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ORIGINAL ARTICLE

Association of Body Mass Index With Progression and Prediction of Multiple Sclerosis

Daliborka Tadić,[1, 2] Vlado Đajić,[1, 2] Sanja Grgić,[1, 2] Siniša Miljković[1, 2]

(1) Clinic of Neurology, University Clinical Centre of the Republic of Srpska, Banja Luka, the Republic of Srpska, Bosnia and Herzegovina;
(2) Faculty of Medicine, University of Banja Luka, Banja Luka, the Republic of Srpska, Bosnia and Herzegovina.

Abstract

Background/Aim: Multiple sclerosis is a disease whose aetiology involves multifactorial interactions among genetic and environmental factors. Obesity is one of the most important environmental factors conducive to the onset and progression of the disease. The aim of the study was to determine the value of body mass index (BMI) in a population of patients with multiple sclerosis compared to the general population, in order to assess the relation between the BMI and physical disability in patients with multiple sclerosis and the influence of the BMI on the course and progression of the disease.
Methods: A cross-sectional study was performed in 100 patients suffering from multiple sclerosis (experimental group) and 50 healthy people (control group). In order to determine the degree of physical disability, the Expanded Disability Status Scale (EDSS) was used. Clinical and demographic data and values of the BMI in both studied groups were collected. Statistical analysis included the descriptive statistics, t-test, chi-square test, analysis of variance, correlation and regression analysis.
Results: Mean body weight and BMI were significantly higher in the control group ($p < 0.05$). There was no significant correlation between EDSS and BMI ($p = 0.574$). There was a correlation between the course of MS and the fact whether BMI was abnormal or normal ($p = 0.031$).
Conclusion: BMI is an environmental factor that significantly correlates with the progression and prediction of multiple sclerosis, but not to the degree of physical disability.

Key words: multiple sclerosis, BMI, progression, prediction, physical disability.

Correspondence:
DALIBORKA TADIĆ
E: tadic.daliborka@gmail.com
M:+387 65 659 651

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Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) that often occurs in a population of young adults, predominantly female.[1] Pathophysiological mechanisms of this disorder include a degenerative and an inflammatory component that covers both grey and white matter of the CNS. These mechanisms are basis for a very heterogeneous relapsing or progressive clinical course of MS, where longer duration of the disease leads to physical and cognitive disability. A reliable long-term individualised prognosis has not yet been possible and represents a subject to intensive research.[2] The aetiology of MS involves multifactorial interactions among genetic and environmental factors. Genetic predisposition is only a part of the risk of MS, while lifestyle and environmental factors are key participants in the development of the disease.[3] Proven risk factors for the development of the disease are

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female gender, smoking, low level of vitamin D, dietary habits, Epstein Barr virus infection and obesity in childhood and adolescence.[4, 5]

According to the previous studies, there is an obvious connection between the disability in MS and obesity. Increased level of disability decreases the level of physical activity and the frequency of overweight or obese status is higher and *vice versa*.[6] This may be associated with loss of mobility, but also with other disorders that accompany MS such as depression, pain, fatigue, loss of social contacts and associated chronic diseases.[7] However, this interdependence also exists at the molecular level. Since obesity is associated with latent inflammatory reactivity, it leads to the release of inflammatory cytokines that influence the immune response and is associated with a possible risk for the development of MS.[8] Adipose tissue secretes hormones that affect the functioning of the immune system, including leptin and interleukin-6, known inhibitors of T-cell activity. Elevated leptin levels in obese people are inversely proportional to the function of T cells in individuals with MS. Another potential mechanism is related to the fact that obese people have lower levels of serum 25-hydroxy vitamin D correlates with leads to an increased risk for MS.[7, 8] Inflammasome is a protein complex that participates in the inflammatory response and it is found in the adipose tissue. Recent studies have shown its significant role in the pathogenesis of autoimmune and inflammatory diseases and demonstrated that elevated levels of these proteins leads to the progression of these diseases, which is particularly applicable to diabetes, atherosclerosis and MS.[9-11]

So far, in several studies the body composition has been studied as a factor influencing the onset and progression of MS, which was mostly related to the body mass index (BMI), total body fat and lean body mass.[12, 13] In well-designed studies, in populations of Sweden and the United States of America (USA), the interactions between HLA genotype and BMI of 20-year-old people were investigated, where it was shown that obesity was associated with an increased risk of MS compared to people with normal weigth body.[14]

The influence of obesity on MS was confirmed by a large longitudinal study, which included nurses in the USA (Nurses Health Study and Nurses Health Study II). The results of this study showed that obesity at the age of 18 years was related to a doubled risk of developing MS, compared to the individuals with normal BMI, while such a correlation was not found in the adult population.[15] Munger et al[16] in a long-term cohort study also examined children from 7-13 years of age and the results showed that obesity in this age carries a higher risk for the development of MS.

A large multinational EnvIMS study that included populations in Italy and Norway has shown that an increased body weight, in particular at the age of 20-25, poses a risk for the MS in Norwegian population, which partly also applies to the Italian population, but without reaching statistical significance. These results are compatible with low levels of vitamin D and a chronic inflammatory condition in the obese, which may originate from the differences in protective exposure to the sun.[17] These data are significant, because in other studies lower levels of vitamin D metabolites in obese human subjects were observed and, among other things, this is why overweight status in infancy may be a risk factor for MS.[18-21] Most recent studies confirmed the impact of obesity on the occurrence of MS in paediatric patients as well as on a weaker response to the drugs of the first-line therapy in the obese patients.[22] It is also important to know that certain genetic structure is a common predictor for the elevated BMI before the onset of MS as well as for the occurrence of the disease.[23]

Why are these findings important? The survey data show that in the period from 2009 to 2010, 16.9 % of children and adolescents in the USA were obese. Although genetic and some other causes that lead to the disease cannot be affected, it is important to influence the environmental factors that are suitable for modification.[24]

The aim of this study was to determine the value of BMI in the population of people with MS compared to the general population, to estimate the association of BMI and the degree of physical disability in patients with MS and to estimate the possible influence of BMI on the course and the progression of the disease.

Methods

This cross-sectional study was conducted at the Clinic of Neurology, University Clinical Centre of the Republic of Srpska, Banja Luka. The sample consisted of 100 MS patients and 50 healthy people (control group) from general population, matched according to sex and age and who were not blood-related to the MS patients, who did not have an inflammatory disease of the CNS nor a cerebrovascular disease and did not use statins (control group). The duration of the study was twelve months.

The research was performed upon prior approval of the Ethics Committee of the University Clinical Centre of the Republic of Srpska, Banja Luka. For this study a general questionnaire, consisting of questions related to the demographic and clinical characteristics of patients and the questionnaire for risk factors for vascular diseases in patients with MS, which was created for the scientific purposes at the Institute of Epidemiology, Faculty of Medicine, University of Belgrade were used. In order to determine the degree of physical disability, the Expanded Disability Status Scale (EDSS) was used.[25] BMI was defined as the body weight (BW) in kilograms divided by the surface area measured in square meters.[26] BMI was determined in both groups of participants and based on its value participants were classified in following groups: reduced BMI (less than 18.5 kg/m^2), normal BMI (18.5-24.9 kg/m^2) and people with increased BMI (more than 25 kg/m^2 - overweight status and over 29.9 kg/m^2 - obesity).

Statistical analyses included methods of descriptive statistics, χ^2 test, Student t-test, variance analysis, correlations and regression analysis.

Results

From a total of 100 patients with MS, 25 % were male and 75 % female. The average age of participants at the beginning of the study was 41.9 ± 10.1 years in the MS group, while participants from the control group were slightly older (average age 42.1 ± 12.3 years). The distribution of patients according to the clinical form of the disease is shown in Figure 1.

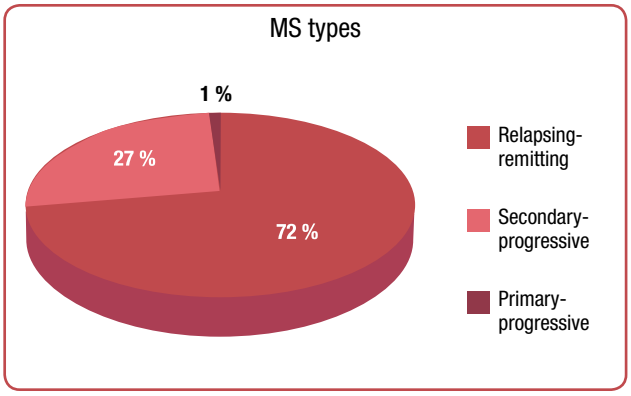

Figure 1. Distribution of clinical types of MS in the group of patients (n=100)

The average value of the EDSS score in the group of patients was 3.7. Based on the quotient of these values and the duration of the disease, the mean value of the index of disease progression was obtained, which in this patient group was 0.9.

Table 1. Parameters of patients with multiple sclerosis (MS) and the control group

Parameter	MS patients (n = 100)	Control group (n = 50)
Age (years)	41.9 ± 10.1	42.1 ± 12.3
Body weight (BW, kg)	67.1 ± 13.2	76.1 ± 16.3*
Body mass indeks (BMI, kg/m^2)	22.7 ± 3.1	36.0 ± 4.4*

**p<0.05 versus the MS group*

In both groups parameters necessary for calculation of the BMI–BW and body height – were registered (Table 1).

Although the MS patients and their controls were matched by age, the average BW and BMI were significantly lower in the MS group. Values of BMI fell within a normal range in the MS group, while they vere increased in terms of obesity in the control group.

The group of patients with MS was analysed according to the form of the disease. In order to establish whether there is a correlation between the clinical types of the disease and the BMI (classified in the pathological and normal level), the chi-square test was used and showed a statistically significant correlation (p = 0.031). More specifically, there was a correlation between the clinical types of MS and the fact whether BMI has pathological or normal values. BMI was a factor that changed during the disease progression and there was a higher incidence of lower values of this parameter with the progression of the disease, ie the transition from relapsing-remitting (RR) in the secondary progressive (SP) form (Figure 2).

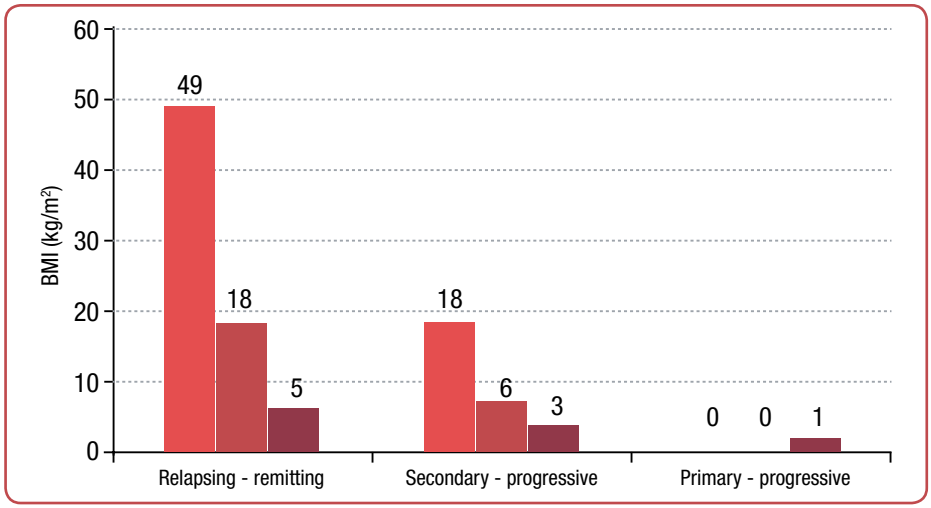

Figure 2. Body mass index (BMI) in different clinical types of MS

Among the patients with RR form, 68.1 % had a normal BMI, 25 % increased and 6.9 % decreased. In the SP group, 66.7 % of patients had a normal BMI, 22.2 % increased and 11.1 % decreased. One patient, suffering from a primary progressive (PP) form of the disease, had decreased BMI.

Using logistic regression methods (univariate analysis) the parameters that could be predictors of MS and thereby determined that the coefficient for the normal BMI was positive, ie that normal values of BMI increase odds ratio and the probability that the patient has MS were analysed.

Discussion

So far, there have been a series of studies involving the assessment of BMI in the population of patients with MS. Our results are in agreement with the hereinafter mentioned best-designed studies conducted on this topic in other environments. A highly significant difference in the values of BMI ($p<0.05$) in the group of MS patients compared to the control group (average value of BMI in the experimental group was within the normal range, whereas it was increased in the control group) is a consequence of the lower BW of this group of patients.

The study of Markianosa et al[27] showed that women suffering from MS had a lower BMI compared to age- and gender-matched controls, while substantial differences were not found among male patients. Their results showed that patients suffering from MS were overweight at a younger age and later on even had a lower BMI, a fact to which attention should be paid, in the context of a possible weight loss with the disease progression in certain populations.

The study of Nortvedt et al[28] observed a gender-mixed population (75 % female) of MS patients compared to healthy individuals, where the average values of the BMI were 23.5 ± 3.6 kg/m², with 11 % of subjects with a BMI below 20 kg/m². Low BMI values was observed in several studies in the population of MS patients compared to healthy controls, wherein there was also a significant, inverse correlation between the high BMI and the risk of developing MS.[29-34]

The study of Pike et al[35] found an average BMI of 23.9 kg/m² for the tested MS population from five European countries, which is within the normal range of values.[35] In some other studies, BMI values in patients with MS were in the range of those in the general population.[36, 37]

A large meta-analysis of clinical trials conducted on this subject also showed a significantly lower BMI in the group of MS patients than in healthy controls and the same results were obtained for patients who had the RR form of the disease.[38] However, some other studies have shown conflicting results to those previously shown and also to this study's results. This may be the case because these investigations were conducted in certain regions of the world where the prevalence of obesity in the general population was higher due to the nutrition style, socio-economic conditions and less physical activity. Besides, some of these studies were performed as retrospective analyses of data from the registries dating from the 1980s, when the awareness of the need for prevention of factors affecting the cardiovascular and other diseases was significantly lower than today.[10]

A study in patients from the NARCOMS registry, the largest registry of MS worldwide, showed that over 50 % of patients with MS were overweight.[39] Similar data on the increased frequency of obesity in the population of MS patients have been shown in other several studies.[40-45]

In the present study, in the experimental group, a lower mean BMI value (although within a normal range) compared to the control group can be interpreted in the context of the application of imunomodulatory therapy. Namely, a significant number of patients had been treated with interferon beta-1b (34 %), whose one of the possible adverse effects is a reduction of BW.[12, 46]

The results obtained in the present study can be explained by the fact that MS patients were under a constant medical supervision, in touch with their therapists who gave them advice on proper diet, need for physical activity and other measures of hygienic and dietetic regimens, which led to the levelling of body weight, as opposed to healthy the individuals in the control group.

Regarding the physical disability and its dependence on the value of the BMI, the results of clinical trials conducted so far were inconsistent. In the present study, there was no correlation between these two parameters, which can be interpreted by the fact that the patients from the experimental group had a higher percentage of normal values of BMI compared to the control group. However, in several studies conducted in a population of MS patients, there was a positive correlation between the degree of physical disability and the BMI.[47-49]

The inverse impact of the BMI on physical disability was also recorded in the research of Flauzino et al[50] In several studies as well as in the present one, it was shown that BMI may be considered as a factor that can change during the progression of the disease and that there was an increased incidence of lower values of this parameter with the progression of the disease ie with the transition from RR to SP form.[39]

Obesity, among other factors such as gender, age, genetic profile and smoking, has a disease-modifying effect by forming its phenotypic presentation and contributes to the occurrence and progression of MS.[51, 52] Research performed at the molecular level showed that high BMI negatively affected the course and form of MS, since the existence of obesity leads to a modulation of the number of monocytes through the ceramide-induced DNA methylation of the antiproliferative genes.[53] MRI studies showed that lifestyle factors, including obesity, influenced the acceleration of cerebral atrophy, and the appearance of new lesions in patients with MS.[54]

Prediction of the MS course is nowadays one of the foci of considerable research. In this study, normal BMI values were shown as a predictive factor for the onset of the MS. However, in other investigations conducted on this topic results were inconsistent. In one of them, BMI has shown a correlation with the progression of the disease and a higher frequency of relapses but was in no correlation with the prediction of the conversion from a clinically isolated syndrome to MS.[55] In other studies it was shown that in a population of MS patients during the one year follow-up there was an increase in physical disability, but there were minimal pieces of evidence that BMI was a predictive factor for this change.[56]

Taiwanese researchers have shown that the BMI values below the normal range with more than four demyelinating lesions are a strong predictor for the conversion from a clinically isolated syndrome to MS.[57] It was also confirmed that the BMI values affected the prediction of cognitive disorders in patients suffering from MS.[58]

Conclusion

So far, in several studies, the BMI has been stu-died as a factor influencing the onset of MS. Results of this study showed that BMI affected the progression and prediction of the disease, but not the degree of physical disability of patients with MS. To prevent these undesirable effects, it is very important to emphasise that this environmental factor is suitable for modification.

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Conflict of interest

None.

References

1. Compston A, Ebers G, Lassmann H, McDonald I, Matthews B, Wekerle H. McAlpine's Multiple Sclerosis. 3rd ed. London: Churchill Livingstone; 1998.
2. Wingerchuk DM, Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. Mayo Clin Proc 2014;89(2):225–40.
3. Waubant E, Lucas R, Mowry E, Graves J, Olsson T, Alfredsson L, et al. Environmental and genetic risk factors for MS: an integrated review. Ann Clin Transl Neurol 2019;6(9):1905-22.
4. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat Rev Neurol 2017;13(1):25-36.
5. Hedström AK. Smoking and its interaction with genetics in MS etiology. Mult Scler 2019;25(2):180-6.
6. Marrie RA, Beck CA. Obesity and HLA in multiple sclerosis: weighty matters. Neurology 2014;82(10):826-7.
7. Marrie R, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T. High frequency of adverse health behaviors in multiple sclerosis. Mult Scler 2009;15(1):105-13.
8. Overs S, Hughes CM, Haselkorn JK, Turner AP. Modifiable comorbidities and disability in multiple sclerosis. Curr Neurol Neurosci Rep 2012;12(5):610-7.
9. Materese G, Carrieri PB, La Cava A, Perna F, Sanna V, De Rosa V, et al. Leptin increase in multiple sclerosis associates with reduced number of CD4+CD25+ regulatory T cells. Proc Natl Acad Sci USA 2005;102(14):5150-5.
10. Lukens JR, Dixit VD, Kanneganti TD. Inflammasome activation in obesity-related inflammatory diseases and autoimmunity. Discov Med 2011;12(62):65-74.
11. Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, et al. Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat Med 1995;1(1):1155–61.
12. Birnbaum G, Cree B, Altafullah I, Zinser M, Reder AT. Combining beta interferon and atorvastatin may increase disease activity in multiple sclerosis. Neurology 2008;71(18):1390–5.
13. Lambert CP, Lee Archer R, Evans WJ. Body composition in ambulatory women with multiple sclerosis. Arch Phys Med Rehabil 2002;83(11): 1559–61.
14. Hedström AK, Olsson T, Alfredsson L. High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women. Mult Scler 2012;18(9):1334-6.
15. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab 1997;82(12):4196–200.
16. Munger KL, Bentzen J, Laursen B, Stenager E, Koch-Henriksen N, Sørensen TI, et al. Childhood body mass index and multiple sclerosis risk: a long-term cohort study. Mult Scler 2013;19(10):1323-9.
17. Wesnes K, Riise T, Bjørnevik T, Myhr KM, Magalhaes S, Wolfson C, et al. The relationship between body size and the risk of multiple sclerosis. Mult Scler 2012;18(4):P253.
18. Bell NH, Epstein S, Greene A, Shary J, Oexmann MJ, Shaw S. Evidence for alteration of the vitamin D-endocrine system in obese subjects. J Clin Invest 1985; 76(1):370–3.
19. Liel Y, Ulmer E, Shary J, Hollis BW, Bell NH. Low circulating vitamin D in obesity. Calcif Tissue Int 1988;43(4):199–201.
20. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72(3):690–3.
21. Hernán MA, Olek MJ, Ascherio A. Geographic variation of MS incidence in two prospective studies of US women. Neurology 1999;53(8):1711–8.
22. Huppke B, Ellenberger D, Hummel H, Stark W, Röbl M, Gärtner J, et al. Association of obesity with multiple sclerosis risk and response to first-line disease modifying drugs in children. JAMA Neurol 2019 Jul 15. doi: 10.1001/jamaneurol.2019.1997.
23. Gianfrancesco MA, Glymour MM, Walter S, Rhead B, Shao X, Shen L, et al. Causal effect of genetic variants associated with body mass index on multiple sclerosis susceptibility. Am J Epidemiol 2017;185(3):162-171.
24. Hedström AK, Lima Bomfim I, Barcellos L, Gianfrancesco M, Schaefer C, Kockum I, et al. Interaction between adolescent obesity and HLA risk genes in the etiology of multiple sclerosis. Neurology 2014; 82:865–872
25. Kurtzke JF. Rating neurologic instrument in multiple sclerosis: an expandede disability status scale (EDSS). Neurology 1983;33(11):1444-52.
26. NHLBI Obesity Task Force. Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults – the evidence report. National Institutes of Health. Obes Res 1998;2:51–209.
27. Markianos M, Evangelopoulos ME, Koutsis G, Davaki P, Sfagos C. Body mass index in multiple sclerosis: associations with CSF neurotransmitter metabolite level. ISRN Neurology Sep 24;2013:981070. doi: 10.1155/2013/981070.
28. Nortvedt MW, Riise T, Maeland JG. Multip sclerosis and lifestyle factors: the Hordaland Health Study. Neurol Sci 2005;26(5):334–9.
29. Alschuler KN, Gibbons LE, Rosenberg DE, Ehde DM, Verrall AM, Bamer AM, et al. Body mass index and waist circumference in persons aging with muscular dystrophy, multiple sclerosis, post-polio syndrome, and spinal cord injury. Disab Health J 2012;5(3):177–84.
30. Ghadirian P, Jain M, Ducic S, Shatenstein B, Morisset R. Nutritional factors in the etiology of multiple sclerosis. Int J Epidemiol 1998;27(5):845-52.
31. Snook EM, Mojtahedi MC, Evans EM, McAuley E, Motl RW. Physical activity and body composition among ambulatory individuals with multiple sclerosis. Int J MS Care 2005/2006;7:137–42.
32. Allen NB, Lichtman JH, Cohen HW, Fang J, Brass LM, Alderman MH. Vascular disease among hospitalized multiple sclerosis patients. Neuroepidemiology 2008;30:234–8.
33. Formica CA, Cosman F, Nieves J, Herbert J, Lindsay R. Reduced bone mass and fat-free mass in women with multiple sclerosis: effects of ambulatory status and glucocorticoid use. Calc Tiss Int 1997;61(2):129–33.

34. Sioka C, Fotopoulos A, Georgiou A, Papakonstantinou S, Pelidou SH, Kyritsis AP, et al. Body composition in ambulatory patients with multiple sclerosis. J Clin Densitom 2011;14(4):465–70.
35. Pike J, Jones E, Rajagopalan K, Piercy J, Anderson P. Social and economic burden of walking and mobility problems in multiple sclerosis. BMC Neurology 2012 Sep 18;12:94. doi: 10.1186/1471-2377-12-94.
36. Mähler A, Steiniger J, Bock M, Brandt AU, Haas V, Boschmann M, et al. Is metabolic flexibility altered in multiple sclerosis patients? PLoS One 2012;7(8): e43675. doi: 10.1371/journal.pone.0043675.
37. Comoglu S, Yardimici S, Okcu Z. Body fat distribution and plasma lipid profiles of patients with multiple sclerosis. Turk J Med Sci 2004;34:43-8.
38. Dardiotis E, Tsouris Z, Aslanidou P, Aloizou AM, Sokratous M, Provatas A, et al. Body mass index in patients with multiple sclerosis: a meta–analysis. Neurolol Res 2019:41(9):836-46.
39. Marrie RA, Horwitz RI, Cutter G, Tyry T, Vollmer T. Association between comorbidity and clinical characteristics of MS. Acta Neurol Scand 2011;124(2):135-41.
40. Slawta JN, Wilcox AR, McCubbin JA, Nalle DJ, Fox SD, Anderson G. Health behaviors, body composition, coronary heart disease risk in women with multiple sclerosis. Arch Phys Med Rehabil 2003;84(12):1823-30.
41. Pilutti LA, Dlugonski D, Pula JH, Motl RW. Weight status in persons with multiple sclerosis: implications for mobility outcomes. J Obes 2012; 2012:868256. doi: 10.1155/2012/868256.
42. White LJ, McCoy SC, Castellano V, Ferguson MA, Hou W, Dressendorfer RH. Effect of resistance training on risk of coronary artery disease in women with multiple sclerosis. Scand J Clin Lab Invest 2006;66(4):351-5.
43. Mojtahedi MC, Snook EM, Motl RW, Evans EM. Bone health in ambulatory individuals with multiple sclerosis: impact of physical activity, glucocorticoid use, and body composition. J Rehabil Res Dev 2008;45(6):851–61.
44. Lalmohamed A, Bazelier MT, Van Staa TP, Uitdehaag BM, Leufkens HG, De Boer A, et al. Causes of death in patients with multiple sclerosis and matched referent subjects: A population-based cohort study. Eur J Neurol 2012;19(7):1007–14.
45. Khurana SR, Bamer AM, Turner AP, Wadwhani RV, Bowen JD, Leipertz SL, et al. The prevalence of overweight and obesity in veterans with multiple sclerosis. Am J Phys Med Rehabil 2009;88(2):83-91.
46. Muñoz D, Escartín A, Dapena D, Coret F, Fernández-Uría D, Pérez D, et al. Adverse events during the titration phase of interferon-beta in remitting-relapsing multiple sclerosis are not predicted by body mass index nor by pharmacodynamic biomarkers. BMC Neurol 2013 Jul 11;13:82. doi: 10.1186/1471-2377-13-82.
47. Zamzam D, Foad M, Swelam M, AbdelHafez M, AbdelNasser A, Mahmoud R, et al. Vitamin D and body mass index in Egyptian multiple sclerosis patients. Mult Scler Relat Disord 2019;28:313-6.
48. Stampanoni Bassi M, Iezzi E, Buttari F, Gilio L, Simonelli I, Carbone F, et al. Obesity worsens central inflammation and disability in multiple sclerosis. Mult Scler 2019 Jun 4:1352458519853473. doi: 10.1177/1352458519853473.
49. Piluti LA, Molti RW. Body composition and disability in people with multiple sclerosis. A dual energy x-ray absorptiometry study. Mult Scler Relat Disord 2019;29:41-7.
50. Flauzino T, Simão ANC, de Carvalho Jennings Pereira WL, Alfieri DF, Oliveira SR, Kallaur AP, et al. Disability in multiple sclerosis is associated with age and inflammatory, metabolic and oxidative/nitrosative stress biomarkers: results of multivariate and machine learning procedures. Metab Brain Dis 2019;34(5):1401-13.
51. Briggs FBS, Yu JC, Davis MF, Jiangyang J, Fu S, Parrotta E, et al. Multiple sclerosis risk factors contribute to onset heterogeneity. Mult Scler Relat Disord 2019;28:11-6.
52. Jakimovski D, Guan Y, Ramanathan M, Weinstock-Guttman B, Zivadinov R. Lifestyle-based modifiable risk factors in multiple sclerosis: review of experimental and clinical findings. Neurodegener Dis Manag 2019;9(3):149-72.
53. Castro K, Ntranos A, Amatruda M, Petracca M, Kosa P, Chen EY, et al. Body mass index in multiple sclerosis modulates ceramide induced DNA methylation and disease course. EBioMedicine 2019;43:392-410.
54. Jakimovski D, Weinstock-Guttman B, Gandhi S, Guan Y, Hagemeier J, Ramasamy DP, et al. Dietary and lifestyle factors in multiple sclerosis progression: results from 5-year longitudinal MRI study. J Neurol 2019;266(4):866-75.
55. Tettey P, Simpson S, Taylor B, Ponsonby AL, Lucas RM, Dwyer T, et al. An adverse lipid profile and increased levels of adiposity significantly predict clinical course after first demyelinating event. J Neurol Neurosurg Psychiatry 2017;88(5):395-401.
56. Pilutti LA, McAuley E, Motl RW. Weigth status and disability in multiple sclerosis: An examination of bi-directional associations over a 24-month period. Mult Scler Relat Disord 2012;1(3):139-44.
57. Ro LS, Yang CC, Lyu RK. A prospective, observational study on conversion of clinically isolated syndrome to multiple sclerosis during 4-year period (MSNEO study) in Taiwan. PLoS One 2019 Jul 15;14(7):e0202453. doi: 10.1371/journal.pone.0202453.
58. Owji M, Ashraf-Ganjouei A, Sahraian MA, Bidadian M, Ghadiri F, Naser Moghadasi A. The relationship between cognitive function and body mass index in multiple sclerosis patients. Mult Scler Relat Disord 2019;32:37-40.
59. Esposito S, Bonavita S, Sparaco M, Gallo A, Tedeschi G. The role of diet in multiple sclerosis: a review. Nutr Neurosci 2018;21(6):377-90.