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Fear of Relapse in Patients Suffering from RRMS Influence Their Quality of life

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Abstract

Multiple Sclerosis (MS) is a chronic, potentially debilitating disease that affects millions of patients worldwide. About 85% of patients experience a disease subtype characterised by relapses and remittance (RRMS). While many studies have investigated factors influencing patients' health-related quality of life (HRQoL) in RRMS, none have taken patients' fear of relapses into account. In this study, we measured the patients' self-reported HRQoL, fear of relapse (FoR), health anxiety (HA), number of relapses, duration of disease, type of medication and perceived level of side effects. Treating neurologists provided an estimate of patients' disease severity. All covariates and demographic (personal and disease-related) characteristics were included in regression modelling of their association with HRQoL. The model showed that HRQoL was most strongly associated with disease severity estimated by neurologists, which was highly correlated with the number of relapses and disease duration. However, upon adjustment for FoR (in the presence of all covariates), this association between disease severity and HRQoL attenuated, and FoR remained the only covariate significantly associated with HRQoL. Notably, our modelling also revealed a significant association between HA and FoR in RRMS patients. This study's findings have important implications for the management of MS in RRMS patients and point to the critical roles of FoR and HA as drivers of HRQoL in RRMS. Given the importance of HRQoL to the patient experience and economically, we argue that a more nuanced understanding is needed of the subjective nature of quality of life and its determinants. Interventions aimed at reducing psychological distress and anxiety should be explored.

Keywords: RRMS, Quality of Life, Health Anxiety, Fear of Relapse, Regression

1. Introduction

Multiple Sclerosis (MS) is a chronic and potentially debilitating disease. In most patients, diagnosis follows a major attack involving a heterogeneous suite of debilitating symptoms. Among these symptoms are visual disturbances, fatigue, motor impairments affecting balance, and sensory symptoms, including numbness, tingling, and pain. While approximately 85% of patients with MS will initially regain part or full-function, an accumulation of disability can ensue over the longer term in 70-75% of patients due to successive relapses followed by an incomplete return of function on remission. These patients are initially diagnosed with Relapsing-Remitting MS (RRMS). Within ten years of diagnosis, more than 50% of patients with RRMS develop a secondary progressive form (SPMS), characterised by a steady progression of disease and disability over time. The current paradigm of care includes the use of disease modifying medications (DMDs) which have demonstrated benefit in reducing relapses rate, slowing disease progression, and postponing the transition to secondary progressive MS (Landfeldt et al., 2018). Disease-modifying medications carry significant side-effects (Landfeldt et al., 2018), which for some, are intolerable or deemed unsafe.

Given their impact and potential significance to disease course and disability accumulation, it is logical that relapses are a critical experience for RRMS patients. Relapses have been linked to increased fatigue and reduced Health-Related QoL (HRQoL) (Maurer et al., 2016).

Consistent with the WHO's recognition of wellbeing as important in "Health" (1947), Health-related quality of life (HRQOL) has become a useful indicator of overall health and the impact of health status on quality of life (Palermo et al., 2008; Revicki et al., 2014), rendering it a useful construct to inform burden of disease. HRQOL is a multidimensional measure comprising self-perceived assessments of physical and mental health status.

Affecting approximately 50% of the adult population, chronic conditions are associated with high disease burden both personally and in economic terms. Identifying modifiable factors that can improve HRQOL in chronic and costly conditions such as RRMS is likely to have far-reaching implications. Understanding the influence of individual factors is crucial in informing the design of interventions (Megari, 2013).

Several studies have investigated QoL, anxiety, and other psychological factors in MS patients in different stages and compared them with disease-free individuals. It has been suggested that

individuals, even at the early stages of the disease, have a lower quality of life and a higher level of anxiety and other psychological complications as compared to disease-free individuals (Janssens et al., 2003; Strober, 2018). Different factors have been suggested to contribute to lowering the quality of life in RRMS patients, including patients' cognitive impairment (Vinck et al., 1997) and type of DMD used (Jongen, 2017), with a disparity documented between perspectives of patients and that of neurologists' regarding contributing factors (Ysrraelit et al., 2017).

We have previously demonstrated that the expectation of relapse and its associated consequences are a significant source of stress in RRMS patients (Khatibi et al., 2020). It is conceivable that patients' anticipatory anxiety regarding relapse can also be another source of discrepancy between the patient and the neurologist's attitudes about the disease and its impact on QoL. The current study investigates the factors associated with the quality of life in patients diagnosed with RRMS comparing patients and the neurologist's attitudes towards QoL.

2. Methods

A total number of 70 RRMS patients (44 females, Mean age=33.69±7.8; age range 21-53) were recruited by advertisement through a charity organisation dedicated to relieving MS patients' problems. Patients agreed to share information about the duration of the disease (since diagnosis, mean years=8.24±5.6, range 1-30 years), the number of relapses recorded in their documents (mean=7.13±4.5, range 1-25), and contact information for their neurologist. The range of education level was from high school diploma to PhD.

A control group of participants matched for age, sex, and educational level without a history of a neurological or psychiatric disorder were recruited by advertisement in social media such as telegram and Instagram (n=70). Control participants (44 females) aged between 20-54 (mean age=33.01±7.5 years). The lowest educational level was a high school diploma, and the highest educational level was PhD or medical doctorate. Both groups of participants received a link to an online survey through which they completed questionnaires. The research was conducted according to the guidelines set by the Helsinki declaration. The Department of Psychology's research ethics committee at Shahid Beheshti University (Tehran, Iran) reviewed and approved the study. All participants have read and agreed to participate and share their information with the research team and their neurologist before their participation.

2.1. Tools

The following questionnaires were completed by both RRMS patients and control group participants:

The Short-Form 36 Questionnaire for the assessment of the health-related quality of life is a 36-item questionnaire widely used in the MS population. This instrument assesses health concerns relevant to patients and the general population and generates eight subscales and two summary scores: Physical Component Scale and Mental Component Scale (each between 0 and 100). This measure was previously translated to Farsi and widely used in Iranian population (Dehvan et al., 2019).

The Health-Anxiety Inventory (HAI-18) is a short form of a measure that measures an individual's experience of current health concerns and how they impacted his/her reaction to possible health-related complaints. Each item consists of four statements, and the respondent chooses the statement that best describes their feeling. Total scores range from 0-54. The HAI has been translated to Farsi and widely used in Iranian population (Rabiei et al., 2013)

In addition to the above-mentioned questionnaires, RRMS patients completed the Fear of relapse Scale (Khatibi et al., 2020). The Fear of Relapse Scale is a 26-item measure developed to assess RRMS patients fear of experiencing a relapse. Each item asks patients to rate the degree to which thoughts related to fear of relapse come to their mind on a 5-point Likert scale. Total scores range from 0-104. The original version of the questionnaire is developed in Farsi and validated in the Iranian population (Khatibi et al., 2020).

Besides, patients were also asked the type of DMD they use and rated tolerability of the DMD's side effects on a VAS (0=I have no problem with the side effects of the DMD, 10=It is extremely difficult for me to tolerate the side-effects of the DMD).

We also contacted the neurologist of each patient and asked them to rate the severity of the disease in the patient on a VAS (0=Not severe at all, 10= the most severe form of RRMS). We asked them to consider the severity of relapses and disability status of the patient into account when they do this rating.

2.2. Statistical analyses

Linear regression analyses were performed with quality of life physical component score as the dependent variable, and later with quality of life mental component as the dependent variable. Chi-square analysis was used to investigate differences between patients and the control group regarding gender and educational level. Independent group t-score analysis was used to test group differences in age

3. Results

No significant differences were observed between patients and matched controls in terms of gender and age (Table 1). As can be seen in table 1, the health anxiety of RRMS patients was significantly higher than matched controls. RRMS patients' quality of life-Mental component was significantly lower than the control group. RRMS patients' quality of life-Physical component was significantly lower than the control group.

-Table 1 about here-

3.1. *Physical HRQOL*

Multivariable linear regression model summary revealed significant associations between covariates in the fourth block and physical health HRQOL (F change(3,59)=24.39, $p < 0.001$, $R^2 = 0.61$). Accordingly, we only report the model with the physical component as the dependent variable and only among RRMS patients. Independent variables were entered in four blocks: the first block included demographics (age, education level, and sex). The second block included information about the disease (years since diagnosis, the total number of relapses). The third block included information about the DMD (type and the patient's evaluation of side-effects). The fourth and last block included Fear of Relapse, Health anxiety and the neurologist estimate of the patient's severity of the disease. The model demonstrated that the fear of relapse is the best predictor of the quality of life in RRMS patients ($b = -0.70$, $t(59) = -7.55$, $p < 0.001$). Before including the third block of variables in the model, the number of relapses was the best predictor of patients' quality of life ($b = -0.43$, $t(64) = -2.27$, $p = 0.027$). Besides, in this model, the neurologist's estimate of the patient's severity of the disease was not a significant predictor of the quality of life-physical component in RRMS patients ($b = -0.30$, $t(59) = -1.878$, $p = 0.08$). After removing the fear of relapse from the fourth block, the neurologist's estimation of the patient's severity of the disease became

the best predictor of the quality of life in patients ($b=-0.63$, $t(60)=-2.77$, $p=0.007$). A significant equation was found for the whole model ($F(9,60)=2.10$, $p=0.043$, $R^2=0.24$).

Next, the fear of relapse was included as the dependent variable and health anxiety as the independent variable. Linear regression indicated that health anxiety was significantly associated with fear of relapse in RRMS patients ($b=0.27$, $t(64)=2.28$, $p=0.026$). A significant equation was found ($F(1,68)=5.21$, $p=0.026$, $R^2=0.07$).

3.2. Mental HRQOL

We found no significant effects among the covariates tested when modelling mental health related QOL as the dependent variable (data not shown).

3.3. Correlation analysis

Figure 1 presents the heatmap correlogram in RRMS patients. As can be seen, the biggest positive correlation is between the neurologist's estimation of the severity of the disease, number of relapses and years since diagnosis. It suggests that the more relapses the patient experiences and the more time passed since the diagnosis of the patient, the power of neurologist estimation for the severity of the disease increases. The biggest negative correlation was between the fear of relapse and the patient's quality of life-physical component (the negative correlation between the fear of relapse and the quality of life-mental component did not reach to significant level). Health anxiety was significantly and positively associated with fear of relapse, showing that the more the patient is anxious about her/his health generally, the more they are fearful of a relapse.

There was a significant negative correlation between health anxiety and the quality of life-physical component among the control group. No other significant correlation was observed in the control group.

-Figure 1 about here-

4. Discussion

In this study, we examined factors hypothesised to contribute to RRMS patients' quality of life. Self-reported health anxiety of RRMS patients was significantly higher than that of non-patients, whereas both physical and mental quality of life was significantly lower among patients compared to non-patients. Among RRMS patients, fear of relapse was the best (and the only significant) predictor of physical quality of life, and health anxiety was a significant predictor of fear of relapse.

Interestingly, neurologists' estimation of the disease severity accounted for no significant unique variance within the combined model that included fear of relapse. However, in the absence of fear of relapse, neurologists' estimation of disease severity became the strongest predictor of physical quality of life in patients. In line with these findings, we found significant positive correlations between the number of relapses experienced, years since diagnosis and neurologists' estimates of disease severity. The number of relapses is a good indicative of future disability. Studies in the literature suggest that relapses have independent contribution to worsening of patients and disability (Koch-Henriksen et al., 2019). In our regression model, the total number of relapses was also a significant predictor of the quality of life in patients. However, after inclusion of the fear of relapse and the neurologist's estimation of the severity of the disease, the total number of relapses became insignificant.

Relapses appear to carry both immediate (direct) and anticipatory effects. The experience of relapse can be devastating for many with RRMS, producing an acute, unexpected disruption of daily life for patients (Brown et al., 2006), and relapses themselves are associated with anxiety, worsening mood and lowered self-esteem (McCabe, 2005). While relapse in and of itself can be devastating for many with RRMS, anticipated secondary consequences related to relapse represent another source of anxiety for RRMS patients (Jose Sa, 2008). A relapse is a potential reminder of the neurodegenerative loss of function and future disability (Brown et al., 2006). This is consistent with research on chronic conditions wherein fear of progression is one of the important factors influencing the psychological wellbeing of patients (Herschbach et al., 2005). Similarly, fear of recurrence is thought to have a substantial impact on cancer patients' quality of life (Hart et al., 2008).

As a construct, fear of relapse and its impact has been largely overlooked in RRMS patients. This is despite relapse being the primary characteristic of RRMS, and pathophysiological processes

that is thought to contribute to disease progression. Others have incorporated fear of relapse into newer measure of the quality of life specific to RRMS (Baroin et al., 2013). However, ours is the first to determine the associations between fear of relapse as a psychological state affecting quality of life, physical and psychological wellbeing. The fear of relapse measure targets patients' fear of the impact of a relapse on their current state of life (e.g., hospitalisation) and fear of the progression of the disease (e.g., losing more abilities). In this study, we have not tried to differentiate them, but it will be valuable to the literature if future studies investigate contribution of each of them separately to the quality of life in patients.

A number of factors have been suggested to be associated with the severity of diseases in RRMS, and they are known to influence the quality of life in patients. Most previous studies looked into the factors that can be objectively measured, such as the duration of the disease, relapses, education level or type of DMD (Rezapour et al., 2017; Yalachkov et al., 2019). However, quality of life is a subjective measure of a person's psychological wellbeing (Hays et al., 2002). Although external factors like health status, economic situation, existing social networks, and etc. may influence a person's understanding of his or her wellbeing, none of them can be directly used to examine the quality of life in a person without taking that person's perspective into account. In the current study, although the duration of the disease (years since the first diagnosis) and the number of relapses were significantly and negatively correlated with the quality of life in RRMS patients, our analyses revealed that when we put them in the same model that considers the subjective evaluation of the patients' fear of relapse, number of relapses lose their power in the prediction of the quality of life. Some previous studies have proposed that factors such as age, and education influence an MS patient's quality of life (Yalachkov et al., 2019). In contrast to those studies, in our study, we did not find any relationship between age, educational level and quality of life (physical and mental in RRMS patients).

Different measures have been used to examine health-related quality of life in patients suffering from chronic conditions. Among them, SF36 is one of the most widely used ones. However, many of those studies used a single total score to measure the quality of life in patients and the validity of the use of a single score has been questioned previously (Lins and Carvalho, 2016). In our study, we did not find differences between the physical and mental components of the quality-of-life measure (SF36) within groups. On average, both scores were lower among RRMS patients than the control group. However, correlational and regression analyses revealed significant associations between scores in the physical component and factors that were suggested to be

correlated with the quality of life in RRMS patients. The physical component includes subscales that consider physical functioning, bodily pain, general health, and role limitations-physical component. The aspects covered in the physical subscales are in the centre of problems associated with complications in MS and the findings of our study confirm these assumptions.

Anxiety in MS is a common problem, and many previous studies suggested a high prevalence of anxiety problems in patients (Jose Sa, 2008). Previous studies suggested that health anxiety (also called illness anxiety in more recent references) is among factors that contribute to lowering the quality of life in RRMS patients (Hayter et al., 2016). The research literature on other chronic disorders such as chronic pain suggests that anxiety is among factors that contribute to the development of fear and in its place this can contribute to disability in patients (Turk and Wilson, 2010). In our study, a higher level of health anxiety was associated with lower quality of life (physical) in both in RRMS patients and disease-free controls. Among RRMS patients, health anxiety could significantly predict the fear of relapse in RRMS patients. Some studies may target changing health anxiety in patients and investigate its influence on fear of relapse and consequently quality of life in patients with RRMS. Previous studies suggest that efforts in the management of anxiety related to a specific target, can lead to reduction of fear (Rossi et al., 2020; Steimer, 2002). Many previous studies suggested that Cognitive Behaviour therapy is an effective way for the management of health anxiety (Cooper et al., 2017). Future studies may examine the relationship between health anxiety, fear of relapse, and other emotional and cognitive factors that play a role in this model and suggest interventions to improve quality of life in RRMS patients.

Another important finding of our study was the fact that comparing the patients' fear of relapse with their neurologist's estimation of the severity of the disease, patients' expression of fear was a better predictor of their perceived quality of life. As stated before, quality of life is a subjective measure and can be influenced by many different factors; however, the most determinant factor is an individual understanding and perception of those factors. Neurologists' estimation of the patient's status and her or his disease severity are mostly based on objective factors that can be assessed by the examination of medical records. In line with this assumption, in our study, the neurologist's estimation was significantly correlated with the number of relapses and the duration of disease in patients and their age. However, when it comes to the prediction of the quality of life in patients, unless we take patients expressed fear of relapse, none of those factors can play a significant role. This finding has clear implications for the clinical practice: understanding RRMS

patient's quality of life is not complete before we take the subjective perception of the patient into account. Previous studies suggest that quality of life is among factors that have an impact on MS patients' adherence to DMDs (Treadaway et al., 2009). Thus, lower quality of life can result in interruption of disease management in MS patients which in turn, can lead to more complications in future which on its own will further reduce the quality of life in patients. However, further studies are needed to examine this inter-relationship.

Our choice of methodology resulted in limitations which should be considered when interpreting results. We were unable to verify patients' medical records and all information collected other than neurologists' assessments were based on patient self-report which may be subject to recall bias. In addition, we were unable to obtain more than one rating by participants' treating neurologists. Future studies can further extend our knowledge with better access to medical records and a more comprehensive estimation by neurologists. Besides, recruitment of patients through a charity organisation and control group's participants by advertisements in social media could have introduced some bias in the study. Optimistically, both groups should be recruited from similar setting to compare their data. In our study, due to the limitations we had because of working with a charity organisation it was not possible to recruit control participants through them.

Altogether, this study is one of the few studies that tried to understand factors that contribute to RRMS patients' quality of life from their perspective in comparison with their neurologist's. The current study revealed associations between health anxiety, fear of relapse in RRMS patients, and patients' perceived quality of life.

Conflict of Interest Statement

Authors declare no conflict of interest regarding the current submission.

Authors' contribution

AK was involved in design, data-collection, analysis and writing. TW was involved in writing. MD was involved in writing.

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Table 1

Comparison between patients and healthy controls in terms of sex, education, age, health anxiety and quality of life

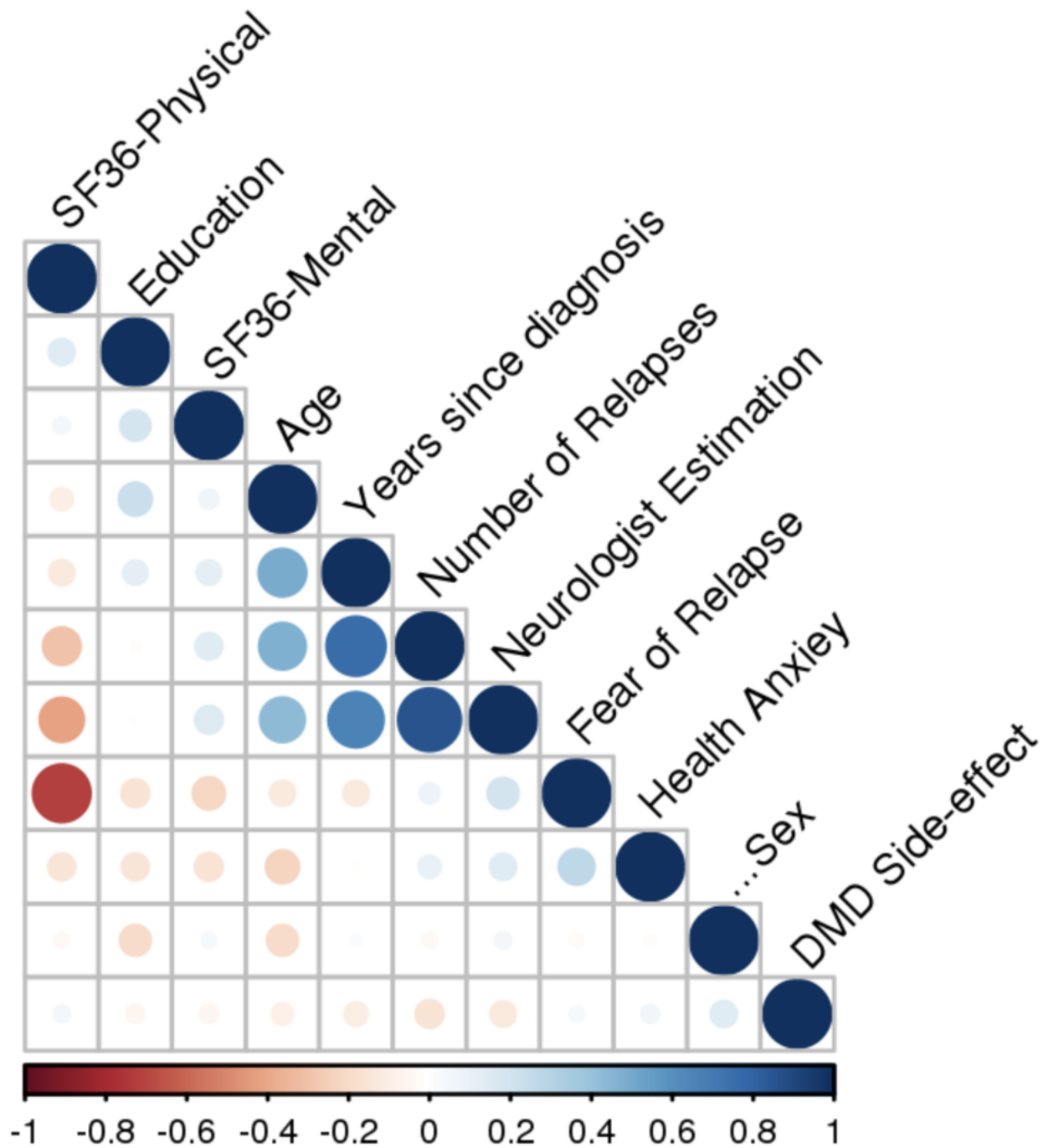
| | | Patients (n=70) | Healthy Control (n=70) | t or chi Square | p or Asymp. Sig. for chi- square |
|-------------------|-------------------------------------|--------------------|---------------------------|--------------------|--|
| Sex | Male | 26 | 26 | | |
| | Female | 44 | 44 | | |
| Education | High-school diploma and below | 17 | 19 | 0.167 ^a | 0.92 |
| | Bachelors and below | 37 | 35 | | |
| | Masters, PhD, MD | 16 | 16 | | |
| Age | | 33.69±7.8 | 32.56±7.3 | 0.88 | 0.38 |
| Health Anxiety | | 21.5±11.1 | 17.00±6.6 | 2.90* | 0.004 |
| SF36 | Mental | 53.09±21.1 | 70.50±12.3 | 5.96* | <0.001 |
| | Physical | 54.03±22.7 | 70.31±11.7 | 5.34* | <0.001 |

^a Chi-Square

* Significant difference between the two groups

Figure Legends

Figure 1-Heatmap Correlogram of dependent variables among RRMS patients, DMD=Disease Modifying Drug,



Highlights

- RRMS patients' quality of life (QoL) is lower than non-patient controls
- Several factors contribute to lowered QoL in RRMS
- Patients' fear of relapse is the best predictor of QoL
- Health anxiety contributes to fear of relapse in RRMS