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UNEXPLAINED FATIGUE IN THE HEALTHY POPULATION: THE ROLE OF DEPRESSION, SLEEP, AND SOCIAL FACTORS

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Abstract

Objectives: Fatigue is characterised as a feeling of exhaustion that arises with a reduction in the ability to engage in physical or mental activities. This study aims to examine the root causes of fatigue symptoms and associated demographic characteristics among persons devoid of any underlying medical disorders.

Materials and Methods: The study included 125 patients who visited the outpatient neurology clinic reporting fatigue. Data was collected using the Chalder Fatigue Scale (CFS), the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale, the Beck Depression Inventory (BDI), and the Beck Anxiety Inventory (BAI).

Results: The mean age of the patients was 46.01±12.10 years, with 67.2% (n=84) being female. The prevalence of individuals who were married (p=0.002), employed (p=0.004), and possessed a university degree (p=0.033) was greater among women compared to men. Elevated BDI scores were (OR: 1.192, 95% CI: 1.057–1.337, p=0.003) and PSQI scores (OR: 1.782, 95% CI: 1.376–2.192, p<0.001) significantly associated with higher fatigue severity. The CFS ratings were significantly elevated in individuals with a university degree relative to those with primary education (OR: 3.032, 95% CI: 1.099–8.122, p=0.031). Unemployment was associated with a markedly reduced probability of experiencing fatigue (OR: 0.083, 95% CI: 0.032-0.232, p<0.001).

Conclusion: Our study demonstrated that elevated educational attainment, unemployment, compromised sleep quality, and heightened depression were associated with fatigue symptoms. The data demonstrate that weariness is associated not only with physiological aspects but also highly impacted by psychological and social factors.

Keywords: Fatigue, depression, sleep disorder, anxiety.

Introduction

Fatigue is characterised as a feeling of exhaustion resulting from diminished physical or mental activity capacity. Fatigue is a significant symptom linked to various chronic health conditions and can adversely affect quality of life.[1] The prevalence in European countries ranges from 20% to 60%, contingent upon the assessment methodologies and the age demographics examined.[2,3] Commonly observed in primary care, weariness detrimentally influences patients' quality of life and diminishes productivity, hence significantly affecting national economies.

Fatigue has been linked to various causes, including physical, psychological, and environmental issues such as lifestyle and occupational circumstances. Studies have shown that sleep disruptions, psychosocial stress, depression, and respiratory illnesses are prevalent causes of chronic fatigue.[4] In contemporary societies, shifts in job and family obligations, coupled with a rise in the incidence of illnesses like metabolic syndrome, anxiety, and depression, have resulted in detrimental modifications to the requisite quantity of sleep for optimal physiological functioning.[5] Furthermore, the wholly subjective nature of fatigue and the absence of definitive diagnostic criteria have compelled neurologists, who often observe this symptom in clinical settings, to investigate its underlying causes. Nonetheless, whereas the majority of current research has concentrated on particular disorders, our study sought to examine the fundamental causes and demographic attributes of fatigue symptoms among persons devoid of any recognised medical conditions.

Materials and Methods

Study design and participants

This prospective study was approved by the Ankara City Hospital Ethics Committee on December 10, 2022 (Protocol No: E2-22-2556), and all procedures adhered to the principles of the Declaration of Helsinki. All participants provided written informed consent. One hundred twenty-five patients presenting with fatigue at the outpatient neurology clinic from November 2022 to March 2025 were included in the study. Patients exhibiting fatigue and having a history of diabetes mellitus, hypertension, rheumatologic diseases, chronic kidney disease, oncologic conditions, chemotherapy, immunologic disorders, thyroid dysfunction, heart disease, anaemia, recent infections, or prior medication use were excluded from the study. Furthermore, pregnant women, individuals below 18 years of age, and those who opted out of participation were excluded from the study. Data on age, sex, marital status, occupational status, and educational attainment were collected for all participants.

Data collection and questionnaires

For data collection, questionnaires were distributed to participants who consented after being fully informed about the study. Questionnaires were collected on the same day they were completed.

This study utilised the Chalder Fatigue Scale (CFS) to evaluate fatigue levels. The CFS comprises 11 items that assess physical and mental fatigue. Items are evaluated using a 4-point scale that ranges from asymptomatic to maximal symptomatology. Likert scoring (0–3) was utilised, resulting in total scores from 0 to 33; elevated scores reflect increased severity of fatigue.[6]

The Pittsburgh Sleep Quality Index (PSQI) was utilised to assess sleep quality. The PSQI consists of seven components that evaluate sleep disturbances and overall sleep quality during the preceding month. The scoring for each item ranges from 0 to 3, resulting in a cumulative score that spans from 0 to 21. Scores exceeding 5 signify inadequate sleep quality.[7]

The overall degree of daytime sleepiness was evaluated utilising the Epworth Sleepiness Scale (ESS). The ESS is an 8-item tool designed to assess the probability of dozing off or falling asleep during routine activities, utilising a 4-point Likert-type scale (0–3) for scoring. Total scores vary between 0 and 24, with scores exceeding 10 signifying excessive daytime sleepiness.[8]

The Beck Depression Inventory (BDI) is a self-report tool intended to evaluate cognitive, emotional, and motivational symptoms related to depression. The instrument comprises 21 items, each rated on a 0–3 scale, with the cumulative score reflecting the severity of depressive symptoms.[9] The Beck Anxiety Inventory (BAI) is a self-report questionnaire consisting of 21 items designed to assess the severity of anxiety symptoms, particularly somatic and cognitive components of anxiety. Each item is scored on a 4-point Likert scale ranging from 0 to 3, with higher total scores indicating greater anxiety severity. The BAI has been widely validated and is commonly used in both clinical and research settings. [10]

Statistical Analysis

In this study, data analysis was performed using IBM SPSS Statistics version 25.0. Descriptive statistics are presented as numbers (n) and percentages (%) for categorical variables, and as mean ± standard deviation for continuous variables. For comparisons between groups, the Independent Samples t-test was used for continuous variables, and the Chi-square test was applied for categorical variables. To identify the factors affecting the CFS, multivariable logistic regression analysis was conducted. Variables included in the multivariable logistic regression model were selected based on clinical relevance and prior evidence from the literature. In addition, variables showing an association with fatigue at a significance level of $p < 0.10$ in

univariate analyses were entered into the multivariable model. The logistic regression analysis was performed using the enter method. For continuous variables found to be significant (PSQI and BDI), receiver operating characteristic (ROC) curves and the area under the curve (AUC) were utilised. A p-value of <0.05 was considered statistically significant.

Although this study was prospective, it was designed as an exploratory, observational study without an interventional hypothesis. Therefore, no a priori sample size calculation was performed. All consecutive patients who met the inclusion criteria during the study period were enrolled.

To assess the adequacy of the final sample size, receiver operating characteristic (ROC) curve analysis was performed for the main predictor variables. The area under the curve (AUC) values were reported together with 95% confidence intervals, and statistical significance was tested against the null hypothesis of AUC = 0.50.

Results

Out of 214 patients presenting to the neurology outpatient clinic with fatigue complaints, 125 were included in the study. Figure 1 illustrates the enrollment process in detail.

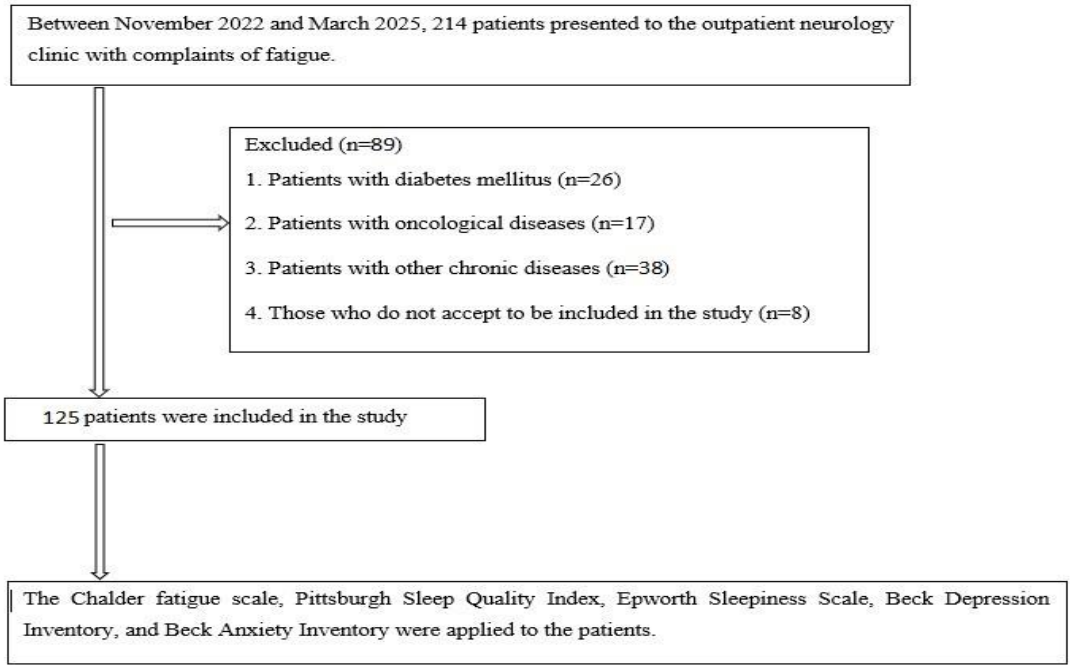

Figure 1. Flow chart of patients included in the study

The demographic characteristics and questionnaire scores of the patients are listed in Table 1. The mean age of the patients was 46.01 ± 12.10 years, and 67.2% (n=84) were female. Of the patients, 64% (n=80) were married, and 50.4% (n=63) had children. Regarding employment status, 48.8% (n=61) were employed, 38.4% (n=48) were unemployed, and 12.8% (n=16) were students. In terms of educational level, 24% (n=30) had a primary school education, 43.2% (n=54) had completed high school, and 32.8% (n=41) held a university degree. The proportion of married, employed, and university-educated patients was higher among women than men (p=0.002, p=0.004, p=0.033). The mean scores on the scales were as follows: Chalder Fatigue Scale 21.21 ± 4.16, Pittsburgh Sleep Quality Index 8.32 ± 2.88, Epworth Sleepiness Scale 9.20 ± 3.55, Beck Depression Inventory 17.43 ± 6.21, and Beck Anxiety Inventory 15.90 ± 5.06. Total scores on all scales were significantly higher in women than in men (p<0.05) (Table 1).

Table 1. Demographic characteristics of patients and questionnaire results

	Male (n=41)	**Female** (n=84)	**Total** (n=125)	**p**
Age(Mean±SD)	48.39 ± 11.88	44.85 ± 12.10	46.01 ± 12.10	0.124
Marital Status				
Married	18 (44%)	62 (74%)	80 (64%)	0.002
Single	23 (56%)	22 (26%)	45 (36%)	
Children				
Yes	30 (73.2%)	33 (39.3%)	63 (50.4%)	0.449
No	11 (26.8%)	51 (60.7%)	62 (49.6%)	
Employment Status				
Employed	14 (34.1%)	47 (55.9%)	61 (48.8%)	0.004
Unemployed	22 (53.7%)	26 (31.0%)	48 (38.4%)	
Student	5 (12.2%)	11 (13.1%)	16 (12.8%)	
Education Level				
Primary school	12 (29.2%)	18 (21.4%)	30 (24%)	0.033
High school	22 (53.7%)	32 (38.1%)	54 (43.2%)	
University	7 (17.1%)	34 (40.5%)	41 (32.8%)	
CFS	18.95±3.89	22.31±3.85	21.21±4.16	< 0.001
PSQI	7.00±2.77	8.96±2.73	8.32±2.88	< 0.001
Epworth SS	7.95±2.86	9.81±3.71	9.20±3.55	0.002
BDI	14.59 ±5.87	18.82 ±5.92	17.43 ±6.21	< 0.001
BAI	13.41±4.95	17.12±4.67	15.90±5.06	< 0.001

CFS: Chalder Fatigue Scale, PSQI: Pittsburgh Sleep Quality Index, Epworth SS: Epworth Sleepiness Scale, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory

Factors associated with fatigue were evaluated using a multivariate logistic regression model. Increased BDI scores were significantly associated with higher fatigue scores (OR: 1.192, 95% CI: 1.057–1.337, p=0.003). Similarly, higher PSQI scores were significantly associated with higher fatigue scores (OR: 1.782, 95% CI: 1.376–2.192, p<0.001). University-educated individuals had higher CFS scores compared to those with primary education (OR: 3.032, 95% CI: 1.099–8.122, p=0.031), while unemployed individuals were significantly less likely to report fatigue (OR: 0.083, 95% CI: 0.032-0.232, p<0.001). (Table 2)

Table 2. Multivariate logistic regression analysis of factors associated with fatigue

Variables	β	SE	**OR (95% CI)**	p
Age	0.016	0.014	1.021 (0.992-1.055)	0.234
Gender (Male)	0.637	0.401	1.588 (0.722-3.492)	0.115
BDI	0.172	0.06	1.192 (1.057-1.337)	**0.003**
BAI	-0.036	0.066	0.965 (0.848–1.098)	0.584
PSQI	0.577	0.101	1.782 (1.376-2.192)	**<0.001**
Epworth SS	0.004	0.069	1.002 (0.871-1.142)	0.953
Education (University)	1.112	0.510	3.032 (1.099-8.122)	**0.031**
Employment (Unemployed)	-2.558	0.549	0.083 (0.032-0.232)	**<0.001**
Children (Yes)	0.276	0.503	1.324 (0.492-3.582)	0.584
Marital Status(Married)	-0.326	0.540	0.722 (0.243-2.112)	0.547

Nagelkerke R^2 = 0.826, SE: standard error, OR: Odds Ratio, CI: confidence interval, PSQI: Pittsburgh Sleep Quality Index, Epworth SS: Epworth Sleepiness Scale, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory

ROC curve analysis was performed to identify cut-off values for the continuous variables that were significant in the logistic regression (PSQI and BDI). The PSQI cut-off value was 8 (specificity: 86%, sensitivity: 86%, AUC: 0.911), and the BDI cut-off value was 17 (specificity: 95%, sensitivity: 77%, AUC: 0.865). (Figure 2)

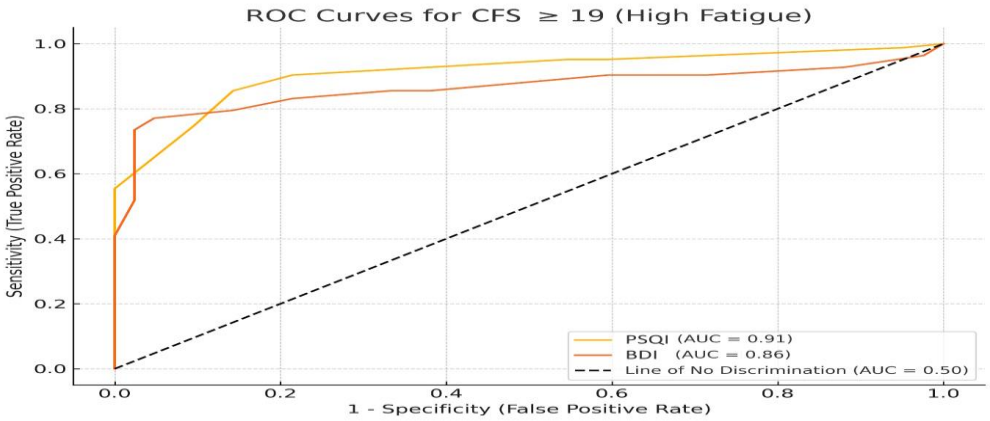

Figure 2. ROC curve analysis for Chalder Fatigue Scale

Discussion

In this study, we investigated the demographic and psychosocial factors associated with fatigue, a symptom frequently encountered in clinical practice, among individuals without a formal medical diagnosis. Our findings demonstrate that higher educational level, unemployment, impaired sleep quality, and increased depression are associated with fatigue symptoms. These results underscore that fatigue is not only related to physiological factors but is also significantly influenced by psychological and social variables.

The majority of individuals presenting with fatigue symptoms were women, and these women were more likely to be married, employed, and highly educated. In a recent nationwide, population-based cross-sectional survey conducted by Cruickshank et al., female sex and lower educational level were associated with a greater risk of fatigue.[11] Conversely, in another study, Knoers et al. reported that fatigue was more prevalent among employed, highly educated women.[12] The elevated fatigue scores observed in working individuals may reflect the cumulative impact of occupational and daily responsibilities, which can deplete an individual's physical and mental resources. The significantly lower fatigue scores in unemployed individuals support this hypothesis. Furthermore, we propose that high educational attainment may contribute to increased fatigue due to heightened expectations and performance anxiety in both occupational and personal domains. Consistent with these findings, we observed that women had significantly higher scores across all questionnaires. We suggest that multiple factors could account for this observation, including higher rates of depression, anxiety, and sleep disturbances among women, as well as differences in healthcare-seeking behaviour and symptom reporting. Additionally, biological, hormonal, and social role differences may also contribute to more pronounced experiences of fatigue in women. The dual burden of managing domestic responsibilities alongside professional commitments can limit time for rest and recuperation, potentially predisposing women to chronic fatigue. Our findings, including higher depression, anxiety, and sleep disturbance scores among female participants, support this multidimensional interplay.

In our study, we observed a strong positive correlation between PSQI and CFS scores and determined an optimal PSQI cut-off value of 8 via ROC analysis. These results suggest that impaired sleep quality is a substantial contributing factor in the emergence of fatigue symptoms. In a study by Ju Kim et al., insomnia severity and daytime sleepiness were found to be closely related to fatigue severity. Their findings indicated that poor sleep quality has considerable effects on daily energy levels and cognitive performance, and that managing insomnia or depression could alleviate fatigue.[13] Prior research has also shown that declining sleep quality and increased fatigue with ageing are associated with reduced quality of life and mortality.[14,15] Moreover, Christie et al. demonstrated that improving sleep in older adults can reduce self-reported fatigue independently of increased physical activity.[16]

Our study revealed a significant correlation between increased fatigue scores and elevated levels of depression. ROC analysis determined a cut-off value of 17 for the Beck Depression Inventory. Depression affects fatigue not only through mood alterations but also via various mechanisms, such as diminished motivation, social withdrawal, and disrupted sleep patterns. A recent population-based study demonstrated an association between depression and both fatigue symptoms and daytime sleepiness.[17] Fatigue, influenced by its emotional and cognitive dimensions, may be linked to various psychiatric and physical diagnoses.[18,19] Research indicates that individuals with medically unexplained fatigue have an approximately 11-fold increased likelihood of being diagnosed with depression relative to those without such fatigue.[20] Our findings align with existing literature, indicating that individuals exhibiting fatigue symptoms report higher levels of depression than the general population.[21] Fatigue must be examined from both medical and psychosocial viewpoints. Mood disturbances, social support levels, coping mechanisms for stress, and lifestyle habits can all affect the severity of fatigue symptoms. The findings of our study indicate a significant correlation among depression, sleep quality, and fatigue, underscoring the importance of a comprehensive evaluation of these symptoms.

Nonetheless, certain limitations exist. The limited sample size and single-centre design may constrain the generalizability of the findings. Furthermore, considering that fatigue is a subjective symptom significantly shaped by individual perception, the objective measurement of this variability is often impractical.

In conclusion, this study indicates that elevated educational attainment, unemployment, poor sleep quality, and heightened depression are associated with fatigue symptoms. The findings suggest that fatigue is related not only to physiological factors but also to psychological and social factors. Future studies with larger sample sizes, preferably multicenter and longitudinal in design, are warranted to provide deeper insights into the mechanisms underlying fatigue symptoms and to improve diagnostic and therapeutic approaches in clinical practice.

Ethical Considerations: The study was approved by Ankara City Hospital Ethics Committee on 12/10/2022, protocol number E2-22-2556, and all procedures were carried out in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest: The authors declare no conflict of interest.

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