

# Northumbria Research Link

Citation: Schoon, Hannah, Slack, Emma, Pearce, Mark, Ng, Wan-Fai and Hackett, Katie (2022) Activity Interference in Patient's with Sjögren's Syndrome: A Cross-Sectional Study of 149 Patients in the UK. *Rheumatology*, 61 (10). pp. 4065-4075. ISSN 1462-0324

Published by: Oxford University Press

URL: <https://doi.org/10.1093/rheumatology/keac053>  
<<https://doi.org/10.1093/rheumatology/keac053>>

This version was downloaded from Northumbria Research Link:  
<https://nrl.northumbria.ac.uk/id/eprint/48251/>

Northumbria University has developed Northumbria Research Link (NRL) to enable users to access the University's research output. Copyright © and moral rights for items on NRL are retained by the individual author(s) and/or other copyright owners. Single copies of full items can be reproduced, displayed or performed, and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided the authors, title and full bibliographic details are given, as well as a hyperlink and/or URL to the original metadata page. The content must not be changed in any way. Full items must not be sold commercially in any format or medium without formal permission of the copyright holder. The full policy is available online: <http://nrl.northumbria.ac.uk/policies.html>

This document may differ from the final, published version of the research and has been made available online in accordance with publisher policies. To read and/or cite from the published version of the research, please visit the publisher's website (a subscription may be required.)



**Northumbria  
University**  
NEWCASTLE



**UniversityLibrary**

**Title:** Activity Interference in Patient's with Sjögren's Syndrome: A Cross-Sectional Study of 149 Patients in the UK

Hannah Schoon<sup>1,2</sup>, Dr. Emma Slack<sup>3</sup>, Dr. Mark Pearce<sup>3</sup>, Prof. Wan-Fai Ng<sup>4</sup>, Dr. Katie L Hackett<sup>5</sup>

<sup>1</sup>Epidemiologist, Southeast Utah Health Department, US

<sup>2</sup>Albion College, Michigan, US

<sup>3</sup>Population Health Sciences Institute, Newcastle University, UK

<sup>4</sup>NIHR Newcastle Biomedical Research Centre, Newcastle University, UK

<sup>5</sup>Department of Social Work, Education and Community Wellbeing, Northumbria University, UK

**Corresponding Author:** Dr. Katie L Hackett, Department of Social Work, Education and Community Wellbeing, Northumbria University, Coach Lane Campus West, Coach Lane, Newcastle upon Tyne, NE7 7XA, UK. email: kate.hackett@northumbria.ac.uk

**Keywords:** Sjögren's Syndrome, activity interference, autoimmunity

**Key messages:**

1. In this group of pSS patients, fatigue had the largest impact on activity interference
2. Longer duration of a clinical diagnosis resulted in better quality of life in pSS patients
3. Activity interferences experienced with pSS are significantly interconnected with one another

**Data availability statement:**

The dataset used and/or analysed during the current study is available from the corresponding author on reasonable request.

1 **Abstract:**

2 **Objectives:** To investigate which five activity interference categories; pain, fatigue, mood, dryness and  
3 brain fog/mental fatigue, scored highest in patients with primary Sjögren’s syndrome (pSS) and to  
4 investigate the association between activity interference and mood and physical functioning in these  
5 patients.

6 **Methods:** The Comprehensive Pain Evaluation Questionnaire (CPEQ) assessed activity interference  
7 (actions done in daily life that are hindered) in 149 UK pSS patients. This was modified to include 4  
8 additional symptoms (fatigue, mood, dryness and brainfog/mental fatigue). Functional impairment was  
9 measured using the Hospital Anxiety and Depression Scale (HADs) and the IMPROVED Health  
10 Assessment Questionnaire (IMPROVED HAQ). Univariable linear regression models were estimated to  
11 investigate the association between CPEQ results and the outcome scores obtained from the HADs and  
12 IMPROVED HAQ. Multivariable linear regression models were estimated adjusting for patient age and  
13 length of disease.

14 **Results:** Fatigue had the biggest impact on 7 activity domains: physical exercise (mean score of 3.49 out  
15 of 5 [SD 1.26]), performing household chores (mean 3.14 [SD 1.18]), gardening or shopping (mean 3.18  
16 [SD 1.20]), socializing with others (mean 2.62 [SD 1.24]), recreation/hobbies (mean 2.88 [SD 1.20]),  
17 sexual relations (mean 3.00 [SD 1.52]), and mental efficacy (mean 2.69 [SD 1.17]). Regression analysis  
18 showed a positive correlation where every point increase in an activity interference category saw the  
19 overall mood and physical functioning scores increase.

20 **Conclusion:** Fatigue has the largest impact on pSS patients’ daily activities in this cohort. Length of  
21 disease reduced the impact of activity interference on patient’s overall health score.

22

## 23 Introduction

24 Primary Sjögren's syndrome (pSS) is classified as the second most common autoimmune disease in the  
25 world, closely behind Rheumatoid Arthritis (RA), with a variable prevalence rate of 0.5-2.0%.<sup>1-3</sup> Incidence  
26 is just as varied, with estimates ranging between 3.9-6.0 per 100,000 people.<sup>1,3-4</sup> Like most autoimmune  
27 diseases, it is more common in women with evidence showing a 20:1 female to male ratio.<sup>4</sup> Those with  
28 pSS disease are classified by defective lacrimal (eye) and salivary glands, along with exocrine gland  
29 inflammation.<sup>5</sup> pSS is a complex disease that is still not completely understood.<sup>4</sup> Research has  
30 consistently reported an increased risk of acquiring secondary diseases (non-Hodgkin B-cell lymphoma  
31 [RR of 13.76, 95% CI 8.53-18.9<sup>6</sup>], lung disease [up to 75% of pSS patients<sup>7</sup>], and myocardial infarctions [p-  
32 value 0.002<sup>8</sup>]) after a pSS diagnosis, causing further complications.<sup>6-8</sup> Oral and eye health are universal  
33 complaints made by both male and female patients.<sup>5</sup> Keratoconjunctivitis sicca that leads to  
34 xerophthalmia (dry eyes disease [DED]) is the most commonly reported eye condition with 95% of  
35 patients reporting symptoms.<sup>5,9</sup>

36

37 Due to pSS chronic and integral pathology, patient's quality of life is significantly affected through  
38 multiple different avenues. Numerous studies have used self-reported questionnaires to look at the  
39 general quality of life affected via pSS.<sup>2,10-12</sup> One study conducted in the United States (US) showed  
40 found that patients in the US with pSS are more likely to be hospitalized, experience infections and  
41 require the use of multiple medications.<sup>10</sup> Out-of-pocket spending on dental care has also been shown  
42 to be three fold higher in those with pSS in the US.<sup>11</sup> Those in the UK are not sheltered from similar  
43 socio-economic effects, with patients spending between £9,800-£15,700 annually on direct (defined as  
44 "the value or resources used in the diagnosis, treatment, and rehabilitation of a disease") and indirect  
45 healthcare costs ("economic productivity lost due to the disease").<sup>12-13</sup> In 2005, the US Sjögren's  
46 Syndrome Foundation surveyed over 3,000 patients and found the average time to diagnosis after the  
47 initial presentation of symptoms took over 6 years.<sup>5</sup> Qualitative evidence suggested that this delay in  
48 diagnosis increased mental and family struggles for patients with pSS.<sup>14-15</sup>

49

50 Compared to other autoimmune diseases, research into pSS is not as advanced and further exploration  
51 into activity interference among these patients is even less. Previous research has only looked at one  
52 symptom, while others take a broader approach and analyse only the quality of life.<sup>2,10-12</sup> This study goes  
53 further by looking at multiple different pSS symptoms to observe possible activity interferences patients  
54 may face in their daily lives. We also evaluate mental health symptoms, using the Hospital Anxiety and

55 Depression Scale (HADs), physical constraints, and an overall health assessment, analysis that to our  
56 knowledge has not previously been explored in depth. By looking at several aspects of patient's  
57 symptoms, including mood, dryness, fatigue, pain, and brain fog/mental fatigue, we can obtain a clearer  
58 insight into pSS patients and their daily struggles. Including HADs allows us to investigate mental health  
59 symptoms experienced by Sjögren's patients. Due to the unclear pathology of pSS, treatment is centred  
60 on symptoms rather than the disease itself. Further knowledge into how these symptoms interfere with  
61 a patient's activity level could shift research focus on treatments that are effective for the most limiting  
62 symptoms.

63

## 64 **Methods**

65 This study uses anonymised, cross-sectional quantitative data on patients with pSS (n=149) from a  
66 previous mixed methods study engaging PSS patients, family members and healthcare professionals to  
67 identify barriers and facilitators to participating life activities.<sup>16</sup> Data collection methods are described in  
68 detail elsewhere.<sup>17</sup> In summary, patients who were diagnosed using the American European Consensus  
69 Group (AECG) classification were recruited to participate in the United Kingdom Sjögren's Syndrome  
70 Registry (UKPSSR).<sup>16-18</sup> This database consists of Primary Sjögren's Syndrome (pSS) patients from  
71 different areas in the United Kingdom who have consented to be contacted for future research.<sup>16-18</sup>  
72 Using the UKPSSR, patient enrolment occurred between February and August of 2014 from 12 locations  
73 throughout England.<sup>16</sup> An invitation packet was mailed out with pSS formulated questionnaires.<sup>16</sup>  
74 Regulations outlined in the Helsinki Declaration were used to obtain consent from all participants.<sup>16,19</sup>  
75 <sup>19</sup> A favourable ethical opinion for the original study was obtained from the Office for Research Ethics  
76 Committee of Northern Ireland [13/NI/0190], and the committee specifically approved this study.  
77 Participants provided written informed consent prior to taking part. The anonymised dataset is available  
78 on request of the corresponding author.

79

## 80 Exposure: Activity Interference Assessment Questionnaires

81 The Comprehensive Pain Evaluation Questionnaire (CPEQ) was developed to understand both physical  
82 and psychological symptoms chronic pain patients suffer from.<sup>20</sup> Only portion A; the activity interference  
83 portion, of the CPEQ was used in this analysis.<sup>20</sup> The original CPEQ asks 'During the past month, how  
84 much did *pain* interfere with the following activities'?<sup>20</sup> Activities such as yard work, sexual relations,  
85 and going to work were included in the questionnaire.<sup>20</sup> Participants were asked to complete the  
86 interference portion 4 further times and the main word *pain* was substituted with four additional

87 symptoms;<sup>16</sup> fatigue, mood, dryness and brain fog/mental fatigue i.e. 'During the past month, how much  
88 did *mood* interfere with the following activities?'<sup>16,20</sup> A total of 5 different versions of the CPEQ were  
89 administered to understand and compare the different activity interferences pSS patients face. Each  
90 CPEQ was scored using a 5-point scale where 1="not at all", 2="a little bit", 3="moderately", 4="quite a  
91 bit" and 5="extremely."<sup>20</sup> Higher scores indicated a greater lifestyle impact. These questionnaires will be  
92 referred to as the Pain Activity Interference Questionnaire, Fatigue Activity Interference Questionnaire,  
93 Mood Activity Interference Questionnaire, Dryness Activity Interference Questionnaire and Brain  
94 Fog/Mental Fatigue Activity Interference Questionnaire for the remainder of this paper. These  
95 additional symptoms were chosen as our previous work has suggested that these symptoms interfere  
96 with the ability to perform daily activities in pSS patients.<sup>18</sup>

97

#### 98 Outcome: Hospital Anxiety and Depression Scale

99 The Hospital Anxiety and Depression Scale (HAD's) was developed in 1983 by Snaith and Zigmond.<sup>16,21</sup>  
100 This self-assessment questionnaire has been used to understand and classify states of anxiety and  
101 depression in patients.<sup>21</sup> The questionnaire is split in half with 7 questions concerning anxiety and 7 on  
102 depression. Questions are scored on a 4-point scale where 0="not at all," 1="from time to  
103 time/occasionally," 2="a lot of the time," and 3="most of the time."<sup>22</sup> The final score is between 0-21  
104 with a higher score correlating to a worse mental prognosis.<sup>22</sup> A score of > 10 on either subscale  
105 indicates a case for anxiety or depression.<sup>22</sup>

106

#### 107 Outcome: IMPROVED Health Assessment Questionnaire

108 The IMPROVED Health Assessment Questionnaire (IMPROVED HAQ) is used to measure physical  
109 function unlike HAD's that measures the mental health symptoms of anxiety and depression.<sup>23</sup> There  
110 are a total of 24 questions that comprise the IMPROVED HAQ; 20 questions that ask about patient's  
111 activity level and 4 that ask about the use of help.<sup>23</sup> The 20 activity questions rate a patient's ability on a  
112 5-point scale with 0="without any difficulty," 1=" with a little difficulty," 2="with some difficulty,"  
113 3="with much difficulty," and 4="unable to do."<sup>16,23</sup> The 20 questions that ask about ability are divided  
114 into 8 different physical functioning domains (eating, walking, arising, dressing, grip, hygiene, reach and  
115 activity).<sup>24</sup> The question that scores the highest in each domain is used as the domain score.<sup>24</sup> The Total  
116 IMPROVED HAQ score is calculated by the sum of all 8 domain scores, divided by 8 then multiplied by  
117 25.<sup>24</sup> The final score is between 0-100 and a higher total score relates to a greater functional

118 impairment.<sup>16,23</sup> Data used in this research is based off the total IMPROVED HAQ score and not the 4  
119 questions concerning the use of patient help.<sup>16</sup>

120

### 121 Additional variables

122 Information was also available on self-reported patient characteristics. Categorical variables included:  
123 employment status with coding 1 -6 (1: unemployed, 2: part time, 3: full time, 4: full time education, 5:  
124 housewife/husband, 6: retired): other adults living in the household (1: yes, 2: no): Dependents (1: yes,  
125 2: no): Paid for non-NHS services (1: yes, 2: no): Qualifications (1: no formal qualifications, 2:GCSE/O  
126 level, 3: A Level, 4: University Degree, 5: Postgraduate Degree): Household income (1: ≤£15,000, 2:  
127 £15,001-£26,000, 3:£26,001-£35,000, 4:£35,001-£50,000, 5:£50,00 -£70,000, 6:≥£70,001): Disability  
128 Allowance (1: yes, 2: no), and Employment and Support Allowance (1: yes, 2: no). Continuous variables  
129 of age and length of disease and binary variable gender (1: Female, 2: Male) were included. All variables  
130 were recorded using methods discussed elsewhere.<sup>17</sup>

131

132

### 133 Statistical Methods / Analysis

134 Descriptive statistics were calculated to summarise patient demographics, exposure information  
135 (activity interference), and outcome (for Hospital Anxiety and Depression Scale and IMPROVED Health  
136 Assessment Questionnaire). Normality for each continuous variable was investigated using the Shapiro-  
137 Wilk test alongside checking distribution visually using histograms. Mean and standard deviation were  
138 calculated for normally distributed data with median and inter-quartile range being calculated for all  
139 non-normal data.

140

141 Correlation coefficient matrixes were calculated using Pearson's correlation coefficient to validate  
142 whether the three outcome questionnaires, normally distributed, were associated with one another. No  
143 questionnaire resulted in a high correlation with another (a result of 0.70 or higher) and allowed the use  
144 of all three to be included in further analysis. Each matrix resulted in eight categories showing strong  
145 correlation with at least one other category. Cronbach's  $\alpha$  score of 0.99 indicated the internal reliability  
146 of these outcome questionnaires.

147

148 Simple linear regression was estimated for the association between the three outcome measures; HAD's  
149 Anxiety score, HAD's Depression score and the IMPROVED HAQ total score and the exposure; all activity

150 interference parameters. Primarily, it was checked that the models met all assumptions of linear  
151 regression; linear association between outcome and exposure, residuals are normally distributed with a  
152 mean of zero, the residuals are independent, and there is no heteroskedascity present. Where the  
153 models did not meet these assumptions; data was transformed and independence of residuals checked,  
154 where there were significant heteroskedascity robust standard errors were used (this was not required).  
155 Linear regression analysis revealed collinearity between the exposure categories, which limited analysis  
156 to only one exposure and one outcome at a time. Multivariable linear regression was used to adjust for  
157 potential confounding variables: patient age and length of disease. Four separate models were  
158 developed for potential confounding variables; model 1: Unadjusted, model 2: adjusted for disease  
159 length, model 3: adjusted for patient age and model 4: adjusted for disease length and patient age.

160

161 Interaction tests were used to investigate if the associations between exposure categories and outcome  
162 results differed due to length of disease. HAD's Anxiety showed to be the only outcome to have a  
163 significant interaction with length of disease in three activity interference questionnaires, fatigue, mood  
164 and dryness. For associations with significant interactions, length of disease was converted to a binary  
165 variable to test if a particular length of disease (in years) caused the significant finding. Due to  
166 participants having a median value of 8 years for length of disease, the continuous variable was  
167 converted to binary with 1 = length of disease 9 years or longer and 0 = all other years. All analysis was  
168 performed used statistical software package Stata/SE 16.1; StatCorp LLC; College Station, TX, USA.

169

## 170 **Results**

171 Table 1 shows the patient demographics of those who participated in this study. Analysis found 88.59%  
172 of participants to identify as female. With a median age of 63.80 years and range of 55.97 (minimum age  
173 of 32 and maximum age of 88), most participants, 50.67%, were retired at the time of study in 2014 and  
174 66.67% had no dependents living at home. A significant portion of participants did not receive disability  
175 living allowance or employment/support allowance, 65.33% and 76.97% respectively.

176

### 177 Activity Interference Assessment Questionnaires

178 Table 2 shows descriptive analysis conducted on the 5 different CPEQs; Pain, Fatigue, Mood, Dryness  
179 and Brain Fog/ Mental Fatigue. Mean and SD was included for normally distributed data with inter-  
180 quartile range and median represented non-normal data. All nine categories in the Fatigue Activity  
181 Interference Questionnaire were normally distributed. 'Physical exercise', with a mean score of 3.49

182 (SD1.26), is the activity most impacted by fatigue. The CPEQ concerning mood found four activity  
183 categories to be normally distributed with 'Sleep' being the most impacted with a median score of 3  
184 (IQR 1,4). The Dryness questionnaire resulted in 'Sleeping' with a mean score of 2.74 (SD 1.40) and  
185 'Sexual Relations' with a mean score or 2.63 (SD 1.56) to be the top two activities impacted. 'Mental  
186 Efficacy' is impacted the greatest due to brain fog/mental fatigue with a mean score of 2.67 (SD 1.28).  
187

#### 188 Hospital Anxiety and Depression Scale (HADs) / Improved Health Assessment Questionnaire Disability 189 Index (IMPROVED HAQ)

190 Descriptive statistics were performed on the three outcome questionnaires. Patients in this study scored  
191 in the "normal" range for anxiety with a median score of 7 (IQR 4,11) and depression with a median  
192 score of 5.50 (IQR 3,8). However, further analysis shows only 53.38% of the participants scored in the  
193 normal range for anxiety while 46.62% scored either "borderline abnormal" or "abnormal".<sup>22</sup> The  
194 IMPROVED HAQ Total Score had a normal distribution with a median value of 15.63 (IQR 37.50).  
195

#### 196 Regression Analysis

197 Due to an overall strong collinearity between the activity variables, simple linear regression was  
198 performed between each CPEQ category and the three outcome questionnaires (Tables 3-5). A trend  
199 can be seen that, for every point increase in a CPEQ activity score, HAD's Anxiety, HAD's Depression and  
200 IMPROVED HAQ total score will also increase indicating increased levels of anxiety/depression and  
201 overall quality of life. The effect size is similar between HAD's Anxiety (1.25 [95% confidence interval (CI)  
202 0.57,1.93]) and HAD's Depression (1.12 [95%CI 0.53,1.71]) while a larger impact is seen in the  
203 IMPROVED HAQ (6.74 [95%CI 2.04,11.44]. In unadjusted models, positive, significant associations were  
204 observed for all categories except 'Sexual Relations' in relation to Pain interference and dryness  
205 interference for the HAD'S anxiety scale, and for dryness interference for the HAD's depression scale  
206 where there was no significant association. Multivariable linear regression adjusted for length of  
207 disease; effect sizes decreased suggesting evidence of confounding. Age was likewise adjusted and not  
208 found to be a confounder.  
209

#### 210 Interaction Tests

211 Multiple linear regression found significant results in two questionnaires, fatigue, and mood, with no  
212 apparent interaction in dryness. Within the fatigue questionnaire, three categories ('Gardening or  
213 Shopping, 'Socializing' and 'Recreation') showed significant interaction with length of disease on HAD's

214 Anxiety [p-value = 0.03, 0.03 and 0.01 respectively]. In the mood questionnaire, two categories  
215 'Gardening or Shopping' (p-value <0.001) and 'Socializing' (p-value = 0.01) displayed significant  
216 interaction with length of disease on HAD's Anxiety. Three categories ('Gardening or Shopping',  
217 'Socializing' and 'Mental Efficacy') in the dryness questionnaire were significant until length of disease  
218 was converted to a binary variable. Table 6 show that all anxiety correlation scores were significantly  
219 reduced after patients had been diagnosed with pSS for 9 years or longer.

220

## 221 **Discussion**

222 Activity interference associated with fatigue was found to have the biggest impact; 60% of the highest  
223 scoring categories originated from the fatigue questionnaire with 'Physical Exercise' being the activity  
224 impacted the most followed by 'Gardening or Shopping' and 'Performing Household Chores.' Correlation  
225 coefficient matrixes displayed strong collinearity between the CPEQ activity categories in each  
226 questionnaire; this highlights the interwoven facet of pSS symptoms. This caused an issue with  
227 performing multiple linear regression analysis between the exposure and outcome questionnaires. If  
228 these statistical tests were conducted, no true relationship between one exposure and an outcome  
229 could have been observed. For example, if multiple regression was performed between HAD's Anxiety  
230 and the mood activity assessment questionnaire, there would be no way to tell if the possible effect on  
231 the anxiety score was caused by 'Recreation/Hobbies' or 'Socializing with Others'.

232

233 However, looking at correlation between the CPEQ categories and outcome questionnaires does pose a  
234 vital argument to why this research is so unique to previous studies conducted on pSS. Previous studies  
235 have conducted analysis using only one outcome measure where three were used here.<sup>2,10-12</sup> Having  
236 HAD's Anxiety, HAD's Depression and the IMPROVED HAQ Score, both a broader and an in-depth look  
237 into pSS patient's lives can be seen. Close evaluation of mental health symptoms and physical  
238 constraints are possible in this study while also allowing for an overall health assessment to be  
239 conducted. Additionally, these findings show there is no clear separation between two exposure  
240 categories. To properly understand the activity interferences experienced in pSS, future research needs  
241 to take physical and mental health into consideration.

242

243 An additional aim of this research was to view what type of relationship activity interference scores had  
244 with separate health outcome measures. Unadjusted analysis revealed that for every score increase in  
245 an exposure category (i.e., 'Going to Work') every outcome score (HAD's Anxiety/Depression and

246 IMPROVED HAQ) would also increase. The sexual relation category seemed to have the least impact on  
247 the outcome scores. However, this could be due to low power from the questionnaire results; overall,  
248 more participants refused to answer questions concerning sexual relations compared to the other eight  
249 categories. The low response rate for the question relating to sexual relations may have introduced  
250 reporting bias if those who responded were systematically different from those who did not.  
251 Multiple linear regression was used to adjust the data for potential confounding variables, age and  
252 length of disease. This indicated that length of disease was the main confounder in this analysis and had  
253 a positive impact (lower scores) to the three health outcomes. After adjusting, HAD's Anxiety, HAD's  
254 Depression and IMPROVED HAQ, length of disease resulted in a lower effect size than the unadjusted  
255 regressions. To our knowledge this is the first quantitative pSS study that adjusted for length of disease.  
256 This analysis indicates that the longer a patient with pSS is diagnosed, better able they are to adapt their  
257 expectations and lifestyle. A qualitative study found similar results where patients learned how to adapt  
258 their lifestyle around pSS and the various symptoms.<sup>14</sup> By modifying their diet, types of physical exercise,  
259 or altering medications, patients were able to modify their lives and create a `new normal`.<sup>14</sup> This trend  
260 is seen in other chronic illness like RA<sup>25</sup> and Crohn's disease<sup>26</sup> where patients feel their condition, over  
261 time, is less of a burden.<sup>14,25-26</sup> This study gives additional insight into which factors limit activity the  
262 most. By tailoring treatment to these key symptoms earlier, patients may learn to manage their  
263 condition sooner after diagnosis.

#### 264 Strengths and Limitations

265 This study used an existing dataset and is therefore limited in terms of data availability. However,  
266 missing data was minimal (n=4 or 2.61% of total data) and missing completely at random, making it  
267 unlikely to influence the final analysis. The total number of participants (n=149) strengthens the findings  
268 of this research. Previous quantitative studies have ranged from 42 to 185 pSS patients, making this  
269 study one of the more robust representations of Primary Sjögren's disease in the U.K.<sup>2,10-12</sup> As this study  
270 used an existing dataset, analysis was limited to the data available. An additional limitation to take into  
271 consideration is the measurement of the exposure variables; exposure questionnaires (mood, fatigue,  
272 dryness, and brain fog/mental fatigue) were adapted from the original CPEQ and not validated before  
273 distributed to participants. This was done as no other questionnaire existed that could measure the  
274 other potential interferences. More work is needed to validate these questionnaires to check that they  
275 measure what they intend to. However, this study sets the scene for these questionnaires to be used for  
276 further research in a larger sample size of patients.

277 Another point of limitation was produced by conducting a cross-sectional study. While clear exposure  
278 and outcome variables were chosen, no temporal relationship can be determined. For example, this  
279 research cannot say if the scores associated with the Dryness Activity Interference Questionnaire caused  
280 the results in the HAD's Depression score or vice versa. Still, a cross-sectional study was the only option  
281 for this research project due to the data available. Using the UKPSSR<sup>16,18</sup>, a snapshot of the pSS  
282 population in the UK could be obtained in a short and inexpensive time frame. This allowed for analysis  
283 to be conducted six years after the initial questionnaires were administered without the need for  
284 participants to be contacted again.

## 285 **Conclusion**

286 This cross-sectional study investigating which pSS symptoms cause the biggest impact in daily activities  
287 using the adapted CPEQ measures found that fatigue had the biggest impact on 7 activity domains:  
288 physical exercise (mean score of 3.49 out of 5 [SD 1.26]), performing household chores (mean 3.14 [SD  
289 1.18]), gardening or shopping (mean 3.18 [SD 1.20]), socializing with others (mean 2.62 [SD 1.24]),  
290 recreation/hobbies (mean 2.88 [SD 1.20]), sexual relations (mean 3.00 [SD 1.52]), and mental efficacy  
291 (mean 2.69 [SD 1.17]). Additionally, this research looked at the relationship activity interference had  
292 with three separate outcome measures: HAD's Anxiety, HAD's Depression and IMPROVED HAQ score. A  
293 positive association is seen between each exposure categories and outcome results. As an activity  
294 interference score increased; the patient experiencing more difficulty, an outcome score will also  
295 increase. However, length of disease has shown to lessen the overall impact of this association.

296 Importantly, this study looked at the association between activity interferences and mental/physical  
297 outcomes, analysis that has not been previously explored. Results found have given further insight into  
298 how pSS affects daily life to provide additional treatment options to patients. This study shows the  
299 importance of early intervention with support for symptom management, particularly fatigue. However,  
300 this research has also highlighted the interconnectedness of symptoms and how they all impact on daily  
301 activity. One possible approach within a self-management support package; a technique that targets  
302 several symptoms at once, may help people with pSS to reduce activity interference of these symptoms  
303 and ultimately increase quality of life.

304

305 **References**

- 306 1. de Paiva CS, Pflugfelder SC. Mechanisms of disease in Sjögren Syndrome—new developments  
307 and directions. *International Journal of Molecular Sciences*. 2020;21(2):650
- 308 2. Meijer JM, Meiners PM, Huddleston Slater JJR, Spijkervet FKL, Kallenberg CGM, Vissink A, et al.  
309 Health-related quality of life, employment and disability in patients with Sjögren’s syndrome.  
310 *Rheumatology (Oxford)*. 2009;48(9):1077–82.
- 311 3. Vivino FB, Bunya VY, Massaro-Giordano G, Johr CR, Giattino SL, Schorpion A, et al. Sjögren’s  
312 syndrome: An update on disease pathogenesis, clinical manifestations and treatment. *Clinical*  
313 *Immunology*. 2019;203:81–121.
- 314 4. Ramos-Casals M, Stone JH, Moutsopoulos HM, editors. *Sjögren’s Syndrome, Diagnosis and*  
315 *Therapeutics*. 2012th ed. London, England: Springer; 2011.
- 316 5. Stone JH, editor. *A clinician’s pearls & myths in rheumatology [Internet]*. 2009th ed. London,  
317 England: Springer; 2009. Available from: <http://dx.doi.org/10.1007/978-1-84800-934-9>
- 318 6. Liang Y, Yang Z, Qin B, Zhong R. Primary Sjögren’s syndrome and malignancy risk: a systematic  
319 review and meta-analysis. *Annals of Rheumatic Diseases*. 2014;73(6):1151–6.
- 320 7. Parambil JG, Myers JL, Lindell RM, Matteson EL, Ryu JH. Interstitial lung disease in primary  
321 Sjögren syndrome. *Chest*. 2006;130(5):1489–95.
- 322 8. Bartoloni E, Baldini C, Schillaci G, Quartuccio L, Priori R, Carubbi F, et al. Cardiovascular disease  
323 risk burden in primary Sjögren’s syndrome: results of a population-based multicentre cohort  
324 study. *Journal of Internal Medicine*. 2015;278(2):185–92.
- 325 9. Mason J, Pearce MS, Walls AWG, Parker L, Steele JG. How do factors at different stages of the  
326 lifecourse contribute to oral-health-related quality of life in middle age for men and women?  
327 *Journal of Dental Research*. 2006;85(3):257–61.
- 328 10. Segal B, Bowman SJ, Fox PC, Vivino FB, Murukutla N, Brodscholl J, et al. Primary Sjögren’s  
329 Syndrome: health experiences and predictors of health quality among patients in the United  
330 States. *Health Qual Life Outcomes*. 2009;7(1):46.
- 331 11. Tensing EK, Solovieva SA, Tervahartiala T, Nordström DC, Laine M, Niissalo S, et al. Fatigue and  
332 health profile in sicca syndrome of Sjögren’s and non-Sjögren’s syndrome origin. *Clinical and*  
333 *Experimental Rheumatology*. 2001;19(3):313–6.
- 334 12. Bowman SJ, St Pierre Y, Sutcliffe N, Isenberg DA, Goldblatt F, Price E, et al. Estimating indirect  
335 costs in primary Sjögren’s syndrome. *Journal of Rheumatology*. 2010;37(5):1010–5.

- 336 13. Callaghan R, Prabu A, Allan RB, Clarke AE, Sutcliffe N, Pierre YS, et al. Direct healthcare costs and  
337 predictors of costs in patients with primary Sjogren's syndrome. *Rheumatology (Oxford)*.  
338 2007;46(1):105–11.
- 339 14. Schoofs N. Seeing the glass half full: living with Sjogren's Syndrome. *Journal of Professional*  
340 *Nursing*. 2001;17(4):194–202.
- 341 15. Lackner A, Ficjan A, Stradner MH, Hermann J, Unger J, Stamm T, et al. It's more than dryness and  
342 fatigue: The patient perspective on health-related quality of life in Primary Sjögren's Syndrome -  
343 A qualitative study. *PLoS One*. 2017;12(2):e0172056.
- 344 16. Ng W-F, Bowman SJ, Griffiths B, UKPSSR study group. United Kingdom Primary Sjogren's  
345 Syndrome Registry--a united effort to tackle an orphan rheumatic disease. *Rheumatology*  
346 (Oxford). 2011;50(1):32–9.
- 347 17. Hackett K. Developing a non-pharmacological intervention model to improve function and  
348 participation in people with primary Sjögren's syndrome [dissertation]. Newcastle Upon Tyne:  
349 Newcastle University;2017.
- 350 18. Hackett KL, Deane KHO, Newton JL, Deary V, Bowman SJ, Rapley T, et al. Mixed-methods study  
351 identifying key intervention targets to improve participation in daily living activities in primary  
352 Sjögren's syndrome patients. *Arthritis Care and Research (Hoboken)*. 2018;70(7):1064–73.
- 353 19. WMA declaration of Helsinki – ethical principles for medical research involving human subjects  
354 [Internet]. Wma.net. [cited 2021 May 19]. Available from: [https://www.wma.net/policies-  
355 post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-  
356 subjects/](https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)
- 357 20. Jamison RN, Rudy TE, Penzien DB, Mosley TH Jr. Cognitive-behavioral classifications of chronic  
358 pain: replication and extension of empirically derived patient profiles. *Pain*. 1994;57(3):277–92.
- 359 21. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatrica*  
360 *Scandinavica*. 1983;67(6):361–70.
- 361 22. Zigmond A, Snaith R. Hospital Anxiety and Depression Scale (HADS) [Internet]. Svri.org. 1983  
362 [cited 202 Jun 4]. Available from: [https://www.svri.org/sites/default/files/attachments/2016-01-  
363 13/HADS.pdf](https://www.svri.org/sites/default/files/attachments/2016-01-13/HADS.pdf)
- 364 23. Maska L, Anderson J, Michaud K. Measures of functional status and quality of life in rheumatoid  
365 arthritis: Health assessment questionnaire disability index (HAQ), modified health assessment  
366 questionnaire (MHAQ), multidimensional health assessment questionnaire (MDHAQ), health  
367 assessment questionnaire II (HAQ-II), improved health assessment questionnaire (improved

368 HAQ), and rheumatoid arthritis quality of life (RAQoL). *Arthritis Care and Research* (Hoboken).  
369 2011;63 Suppl 11(S11):S4-13.

370 24. Elliott C, Frith J, Pairman J, Jones DEJ, Newton JL. Reduction in functional ability is significant  
371 postliver transplantation compared with matched liver disease and community dwelling  
372 controls: Functional ability postliver transplant. *Transplant International*. 2011;24(6):588–95.

373 25. Strömbeck B, Ekdahl C, Manthorpe R, Wikström I, Jacobsson L. Health-related quality of life in  
374 primary Sjögren's syndrome, rheumatoid arthritis and fibromyalgia compared to normal  
375 population data using SF-36. *Scandinavian Journal of Rheumatology*. 2000;29(1):20–8.

376 26. Jäghult S, Saboonchi F, Johansson U-B, Wredling R, Kapraali M. Identifying predictors of low  
377 health-related quality of life among patients with inflammatory bowel disease: comparison  
378 between Crohn's disease and ulcerative colitis with disease duration: HRQOL in inflammatory  
379 bowel disease. *Journal of Clinical Nursing*. 2011;20(11–12):1578–87.

380

1 Table 1: Primary Sjögren's Syndrome Patient Demographics

Variable	n [149]	%
Gender		
Female	132	88.59
Male	17	11.41
Employment Status		
Unemployed	7	4.70
Part Time	19	12.75
Full Time	15	10.07
Full Time Education	1	0.67
Housewife/husband	5	3.36
Retired	76	50.02
Unanswered	26	17.45
Other Adults in Household		
Yes	92	61.75
No	32	21.48
Unanswered	25	16.78
Dependents		
No Dependents	100	67.11
Dependents in home part time	19	12.75
Dependents in home full time	4	2.68
Unanswered	26	17.45
Paid for non-NHS services		
Yes	28	18.79
No	96	64.43
Unanswered	25	16.78
Qualifications		
No Formal Qualifications	27	18.12
GCSE/O Level	32	21.48
A Level	21	14.09
University Degree	20	13.42
Postgraduate Degree	20	13.42
Unanswered	29	19.46
Household Income (£)		
≤15,000	28	18.79
>15,000-26,000	21	14.09
>26,000-35,000	13	8.72
>35,000-50,000	13	8.72
>50,000-70,000	8	5.37
≥70,000	5	3.36
Prefer Not to Say	36	24.16
Unanswered	25	16.78
Disability Living Allowance		
Yes	26	17.45
No	98	65.77
Unanswered	25	16.78
Employment and Support Allowance		
Yes (1)	9	6.04
No (2)	115	77.18
Unanswered	25	16.78

Table 2: Activity Interference (CPEQ) Questionnaire results for the domains; pain, fatigue, mood, dryness and brain fog/mental activity

	Activity interference domain								
	Going to Work	Performing Household Chores	Gardening or Shopping	Socializing with others	Recreation / Hobbies	Sexual Relations	Physical Exercise	Sleeping	Mental Efficacy
<b>Pain</b>									
Mean (SD)	-	2.72 (1.22)	2.85 (1.25)	-	2.61 (1.27)	2.61 (1.56)	3.12 (1.35)	2.95 (1.36)	-
Median (IQR)	2 (1,3)	-	-	2 (1,3)	-	-	-	-	2 (1,3)
<b>Fatigue</b>									
Mean (SD)	2.73 (1.37)	3.14 (1.18)	3.18 (1.20)	2.62 (1.24)	2.88 (1.20)	3.00 (1.52)	3.49 (1.26)	2.98 (1.35)	2.69 (1.17)
Median (IQR)	-	-	-	-	-	-	-	-	-
<b>Mood</b>									
Mean (SD)	-	2.32 (1.16)	2.32 (1.22)	-	-	2.53 (1.48)	2.73 (1.35)	-	-
Median (IQR)	2 (1,3)	-	-	2 (1,3)	2 (1,3)	-	-	3 (1,4)	2 (1,3)
<b>Dryness</b>									
Mean (SD)	-	-	-	-	-	2.63 (1.56)	2.60 (1.38)	2.74 (1.40)	-
Median (IQR)	2 (1,3)	2 (1,3)	2 (1,3)	2 (1,3)	2 (1,3)	-	-	-	2 (1,3)
<b>Brain fog/ mental fatigue</b>									
Mean (SD)	-	-	2.48 (1.24)	-	2.52 (1.20)	-	2.59 (1.33)	-	2.67 (1.28)
Median (IQR)	2 (1,3)	2 (1,3)	-	2 (1,3)	-	2 (1,3)	-	2 (1,3)	-

Table 3: Linear Regression Analysis of HAD's Anxiety

Activity interference variable	HAD's Anxiety		
	Unadjusted, [95% CI], <i>p-value</i>	Adjusted for of Disease Length, [95% CI], <i>p-value</i>	Adjusted for age, [95% CI], <i>p-value</i>
<b>Pain interference</b>			
Going to Work	1.25, [0.57,1.93], <i>p</i> < 0.001	0.80, [0.01,1.49], <i>p</i> = 0.03	1.18, [0.48,1.89], <i>p</i> = 0.001
Performing Household Chores	1.17, [0.56,1.78], <i>p</i> < 0.001	0.83, [0.19,1.46], <i>p</i> = 0.01	1.14, [0.53,1.75], <i>p</i> < 0.001
Gardening or Shopping	1.28, [0.70,1.87], <i>p</i> < 0.001	0.97, [0.35,1.59], <i>p</i> = 0.002	1.27, [0.69,1.85], <i>p</i> < 0.001
Socializing with others	1.44, [0.87,2.01], <i>p</i> < 0.001	1.17, [0.57,1.78], <i>p</i> < 0.001	1.40, [0.82,1.98], <i>p</i> < 0.001
Recreation / Hobbies	1.41, [0.85,1.97], <i>p</i> < 0.001	1.15, [0.56,1.73], <i>p</i> < 0.001	1.38, [0.81,1.94], <i>p</i> < 0.001
Sexual Relations	0.13, [-0.43,0.67], <i>p</i> = 0.66	0.02, [-0.55,0.58], <i>p</i> = 0.96	0.09, [-0.47,0.65], <i>p</i> = 0.75
Physical Exercise	1.01, [0.46,1.56], <i>p</i> < 0.001	0.84, [0.27,1.41], <i>p</i> = 0.004	0.98, [0.43,1.53], <i>p</i> = 0.001
Sleeping	1.32, [0.75,1.90], <i>p</i> < 0.001	1.05, [0.49,1.61], <i>p</i> < 0.001	1.31, [0.79,1.83], <i>p</i> < 0.001
Mental Efficacy	1.49, [0.88,2.11], <i>p</i> < 0.001	1.19, [0.60,1.78], <i>p</i> < 0.001	1.45, [0.85,2.05], <i>p</i> < 0.001
<b>Fatigue Interference</b>			
Going to Work	1.38, [0.75,2.01], <i>p</i> < 0.001	0.85, [0.15,1.55], <i>p</i> = 0.02	1.28, [0.64,1.92], <i>p</i> < 0.001
Performing Household Chores	1.75, [1.14,2.36], <i>p</i> < 0.001	1.22, [0.57,1.87], <i>p</i> < 0.001	1.71, [1.13,2.30], <i>p</i> < 0.001
Gardening or Shopping	1.79, [1.21,2.37], <i>p</i> < 0.001	1.45, [0.82,2.09], <i>p</i> < 0.001	1.77, [1.20,2.35], <i>p</i> < 0.001
Socializing with others	1.80, [1.22,2.38], <i>p</i> < 0.001	1.47, [0.86,2.08], <i>p</i> < 0.001	1.77, [1.21,2.33], <i>p</i> < 0.001
Recreation / Hobbies	1.97, [1.42,2.53], <i>p</i> < 0.001	1.63, [1.00,2.25], <i>p</i> < 0.001	1.94, [1.38,2.50], <i>p</i> < 0.001
Sexual Relations	0.55, [-0.43,1.14], <i>p</i> = 0.07	0.34, [-0.28,0.96], <i>p</i> = 0.27	0.54, [-0.04,1.13], <i>p</i> = 0.07
Physical Exercise	1.40, [0.80,2.00], <i>p</i> < 0.001	1.11, [0.51,1.72], <i>p</i> < 0.001	1.36, [0.79,1.94], <i>p</i> < 0.001
Sleeping	1.62, [1.07,2.17], <i>p</i> < 0.001	1.36, [0.78,1.93], <i>p</i> < 0.001	1.62, [1.12,2.12], <i>p</i> < 0.001
Mental Efficacy	1.79, [1.21,2.37], <i>p</i> < 0.001	1.66, [1.03,2.30], <i>p</i> < 0.001	1.75, [1.15,2.35], <i>p</i> < 0.001
<b>Mood Interference</b>			
Going to Work	2.02, [1.26,2.79], <i>p</i> < 0.001	1.52, [0.75,2.28], <i>p</i> < 0.001	1.94, [1.27,2.61], <i>p</i> < 0.001
Performing Household Chores	2.53, [1.99,3.06], <i>p</i> < 0.001	2.23, [1.63,2.82], <i>p</i> < 0.001	2.49, [1.98,3.01], <i>p</i> < 0.001
Gardening or Shopping	2.22, [1.58,2.85], <i>p</i> < 0.001	1.82, [1.22,2.42], <i>p</i> < 0.001	2.23, [1.72,2.73], <i>p</i> < 0.001
Socializing with others	2.83, [2.38,3.28], <i>p</i> < 0.001	2.60, [2.07,3.13], <i>p</i> < 0.001	2.82, [2.36,3.28], <i>p</i> < 0.001
Recreation / Hobbies	2.45, [1.95,2.96], <i>p</i> < 0.001	2.29, [1.71,2.87], <i>p</i> < 0.001	2.42, [1.92,2.93], <i>p</i> < 0.001
Sexual Relations	1.19, [0.62,1.77], <i>p</i> < 0.001	1.02, [0.41,1.64], <i>p</i> = 0.001	1.17, [0.59,1.75], <i>p</i> < 0.001
Physical Exercise	1.80, [1.27,2.32], <i>p</i> < 0.001	1.53, [1.00,2.06], <i>p</i> < 0.001	1.78, [1.30,2.27], <i>p</i> < 0.001
Sleeping	1.96, [1.51,2.40], <i>p</i> < 0.001	1.79, [1.30,2.27], <i>p</i> < 0.001	1.93, [1.49,2.37], <i>p</i> < 0.001
Mental Efficacy	2.33, [1.80,2.87], <i>p</i> < 0.001	2.12, [1.55,2.68], <i>p</i> < 0.001	2.33, [1.80,2.86], <i>p</i> < 0.001

Activity interference variable	HAD's Anxiety		
	Unadjusted, [95% CI], <i>p-value</i>	Adjusted for of Disease Length, [95% CI], <i>p-value</i>	Adjusted for age, [95% CI], <i>p-value</i>
<b>Dryness Interference</b>			
Going to Work	1.14, [0.50,1.77], <i>p</i> = 0.001	0.96, [0.34,1.57], <i>p</i> = 0.003	1.04, [0.39,1.70], <i>p</i> = 0.002
Performing Household Chores	0.60, [-0.02,1.21], <i>p</i> = 0.06	0.48, [-0.15,1.10], <i>p</i> = 0.13	0.60, [-0.01,1.21], <i>p</i> = 0.05
Gardening or Shopping	0.54, [-0.06,1.13], <i>p</i> = 0.08	0.39, [-0.22,1.01], <i>p</i> = 0.21	0.59, [-.001,1.17], <i>p</i> = 0.05
Socializing with others	0.75, [0.15,1.35], <i>p</i> = 0.02	0.66, [0.05,1.28], <i>p</i> = 0.03	0.73, [0.13,1.33], <i>p</i> = 0.02
Recreation / Hobbies	0.81, [0.22,1.41], <i>p</i> = 0.008	0.63, [0.02,1.25], <i>p</i> = 0.04	0.80, [0.21,1.40], <i>p</i> = 0.008
Sexual Relations	-0.001, [-0.57,0.57], <i>p</i> = 1.00	0.03, [-0.54,0.61], <i>p</i> = 0.91	-0.01, [-0.58,0.56], <i>p</i> = 0.97
Physical Exercise	0.59, [0.05,1.14], <i>p</i> = 0.03	0.52, [-0.05,1.09], <i>p</i> = 0.08	0.63, [0.09,1.18], <i>p</i> = 0.02
Sleeping	0.82, [0.29,1.35], <i>p</i> = 0.003	0.83, [0.28,1.38], <i>p</i> = 0.003	0.79, [0.25,1.32], <i>p</i> = 0.004
Mental Efficacy	1.83, [1.23,2.43], <i>p</i> < 0.001	1.72, [1.12,2.33], <i>p</i> < 0.001	1.78, [1.17,2.39], <i>p</i> < 0.001
<b>Brain Fog / Mental Fatigue Interference</b>			
Going to Work	1.77, [1.09,2.45], <i>p</i> < 0.001	1.28, [0.60,1.96], <i>p</i> < 0.001	1.76, [1.08,2.44], <i>p</i> < 0.001
Performing Household Chores	1.73, [1.04,2.42], <i>p</i> < 0.001	1.13, [0.43,1.84], <i>p</i> = 0.002	1.69, [1.07,2.31], <i>p</i> < 0.001
Gardening or Shopping	1.77, [1.23,2.32], <i>p</i> < 0.001	1.31, [0.69,1.94], <i>p</i> < 0.001	1.75, [1.21,2.29], <i>p</i> < 0.001
Socializing with others	1.70, [1.14,2.26], <i>p</i> < 0.001	1.26, [0.64,1.88], <i>p</i> < 0.001	1.66, [1.10,2.23], <i>p</i> < 0.001
Recreation / Hobbies	1.88, [1.32,2.44], <i>p</i> < 0.001	1.43, [0.79,2.07], <i>p</i> < 0.001	1.84, [1.28,2.41], <i>p</i> < 0.001
Sexual Relations	0.91, [0.30,1.52], <i>p</i> = 0.004	0.46, [-0.19,1.10], <i>p</i> = 0.16	0.90, [0.28,1.51], <i>p</i> = 0.004
Physical Exercise	1.46, [0.94,1.98], <i>p</i> < 0.001	1.09, [0.51,1.67], <i>p</i> < 0.001	1.45, [0.93,1.97], <i>p</i> < 0.001
Sleeping	1.54, [1.01,2.07], <i>p</i> < 0.001	1.33, [0.74,1.92], <i>p</i> < 0.001	1.51, [0.98,2.04], <i>p</i> < 0.001
Mental Efficacy	1.70, [1.17,2.24], <i>p</i> < 0.001	1.50, [0.92,2.07], <i>p</i> < 0.001	1.67, [1.12,2.22], <i>p</i> < 0.001

Table 4: Linear Regression Analysis of HAD's Depression

Activity interference variable	HAD's Depression		
	Unadjusted, [95% CI], <i>p</i> -value	Adjusted for of Disease Length, [95% CI], <i>p</i> -value	Adjusted for age, [95% CI], <i>p</i> -value
<b>Pain Interference</b>			
Going to Work	1.12, [0.53,1.71], <i>p</i> < 0.001	0.76, [0.18,1.35], <i>p</i> = 0.01	1.07, [0.47,1.68], <i>p</i> = 0.001
Performing Household Chores	1.29, [0.80,1.78], <i>p</i> < 0.001	1.15, [0.65,1.65], <i>p</i> < 0.001	1.27, [0.78,1.76], <i>p</i> < 0.001
Gardening or Shopping	1.31, [0.85,1.78], <i>p</i> < 0.001	1.27, [0.78,1.76], <i>p</i> < 0.001	1.30, [0.84,1.77], <i>p</i> < 0.001
Socializing with others	1.38, [0.94,1.83], <i>p</i> < 0.001	1.31, [0.84,1.77], <i>p</i> < 0.001	1.35, [0.90,1.81], <i>p</i> < 0.001
Recreation / Hobbies	1.29, [0.78,1.80], <i>p</i> < 0.001	1.23, [0.77,1.69], <i>p</i> < 0.001	1.26, [0.80,1.71], <i>p</i> < 0.001
Sexual Relations	0.54, [0.07,1.01], <i>p</i> = 0.03	0.50, [0.04,0.95], <i>p</i> = 0.03	0.50, [0.03,0.97], <i>p</i> = 0.04
Physical Exercise	0.98, [0.53,1.42], <i>p</i> < 0.001	0.99, [0.83,1.45], <i>p</i> < 0.001	0.95, [0.50,1.40], <i>p</i> < 0.001
Sleeping	1.07, [0.63,1.51], <i>p</i> < 0.001	0.83, [0.36,1.31], <i>p</i> = 0.001	1.06, [0.62,1.49], <i>p</i> < 0.001
Mental Efficacy	1.47, [0.92,2.01], <i>p</i> < 0.001	1.29, [0.83,1.76], <i>p</i> < 0.001	1.45, [0.97,1.93], <i>p</i> < 0.001
<b>Fatigue Interference</b>			
Going to Work	1.60, [1.09,2.10], <i>p</i> < 0.001	1.28, [0.72,1.84], <i>p</i> < 0.001	1.55, [1.04,2.07], <i>p</i> < 0.001
Performing Household Chores	2.03, [1.56,2.49], <i>p</i> < 0.001	1.78, [1.30,2.25], <i>p</i> < 0.001	2.00, [1.57,2.44], <i>p</i> < 0.001
Gardening or Shopping	2.01, [1.56,2.46], <i>p</i> < 0.001	1.88, [1.42,2.33], <i>p</i> < 0.001	1.99, [1.57,2.42], <i>p</i> < 0.001
Socializing with others	1.85, [1.40,2.29], <i>p</i> < 0.001	1.73, [1.29,2.18], <i>p</i> < 0.001	1.83, [1.41,2.25], <i>p</i> < 0.001
Recreation / Hobbies	2.02, [1.61,2.43], <i>p</i> < 0.001	1.90, [1.45,2.35], <i>p</i> < 0.001	1.99, [1.58,2.40], <i>p</i> < 0.001
Sexual Relations	0.97, [0.49,1.45], <i>p</i> < 0.001	0.77, [0.29,1.26], <i>p</i> = 0.002	0.96, [0.49,1.44], <i>p</i> < 0.001
Physical Exercise	1.70, [1.25,2.15], <i>p</i> < 0.001	1.63, [1.18,2.07], <i>p</i> < 0.001	1.67, [1.24,2.11], <i>p</i> < 0.001
Sleeping	1.41, [1.00,1.83], <i>p</i> < 0.001	1.19, [0.72,1.67], <i>p</i> < 0.001	1.41, [1.00,1.82], <i>p</i> < 0.001
Mental Efficacy	1.79, [1.33,2.25], <i>p</i> < 0.001	1.75, [1.26,2.24], <i>p</i> < 0.001	1.77, [1.30,2.24], <i>p</i> < 0.001
<b>Mood Interference</b>			
Going to Work	1.56, [0.96,2.16], <i>p</i> < 0.001	1.25, [0.57,1.94], <i>p</i> < 0.001	1.50, [0.89,2.11], <i>p</i> < 0.001
Performing Household Chores	1.98, [1.53,2.44], <i>p</i> < 0.001	1.90, [1.39,2.40], <i>p</i> < 0.001	1.96, [1.50,2.41], <i>p</i> < 0.001
Gardening or Shopping	1.60, [1.16,2.05], <i>p</i> < 0.001	1.43, [-0.93,1.93], <i>p</i> < 0.001	1.61, [1.18,2.05], <i>p</i> < 0.001
Socializing with others	2.13, [1.71,2.54], <i>p</i> < 0.001	2.03, [1.56,2.50], <i>p</i> < 0.001	2.11, [1.69,2.53], <i>p</i> < 0.001
Recreation / Hobbies	2.01, [1.59,2.44], <i>p</i> < 0.001	1.94, [1.48,2.41], <i>p</i> < 0.001	1.98, [1.56,2.41], <i>p</i> < 0.001
Sexual Relations	1.14, [0.66,1.62], <i>p</i> < 0.001	0.92, [0.44,1.41], <i>p</i> < 0.001	1.11, [0.64,1.59], <i>p</i> < 0.001
Physical Exercise	1.53, [1.11,1.95], <i>p</i> < 0.001	1.45, [1.03,1.88], <i>p</i> < 0.001	1.52, [1.13,1.91], <i>p</i> < 0.001
Sleeping	1.38, [0.99,1.77], <i>p</i> < 0.001	1.35, [0.93,1.77], <i>p</i> < 0.001	1.35, [0.96,1.74], <i>p</i> < 0.001
Mental Efficacy	1.92, [1.49,2.35], <i>p</i> < 0.001	1.84, [1.38,2.30], <i>p</i> < 0.001	1.91, [1.47,2.35], <i>p</i> < 0.001

Activity interference variable	HAD's Anxiety		
	Unadjusted, [95% CI], <i>p</i> -value	Adjusted for of Disease Length, [95% CI], <i>p</i> -value	Adjusted for age, [95% CI], <i>p</i> -value
<b>Dryness Interference</b>			
Going to Work	1.00, [0.45,1.55], <i>p</i> < 0.001	0.94, [0.41,1.47], <i>p</i> = 0.001	0.93, [0.36,1.50], <i>p</i> = 0.002
Performing Household Chores	0.73, [0.21,1.25], <i>p</i> = 0.006	0.87, [0.34,1.39], <i>p</i> = 0.001	0.74, [0.22,1.25], <i>p</i> = 0.005
Gardening or Shopping	0.51, [-0.02,1.00], <i>p</i> = 0.04	0.55, [0.06,1.04], <i>p</i> = 0.03	0.55, [0.07,1.04], <i>p</i> = 0.03
Socializing with others	0.69, [0.20,1.18], <i>p</i> = 0.006	0.81, [0.32,1.30], <i>p</i> = 0.001	0.67, [0.18,1.16], <i>p</i> = 0.007
Recreation / Hobbies	0.88, [0.41,1.36], <i>p</i> < 0.001	0.92, [0.43,1.40], <i>p</i> < 0.001	0.88, [0.40,1.35], <i>p</i> < 0.001
Sexual Relations	0.17, [-0.33,0.66], <i>p</i> = 0.48	0.35, [-0.13,0.82], <i>p</i> = 0.15	0.16, [-0.32,0.64], <i>p</i> = 0.50
Physical Exercise	0.36, [-0.09,0.82], <i>p</i> = 0.11	0.48, [0.01,0.95], <i>p</i> = 0.05	0.40, [-0.05,0.85], <i>p</i> = 0.08
Sleeping	0.57, [0.12,1.02], <i>p</i> = 0.01	0.69, [0.23,1.15], <i>p</i> = 0.003	0.54, [0.09,0.99], <i>p</i> = 0.02
Mental Efficacy	1.23, [0.72,1.74], <i>p</i> < 0.001	1.24, [0.73,1.76], <i>p</i> < 0.001	1.19, [0.67,1.71], <i>p</i> < 0.001
<b>Brain Fog / Mental Fatigue Interference</b>			
Going to Work	1.52, [1.00,2.03], <i>p</i> < 0.001	1.36, [0.80,1.91], <i>p</i> < 0.001	1.54, [0.98,2.09], <i>p</i> < 0.001
Performing Household Chores	1.64, [1.15,2.12], <i>p</i> < 0.001	1.35, [0.80,1.90], <i>p</i> < 0.001	1.60, [1.12,2.09], <i>p</i> < 0.001
Gardening or Shopping	1.54, [1.10,1.98], <i>p</i> < 0.001	1.33, [0.84,1.83], <i>p</i> < 0.001	1.52, [1.08,1.95], <i>p</i> < 0.001
Socializing with others	1.65, [1.17,2.12], <i>p</i> < 0.001	1.46, [0.98,1.93], <i>p</i> < 0.001	1.62, [1.18,2.05], <i>p</i> < 0.001
Recreation / Hobbies	1.67, [1.16,2.19], <i>p</i> < 0.001	1.53, [1.04,2.03], <i>p</i> < 0.001	1.64, [1.20,2.09], <i>p</i> < 0.001
Sexual Relations	1.01, [0.51,1.52], <i>p</i> < 0.001	0.65, [0.12,1.18], <i>p</i> = 0.02	1.00, [0.50,1.50], <i>p</i> < 0.001
Physical Exercise	1.39, [0.98,1.80], <i>p</i> < 0.001	1.26, [0.81,1.71], <i>p</i> < 0.001	1.38, [0.97,1.79], <i>p</i> < 0.001
Sleeping	1.04, [0.59,1.49], <i>p</i> < 0.001	1.02, [0.52,1.51], <i>p</i> < 0.001	1.01, [0.56,1.46], <i>p</i> < 0.001
Mental Efficacy	1.53, [1.11,1.96], <i>p</i> < 0.001	1.52, [1.08,1.96], <i>p</i> < 0.001	1.51, [1.08,1.94], <i>p</i> < 0.001

Table 5: Linear Regression Analysis of IMPROVED HAQ Score

Activity interference variable	IMPROVED HAQ Score		
	Unadjusted, [95% CI], <i>p</i> -value	Adjusted for of Disease Length, [95% CI], <i>p</i> -value	Adjusted for age, [95% CI], <i>p</i> -value
<b>Pain Interference</b>			
Going to Work	6.74, [2.04,11.44], <i>p</i> = 0.005	4.35, [0.38,8.31], <i>p</i> = 0.032	7.91, [4.05,11.77], <i>p</i> < 0.001
Performing Household Chores	12.56, [9.01,16.12], <i>p</i> < 0.001	12.15, [9.07,15.24], <i>p</i> < 0.001	12.78, [9.81,15.76], <i>p</i> < 0.001
Gardening or Shopping	12.97, [10.10,15.83], <i>p</i> < 0.001	12.85, [9.89,15.82], <i>p</i> < 0.001	13.04, [10.20,15.88], <i>p</i> < 0.001
Socializing with others	9.97, [6.57,13.37], <i>p</i> < 0.001	9.29, [5.96,12.63], <i>p</i> < 0.001	10.91, [7.82,14.00], <i>p</i> < 0.001
Recreation / Hobbies	10.90, [7.50,14.29], <i>p</i> < 0.001	10.49, [7.43,13.56], <i>p</i> < 0.001	11.28, [8.34,14.21], <i>p</i> < 0.001
Sexual Relations	5.46, [2.65,8.26], <i>p</i> < 0.001	4.89, [2.01,7.75], <i>p</i> = 0.001	5.76, [2.98,8.54], <i>p</i> < 0.001
Physical Exercise	8.80, [5.85,11.75], <i>p</i> < 0.001	8.94, [5.90,11.97], <i>p</i> < 0.001	9.09, [6.17,12.01], <i>p</i> < 0.001
Sleeping	10.93, [8.11,13.76], <i>p</i> < 0.001	10.08, [7.14,13.03], <i>p</i> < 0.001	11.00, [8.31,13.70], <i>p</i> < 0.001
Mental Efficacy	9.94, [6.74,13.13], <i>p</i> < 0.001	9.50, [5.93,12.46], <i>p</i> < 0.001	11.39, [8.19,14.60], <i>p</i> < 0.001
<b>Fatigue Interference</b>			
Going to Work	9.84, [5.77,13.91], <i>p</i> < 0.001	6.66, [2.94,10.36], <i>p</i> = 0.001	10.70, [7.44,13.95], <i>p</i> < 0.001
Performing Household Chores	14.77, [11.81,17.73], <i>p</i> < 0.001	13.46, [10.22,16.71], <i>p</i> < 0.001	15.04, [12.18,17.90], <i>p</i> < 0.001
Gardening or Shopping	14.95, [12.01,17.88], <i>p</i> < 0.001	14.21, [11.19,17.23], <i>p</i> < 0.001	15.05, [12.29,17.82], <i>p</i> < 0.001
Socializing with others	11.26, [8.19,14.33], <i>p</i> < 0.001	9.85, [6.42,13.27], <i>p</i> < 0.001	12.25, [9.26,15.24], <i>p</i> < 0.001
Recreation / Hobbies	13.09, [10.07,16.11], <i>p</i> < 0.001	12.14, [8.81,15.47], <i>p</i> < 0.001	13.58, [10.66,16.50], <i>p</i> < 0.001
Sexual Relations	6.20, [3.32,9.08], <i>p</i> < 0.001	4.50, [1.39,7.61], <i>p</i> = 0.005	6.22, [3.34,9.09], <i>p</i> < 0.001
Physical Exercise	12.35, [9.57,15.14], <i>p</i> < 0.001	11.45, [8.30,14.61], <i>p</i> < 0.001	12.77, [9.86,15.67], <i>p</i> < 0.001
Sleeping	10.78, [8.03,13.53], <i>p</i> < 0.001	9.49, [6.33,12.65], <i>p</i> < 0.001	10.78, [8.02,13.54], <i>p</i> < 0.001
Mental Efficacy	9.57, [6.12,13.02], <i>p</i> < 0.001	8.70, [4.88,12.51], <i>p</i> < 0.001	10.48, [7.02,13.93], <i>p</i> < 0.001
<b>Mood Interference</b>			
Going to Work	6.44, [2.33,10.54], <i>p</i> = 0.002	1.63, [-2.94,6.20], <i>p</i> = 0.48	7.09, [2.92,11.26], <i>p</i> = 0.001
Performing Household Chores	11.26, [7.96,14.59], <i>p</i> < 0.001	9.96, [6.16,13.76], <i>p</i> < 0.001	11.51, [8.20,14.81], <i>p</i> < 0.001
Gardening or Shopping	11.54, [8.54,14.55], <i>p</i> < 0.001	9.89, [6.40,13.38], <i>p</i> < 0.001	11.51, [8.51,14.51], <i>p</i> < 0.001
Socializing with others	9.29, [5.93,12.65], <i>p</i> < 0.001	6.25, [2.29,10.21], <i>p</i> = 0.002	9.91, [6.54,13.27], <i>p</i> < 0.001
Recreation / Hobbies	10.28, [7.05,13.51], <i>p</i> < 0.001	8.95, [5.23,12.67], <i>p</i> < 0.001	10.65, [7.43,13.86], <i>p</i> < 0.001
Sexual Relations	6.15, [3.19,9.10], <i>p</i> < 0.001	4.06, [0.86,7.26], <i>p</i> = 0.01	6.27, [3.32,9.23], <i>p</i> < 0.001
Physical Exercise	9.47, [6.65,12.30], <i>p</i> < 0.001	8.16, [5.03,11.28], <i>p</i> < 0.001	9.52, [6.71,12.34], <i>p</i> < 0.001
Sleeping	7.92, [5.14,10.70], <i>p</i> < 0.001	7.10, [4.00,10.19], <i>p</i> < 0.001	8.15, [5.37,10.92], <i>p</i> < 0.001
Mental Efficacy	9.48, [6.21,12.75], <i>p</i> < 0.001	8.08, [4.44,11.71], <i>p</i> < 0.001	10.50, [7.20,13.80], <i>p</i> < 0.001

Activity interference variable	IMPROVED HAQ Score		
	Unadjusted, [95% CI], <i>p-value</i>	Adjusted for of Disease Length, [95% CI], <i>p-value</i>	Adjusted for age, [95% CI], <i>p-value</i>
<b>Dryness Interference</b>			
Going to Work	4.49, [0.31,8.67], <i>p</i> = 0.04	3.35, [-0.09,6.78], <i>p</i> = 0.06	5.27, [1.63,8.91], <i>p</i> = 0.005
Performing Household Chores	7.28, [3.34,11.21], <i>p</i> < 0.001	7.79, [4.26,11.33], <i>p</i> < 0.001	7.25, [3.80,10.70], <i>p</i> < 0.001
Gardening or Shopping	6.70, [3.11,10.29], <i>p</i> < 0.001	6.62, [3.25,9.98], <i>p</i> < 0.001	6.55, [3.30,9.79], <i>p</i> < 0.001
Socializing with others	6.58, [2.86,10.30], <i>p</i> = 0.001	6.83, [3.42,10.24], <i>p</i> < 0.001	6.73, [3.41,10.05], <i>p</i> < 0.001
Recreation / Hobbies	7.98, [4.32,11.65], <i>p</i> < 0.001	7.53, [4.14,10.92], <i>p</i> < 0.001	8.03, [4.81,11.25], <i>p</i> < 0.001
Sexual Relations	5.02, [2.08,7.96], <i>p</i> = 0.001	5.36, [2.42,8.29], <i>p</i> < 0.001	5.06, [2.12,7.80], <i>p</i> = 0.001
Physical Exercise	6.08, [2.71,9.46], <i>p</i> < 0.001	6.23, [3.05,9.42], <i>p</i> < 0.001	5.95, [2.92,8.97], <i>p</i> < 0.001
Sleeping	6.44, [3.47,9.41], <i>p</i> < 0.001	7.10, [4.01,10.18], <i>p</i> < 0.001	6.68, [3.72,9.64], <i>p</i> < 0.001
Mental Efficacy	7.58, [3.99,11.18], <i>p</i> < 0.001	6.86, [3.17,10.55], <i>p</i> < 0.001	8.23, [4.64,11.83], <i>p</i> < 0.001
<b>Brain Fog / Mental Fatigue Interference</b>			
Going to Work	6.23, [2.47,9.99], <i>p</i> = 0.001	1.97, [-2.07,6.01], <i>p</i> = 0.34	8.01, [4.10,11.93], <i>p</i> < 0.001
Performing Household Chores	10.67, [6.66,14.67], <i>p</i> < 0.001	8.01, [4.01,12.01], <i>p</i> < 0.001	11.12, [7.71,14.52], <i>p</i> < 0.001
Gardening or Shopping	10.88, [7.76,14.00], <i>p</i> < 0.001	8.97, [5.40,12.54], <i>p</i> < 0.001	11.06, [8.03,14.08], <i>p</i> < 0.001
Socializing with others	9.34, [6.03,12.65], <i>p</i> < 0.001	6.71, [3.06,10.37], <i>p</i> < 0.001	9.79, [6.58,12.99], <i>p</i> < 0.001
Recreation / Hobbies	10.42, [7.19,13.65], <i>p</i> < 0.001	8.51, [4.78,12.32], <i>p</i> < 0.001	10.84, [7.63,14.04], <i>p</i> < 0.001
Sexual Relations	7.42, [4.32,10.52], <i>p</i> < 0.001	4.61, [1.19,8.03], <i>p</i> = 0.009	7.52, [4.43,10.60], <i>p</i> < 0.001
Physical Exercise	8.36, [5.39,11.34], <i>p</i> < 0.001	6.30, [2.98,9.62], <i>p</i> < 0.001	8.43, [5.47,11.38], <i>p</i> < 0.001
Sleeping	7.26, [4.12,10.40], <i>p</i> < 0.001	6.31, [2.77,9.85], <i>p</i> = 0.001	7.53, [4.41,10.66], <i>p</i> < 0.001
Mental Efficacy	8.15, [4.50,11.29], <i>p</i> < 0.001	7.14, [3.70,10.57], <i>p</i> < 0.001	9.05, [5.90,12.20], <i>p</i> < 0.001

Table 6: Interaction Analysis of the Binary Variable Length of Disease

Activity Interference Variable	HAD's Anxiety		
	Unadjusted, [95% C.I.], <i>p-value</i>	Adjusted for Disease Length, [95% C.I.], <i>p-value</i>	Adjusted Interaction Length of Disease ≥ 9 years, [95% C.I.], <i>p-value</i>
<b>Fatigue Interference</b>			
Gardening or Shopping	1.79, [1.21,2.37], <i>p</i> < 0.001	1.45, [0.82,2.09], <i>p</i> < 0.001	1.33, [0.17,2.49], <i>p</i> = 0.03
Socializing with others	1.80, [1.22,2.38], <i>p</i> < 0.001	1.47, [0.86,2.08], <i>p</i> < 0.001	1.24, [0.15,2.32], <i>p</i> = 0.03
Recreation / Hobbies	1.97, [1.42,2.53], <i>p</i> < 0.001	1.63, [1.00,2.25], <i>p</i> < 0.001	1.40, [0.30,2.50], <i>p</i> = 0.01
<b>Mood Interference</b>			
Gardening or Shopping	2.22, [1.58,2.85], <i>p</i> < 0.001	1.82, [1.22,2.42], <i>p</i> < 0.001	2.00, [0.99,3.00], <i>p</i> < 0.001
Socializing with others	2.83, [2.38,3.28], <i>p</i> < 0.001	2.60, [2.07,3.13], <i>p</i> < 0.001	1.20, [0.29,2.11], <i>p</i> = 0.01