# Quality of life of multiple sclerosis patients receiving medical care at the Palestinian ministry of health's directorates in the west bank, occupied Palestinian territory (oPt) and associated factors

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## **ABSTRACT**

Multiple Sclerosis (MS) is a neurological disease where the immune system attacks the myelin sheath of neuron axons leading to considerable symptoms. The disease has detrimental effects on patients' health-related quality of life (HRQoL). This study assesses the quality of life (QoL) of MS patients receiving medical care at Palestinian Ministry of Health's (PMoH) directorate in the West Bank. 150 patients were included, with ages between 20 and 65 years. A standardized questionnaire was used, it is divided into 2 sections: the first section with questions on basic demographic and socio-economic characteristics; the second focuses on the patient's QoL by assessing physical, mental and emotional health's factors. The MSQoL-54 scale scores were created using the Likert method by averaging items within the scales. Then the row scores were linearly transformed into 0-100 scales. Calculation of the score of physical health composite and the mental health composite, and multiplying these constructed variables by the weight given to each variable and finding subtotals for each composite. Patients had a mean age of 35 years. 68.7% were females. 99.3% were diagnosed as with Relapsing Remitting Multiple Scleroses (RRMS). Overall quality of life mean was 58.71(standard deviation (SD): 22.06), role limitations due to physical and emotional problems means: 32(SD: 39.51) and 32(SD: 40.11) respectively, and health distress mean: 3.19 (SD: 1.38). Both physical and mental health composite mean were: 40.94(SD: 38.97) and 39.91(SD: 36.67) respectively. All patients had low physical and mental HRQoL scores. The most affected parts of QoL in the sample were those related to role limitations due to physical and emotional problems, physical function, emotional well-being, fatigue, and health perception. Health distress was found to be the most powerful predictor of QoL of MS patients. The results are beneficial to the PMoH in developing plans to improve the quality of life of MS patients.

**Keywords:** Multiple Sclerosis, Quality of Life, Neurological Disease, Relapsing Remitting Multiple Scleroses.

# INTRODUCTION

Multiple Sclerosis (MS) is one of the most common neurological diseases [1]. This disease is detected by the presence of multifocal spots of demyelination in the central nervous system [1, 2], in which the immune system attacks the myelin sheath of axons in neurons [3, 4] causing neurological disability in young adults [5, 6]. MS is relatively common in Europe, the United States, Canada, New Zealand [[7]. It is affecting 2 million people worldwide with 350,000 people in the United States alone [8]. The risk of disease is greater in women than in men [7]. Median and mean age of onset were

23.5 and 30 years, respectively. Incidence is low in childhood, increasing rapidly after age 18 [7-9]. Even though the cause of the disease is still unknown[5] there is a complex of genetic and environmental factors related to the occurrence of this disease [10]. One of the genetic factors in the development of this disease is Zn deficiency, which affects several functions in the immune system [1, 5]. Environmental factors include bacterial or viral infections that cause T-cells to confuse myelin proteins for these antigens [4]. Occupational exposure to sunlight which may lead to the occurrence of multiple sclerosis [10]. There are studies showing that vitamin D intake by regular fish consumption and cod

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liver oil has a positive impact on the prevention of this disease progression, this has been observed in a recent Norwegian casecontrol study. [11]. However, there are no prospective studies confirming that vitamin D deficiency is a risk factor for multiple sclerosis [12]. There is also an association between smoking and MS, where the relationship is dose-response, in which an increased frequency of smoking will increase the progression of MS in both males and females [13, 14]. MS is generally divided into three clinical subtypes; 1- Relapsing-Remitting Multiple Sclerosis (RRMS). periods of neurological dysfunction followed by complete or incomplete remission, 2-Secondary Progressive (SPMS) (uninterrupted progression), 3- Primary Progressive (PPMS), as MS can begin in some of the patients with a progressive disease course [2, 5]. The diagnosis of this disease is based on clinical findings and Magnetic Resonance Imaging (MRI). There are some considerable symptoms across multiple sclerosis patients, including loss of function or feeling in the limbs, loss of bowel or bladder control, sexual dysfunction, fatigue, blindness due to optic neuritis, double vision, loss of balance, pain, loss of cognitive functioning, and emotional changes [4]. The first sign of the onset of the disease is urinary disorder, which has been found to occur in 2% to 10% of multiple sclerosis patients [15].

MS disorder was found to have detrimental effects on patients' health-related quality of life (HRQoL) [16]. Globally, The World Health Organization (WHO), has defined quality of life (QOL) as: "the individual's perception of his/her position in life in the context of the culture, the value systems in which he/she lives, and in relation to his/her goals, expectations, standards and concerns [17]. According to several studies and by comparing with other chronic medical illnesses, the quality of life includes several domains: physical, social, and emotional aspects to determine the patient's satisfaction level with life [16]. It is worth to mention that a proper assessment of (HRQoL) can only be assessed by the patients themselves, not by the physicians [18]. Researchers found many aspects to affect the quality of life through MS patients' lifespan. As it can be seen in MS

patients who have a shorter lifespan compared to matched age and sex individuals [19]. However, when MS patients become older, they may face different problems than younger individuals, which leads them to feel depressed affecting both the mental and physical domains of HRQoL, due to impaired motivation, interest, limited physical progress, limited social support, changes relationships, and decreased accessibility to the environment. [19, 20]. Education and employment may decrease the chances of being mentally destroyed [19].

Moreover, damaging of different cells in the brain which causes fatigue, functional limitations that affect daily activities[17]. A study conducted in Germany, France, and the United Kingdom showed that QoL was significantly different among the control group and those who had MS disease, in which physical functions including; self-care, walking indoors, shopping, use of public transport, running, and lifting heavy objects, in addition to general wellbeing were 40%-50% less than the control group. Moreover, psychological function and social role functions were 20% lower than in the control [21]. Psychological symptoms experienced by MS patients were anxiety, depression, cognitive decline, irritability, and anger [16].

The importance of the treatment is to avoid temporary disability due to relapses, delay disease progression of multiple sclerosis, and to avoid permanent disability [22], for that treating patients with early diagnosis was considered more beneficial to the patients and society [22].

Assessing the quality of life (QoL) among MS patients is still essential, as it helps in measuring and monitoring challenging symptoms, treatments, side-effects [18], and encourages successful treatment by health care providers [23]. A low awareness about MS complications is considered an important issue that may contribute to MS patients who live in the West Bank, suffering from this disease, thus, affecting their QoL. Therefore, it is necessary to focus on the main difficulties/challenges that MS patients face and suffer from, to relive their serious physical and psychological problems.

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## **METHODS**

# Research Question

How is the quality of life of Multiple Sclerosis (MS) patients receiving medical care in the Palestinian Ministry of Health's (MOH) directorate in the West Bank and associated factors?

# Sub-research questions

- 1. What is the quality of life of a sample of MS Palestinian patients in the West Bank?
- 2. What are the factors associated with the quality of life of this sample of MS patients?

# Study design

This is a quantitative cross-sectional study covering all MS patients (200) receiving medical care at the MOH's directorate and living in the West Bank during the period between March to December in 2019.

# Sampling

We collected data from all districts (Jerusalem, Bethlehem, Hebron, Ramallah, Nablus, Salfeet, Qalqelya, Tubas, Jeneen, and Jericho). We then divided the district into 3 strata, north, middle, and south.

Pharmacists who work in (MoH) directorates distributed the questionnaires to the MS patients and helped when necessary.

The total population of MS patients receiving medications from the Ministry of Health (MoH) clinics in the West Bank was 200. Of those, 150 patients were willing to join this study at 75% of all patients. We obtained 43 cases from the North of the West Bank (28.7%) of all cases), 68 from the middle of the West Bank (45.3% of all cases), and 39 from the South West Bank (26%) of all cases). Inclusion criteria included patients diagnosed with MS diseased, that was confirmed by a neurologist, with the existence of clinical symptoms, and the indication of the presence of the lesion in the central nervous system, and received medication in (MoH) directorates [17]. Exclusion criteria MS patients who are not receiving medication from (MoH) clinics in the West Bank.

#### Instrument

The measurement instrument aimed to assess the quality of life and its associated factors among MS patients who are receiving medical care at the health centers of the MoH. A standardized questionnaire was used with minor modifications to suit the Palestinian context. "Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument " [24]. It is an appropriate measuring tool for assessing health-related quality of life; in addition, patients' demographic characteristics were collected.

The self-administered questionnaire is divided into 2 sections: the first section encompasses a series of brief questions to ascertain basic demographic and socioeconomic characteristics, data related to age, sex, marital status, education level, income, employment, residence, the second section focuses on the patient's quality of life by assessing physical health, role limitation due to physical health problems, role limitations due to emotional problems, pain, emotional well-being, energy, health perception, social function, cognitive function, health distress, sexual function, change in health, satisfaction with sexual function, and overall quality of life. The Questions also included the date when multiple sclerosis was diagnosed, the availability of MS medications at the (MoH) directorate, and compliance to treatment.

## Statistical analysis

Univariate analyses were initially performed; using frequencies for categorical variables, mean and standard deviation for continuous variables. Bivariate analysis was used to identify significant demographic and socio-economic factors related to the dependent variable, chi-square (chi-2) for categorical variables and the Independent T-test for continuous variables. SPSS V.22 was used for statistical analysis.

The MSQoL-54 scale scores were created using the Likert method by averaging items within the scales, and then the row scores were linearly transformed into 0–100 scales to clarify the factors that affect the quality of life of MS patients. Higher score indicates better quality of life.

Using the constructed variable overall quality of life after Likert analysis as the cutoff point to assess the quality of life in all domains, and the average calculation of any item related to physical and mental health was considered good if it is higher than this point, and bad if it is less than this point.

We calculate the score of physical health composite included (physical function, health perceptions, energy/fatigue, role limitations – physical pain, sexual function (M+W), social function, health distress) and mental health composite included (health distress, overall quality of life, emotional well-being, role limitations – emotional, cognitive function) after multiplying these constructed variables by the weight were given to each variable and find the subtotal of each composite as shown in the table below, this is to determine how are all physical and mental health aspects can affect quality of life.

The internal reliabilities of MSQoL-54 were assessed on multiple item scales by using Cronbach's alpha coefficient, which ranges from 0–1, where 1 means perfect reliability.

## Ethical issues

1. Approval from the primary health care of Palestinian Minister of Health (PMoH)

- was obtained to conduct the study on MS patients receiving medical care at the PMoH Directorate.
- 2. Full consent was obtained from all participants prior to starting the questionnaire, and their confidentiality was ensured.

# **RESULTS**

In the sample of 150 MS patients receiving medications from the Ministry of Health (MoH) clinics in the West Bank, 68.7% were females, 55.3% were 35 years old or less, 28.7% lived in the north of Palestine, 45.3% in the middle of Palestine and 26% in the south of Palestine, 52% had a university degree, 67.3% were married, the majority of the study population (76%) had a monthly income equating the average wages in Palestine, 51.3% were unemployed, 54.7% live in cities, 72.7 % of patients were diagnosed with MS early whine the first year of the appearance of symptoms, 84.7% toke medication regularly, 50.7% of patients benefitted from medication, 99.3 % of the sample were diagnosed with Relapsing Remitting Multiple Scleroses (RRMS).

**Table (1):** Frequency of all demographic and clinically variables.

Varia	Statistical summary		
Sex	Female	103(68.7%)	
	Male	47(31.3%)	
Age (year)	Mean(SD)	35.05(10.90)	
Age category	35 years or less	83(55.3%)	
	Above 35 years	67(44.7%)	
	North	43(28.7%)	
District	Middle	68(45.3%)	
	South	39(26%)	
	Less than secondary	42(28%)	
Education	Secondary	30(20%)	
	Post-secondary	78(52%)	
Marital status	Single	41(27.3%)	
	married	101(67.3%)	
	Widow / divorced	8(5.3%)	
El	Less than others	33(22%)	
Evaluate your income compared to the people around you	As others	114(76%)	
to the people around you	More than others	3(2%)	

Varia	Statistical summary	
	Student	13(8.7%)
Employment status	Unemployment	77(51.3%)
	Employment	60(40%)
	Camp	7(4.6%)
Residence	Village	61(40.7%)
	City	82(54.7%)
Discovered disease	Early within the first year of A the appearance of symptom	109(72.7%)
	Late after one year of the appearance of symptom	41(27.3%)
	Yes	127(84.7%)
Take medication regularly	Some time	20(13.3%)
	No	3(2%)
N. 1: 1	Yes	76(50.7%)
Medicine has positive effect on your health	Some time	66(44%)
	No	8(5.3%)
MS classification	relapsing Remitting	149(99.3%)
MS classification	Secondary progressive	1(.7%)

Used overall quality of life as cut-off point, mean and SD 58.38(22.15), role limitations due to physical and emotional problems 32(39.51), 32(40.11) respectively, physical function 35.8(20.82), emotional

well-being 45.94(17.88), fatigue 40.74(17.91), health perception 42.86(21.80), and health distress 3.19(1.38). Both physical and mental health composite 40.93(38.97), 39.84(36.67) respectively.

Table (2): MSQOL-54 Scoring Form, mean and SD of all constructed variables.

	Item	Mean	SD	Cronbach's alpha	NO. of item
1	Physical function	35.80	20.82	.911	10
2	Role limitations due to physical problems	32	39.51	.869	4
3	Role limitations due to emotional problems	32	40.11	.828	3
4	Pain	56.35	22.06	.642	3
5	Emotional well-being	45.94	17.88	.664	5
6	Energy/fatigue	40.74	17.91	.737	5
7	Health Perceptions	42.86	21.80	.827	5
8	Social function	57.65	21.10	.516	3
9	Cognitive function	52.60	27.89	.909	4
10	Health distress	3.19	1.38	.932	4
	Sexual function men +	69.36	34	.937	4
	Sexual function women	66.79	32.90	.925	4
11	Sexual function M&W	67.59	00		
12	Change in health	52.87	22.49	a	1
13	Satisfaction with sexual function	56.77	30.24	a	1
14	OVERALL QUALITY OF LIFE	58.71	22.06	.837	2

SD-standard deviation

Table (3): Calculating MSQOL-54 Physical Health Composite Score.

MSQOL-54 Scale	Final Scale Score	* (Weight )	Subtotal
Physical function	35.80	.17	6.08
Health perceptions	42.86	.17	7.28
Energy/fatigue	40.74	.12	4.88
Role limitations - physical	32	.12	3.84
Pain	56.35	.11	6.20
Sexual function (M+W)	67.59	.08	5.40
Social function	57.65	.12	6.91
Health distress	3.19	.11	.35
			40.94

**Table (4):** Calculating MSQOL-54 Mental Health Composite Score.

MSQOL-54 Scale	Final Scale Score	*Weight	Subtotal
Health distress	3.19	.14	.44
Overall quality of life	58.71	.18	10.56
Emotional well-being	45.94	.29	13.32
Role limitations - emotional	32	.24	7.68
Cognitive function	52.60	.15	7.9
			39.91

**Table (5):** Descriptive statistics MSQOL-54 Composite Score.

Item	Mean	SD
Physical Health Composite	40.94	38.97
Mental Health Composite	39.91	36.67

SD-standard deviation.

The percentage of those who have good quality of life among patients who live in the middle of Palestine was 43(63.2%), compared to those who live in the north and south of Palestine, 28(65.1%), 11(28.2%) respectively, [chi-2=14.929, p=.001]. Among those who had a monthly income equating the average wage in Palestine 70(61.4%), compared to those who had a monthly income less or more the average than wage in Palestine 11(33.3%),1(33.3%), respectively, [ chi-2=8.699, p= .013]. Among those who live in cities 51(62.2%), compared to those who live in camps and villages, 1(14.3%),51(62.2%), respectively, [chi-2= 7.222, p=.027], Among those who were diagnosed early within the first year of the appearance of symptoms 69(63.3%) compared to those who were diagnosed late after one year from the appearance of symptoms 13(31.7%), [chi-2=12.001, p=.001]. Among those who were taking medication regularly, 75(59.1%),

compared with those who were taking medication irregularly or not taking medication at all, 5(25%),2(66.7%), respectively [chi-2=8.264, p=.016].

Table (6): Bivariate analysis.

variable name		Quality of life of MS patients		Pearson Chi 2 test	
		Good	Bad	Chi 2 test	P value
Sex	Male	22(46.8%)	25(53.2%)	1.706	102
	Female	60(58.3%)	43(41.7%)	1.706	.192
Ago	35 years and less	51(61.4%)	32(38.6%)	3.446	0.62
Age	Above 35 years	31(46.3%)	36(53.7%)	3.440	.063
	North	28(65.1%)	15(34.9%)		.001
District	Middle	43(63.2%)	25(36.8%)	14.929	
	South	11(28.2%)	28(71.8%)		
E1	Less than secondary	23(54.8%)	19(45.2%)	020	006
Education	Secondary	16(53.3%)	14(46.7%)	.028	.986
	Post-secondary	43(55.1%)	35(44.9%)		
	Single	26(63.4%)	15(36.6%)		
Marital status	Married	51(50.5%)	50(49.5%)	2.173	.337
Wartar status	Widow / divorced	5(62.5%)	3(37.5%)	- 2.173	.557
Evaluate your	Less than others	11(33.3%)	22(66.7%)		.013
income	As others	70(61.4%)	44(38.6%)	8.699	
compared to the people around you	More than others	1(33.3%)	2(66.7%)		
	Student	11(84.6%)	2(15.4%)	5.586	.061
Employment status	Unemployment	38(49.4%)	39(50.6%)		
status	Employment	33(55%)	27(45%)		
	Camp	1(14.3%)	6(85.7%)		.027
Residence	Village	30(49.2%)	31(50.8%)	7.222	
	City	51(62.2%)	31(37.8%)		
Diagnose	Early before one year from symptom	69(63.3%)	40(36.7%)	12.001	.001
disease	Late after one year from symptom	13(31.7%)	28(68.3%)	12.001	.001
Take	Yes	75(59.1%)	52(40.9%)		.016
medication	Some time	5(25%)	15(75%)	8.264	
regularly	No	2(66.7%)	1(33.3%)		
Medicine has	Yes	46(60.5%)	30(39.5%)	4.159	.125
positive effect	Some time	34(51.5%)	32(48.5%)		
on your health	No	2(25%)	6(75%)		
MS	Relapsing Remitting	81(54.4%)	68(45.6%)	.835	.361
classification	Secondary progressive	1(100%)	00	.055	.501

#### DISCUSSION

The purpose of this study is to assess the quality of life and its associated factors for MS patients who are receiving medical care at the health centers of PMoH in West Bank directorate. QoL measures not only relate to happiness and satisfaction, but have also become an important factor in manifestation of disease outcomes, patient care, management, and improving function in society. [25, 26] For that we have used a selfadministered questionnaire (Multiple (MSQOL)-54 Sclerosis Quality of Life Instrument ) [24]. The instrument was easy to administer and was well accepted by 75% of our sample of MS patients. The average time to complete the questionnaire was from 5 to 15 minutes, the questionnaire was not difficult to understand, and similar results were found in other studies, where the average time to complete the questionnaire was from 4 to 20 minutes [7, 9]. Most of the patients were able to complete the questionnaire without any intervention by the research team, only a small percentage of patients who were uneducated needed assistance from a pharmacist.

In our study, we found the internal consistency reliability index for these scales to be (0.877) by conducting the coefficient of stability Cronbach's alpha test. The Internal reliabilities of the instrument ranged from (0.516) on social function to (0.937) on sexual function for men. MSQoL-54 scales were reliable in MS Palestinian patients in the West Bank as elsewhere [9].

We found that MS patients suffer from a low score in overall quality of life with mean: 58.38(SD: 22.15), patients also had a score below the recommended cut-off point (overall quality of life) in the following domains: role limitations due to physical and emotional problems with means: 32(SD: 35.8) and 32(SD:40.11) respectively, physical function mean: 35.8(SD: 20.82), emotional well-being mean: 45.94(17.88), fatigue mean: 40.74(SD: 17.91), health perception mean: 42.86 (SD:21.80), and health distress mean: 3.19 (SD: 1.38).Both physical and mental health composite mean: 40.93(SD:38.97) 39.84(SD:36.67) respectively. Similar lower physical and mental components of the OoL

scores were also found in MS patients in Bosnia and Herzegovina, Slovenian, and Italy.[2-4] The previous literature has shown that the lower quality of life was a result of some physical and psychological conditions which affect MS patients negatively and so exacerbate the disease effect [27, 28].

51.3% of MS patients in our sample were unemployed due to the variety of different symptoms that MS patients suffer from, including: fatigue and functional limitations which affect daily activities [17], loss of function or feeling in the limbs, loss of balance, pain, loss of cognitive function, and emotional changes [4]. As a consequence of these symptoms, patients were unable to work and became dependent on others.

We found that health distress in our sample had a major influence on HRQOL. As in the literature, patients with MS had impaired motivations, interest, and collaboration. and felt restricted from participating in social life and family relationships, leading to mental problems among MS patients [17]. While sexual function and satisfaction of sexual function had higher scores than the cutoff point, this may be due to the reason that most patients were not willing to answer the questions related to this subscale, resulting in missing

(71.8%) of patients who were from the south had bad quality of life, this percentage is higher than those patients who were from the middle and north of Palestine (36.8%) (34.9%) respectively, there is no clear explanation for this; however, it may be due to the bad status of all patients who participated from the south.

In our sample, we found younger patients to have better quality of life than older patients, this is similar to previous studies [7, 29]. Younger patients have more hope and optimism to face the disease in early stages [29]. Elderly patients may face different problems than younger individuals, which may lead them to suffer from depression affecting both the mental and physical domains of HRQoL, impaired motivations, interest, limited social support, and changes in relationships [19, 20].

Among our sample of MS patients, we found that those who had an early diagnosis of the disease and took medications regularly had better quality of life. As in the previous literature, early diagnosis of the disease and treatment were considered more beneficial to the patients and society, which prevents the progression of the disease, avoiding severe cases, and permanent disability [22].

The Strength of this study: it is the first study conducted to assess the quality of life of MS patients in Palestine –West Bank.

The limitations of this study: not all patients were willing to join this study, only 75% of MS patients receiving treatment in MoH in West Bank agreed to complete the questionnaire. The sample size is too small, 150 patients, it is can't generalize the result globally.

We sent a questionnaire to all districts according to the number of MS patients in each district but not all patients willing to join this study, especially in the south, where 68 (45.3%) of the patients were from the middle of the West Bank, 43 (28.7 %) were from the north and 39 (26%) were from the south. We attribute this to the difference in the culture of patients from the middle to the north and south of West Bank in terms of disclosing and about the disease due talking embarrassment. Pharmacists in the south directorate had some difficulty in convincing patients to fill the questionnaire, because patients in the south had a fear of disclosing their illness and suffering. For the subscales sexual function and satisfaction of sexual function caused embarrassment for some patients as found in other studies [8, 9], 28.6% of our sample had no desire to answer these questions, especially in single patients who have no experience in this domain. Selfadministrated questionnaires may lead to information bias as some of the questions could not be well understood, which might have an impact on measuring the variables of interest.

# **CONCLUSIONS**

This study highlighted the importance of assessing the QoL of MS patients in the oPt. All patients had low physical and mental HRQoL scores. The most affected parts of

QoL in the sample were those related to role limitations due to physical and emotional problems, physical function, emotional wellbeing, fatigue, and health perception. Health distress was found to be the most powerful predictor of QoL of MS patients. The results are beneficial to the PMoH in developing plans to improve the quality of life of MS patients. More studies are needed to determine the factors that positively affect QoL of MS patients.

## RECOMMENDATION

- 1. The PMoH must improve MS medication availability and commit to providing MS patients with their medications regularly without interruption. Ensuring the continuous availability of medications is necessary to prevent the progression and severity of the disease.
- The PMoH could work on providing psychological counseling and support for MS patients and their families or caregivers as both could suffer from psychological distress.
- 3. Civil society organizations and associations could assist by providing support to MS patients and their families in as much as they can.
- 4. Further research is needed to assess the quality of life of all MS patients for use in future policies and interventions.

## REFERENCES

- Saroukolaei SA, Ghabaee M, Shokri H, Badiei A, Ghourchian S. The role of Candida albicans in the severity of multiple sclerosis. Mycoses. 2016; 59(11): 697-704.
- 2) Kutzelnigg A, Lucchinetti CF, Stadelmann C, Bruck W, Rauschka H, Bergmann M, et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain. 2005; 128(Pt 11): 2705-2712.
- 3) Dorland. Dorland's medical reference works. 2016. <a href="https://www.elsevier.com/books/dorlands-illustrated-medical-dictionary/dorland/978-1-4160-6257-8">https://www.elsevier.com/books/dorlands-illustrated-medical-dictionary/dorland/978-1-4160-6257-8</a> (accessed December 25 2020).

- Mohr DC, Hart SL, Julian L, Cox D, Pelletier D. Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis. BMJ. 2004; 328(7442): 731.
- 5) Bredholt M, Frederiksen JL. Zinc in Multiple Sclerosis: A Systematic Review and Meta-Analysis. ASN Neuro. 2016; 8(3): 1759091416651511.
- 6) Marck CH, Neate SL, Taylor KL, Weiland TJ, Jelinek GA. Prevalence of Comorbidities, Overweight and Obesity in an International Sample of People with Multiple Sclerosis and Associations with Modifiable Lifestyle Factors. PLoS One. 2016; 11(2): e0148573.
- Catic T, Culig J, Suljic E, Masic A, Gojak R. Validation of the Disease-specific Questionnaire MSQoL-54 in Bosnia and Herzegovina Multiple Sclerosis Patients Sample. Med Arch. 2017; 71(2): 103-106.
- 8) Stern B, Hojs Fabjan T, Rener-Sitar K, Zaletel-Kragelj L. Validation of The Slovenian Version of Multiple Sclerosis Quality of Life (MSQOL-54) Instrument. Zdr Varst. 2017; 56(4): 260-267.
- Solari A, Filippini G, Mendozzi L, Ghezzi A, Cifani S, Barbieri E, et al. Validation of Italian multiple sclerosis quality of life 54 questionnaire. J Neurol Neurosurg Psychiatry. 1999; 67(2): 158-162.
- 10) Marrie RA. Environmental risk factors in multiple sclerosis aetiology. Lancet Neurol. 2004; 3(12): 709-718.
- 11) Smolders J, Damoiseaux J, Menheere P, Hupperts R. Vitamin D as an immune modulator in multiple sclerosis, a review. J Neuroimmunol. 2008;194(1-2):7-17.
- 12) Munger KL, Zhang SM, O'Reilly E, Hernan MA, Olek MJ, Willett WC, et al. Vitamin D intake and incidence of multiple sclerosis. Neurology. 2004; 62(1): 60-65.
- 13) Hedström AK, Bäärnhielm M, Olsson T, Alfredsson L. Tobacco smoking, but not Swedish snuff use, increases the risk of

- multiple sclerosis. Neurology. 2009; 73(9): 696-701.
- 14) Riise T, Nortvedt MW, Ascherio A. Smoking is a risk factor for multiple sclerosis. Neurology. 2003; 61(8): 1122-1124.
- 15) Bonniaud V, Parratte B, Amarenco G, Jackowski D, Didier JP, Guyatt G. Measuring quality of life in multiple sclerosis patients with urinary disorders using the Qualiveen questionnaire. Arch Phys Med Rehabil. 2004; 85(8): 1317-1323.
- 16) Ashjazadeh N, Hadianfard H, Feridoni S, Farjam E. Assessment of health-related quality of life in patients with multiple sclerosis living in the Fars province of Iran. Neuroimmunol Neuroinflamm. 2016; 3:57-62.
- 17) Salehpoor G, Rezaei S, Hosseininezhad M. Quality of life in multiple sclerosis (MS) and role of fatigue, depression, anxiety, and stress: A bicenter study from north of Iran. Iran J Nurs Midwifery Res. 2014; 19(6): 593-599.
- 18) Al-Tahan AM, Al-Jumah MA, Bohlega SM, Al-Shammari SN, Al-Sharoqi IA, Dahdaleh MP, et al. The importance of quality-of-life assessment in the management of patients with multiple sclerosis. Recommendations from the Middle East MS Advisory Group. Neurosciences (Riyadh). 2011; 16(2): 109-113.
- 19) Buhse M, Banker WM, Clement LM. Factors associated with health-related quality of life among older people with multiple sclerosis. Int J MS Care. 2014; 16(1): 10-19.
- 20) Lobentanz IS, Asenbaum S, Vass K, Sauter C, Klosch G, Kollegger H, et al. Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. Acta Neurol Scand. 2004; 110(1): 6-13.
- 21) Murphy N, Confavreux C, Haas J, Konig N, Roullet E, Sailer M, et al. Quality of life in multiple sclerosis in France, Germany, and the United Kingdom. Cost

- of Multiple Sclerosis Study Group. J Neurol Neurosurg Psychiatry. 1998; 65(4): 460-466.
- 22) Kobelt G, Berg J, Lindgren P, Fredrikson S, Jonsson B. Costs and quality of life of patients with multiple sclerosis in Europe. J Neurol Neurosurg Psychiatry. 2006; 77(8): 918-926.
- 23) Lysandropoulos AP, Havrdova E, Paradig MSG. 'Hidden' factors influencing quality of life in patients with multiple sclerosis. Eur J Neurol. 2015; 22 Suppl 2:28-33.
- 24) National Multiple Sclerosis Society. Multiple sclerosis quality of life (MSQOL)-54 instrument. 1995.
  - https://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Multiple-Sclerosis-Quality-of-Life-54-(MSQOL-54) (accessed December 25 2020).
- 25) Pittock SJ, Mayr WT, McClelland RL, Jorgensen NW, Weigand SD, Noseworthy JH, et al. Quality of life is favorable for most patients with multiple

- sclerosis: a population-based cohort study. Arch Neurol. 2004; 61(5): 679-686.
- 26) Zwibel HL, Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. Am J Manag Care. 2011; 17 Suppl 5 Improving: S139-145.
- 27) Berrigan LI, Fisk JD, Patten SB, Tremlett H, Wolfson C, Warren S, et al. Health-related quality of life in multiple sclerosis: Direct and indirect effects of comorbidity. Neurology. 2016; 86(15): 1417-1424.
- 28) Papuc E, Stelmasiak Z. Factors predicting quality of life in a group of Polish subjects with multiple sclerosis: accounting for functional state, sociodemographic and clinical factors. Clin Neurol Neurosurg. 2012; 114(4): 341-346.
- 29) Goretti B, Portaccio E, Zipoli V, Hakiki B, Siracusa G, Sorbi S, et al. Coping strategies, psychological variables and their relationship with quality of life in multiple sclerosis. Neurol Sci. 2009; 30(1): 15-20.