials and Methods

Patient selection and sample size

This cross-sectional study was conducted in the Adult Immunology and Allergy Clinic, Department of Internal Medicine, between 2023 and 2024. In all, 65 HAE patients followed in our clinic were screened, and 40 HAE-C1-INH-diagnosed patients who met the appropriate criteria were included in the study. Inclusion criteria in the study comprised patients aged 18-65 years, voluntary participation in the study, and complete answering of all questions in the scales. Patients with low C1-INH levels and functioning were classified as type-1 HAE, and those with normal/high C1-INH levels but low functioning were classified as type-2 HAE. In addition, 40 healthy individuals from the general population were included in the study as a control group. Individuals with a known diagnosis of HAE, chronic inflammatory diseases, psychiatric disorders, or medical conditions that could directly affect sleep quality or sexual function were excluded. Control group patients were selected to be comparable to the patient group with respect to age and sex distribution. Formal matching of socioeconomic variables, such as education level and employment status, was not performed, as the study was designed as an exploratory analysis, and the available sample size limited the feasibility of multivariable adjustment without increasing the risk of model overfitting. Potential differences in sociodemographic characteristics between groups were therefore acknowledged and considered in the interpretation of psychometric outcomes. In both groups, having a diagnosis of sleep disorder and using medical treatment or devices for this purpose were taken as exclusion criteria. After explaining the study, written informed consent was obtained from all participants, and the study was conducted with a total of 80 participants (Figure 1).

Sample size justification

The required sample size was determined prior to data collection using G*Power, version 3.1.9.2. Since the main aim of this study was to compare sleep quality and sexual function between HAE patients and healthy controls, the power calculation was based on two primary outcome variables: the Pittsburgh Sleep Quality Index (PSQI) and the Arizona Sexual Experience Scale (ASEX). These scales were selected because they represent the central domains evaluated in this study, and previous research has reported moderate-to-large differences between patient populations and controls.^{3,6,12,15}

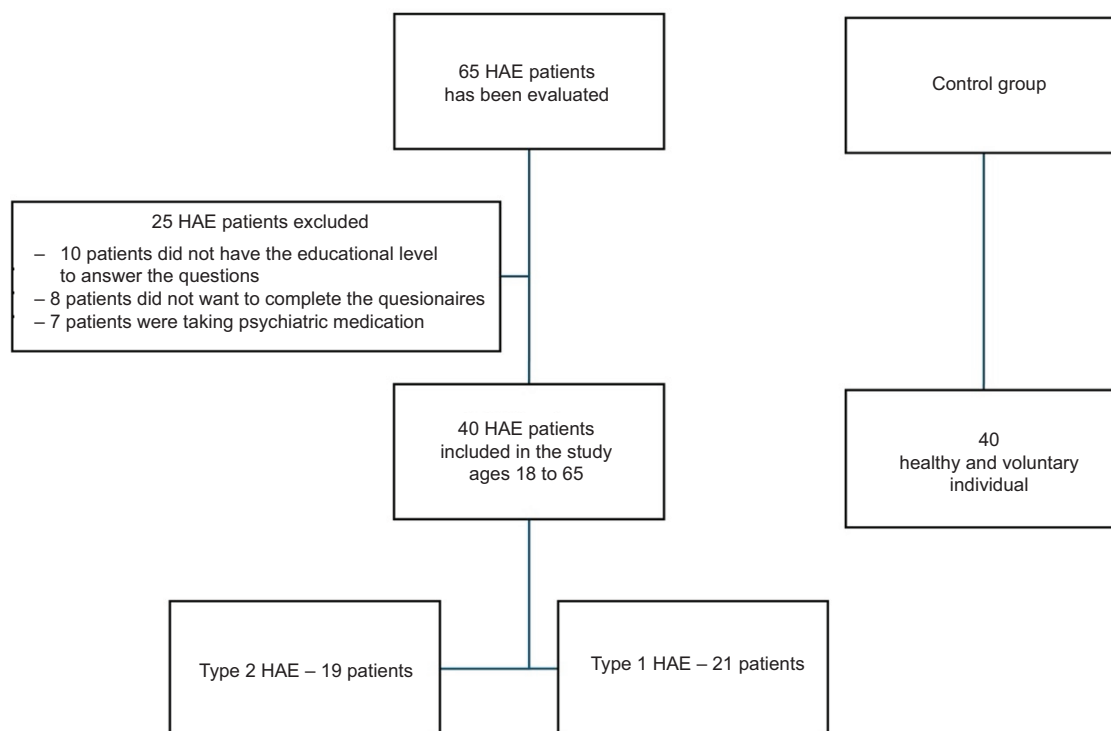


Figure 1 Patient selection flowchart in the study. HAE: hereditary angioedema.

Based on previous studies examining sleep quality and sexual function in chronic illnesses—including HAE—an effect size of Cohen’s $d = 0.70$ was considered clinically meaningful and appropriate for detecting group differences in both PSQI and ASEX scores.

An *a priori* power analysis was performed in G*Power to determine the minimum required sample size. The test family was set to *t*-tests, and the statistical procedure, “difference between two independent means,” was selected. A two-tailed analysis was applied with an assumed effect size of Cohen’s $d = 0.70$, an error probability, α , of 0.05, a power (1- β) of 0.85, and an allocation ratio (N2:N1) of 1.

With these parameters, the minimum required sample size was calculated as 78 participants (39 per group). To ensure adequate statistical power and account for possible missing data, 40 HAE patients and 40 healthy controls were included in the study, exceeding the required sample size.

Study design

The participants were administered pre-designed data forms. PSQI, ASEX, and Hospital Anxiety and Depression Scale (HADS) were applied face-to-face by their attending physicians. After the completion of all scales, they were reviewed together with an attending physician and a psychiatrist, and interpreted by the psychiatrist.

Sociodemographic data form

A personal information form was used to collect demographic data from both patients and control group. This

information included age, gender, education level, marital status, employment status, income level, living situation, and smoking and alcohol habits.

Clinical findings and medical data form

To gather information on comorbidities and disease-specific details within the patient group, medical data forms were utilized. These forms documented accompanying illnesses, history of HAE, the most frequent site of angioedema attacks, monthly attacks’ frequency, use of short- or long-term prophylaxis, and the treatments administered. A frequency of four or more angioedema attacks per month was defined as frequent attacks. Serum C4, C1-INH levels, and C1-INH function levels at the time of HAE diagnosis were recorded from the hospital’s electronic medical record system.

Blood sample collection

Blood samples were centrifuged at 4000 rpm for 5 min at room temperature and stored at -20°C until C1-INH function levels were tested.

Measurement of complement level

C1-INH levels were measured using the Neph 630 device (Siemens, Erlangen, Germany), which relies on a nephelometric method. C1-INH function was assessed using a coagulation device (Cs-2500; Siemens) based on a chromogenic

method. The C4 esterase inhibitor (C4-INH) level was measured using the Architect C8000 device (Abbott, Des Plaines, IL, USA).

Pittsburgh sleep quality index (PSQI)

This scale is used to assess sleep quality over the past month. Its validity and reliability in our country was established by Ağargün et al., who reported a high level of internal consistency.¹⁶ The scale provides reliable data on sleep quality. The first 18 items of the 24-item scale are self-reported and included in the scoring. Each item is scored 0-3, and these 18 items are evaluated in seven areas. The total score of these seven areas gives the total score of PSQI. The total score ranges from 0 to 21. A total PSQI score of >5 indicates poor sleep quality, and the higher the score, the worse the sleep quality.¹⁷

Arizona sexual experiences scale (ASEX)

This scale was developed by McGahuey et al.¹² to evaluate sexual functions of men and women. The male and female forms of Likert-type ASEX are different. There are five items on each scale. Each item is scored 1-6, with a high score being associated with poor sexual function. A total score of ≥ 19 , a score of ≥ 5 for any response on the scale, or a score of 4 for three of the five items has been identified as indicators of sexual dysfunction.¹² In the Turkish validity and reliability study, a score of ≥ 11 was considered as the cut-off score for sexual dysfunction.¹⁸

Hospital anxiety and depression scale (HADS)

This scale, developed by Zigmond and Snaith,¹⁹ measures anxiety and depression levels and is particularly suitable for individuals with physical illnesses. In all, it comprises 14 items, of which seven items assess anxiety and remaining seven items assess depression. Each item is scored 0-3; score of 0-1 indicates the absence of illness, 2 indicates borderline illness, and score of 2-3 indicates severe illness. Each subscale yields a total score ranging from 0 to 21. This scale is used for screening purposes, rather than for diagnostic use.¹⁹ The Turkish validity and reliability of the scale were established by Aydemir et al.²⁰

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as median (interquartile range) or mean \pm standard deviation (SD), as appropriate, while categorical variables were expressed as frequencies and percentages.

The normality of continuous variables was evaluated using visual inspection of histograms and the Shapiro-Wilk test. As several variables did not conform to a normal distribution, between-group comparisons (HAE patients vs. controls) were conducted using the Mann-Whitney U test

for continuous variables and the Chi-squared test for categorical variables.

Associations between psychometric scale scores, sociodemographic characteristics, and clinical parameters within the HAE patient group were examined using Spearman's rank correlation coefficient, given the ordinal nature of psychometric measures and the non-normal distribution of the data.

To explore factors associated with sexual function, multivariate linear regression analyses were performed, with ASEX total score as the dependent variable. Regression models were constructed in an exploratory manner, with independent variables selected based on clinical relevance and previous literature, rather than causal assumptions.

Prior to regression modeling, multicollinearity among independent variables was assessed using variance inflation factors (VIF). All VIF values were below 2.0, indicating no significant collinearity. Model assumptions—including linearity, normality of residuals, homoscedasticity, and independence of errors—were evaluated using standard diagnostic plots and statistical criteria.

All statistical tests were two-tailed, and $P \leq 0.05$ was considered statistically significant.

Results

Descriptive statistics

In this study, we enrolled 40 HAE patients and 40 healthy controls, ensuring an equal gender distribution across both groups. The mean age in the patient group was 40.82 years, comparable to that in the control group. Notably, the patient group had a significantly lower education level ($P = 0.002$), and a significantly higher unemployment rate ($P = 0.005$), compared to healthy controls. There was no significant difference in smoking habits between both groups; however, the patient group reported lower alcohol consumption. Other sociodemographic data did not reveal any significant differences between both groups. The sociodemographic characteristics of the patients and healthy controls, along with group comparisons, are detailed in [Table 1](#).

Clinical characteristics of patients with hereditary angioedema

Among the patient cohort, 37.5% presented with other medical comorbidities, with hypertension being the most prevalent disorder, observed in 10% of cases. Frequent attacks were reported by 57.5% of the patients, with the extremities being the most common site. Genital attacks were reported in 30% of the patients. Long-term prophylaxis was utilized by 37.5% of the patients ([Table 2](#)).

Comparison of psychometric tests of patients and healthy control groups

The patient group exhibited significantly higher PSQI and ASEX scores, compared to the healthy control group

Table 1 Comparison of sociodemographic features of patients and healthy control groups.

Parameter	Patients with HAE group (n = 40)	HC group (n = 40)	t/ χ^2	P value
Age (Mean \pm SD)	40.82 \pm 12.56	41.05 \pm 8.04	0.95	0.924
Gender, n (%)			0.000	1.000
Female	20 (50)	20 (50)		
Male	20 (50)	20 (50)		
Education level, n (%)			12.467	0.002*
Primary school	23 (57.5)	8 (20)		
High school	8 (20)	19 (47.5)		
University	9 (22.5)	13 (32.5)		
Marital status, n (%)			1.569	0.210
Single	8 (20)	4 (10)		
Married	32 (80)	36 (90)		
Number of children, n (%)			1.410	0.494
None	10 (25)	6 (15)		
One	5 (12.5)	7 (17.5)		
Two or more	25 (62.5)	27 (67.5)		
Occupational status, n (%)			10.748	0.005*
Unemployed	21 (52.5)	8 (20)		
Employed	18 (45)	32 (80)		
Student	1 (2.5)	0 (0)		
Income, n (%)			4.885	0.087
High	5 (12.5)	12 (30)		
Moderate	26 (65)	24 (60)		
Low	9 (22.5)	4 (10)		
Living status, n (%)			3.013	0.222
Alone	0 (0)	1 (2.5)		
With family	38 (95)	39 (97.5)		
Other	2 (5)	0 (0)		
Smoking status, n (%)	17 (42.5)	17 (42.5)	0.000	1.000
Alcohol consumption, n (%)	1 (2.5)	10 (25)	8.538	0.003*

Notes. * $P \leq 0.05$, Chi-squared and independent sample t -tests were used. The statistical test applied to each variable is indicated in the “ t/χ^2 ” column.

Although age and gender distributions were comparable across groups, differences were observed in education level and employment status. Owing to sample size limitations, these variables were not included in multivariate analyses and are addressed under “Limitations” section.

HC: healthy controls; SD: standard deviation; HAE: hereditary angioedema.

($P = 0.024$ and $P < 0.001$, respectively). However, there was no significant difference between two groups in terms of HADS-A and HADS-D scores. The comparison of psychometric tests between patients and healthy controls is shown in [Table 3](#) and [Figure 2](#).

Correlations between sociodemographic characteristics, psychometric test scores, and complement levels in the patient group

In correlation analysis ([Figure 3](#)), several clinically meaningful associations were identified. Sexual dysfunction (ASEX score) demonstrated a moderate positive correlation with depressive symptoms (HADS-D; Spearman’s correlation coefficient r (or ρ , p) = 0.48, $P < 0.01$) and a weaker yet statistically significant correlation with anxiety levels (HADS-A; $r = 0.34$, $P < 0.05$). Sleep quality (PSQI) showed

a moderate positive association with anxiety symptoms (HADS-A; $r = 0.48$, $P < 0.01$) and was inversely correlated with sleep efficiency ($r = -0.39$, $P < 0.05$), a pattern consistent with established pathophysiological mechanisms. Complement markers exhibited small-to-moderate correlations, including a positive relationship between C4 levels and sleep efficiency ($r = 0.35$, $P < 0.05$).

These correlations do not imply causality; however, they reflect clinically meaningful patterns within the patient cohort. Multicollinearity was minimal, and no set of variables demonstrated excessively strong interdependence. Given the number of comparisons, the results were interpreted cautiously to avoid overestimating the strength of weak or nonsignificant associations. Key relationships were further illustrated through scatter plots for ASEX-HADS-D ([Figure 4](#)) and PSQI-HADS-A ([Figure 5](#)), complementing the color-coded correlation matrix presented in [Figure 3](#).

Table 2 Clinical features of the patients with hereditary angioedema.

Number of patients, n	40
Disease Type, n (%)	
Type 1	21 (52.5)
Type 2	19 (47.5)
Comorbidity, n (%)	
No	25 (62.5)
Yes	15 (37.5)
Monthly attack frequency, n (%)	
No	4 (10)
Few	13 (32.5)
Frequent	23 (57.5)
Attacks mostly located in, n (%)	
Hands, arms, and legs	10 (25)
Abdomen/GIS	2 (5)
Extremity + abdomen	8 (20)
Extremity + abdomen + genital	5 (12.5)
Face + extremity + abdomen	1 (2.5)
Larynx + extremity	1 (2.5)
Extremity + genital	4 (10)
Face + extremity	2 (5)
Genital + abdomen/GIS	2 (5)
Entire body	1 (2.5)
History of attacks on face and tongue, n (%)	
No	36 (90)
Yes	4 (10)
History of larynx attack, n (%)	
No	28 (70)
Yes	12 (30)
History of extremity attack, n (%)	
No	8 (20)
Yes	32 (80)
History of genital attack, n (%)	
No	28 (70)
Yes	12 (30)
History of abdomen/GIS attack, n (%)	
No	21 (52.5)
Yes	19 (47.5)
Long-term prophylaxis, n (%)	
No	25 (62.5)
Yes	15 (37.5)
Long-term prophylaxis medication, n (%)	
None	25 (62.5)
C1 esterase inhibitor	9 (22.5)
Danazol	6 (15)

Note. C: complement; GIS: gastrointestinal system.

Impact of sociodemographic characteristics and sleep quality on sexual function in HAE patients

In regression analyses, longer disease duration, a history of genital attacks, and higher PSQI scores were significantly associated with higher ASEX scores. The regression model demonstrated acceptable explanatory power (adjusted $R^2 = 0.342$), and diagnostic evaluations supported the appropriateness of the model. [Table 4](#) illustrates the impact of

sociodemographic characteristics and sleep quality on sexual function in HAE patients.

Adjusted $R^2 = 0.342$. Variables were selected based on clinical relevance and the literature. Multicollinearity was assessed using variance inflation factors (VIF), which were within acceptable limits. Standard linear regression assumptions were evaluated and satisfied. CI: confidence interval; PSQI: Pittsburgh Sleep Quality Index; ASEX: Arizona Sexual Experiences Scale.

Discussion

In this study, sleep quality and sexual function were comprehensively evaluated in adult HAE patients. The literature had limited studies examining the relationship between HAE and sexual health, with the existing research primarily focusing on the potential of sexual activity to trigger attacks. Our findings show that both PSQI and ASEX scores were significantly higher in HAE patients, compared to the control group, demonstrating a significant association between HAE and impaired sleep quality and sexual function. Sexual dysfunction was positively correlated with both depression and anxiety levels; higher depression scores were associated with reduced sleep efficiency, while increased anxiety levels were related to poorer sleep quality. Regression analyses indicated that longer duration of disease, a history of genital attacks, and poor sleep quality were significantly associated with higher ASEX scores. These findings suggest that sexual dysfunction in HAE is related to a multidimensional psychosocial and clinical context.

Hereditary angioedema is characterized by angioedema attacks that can affect the face, extremities, upper respiratory tract, trunk, genital organs, and gastrointestinal system.²¹ In this study, extremity attacks were more frequent in HAE patients, followed by abdominal attacks. The proportion of genital attack was 30%, which was lower than the proportions reported in the literature.²² This discrepancy is attributed to the assessment of the proportion of patients who experienced a specific attack, rather than the total number of attacks. Nevertheless, our findings support the predominance of extremity involvement in the clinical course of HAE.

In HAE-C1-INH, the frequency and severity of attacks typically increase after puberty.²³ However, in rare cases, some patients remain entirely asymptomatic.⁴ The unpredictable nature, high frequency, and severity of these attacks—coupled with their painful and debilitating effects—adversely impact patients' work, education, social, and family life.²⁴ One study reported that HAE patients experienced work absenteeism due to the disease and that coping with attacks reduced their productivity.¹⁴ Another study involving working or school-attending patients found that 51% indicated HAE impeded their career or educational achievements.²⁵ In the present study, educational attainment was significantly lower compared to the healthy control group, while the unemployment proportion was markedly elevated at 52.5%. Our findings corroborate the literature results by demonstrating that HAE negatively affects occupational and academic life relative to both general population and healthy controls.

Table 3 Comparison of psychometric test scores of HAE patients and healthy control groups.

Test scores (Mean \pm SD)	Patients with HAE group (n = 40)	HC group (n = 40)	Z	P value*
PSQI	5.6 \pm 2.71 (6)	4.18 \pm 2.6 (4)	-2.264	0.024
HADS-A	6.17 \pm 2.66 (6)	5.83 \pm 3.74 (6)	-1.428	0.153
HADS-D	6.02 \pm 3.01 (5)	5.3 \pm 3.75 (4.5)	-0.975	0.329
ASEX	16.53 \pm 5.57 (15)	11.07 \pm 3.54 (11)	-4.564	<0.001

Notes. * $P \leq 0.05$, Mann-Whitney's U test was performed.

PSQI: Pittsburgh Sleep Quality Index; HADS-A: Hospital Anxiety Depression Scale - Anxiety; HADS-D: Hospital Anxiety Depression Scale - Depression; ASEX: Arizona Sexual Experiences Scale; SD: standard deviation; HC: healthy controls; HAE: hereditary angioedema.

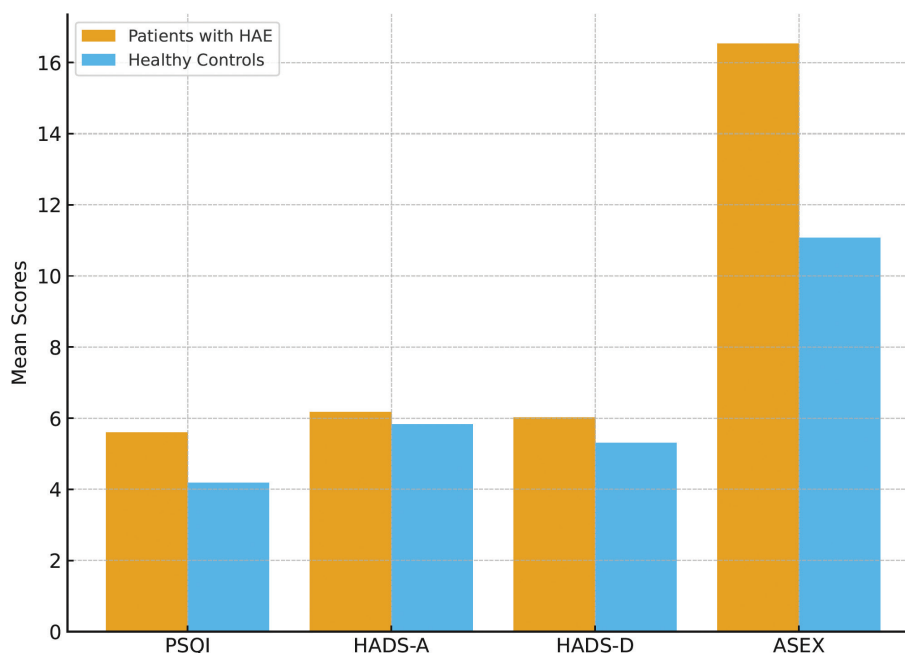


Figure 2 Comparison of psychometric test scores (HAE vs. healthy controls). PSQI: Pittsburgh Sleep Quality Index; HADS-A: Hospital Anxiety Depression Scale - Anxiety; HADS-D: Hospital Anxiety Depression Scale - Depression; ASEX: Arizona Sexual Experiences Scale; HAE: hereditary angioedema.

Sleep disturbances, one of the factors influencing quality of life, are particularly prevalent among individuals with chronic diseases.²⁶ A recent study has demonstrated poor sleep quality even during attack-free periods in HAE patients.³ Previous research has also documented most sleep disturbances in the non-severe HAE group.²⁷ In the present study, PSQI scores were significantly higher in the HAE patient group, consistent with the limited literature. Moreover, comparison with the healthy control group indicated that the overall sleep health and quality was more substantially impaired in HAE patients, relative to both national and global populations.²⁸⁻³⁰ Additionally, a positive correlation was identified between C4 levels and sleep efficiency. The literature provides insufficient data on this relationship. However, studies investigating associations between disease severity, attack frequency, and complement levels have reported a negative correlation between

C4 levels and attack frequency, highlighting its potential as a predictor of disease severity.³¹ Given that increased attack frequency may impair sleep efficiency, C4-INH levels may be indirectly related to sleep efficiency.

Stress and trauma represent the most well-established triggers of attacks in HAE. Sexual intercourse, by inducing localized trauma, has the potential to precipitate attacks. Prior studies have predominantly focused on the impact of sexual activity on HAE attacks, with insufficient investigation on the effects on sexual function among HAE patients.^{32,33} The present study reveals that sexual function is significantly impaired in HAE patients, compared to healthy controls. The fear that sexual activity may trigger attacks, along with the perception that it constitutes a medical contraindication, is posited to contribute substantially. Furthermore, chronic diseases, their treatments, and impaired sleep quality can exert adverse effects on sexual

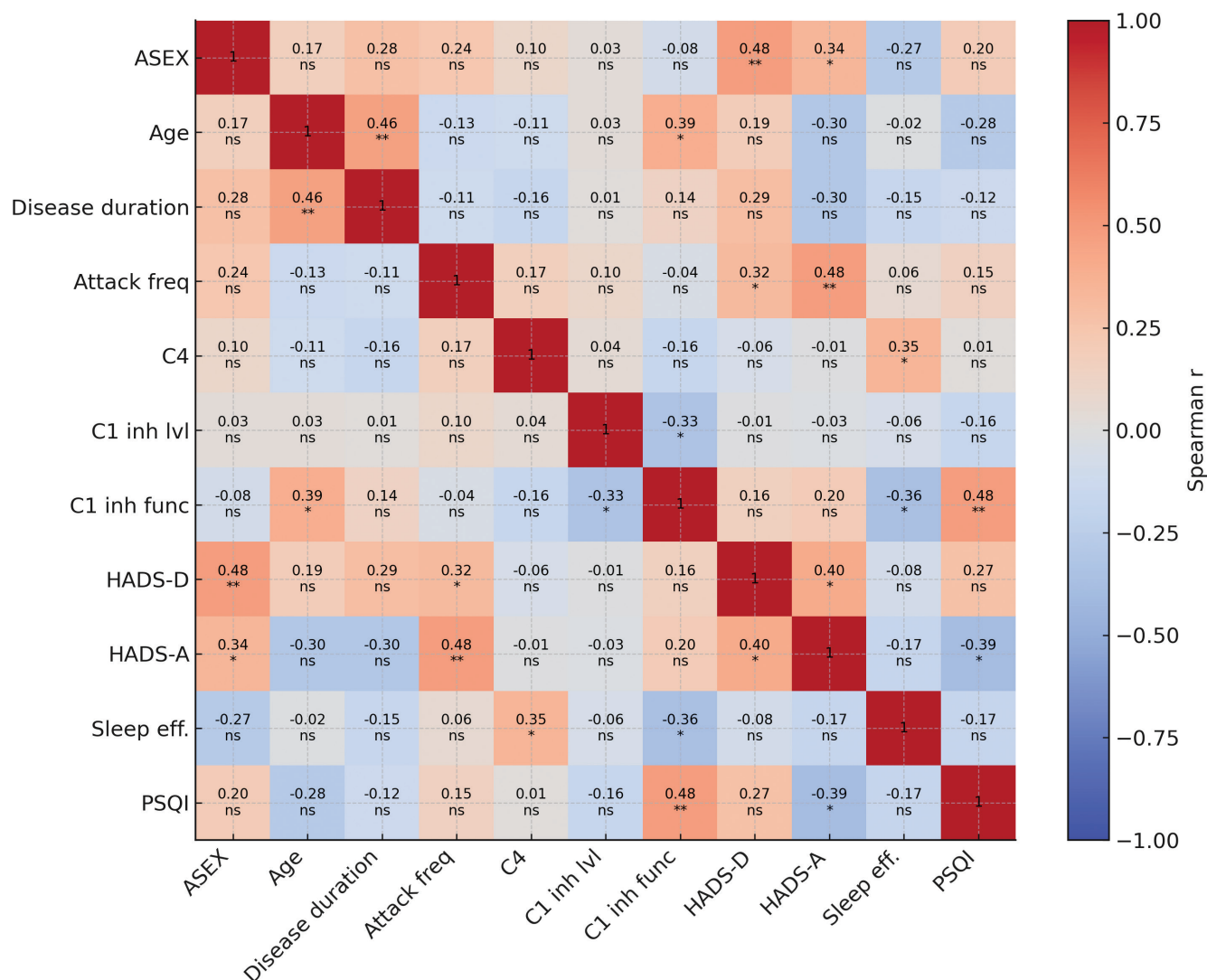


Figure 3 Color-coded correlation matrix (r and P values). Notes. Color-coded Spearman's correlation matrix demonstrating relationships between sociodemographic variables, clinical parameters, psychometric test scores, and complement levels in the patient group. Each cell displays correlation coefficient r (or rho, ρ) in the first line and the corresponding level of statistical significance in the second line (P value: nonsignificant (ns), * $P < 0.05$, ** $P < 0.01$). Darker warm colors represent stronger positive correlations, whereas cooler colors indicate negative relationships. Clinically meaningful associations were observed particularly between ASEX-HADS-D, HADS-A-PSQI, and sleep efficacy-C4 levels. Dark red: strong positive correlation; dark blue: strong negative correlation; and light shades: weak association. PSQI: Pittsburgh Sleep Quality Index; HADS-A: Hospital Anxiety Depression Scale - Anxiety; HADS-D: Hospital Anxiety Depression Scale - Depression; ASEX: Arizona Sexual Experiences Scale; attack freq: attack frequency; C: complement; C1 inh lvl: complement 1 inhibitor level; C1 inh func: C1 inhibitor function; and sleep eff: sleep efficiency.

function.⁶ However, data pertaining to sexual life are frequently underreported due to humiliation, cultural norms, or fear of stigmatization.^{7,8} Face-to-face administration of questionnaires by physicians may introduce social desirability bias. Moreover, ASEX scores are known to vary according to gender.⁷ Consequently, future implementation of anonymous or digital applications could enable more accurate evaluations of sexual life.

In HAE patients, feelings of isolation over time, guilt arising from activity restrictions, and the experience of living with a rare disease that can have serious consequences, including death, contribute to the development of anxiety

and depressive symptoms.^{15,34} A study applying HADS to the general population reported elevated anxiety and depression scores.³⁵ The lack of difference in HADS scores between the patient and healthy control groups in our study is attributed to the already high levels in the general population. Similarly, a previous study found no increased risk of depression and anxiety in HAE patients who experienced genital attacks or attacks triggered by sexual activity.³³ However, in the present study, significant positive correlations were observed between ASEX scores and both HADS-A and HADS-D scores in HAE patients, compared to healthy controls. This suggests that risk of anxiety and

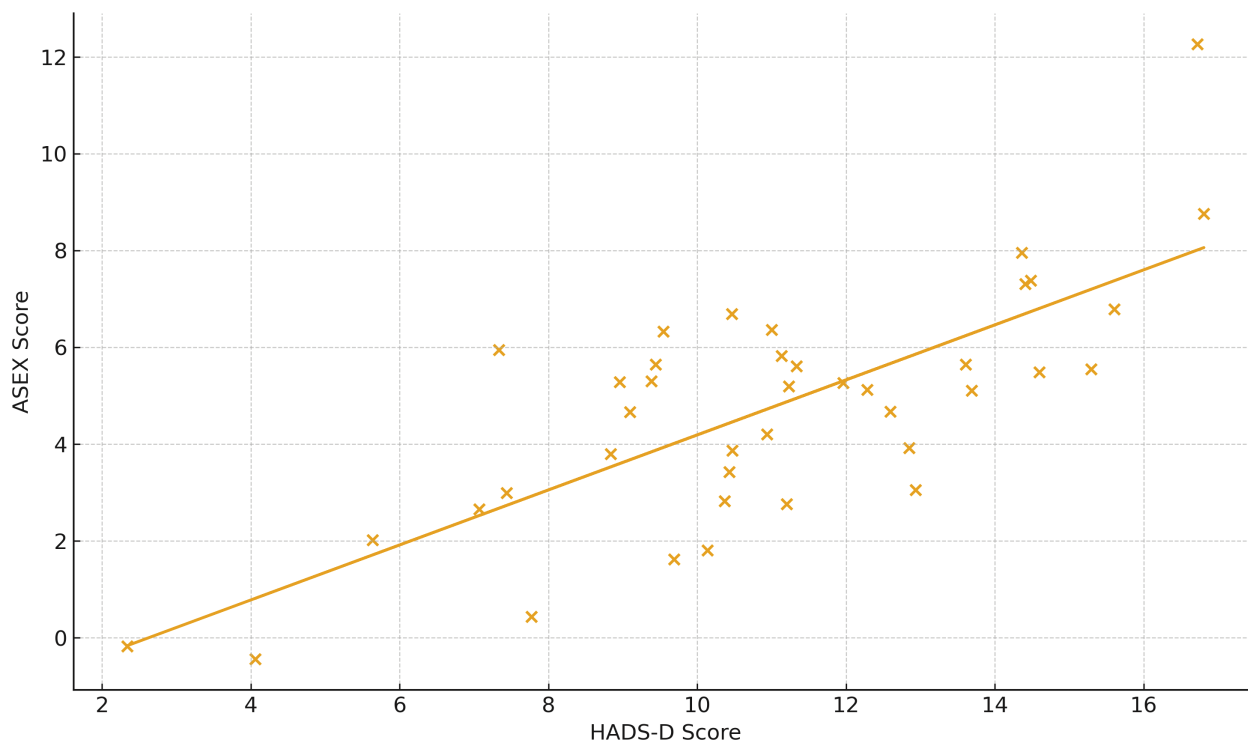


Figure 4 ASEX versus HADS-D. Notes. Scatter plot demonstrates the relationship between ASEX and HADS-D scores. A moderate positive association is visible, with higher depressive symptoms tending to coincide with greater sexual dysfunction. The regression line reflects the direction of association; however, the plot does not imply causality. ASEX: Arizona Sexual Experiences Scale; HADS-D: Hospital Anxiety Depression Scale - Depression.

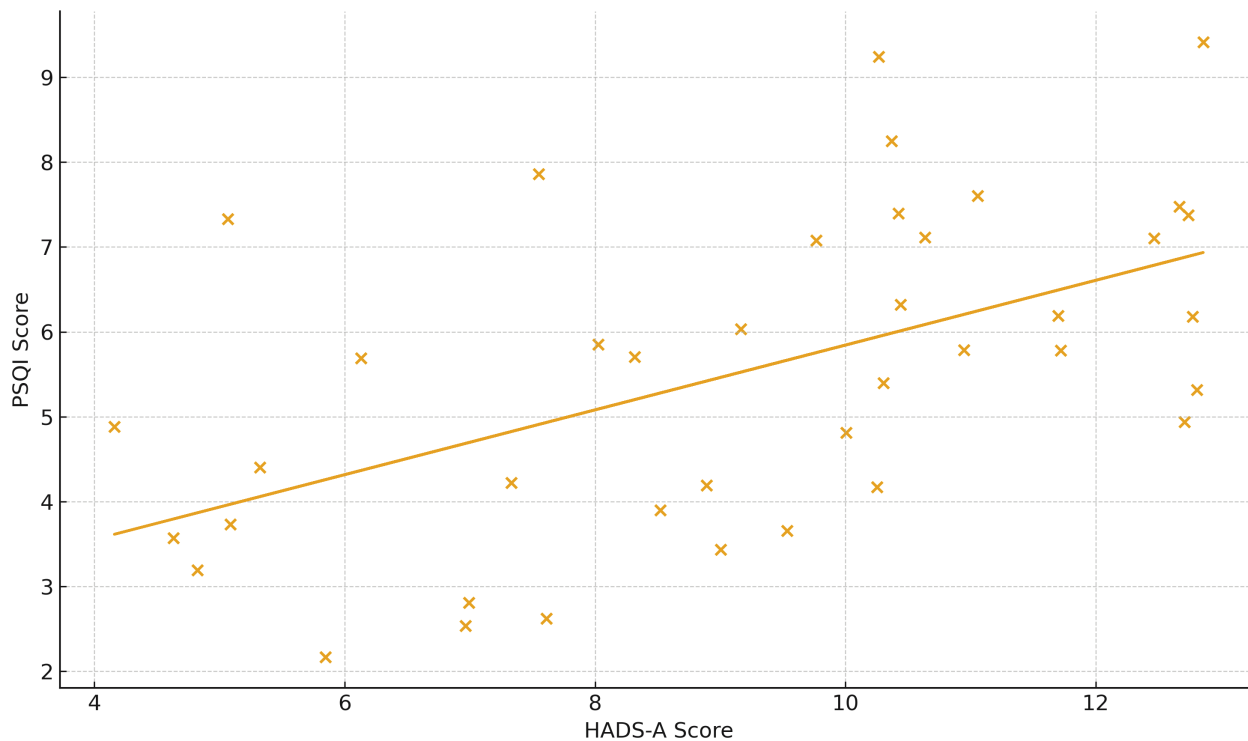


Figure 5 PSQI versus HADS-A. Notes. Scatter plot visualizing the association between PSQI and HADS-A scores. Anxiety symptoms show a moderate-to-strong positive relationship with poorer sleep quality. The regression line illustrates the upward trend in this association, without implying a causal effect. PSQI: Pittsburgh Sleep Quality Index; HADS-A: Hospital Anxiety Depression Scale - Anxiety.

Table 4 Effect of sociodemographic characteristics and sleep quality on sexual functions in HAE patients.

Independent variables	ASEX		
	Beta	95.0% CI for β coefficient	P value
Constant	13.775	8.819-18.731	<0.001*
History of genital attack (1 = No)	-5.874	-9.187--2.560	0.001*
Disease duration	0.158	0.032-0.283	<0.015*
PSQI	0.612	0.05-1.174	0.034*
Number of attacks per month	0.245	-0.297-0.788	0.364

Notes. * $P \leq 0.05$. Multivariate linear regression analysis was used.

depression may be elevated in HAE patients with sexual dysfunction. Considering the contribution of inflammatory mediators to the development of anxiety and depression in HAE patients,¹⁵ the increased risk specifically in those with sexual dysfunction implies that sexual life provides an additional contribution to anxiety and depression in these individuals.

Anxiety is prevalent, particularly among HAE patients experiencing severe or frequent attacks, and substantially impairs their quality of life.^{14,36} A study utilizing the Hamilton Depression Scale demonstrated that depression scores increase with greater attack severity.³⁷ Another study reported that elevations in attack frequency and severity adversely affect quality of life and contribute to heightened fear and anxiety.³⁸ Consistent with these prior findings, the present study observed that increase in the frequency of monthly attacks was significantly associated with elevated depression and anxiety scores. Additionally, higher depression scores correlated with reduced sleep efficiency, while a strong positive correlation existed between anxiety scores and PSQI scores ($P < 0.05$). A previous study indicated that sleep disturbances in HAE patients may be associated with nocturnal attacks (initiating or persisting at night), related anxiety, or psychological distress.¹⁵ Another investigation identified similarly elevated proportions of depression, anxiety, and sleep disturbance symptoms among HAE patients (88.2%, 76.5%, and 76.5%, respectively).³⁹ Our findings corroborate that depression and anxiety negatively impact sleep health in these patients. Consequently, psychometric assessments represent valuable tools for evaluating quality of life, mental health, and sleep health issues, supporting their routine integration into the monitoring and management of HAE patients.⁴⁰

In this study, regression analyses demonstrated that longer disease duration, history of genital attacks, and higher PSQI scores were significantly associated with higher ASEX scores. The rarity of HAE and lack of awareness often lead to delayed diagnosis, thereby prolonging disease duration and increasing comorbidities. Accordingly, our findings support an increased risk of adverse effects on sexual function with longer duration of disease.^{3,41} HAE causes substantial psychological distress and misconceptions regarding triggers.^{32,33} In particular, attacks in the genital region lead to anticipatory anxiety, sexual avoidance, and diminished relationship satisfaction. Consistent with the literature, our study reinforces the idea that a history of

genital attacks can predict sexual dysfunction.^{14,32,33} Recent research indicates that inadequate sleep and sleep disorders impact various aspects of human health, including sexual function.⁴² Chronic sleep deprivation is linked to reduced testosterone levels,⁴³⁻⁴⁵ and decrease testosterone level exerts negative effects on health and quality of life, including sexual function.⁴⁶⁻⁴⁸

Furthermore, poor sleep quality is associated with sexual dysfunction in women. These observations underscore the interplay between sleep and neuro-immuno-endocrine homeostasis.⁴⁹ Collectively, the association between elevated PSQI scores and sexual dysfunction in our study suggests that sleep disturbances in HAE patients may influence sexual life through mechanisms distinct from psychological effects.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, the retrospective and cross-sectional design limits the ability to infer causality, and the results should therefore be interpreted as associations, rather than causal relationships. Variations in participants' perceptions and the potential for recall bias may have influenced self-reported outcomes. Second, the relatively small sample size, although expected, given the rarity of HAE, may have reduced the statistical power and limited the ability to adjust for multiple potential confounding variables. Consequently, the findings should be interpreted within the context of an exploratory analysis. Third, all outcome measures were derived from validated but subjective questionnaires, which may be influenced by individual reporting tendencies. Importantly, all questionnaires were administered face-to-face by the same treating physician, which may have introduced response bias, including social desirability bias, particularly in sensitive domains, such as sexual function and mental health.

Participants may have underreported symptoms or concerns because of discomfort or perceived expectations. Adjustments for socioeconomic factors, comorbidities, use of medication, and psychiatric history could have further strengthened the analyses. Although age and gender were comparable in the healthy control group, matching for education level and employment status could not be achieved. Owing to the limited sample size and the risk of

model overfitting in multivariate regression analyses, these adjustments were not performed.

Finally, while including a healthy control group enhances the study's comparative value, validating the findings in larger, multicenter cohorts would be beneficial. Future studies incorporating objective assessments of sleep quality and sexual function, along with anonymous or self-administered data collection methods, could help to reduce bias and improve the generalizability of results.

Conclusion

This study demonstrates that both sleep quality and sexual function are more impaired in HAE patients, compared to healthy controls. The associations identified between clinical features, such as sleep disturbance, prolonged disease duration, and history of genital attacks with sexual function, suggest that these domains warrant consideration in management of HAE. Furthermore, relationships between anxiety, depression, sleep, and sexual function underscore the necessity of incorporating psychosocial evaluations into routine follow-up. Accordingly, a holistic assessment of HAE patients, with collaboration among relevant specialists as needed, is recommended. Future studies utilizing larger sample sizes and objective measurement methods will more clearly delineate the quality and clinical significance of these associations.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Ethics Approval and Consent to Participate

This study, involving human subjects, was conducted in accordance with the principles of the Declaration of Helsinki (1975) and was approved by the local ethics committee of Necmettin Erbakan University Medical Faculty Hospital, Konya, Türkiye (Decision No. 2023/4715). All participants provided their written informed consent to participate in this study. Furthermore, explicit consent was obtained to publish the data collected from the participants. The consent forms used specifically stated that the participants acknowledged that their anonymized data could be used for scientific publication.

Author Contributions

All authors contributed equally to this article.

Conflict of Interest

The authors declared no potential conflict of interest with respect to research, authorship, and/or publication of this article.

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