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The Metabolic Syndrome in Multiple Sclerosis Patients

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Abstract: Background: The impact of comorbidity on multiple sclerosis (MS) is a new area of interest. Limited data on the risk factors of metabolic syndrome (MetS) is currently available. This study was conducted to study the prevalence of metabolic syndrome in MS patients and to identify components of metabolic syndrome in MS patients and get find the relationship between different components of metabolic syndrome and different types of MS. Patients and methods: A total of 60 cases with MS were included in the study. All cases were subjected to complete history taking, thorough physical examination, and routine laboratory investigations. EDSS, and the criteria of metabolic syndrome were assessed in all cases. Results: The study cases with MS who were classified into two groups: Group A: metabolic syndrome (14 subjects), and Group B: with no metabolic syndrome (46 subjects). The age was significantly higher in the metabolic syndrome group. A positive correlation was detected between EDSS with disease duration, number of relapse and number of steroid pulses. On multivariate regression analysis, increased blood pressure, increased body weight, increased waist circumference and higher BMI were revealed to be an independent risk factors for development of metabolic syndrome. Conclusion: Older age is a significant risk factor for having metabolic syndrome in multiple sclerosis patients. Moreover, metabolic syndrome negatively affects EDSS in MS cases.
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1. Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that affects over 400,000 Americans and approximately 2.3 million people worldwide(1). characterized by the presence of inflammation, neurodegeneration, and demyelinating lesions of white and gray matter. Its onset is more common in young adults and the disease has a female predominance (2).

MS is a heterogeneous, multifactorial, immune-mediated disease that is caused by complex gene–environment interactions. The clinical manifestations and course of MS are heterogeneous; in most patients, reversible episodes of neurological deficits (known as relapses) that usually last for days or weeks characterize the initial phases of the disease (clinically isolated syndrome (CIS) and relapsing–remitting MS (RRMS). Over time, the development of permanent neurological deficits and the progression of clinical disability become prominent (known as secondary progressive MS(3).

A minority of patients have a progressive disease course from onset, which is referred to as primary progressive MS(3). Each subtype of MS can be classified as active or not active on the basis of clinical assessment of relapse occurrence or lesion activity detected using MRI (4).

Diagnosis is based on the demonstration of the dissemination of demyelinating lesions to different regions of the CNS (dissemination in space (DIS)) and over time (dissemination in time (DIT)), which can be demonstrated using clinical evaluation or Para clinical tools once MS-mimicking disorders have been excluded**(4).**

MS is a complex disease, and besides genetic variants, lifestyle and environmental factors can be important contributors to disease risk. A combined analysis of both prominent genetic and environmental risk factors showed that a major fraction of MS risk could be explained by currently known risk factors(5).

The lifestyle and environmental factors that increase the risk of MS include exposure to tobacco smoke and organic solvents, Epstein–Barr virus (EBV) infection, lack of sun exposure or low levels of vitamin D and strong evidence now supports obesity during adolescence as a factor increasing MS risk(6)ز

The metabolic syndrome (MetS) is defined by a constellation of an interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of atherosclerotic

cardiovascular disease (ASCVD), T2DM, and all-cause mortality**.** This collection of unhealthy body measurements and abnormal laboratory test results include atherogenic dyslipidemia, hypertension, glucose intolerance, proinflammatory state, and a prothrombotic state(7).

There have been several definitions of MetS, but the most commonly used criteria for definition at present are from the World Health Organization (WHO)(8)**,** the European Group for the study of Insulin Resistance (EGIR) (9)**,** the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)(10)**,** American Association of Clinical Endocrinologists (AACE) (11), and the International Diabetes Federation (IDF)(12).

The worldwide prevalence of MetS is between 10 and 84% depending on the ethnicity, age, gender and race of the population, whereas the IDF estimates that one-quarter of the world's population has MetS(13).

Patients and methods

Study design

This is a prospective study including Egyptian patients who presented with Multiple sclerosis at Al-Azhar university hospitals (El-Hussien and Bab El-shearia hospitals) outpatient clinics during the period between from 2015 to 2018. The aim of this study is to study the prevalence of metabolic syndrome in MS patients and to identify components of metabolic syndrome in MS patients and get find the relationship between different components of metabolic syndrome and different types of MS.

Patient sample

Sixty patients (n = 60) with definite diagnosis with Multiple sclerosis. They were classified into two groups according to metabolic syndrome: Group A: metabolic syndrome (14 subjects), and Group B: with no metabolic syndrome (46 subjects).

Patient consent

A written formal consent was obtained from the patients before participating in this clinical study. The study was approved by the local ethical committee.

Patient evaluation

All the included cases were subjected to complete history taking, full clinical and neurological examination in addition to clinically definite MS using " McDonald criteria 2017 ", general and neurological examination: including weight, height, waist circumference and blood pressure measurement.

Additionally, Neurological impairment was evaluated and scoredfrom 0 to 10 based on Kurtzk's Expanded disability status score (EDSS) which is an eight functional system scale include: Motor, sensory, cerebellar, brain stem, visual, mental, Sphincteric and ambulation.

Metabolic syndrome was defined according to the National Cholesterol Education Program: Adult Treatment Panel III (NCEP/ATP III) criteria(10).

The presence of any three of the following five components was sufficient: (i) central obesity as measured by waist circumference (males >102 cm, females >88 cm); (ii) TG ≥ 150 mg/dl; (iii) HDL-C <40 mg/dl for males and<50 mg/dl for females; (iv) blood pressure >135/85 mmHg; and (v) fasting hyperglycemia glucose ≥100 mg/dl.

Statistical analysis

The study was performed at 95% level of significance and power of 80%. The collected data were coded, processed and analysed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (SPSS Inc, Chicago, IL, USA). Qualitative data was presented as number (frequency) and Percent. Comparison between groups was done by Chi-Square test ($\chi 2$). Quantitative data was tested for normality by Kolmogorov-Smirnov test. Not normally distributed data was presented as median (min-max). Mann Whitney U test was used to compare between two groups. Spearman correlation was used to evaluate the relation between EDSS and other study parameters. Univariate and multivariate analyses were used to identify the predictors of metabolic syndrome. $P < 0.05$ was considered to be statistically significant.

Results

Regarding the components of metabolic syndrome in the cases with MS (n=14), HTN was found in 35.7% of the cases, high waist circumference in 64.3% of the cases, high TGs was detected in 85.7% of the cases, low HDL in 90.9% of the cases (higher percentage) and high blood sugar level in 57.1% of the cases. Table (1) illustrates these data.

Table (1): Components of metabolic syndrome among the cases with MS.

Components	Number (percentage) total = 14
Elevated BP	5 (35.7%)
Waist circumference (> 102 cm in males or > 88 cm in females)	9 (64.3%)
High TGs (> 150 mg/dl)	12 (85.7%)
Low HDL (< 40 mg/dl)	10 (90.9%)
High blood sugar (> 110 mg/dl)	8 (57.1%)

There was a statistically significant difference in the mean age of the cases within the two groups, being higher in the metabolic syndrome group (p< 0.001). The sex distribution didn't show significant difference between the two groups with more females (39 cases) than females. There was a statistically significant difference in the marital status within the cases in the two study groups (29.2%) married in metabolic syndrome group vs 52.2% married in the cases with no metabolic syndrome. These data are illustrated at table (2).

Table (2): Analysis of demographic data of the cases in the two study groups.

		Groups				Test of significance
		Metabolic syndrome (N=14)		No metabolic syndrome (N=46)		
Age (years)		41.14± 7.25		28.41± 6.54		t= 6.218 p< 0.001*
Sex	Males	5	35.7%	16	34.8%	χ2= 0.004 P= 0.949
	Females	9	65.2%	30	65.2%	
Marital status	Single	1	7.1%	22	47.8%	χ2= 7.515 P= 0.006*
	Married	13	92.9%	24	52.2%	

The age of the MS was earlier and the duration of the disease with longer in the cases with no metabolic syndrome with statistically significant difference as compared with the metabolic syndrome group (p< 0.001 and 0.002 respectively). The number of disease relapse, number of pulse steroid and current treatment plan didn't reveal a statistically significant difference between the two groups. Table (3) illustrates these data.

Table (3): Analysis of the disease criteria in the cases within the two groups.

		Groups				Test of significance
		Metabolic syndrome (N=14)		No metabolic syndrome (N=46)		
Age of onset (years)		33.14± 6.84		24.76± 6.02		t= 4.421 p< 0.001*
Duration of the disease (Duration)		3 (0-12)		8 (0-14)		z= -3.095 p= 0.002*
Number of relapse		3 (1-15)		3 (2-6)		z= -1.370 p= 0.171
Number of pulse steroid		2 (0-10)		2 (2-5)		z= -1.927 p= 0.054
Current treatment plan	Disease modifying drugs	12	85.7%	45	97.8%	χ2= 3.315 P= 0.069
	immunosuppressant	2	14.3%	1	2.2%	

The distribution of the initial manifestation of MS disease in the cases with and without metabolic syndrome didn't show a significant difference between the two groups. The most prevalent symptom was visual symptoms, motor symptoms and sensory symptoms. These data are illustrated at table (4).

Table (4): Analysis of risk factors and chronic diseases in the cases within the two groups

		Groups				Test of significance
		Metabolic syndrome (N=14)		No metabolic syndrome (N=46)		
Initial manifestations	Motor	5	35.7%	16	34.8%	χ2= 5.527 P= 1.021
	Sensory	2	14.3%	16	34.8%	
	Visual	6	42.9%	16	34.8%	
	Cerebellar	1	7.1%	2	4.3%	
	Sphincter	1	7.1%	1	2.2%	

The weight, BMI and waist circumference were statistically significant higher in the cases with metabolic syndrome as compared with the cases with no metabolic syndrome group (p< 0.001).

The number of cases with elevated BP, the serum glucose level and serum TGs level with statistically significant higher in the cases with metabolic syndrome. These data are illustrated at table (6).

Table (5): Analysis of the anthropometric measures in the cases within the two groups.

	Groups		Test of significance
	Metabolic syndrome (N=14)	No metabolic syndrome (N=46)	
Weight (Kg)	90.79 ± 9.721	73.67 ±11.421	t= 5.068 p< 0.001*
Height (cm)	164.93±7.416	164.80± 6.462	t= 0.061 p= 0.956
BMI (kg/m^2)	33.36 ±4.254	27.09± 3.788	t= 5.271 p< 0.001*
Waist circumference (cm)	100.71±11.262	88.39± 9.703	t= 4.008 p< 0.001*

Table (6): Analysis of the metabolic profile of the cases in the two study groups.

		Groups				Test of significance
		Metabolic syndrome (N=14)		No metabolic syndrome (N=46)		
Blood pressure	Normal	9	64.3%	45	97.8%	χ2= 13.416 p < 0.001*
	Elevated	5	35.7%	1	2.2%	
EDSS		1.5 (0-6)		1 (0-6)		z=- 0.304 p= 0.761
FBS		107.64± 23.99		81.57± 10.22		t= 5.894 p < 0.001*
TGs		167.71± 37.36		90.24± 37.81		t= 6.731 p < 0.001*
HBS		40 ± 12.55		44.72± 6.54		t= -1.729 p= 0.078

The course of the disease showed a statistically significant difference between the two groups. There was more case with SPMS in the cases with MS. Table (7) illustrates these data.

Table (7): Analysis of the type of course of the MS in the two study groups.

		Groups				Test of significance
		Metabolic syndrome (N=14)		No metabolic syndrome (N=46)		
Course of the disease	Relapsing remitting (RRMS)	11	78.6%	44	95.7%	χ2= 4.099 p = 0.042*
	Secondary progressive (SPMS)	3	21.4%	2	4.3%	

There was a statistically significant moderate positive correlation between EDSS with disease duration, number of relapse and number of steroid pulse in the cases included in the study. Table (8) illustrates these data.

With the univariate risk analysis, increased blood pressure, longer disease duration, increased body weight, increased waist circumference, higher BMI and progressive course of the disease was reported to be risk factors for development of metabolic syndrome, however with the multivariate regression analysis increased blood pressure, increased body weight, increased waist circumference and higher BMI were revealed to be an independent risk factors for development of metabolic syndrome. Table (9) illustrates these data.

Table (8): Correlation between EDSS and other parameters in the study.

	r	p
Age	0.189	0.149
Age of onset	-0.069	0.609
Disease duration	0.629	<0.001*
Number of relapses	0.633	<0.001*
Number of pulse steroid	0.323	0.012*
Weight	-0.169	0.189
Height	-0.193	0.139
BMI	-0.067	0.611
Waist circumference	0.003	0.911
FBS	0.001	0.998
HDL	0.298	0.021
LDL	-0.088	0.561

Table (9): Univariate and multivariate analysis of predictors of metabolic syndrome among cases with MS (n=14).

Variables	Univariate analysis	Multivariate analysis		
		B	95% CI	P value
Age	0.169			
Sex	0.215			
Smoking	0.053			
Family Hx of MS	0.126			
DM	0.372			
Elevated Blood pressure	0.004*	1.472	1.251– 1.826	0.04*
Age of onset	0.319			
Disease duration	0.035*	0.645	0.308-1.31	0.126
Number of relapses	0.114			
Number of pulse steroid	0.327			
Weight	< 0.001*	1.824	1.273- 2.982	0.043*
Height	0.247			
BMI	0.001*	1.365	1.045– 2.125	0.045*
Waist circumference	< 0.001*	2.116	1.857- 2.784	0.005*
FBS	0.215			
HDL	0.441			
LDL	0.327			
EDSS	0.135			
Progressive course of the disease	0.044*	0.735	0.236-1.08	0.436

4. Discussion

Multiple Sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system and has a high impact on the health-related quality of life of patients, their families and society(14). It is one of the most common causes of neurological disability in young adults and its prevalence is increasing throughout Europe(15).

Comorbidity is common in patients who suffer chronic disease; including individuals suffering from MS(16). The association of comorbidity with health-related quality of life and disability progression has resulted in comorbidity being an area of increasing importance in MS research (17).

Rates of mortality and comorbidities have been shown to be higher in MS patients compared to non-MS patients. A recent observational study of the United States Department of Defence administrative claims database showed that MS patients (vs. a non-MS cohort) had an increased risk of developing a broad spectrum of comorbidity such as sepsis, ischemic stroke, suicide ideation, ulcerative colitis, and cancer (lymphoproliferative disorders and melanoma) (18).

The metabolic syndrome (MetS) is a global public-health challenge and a complex disorder characterized by a cluster of interconnected factors which lead to an increased risk of cardiovascular disease (CVD) and diabetes mellitus type 2 (19).

Previous research has shown that for individuals with autoimmune diseases, the prevalence of MetS is higher than national averages (20). However, only

limited and inconsistent data on MetS risk factors exists for patients with MS (21).

Therefore, the aim of this study was to analyze the prevalence and risk factors of MetS in cases with MS.

The study included 60 cases with MS who were classified into two groups according to metabolic syndrome; group A: metabolic syndrome (14 subjects) and group B: with no metabolic syndrome (46 subjects).

The prevalence of metabolic syndrome among the cases with MS in our study was 23.3%.

This came in accordance with the ENRICA study showed a MetS prevalence of 22.7% (95% CI: 21.7–23.7%) in a sample of 11,143 adult subjects in Spain (22). In another study, the overall prevalence of MetS was 31.1% (95% CI: 25.0–37.2%) (23).

Similar results was reported in another study where Our results from a large international sample of MS showed that overall, 22.5% were overweight and an additional 19.4% were obese (24).

In this study, regarding the components of metabolic syndrome in the cases with MS (n=14), HTN was found in 35.7% of the cases, high waist circumference in 64.3% of the cases, high TGs was detected in 85.7% of the cases, low HDL in 90.9% of the cases (higher percentage) and high blood sugar level in 57.1% of the cases.

This came in accordance with Pinhas‐Hamiel et al. (2015) who showed that regarding specific components of the MetS of the cases included in their study, 56.1% of disabled MS patients had central obesity by waist circumference, 27.7% were treated for hypertension, 17.7% had elevated blood pressure, 10% had type 2 diabetes mellitus, 35.5% had fasting hyperglycemia, 31.3% had treated dyslipidemia, 26.1% had elevated TG level and 28% had low HDL-C. Prevalence rates of components of the MetS in the MS cohort compared to rates in the general population (25)

Similar results were revealed by Sicras-Mainar et al. (2017) who showed that Fasting blood glucose >110 mg/dL was present in 11.2% of the cases, Triglycerides >150 mg/dL that was present in 17.1% of the cases and HDL-c < 40 (men) or <50 (women) mg/dL had the highest prevalence in 38.7% of the cases (23)

Other studies showed similar or increased prevalence of overweight and obesity amongst individuals with MS (26, 27).

However, in another study, the rate central obesity by waist circumference was lower and detected in 21% and 39% in males and females, respectively, among MS cases included in the study (28)

The difference may be due to the fact that waist circumference was measured rather than relying on a self-report value and actual waist circumference showed marked discrepancy with up to 14.2% under-reported waist circumference values (29).

In this study, HTN was found in 35.7% of the cases with metabolic syndrome.

This came in consistent with the finding of the NARCOMS study in which 30% of patients with MS reported hypertension (30)

A case control study consisting of 677 controls and 1,548 MS patients found that MS patients are 48% more likely to have a diagnosis of hypertension(31).

In this study, there was a statistically significant difference in the mean age of the cases within the two groups, being higher in the metabolic syndrome group ($p< 0.001$).

This came in agreement with Pinhas‐Hamiel et al. (2015) who showed that MS patients with the MetS were significantly older than those without MetS (59.1 ± 5.8 vs. 54.3 ± 5.5 years, $P < 0.0001$) (25)

The prevalence of elevated FBG was different from the previously reported prevalence among MS patients that was shown to range between 0 and 27% (32).

In this study, the mean FBG level in the cases with metabolic syndrome was 107.64± 23.99 gm/dl vs 81.57±10.22 gm/dl in the cases without metabolic syndrome with high statistically significant difference between the two groups ($p< 0.001$).

This came in agreement with Pinhas‐Hamiel et al. (2015) who showed that there was a statistically significant difference in the mean serum glucose level among the MS cases with and without metabolic syndrome (25)

This came in accordance with Liu et al. (2016) who showed higher serum triglycerides, total cholesterol, and LDL-cholesterol levels in obese MS cases as compared with healthy controls and normal weight MS cases. Moreover, longer disease duration was associated with high triglycerides while high HDL-cholesterol was associated with a trend toward low disability scores (33).

A prospective cohort design in patients with MS found that high levels of total cholesterol were associated with increased disability, and increased total cholesterol/HDL ratio was associated with annual accumulating disability (34).

In this study, the age of the MS was earlier and the duration of the disease with longer in the cases with no metabolic syndrome with statistically significant difference as compared with the metabolic syndrome group ($p< 0.001$ and 0.002 respectively). The number of disease relapse, number of pulse steroid and current treatment plan didn't reveal a

statistically significant difference between the two groups.

This partially agreed with Pinhas‐Hamiel et al. (2015) who reported that there was no difference in mean disease duration (17.7 ±9.9 vs. 18.5 ± 10.2 years, P = 0.6) or in the number of steroid courses (6.5 ± 10.1 vs. 6.4 ± 8.2) between those with the MetS and those without (25)

In this study, the median (range) EDSS was 1.5 (0-6) in cases with metabolic syndrome vs 1 (0-6) in cases with no metabolic syndrome with no statistically significant difference between the two groups.

This came in agreement with Pinhas‐Hamiel et al. (2015) who showed that the mean EDSS was 5.4 ± 1 vs 5.8 ± 0.8 in cases with and without metabolic syndrome with no statistically significant difference.

Some limitations were reported in this study, which could decrease the power of the reported results including it is a single center study and the relatively small sample size. Although the descriptive nature of the study is considered from the major limitations for obtaining powerful results.

Conclusion

Based on our study results, the age of the multiple sclerosis patients was earlier and duration was longer with nometabolic syndrome with no statisticallysignificant difference as compared with metabolic syndrome group ($p < 0.001$ and 0.002). Moreover, increased waist circumference was found to be particularly prevalent amongst adult disabled MS and metabolic syndrome negatively affects EDSS in MS patients.

References

1. Dilokthornsakul P, Valuck RJ, Nair KV, Corboy JR, Allen RR, Campbell JD. Multiple sclerosis prevalence in the United States commercially insured population. Neurology. 2016;86(11):1014-21.
2. Amato MP, Derfuss T, Hemmer B, et al. Environmental modifiable risk factors for multiple sclerosis: Report from the 2016 ECTRIMS focused workshop. Multiple Sclerosis Journal. 2018;24(5):590-603.
3. Filippi M, Bar-Or A, Piehl F, et al. Multiple sclerosis (Primer). Nature Reviews: Disease Primers. 2018.
4. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83(3):278-86.
5. Van der Mei I, Lucas RM, Taylor B, et al. Population attributable fractions and joint effects of key risk factors for multiple sclerosis. Multiple Sclerosis Journal. 2016;22(4):461-9.
6. Ascherio A. Environmental factors in multiple sclerosis. Expert review of neurotherapeutics. 2013;13(sup2):3-9.
7. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation. 2005;112(17):2735-52.
8. Alberti KGMM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. Diabetic medicine. 1998;15(7):539-53.
9. Balkau B. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet med. 1999;16:442-3.
10. Cleeman J, Grundy S, Becker D, et al. cholesterol Educ program, executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). Jama-J Am Med Assoc. 2001;285:2486-97.
11. Einhorn M, FACP, FACE, Daniel. American College of Endocrinology position statement on the insulin resistance syndrome. Endocrine practice. 2003;9(Supplement 2):5-21.
12. Zimmet P, Alberti K, Shaw J. International Diabetes Federation: the IDF consensus worldwide definition of the metabolic syndrome. Diabetes voice. 2005;50:31-3.
13. Kaur J. A comprehensive review on metabolic syndrome. Cardiology research and practice. 2014;2014.
14. Ayuso G. Multiple sclerosis: socioeconomic effects and impact on quality of life. Medicina clinica. 2014;143:7-12.
15. Howard J, Trevick S, Younger DS. Epidemiology of multiple sclerosis. Neurologic clinics. 2016;34(4):919-39.
16. Estruch B. Cormorbidity in multiple sclerosis and its therapeutic approach. Medicina clinica. 2014;143:13-8.
17. Culpepper WJ. The incidence and prevalence of comorbidity in multiple sclerosis. Mult Scler. 2015;21(3):261-2.
18. Hajiebrahimi M, Montgomery S, Burkill S, Bahmanyar S. Risk of premenopausal and postmenopausal breast cancer among multiple sclerosis patients. PloS one. 2016;11(10):e0165027.

19. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC medicine. 2011;9(1):48.
20. Versini M, Jeandel P-Y, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. Autoimmunity reviews. 2014;13(9):981-1000.
21. Wens I, Dalgas U, Stenager E, Eijnde BO. Risk factors related to cardiovascular diseases and the metabolic syndrome in multiple sclerosis–a systematic review. Multiple Sclerosis Journal. 2013;19(12):1556-64.
22. Guallar-Castillón P, Pérez RF, García EL, et al. Magnitude and management of metabolic syndrome in Spain in 2008-2010: the ENRICA study. Revista Española de Cardiología (English Edition). 2014;67(5):367-73.
23. Sicras-Mainar A, Ruíz-Beato E, Navarro-Artieda R, Maurino J. Comorbidity and metabolic syndrome in patients with multiple sclerosis from Asturias and Catalonia, Spain. BMC neurology. 2017;17(1):134.
24. 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.
25. Pinhas‐Hamiel O, Livne M, Harari G, Achiron A. Prevalence of overweight, obesity and metabolic syndrome components in multiple sclerosis patients with significant disability. European journal of neurology. 2015;22(9):1275-9.
26. Slawta JN, Wilcox AR, McCubbin JA, Nalle DJ, Fox SD, Anderson G. Health behaviors, body composition, and coronary heart disease risk in women with multiple sclerosis. Archives of physical medicine and rehabilitation. 2003;84(12):1823-30.
27. Khurana SR, Bamer AM, Turner AP, et al. The prevalence of overweight and obesity in veterans with multiple sclerosis. American journal of physical medicine & rehabilitation. 2009;88(2):83-91.
28. Alschuler KN, Gibbons LE, Rosenberg DE, et al. Body mass index and waist circumference in persons aging with muscular dystrophy, multiple sclerosis, post-polio syndrome, and spinal cord injury. Disability and health journal. 2012;5(3):177-84.
29. Rubin D, Schneider‐Muntau A, Klapper M, et al. Functional analysis of promoter variants in the microsomal triglyceride transfer protein (MTTP) gene. Human mutation. 2008;29(1):123-9.
30. Marrie RA, Bo NY, Leung S, et al. Prevalence and incidence of ischemic heart disease in multiple sclerosis: a population-based validation study. Multiple sclerosis and related disorders. 2013;2(4):355-61.
31. Saroufim P, Zweig SA, Conway DS, Briggs FB. Cardiovascular conditions in persons with multiple sclerosis, neuromyelitis optica and transverse myelitis. Multiple sclerosis and related disorders. 2018;25:21-5.
32. Marrie RA, Reider N, Cohen J, et al. A systematic review of the incidence and prevalence of cardiac, cerebrovascular, and peripheral vascular disease in multiple sclerosis. Multiple Sclerosis Journal. 2015;21(3):318-31.
33. Liu J, Li M, Wang X, Yi H, Xu L, Peng F-h. Elevated lipid profiles in patients with acute transverse myelitis. European neurology. 2016;75(3-4):142-8.
34. Tettey P, Simpson Jr S, Taylor B, et al. An adverse lipid profile is associated with disability and progression in disability, in people with MS. Multiple Sclerosis Journal. 2014;20(13):1737-44.

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