Association between obesity during different age periods and multiple sclerosis in Saudi Arabia: A multicenter case–control study

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ABSTRACT

الأهداف: تحديد ما إذا كان حجم الجسم خلال الفترات العمرية المختلفة مرتبطًا بزيادة خطر الإصابة بالتصلب المتعدد في المملكة العربية السعودية.

المنهجية: تم اختيار 307 مرضى مصابين بمرض التصلب العصبي المتعدد و 307 حالة ضابطة من العيادات وأجنحة المستشفيات في ثلاث مدن في جميع أنحاء المملكة العربية السعودية (2016-2017). تم استخدام صور ظلية قياسية للجسم لتقييم حجم أجسام المشاركين (من 1 إلى 9) خلال فترات عمرية مختلفة (مراحل المدرسة). تم حساب نسبة الأرجحية المعدلة مع نطاق الثقة 95%. تم إجراء تحليل متعدد المتغيرات مضبوطا بالعمر والجنس.

النتائج: ارتبط حجم الجسم الأكبر (الصور الظلية 6–9) وحجم الجسم 5 خلال المرحلة المتوسطة بزيادة خطر الإصابة بمرض التصلب العصبي المتعدد (نسبة الأرجحية المعدلة = 3.75، نطاق الثقة 95% 1.41–10 = ونسبة الأرجحية المعدلة=3.75، نطاق الثقة 95%1.10–12.78، على التوالي). ارتبط أصغر حجم للجسم (1) خلال المرحلة المتوسطة بإنخفاض خطر الإصابة بمرض التصلب العصبي المتعدد (نسبة الأرجحية المعدلة = 0.39، نطاق الثقة95%=0.17–0.90، مقارنة بحجم الجسم (3).

الخلاصة: يزداد خطر الإصابة بالتصلب المتعدد مع زيادة الوزن والسمنة خلال فترة الدراسة في المرحلة المتوسطة خصوصاً للإناث بين عمر 13–15 سنة.

Objectives: To determine whether body size in different age periods is associated with an increased risk of MS in Saudi Arabia.

Methods: This study included 307 MS patients and 307 healthy controls from clinics and hospital wards in three cities (Riyadh, Jeddah, and Dammam) in Saudi Arabia (2016-2017). We used Stunkard's standard body silhouettes to determine the participants' body sizes (from 1 to 9) during different age periods (school levels). We calculated adjusted odds ratios (AORs) and 95% confidence intervals (CIs) and performed multivariable analysis adjusted for age and gender.

Results: : Large body sizes (silhouettes 6–9) and body size 5 during intermediate school were associated with an increased risk of MS (AOR: 3.75, 95% CI: 1.10–12.78 and AOR: 3.75, 95% CI: 1.41–10, respectively). The smallest body size (1) during intermediate school was associated with a lower risk of MS (AOR: 0.39, 95% CI: 0.17–0.90) compared to body size 3.

Conclusion: Overweight and obesity during the intermediate school period (ages 13–15 years) are associated with an increased risk of MS, particularly among females.

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Multiple sclerosis (MS) is a chronic disease characterized by inflammation, demyelination, and neurodegeneration in the central nervous system.[1] MS has a multifactorial etiology and is triggered by environmental factors in individuals with complex

genetic profiles.[2-6] Obese individuals may have a higher risk of developing MS. A previous study showed that individuals with a body mass index (BMI) of more than 27 kg/m^2 at age 20 years had twice the risk of developing MS than normal-weight individuals.[7] Another study conducted in Norway involving individuals aged 5, 10, 15, 20, 25, and 30 years found that large body sizes (Stunkard's standard body silhouettes 6–9) were associated with an increased risk of MS compared to silhouette 3, particularly at age 25 among female participants.[8] Information on risk factors such as obesity/overweight is essential for the prevention and control of MS. This type of information is particularly important for young people in Saudi Arabia—especially women, who are more frequently affected by MS. According to recent Saudi MS registry reports, MS cases are increasing.[9] Since there have been no changes in the genetic profiles of Saudi people, this increase is likely due to environmental factors. In this study, we aimed to assess whether body size during different age periods (expressed as school levels) is associated with an increased risk of MS in Saudi Arabia.

Methods. ***Study design and settings.*** This case–control study was conducted at 5 governmental hospitals in the 3 main cities of Saudi Arabia (2016-2017). King Fahad Medical City, King Saud Medical City, and King Fahad National Guard Hospital are tertiary hospitals located in Riyadh. King Fahad General Hospital is located in Jeddah. Dammam Central Hospital is located in Dammam. The total sample size was 614 participants divided equally between cases and controls, matched for age and gender.

Participants. The cases were patients diagnosed with MS according to the McDonald Criteria 2010 and recruited in the hospitals' neurological departments (clinics and wards). We included patients diagnosed with MS no more than 4 years previously, aged 18 years or older, and able to understand the administered questionnaire. We excluded patients diagnosed with MS more than 4 years previously and patients younger than 18 years.

The controls included healthy companions of patients in other departments (medicine, surgery, and pediatrics) with no history of MS and were matched to the cases in terms of age (± 3 years), gender, and hospital. Controls with a history of MS or aged less than 18 years were excluded.

Data collection. We adopted a self-administered questionnaire for the purpose of this study and distributed it to the participants in clinics and wards. We used Stunkard's silhouettes to assess body sizes at different school levels. Primary, intermediate, secondary, and university levels corresponded to age groups 7–12, 13–15, 16–18, and 19–22 years, respectively. The silhouette scale uses body size codes 1 to 9, with 1 representing the smallest body size and 9 representing the largest, and it has frequently been used in research.[8] A body size code was obtained via self-selection of a body size that closely matched each participant's body image. Moreover, we used self-reported weight and height to estimate each participants' BMI at the time of the study and validate the silhouette questionnaire.

Statistical analysis. We used IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA) for the statistical analysis. We calculated the variables as frequencies and percentages. We also calculated the mean BMI for each body size. We defined a large body size as silhouettes 6–9 and compared body sizes 1, 2, 4, and 5 to body size 3 as a reference. We selected body size 3 as a reference because the mean BMI for each body size was within the normal range of body weight and because it was similar to that used in previous studies applying Stunkard's scale. This allowed us to compare our results with those of other studies. Owing to the small number of participants with larger body sizes, we created a large body size category by combining body sizes 6–9.

We calculated Spearman's rank correlations between BMI and body sizes at the time of the study. In unadjusted analysis, we assessed the associations between categorical variables using logistic regression for each school level. In multivariable analyses, we used conditional logistic regression adjusted for age and gender, with the cases and controls as dependent variables and body sizes 1, 2, 3 (reference), 4, 5, and 6–9 as independent variables for different school levels for all participants and for females only since there were sufficient participants for each body size. Two-tailed *p*-value of 0.05 was considered a strong evidence against the null hypothesis.

Results. The response rate was approximately 91% for both cases (307/336) and controls (307/340). The mean age for MS cases and healthy controls was 32.9 years with standard deviation (SD) of (8.8) and (8.6) respectively, and female to male ratio was 3:1.

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Table 1 - Mean body mass index for each body silhouette of male and female participants at the time of the study.

Gender /Group	Body silhouette								
	1	2	3	4	5	6	7	8	9
Male									
MS patients	23.9	21.7	23.4	25.7	26.9	31.2	31.6	37.2	44.7
Controls	N/A	22.3	23.1	26.7	26.5	30.3	30.9	38.4	N/A
Female									
MS patients	19.7	21	23.5	25.7	27.7	30.7	35.3	39.9	33.8
Controls	19.5	21.1	23.7	26.8	29.9	32.9	35.9	38.1	38.5

All values are means, MS - multiple sclerosis, N/A - not available

Table 2 - Unadjusted analysis of the association between body size during different school levels and the odds of developing multiple sclerosis.

School level /Body size	MS patients n=307	Controls n=307 n (%)	Crude OR (95% CI)	*P*-value
Primary school				
1	99 (32)	117 (38)	0.67 (0.40–1.13)	0.134
2	83 (27)	92 (30)	0.72 (0.42–1.22)	0.223
3	44 (14)	35 (11)	Reference	
4	31 (10)	46 (15)	0.54 (0.28–1.01)	0.055
5	23 (8)	13 (4)	1.41 (0.63–3.17)	0.410
6–9	27 (9)	4 (1)	5.37 (1.72–16.79)	0.004
Intermediate school				
1	46 (15)	77 (25)	0.70 (0.40–1.21)	0.199
2	94 (31)	93 (30)	1.18 (0.71–1.95)	0.520
3	42 (14)	49 (16)	Reference	
4	46 (15)	59 (19)	0.91 (0.52–1.60)	0.742
5	40 (13)	17 (6)	2.75 (1.36–5.54)	0.005
6–9	39 (13)	12 (4)	3.79 (1.76–8.17)	0.001
Secondary school				
1	30 (10)	48 (16)	0.94 (0.53–1.67)	0.827
2	80 (26)	66 (22)	1.80 (1.11–2.90)	0.018
3	50 (16)	77 (25)	Reference	
4	62 (20)	65 (21)	1.41 (0.86–2.32)	0.177
5	36 (12)	33 (11)	1.64 (0.91–2.96)	0.103
6–9	49 (16)	18 (6)	4.08 (2.14–7.81)	<0.001
University				
1	32 (11)	37 (12)	1.04 (0.57–1.89)	0.895
2	64 (21)	55 (18)	1.38 (0.83–2.29)	0.219
3	54 (18)	67 (22)	Reference	
4	52 (17)	77 (25)	0.80 (0.49–1.33)	0.392
5	52 (17)	44 (15)	1.42 (0.83–2.44)	0.201
6–9	48 (16)	24 (8)	2.41 (1.31–4.43)	0.005

MS - multiple sclerosis, OR - odds ratio, CI - confidence interval

The mean BMI for each body silhouette is shown in **Table 1**. The mean BMIs correlated well with the respective silhouettes (r=0.82).

The unadjusted analysis showed that the odds of developing MS among participants with a large body size during primary school were more than 5 times higher than among those with body size 3 (OR: 5.37, 95% CI: 1.72–16.79). Body sizes 1, 2, 4, and 5 showed no statistically significant associations. The odds of developing MS among participants with a large body size during intermediate school were over 3 times higher than among those with body size 3 (OR: 3.79, 95%

Table 3 - Multivariable analysis of the association between body size during different school levels and the odds of developing multiple sclerosis.

School level /Body size	All*		Females	
	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Primary school				
1	1.12 (0.55–2.26)	0.762	1.70 (0.75–3.88)	0.206
2	0.85 (0.45–1.60)	0.614	1.18 (0.56–2.49)	0.671
3	Reference		Reference	
4	0.36 (0.17–0.76)	0.007	0.41 (0.18–0.95)	0.039
5	0.51 (0.18–1.45)	0.207	0.96 (0.26–3.51)	0.951
6–9	1.57 (0.41–6.05)	0.516	1.04 (0.24–4.60)	0.958
Intermediate school				
1	0.39 (0.17–0.90)	0.029	0.25 (0.09–0.66)	0.005
2	0.87 (0.46–1.65)	0.675	0.46 (0.21–0.98)	0.045
3	Reference		Reference	
4	1.07 (0.54–2.14)	0.845	0.87 (0.39–1.95)	0.740
5	3.75 (1.41–10)	0.008	3.04 (1.01–9.11)	0.047
6–9	3.75 (1.10–12.78)	0.035	4.59 (1.01–20.86)	0.048
Secondary school				
1	0.82 (0.32–2.16)	0.694	0.87 (0.30–2.48)	0.788
2	1.68 (0.90–3.12)	0.101	1.79 (0.88–3.63)	0.109
3	Reference		Reference	
4	1.40 (0.73–2.68)	0.311	1.61 (0.73–3.55)	0.242
5	1.23 (0.49–3.07)	0.656	1.61 (0.53–4.87)	0.400
6–9	1.49 (0.45–4.90)	0.515	1.44 (0.34–6.09)	0.617
University				
1	1.92 (0.80–4.60)	0.144	1.69 (0.67–4.26)	0.269
2	1.31 (0.72–2.39)	0.378	1.56 (0.80–3.05)	0.194
3	Reference		Reference	
4	0.60 (0.33–1.07)	0.084	0.68 (0.33–1.40)	0.291
5	1.03 (0.51–2.09)	0.930	0.92 (0.39–2.16)	0.851
6–9	0.97 (0.37–2.57)	0.950	0.79 (0.24–2.58)	0.696

*Adjusted for age, gender, and hospital, OR - odds ratio, CI - confidence interval

CI: 1.76–8.17) and more than twice as high among those with body size 5 (OR: 2.75, 95% CI: 1.36–5.54). Body sizes 1, 2, and 4 showed no statistically significant associations. The odds of developing MS among participants with a large body size during secondary school were about 4 times higher than those with body size 3 (OR: 4.08, 95% CI: 2.14–7.81) and nearly twice as high among participants with body size 2 (OR: 1.80, 95% CI: 1.11–2.90). Body sizes 1, 4, and 5 showed no statistically significant associations. The odds of developing MS among participants with a large body size during university were nearly 2.5 times higher than among those with body size 3 (OR: 2.41, 95% CI: 1.31–4.43). Body sizes 1, 2, 4, and 5 showed no statistically significant associations (**Table 2**).

In multivariable analysis adjusted for age and gender for all participants, body size 4 during primary school was independently associated with decreased odds of developing MS (AOR: 0.36, 95% CI: 0.17–0.76). Large body sizes (6–9) and body size 5 during intermediate school were independently associated with increased odds of MS (AOR: 3.75, 95% CI: 1.10–12.78 and AOR: 3.75, 95% CI: 1.41–10, respectively). The smallest body size (1) during intermediate school was associated with lower odds of developing MS (AOR: 0.28, 95% CI: 0.13–0.61).

Multivariable analysis of female participants only showed that body sizes 1 and 2 during intermediate school were independently associated with decreased odds of developing MS (AOR: 0.25, 95% CI: 0.09–0.66 and AOR: 0.46, 95% CI: 0.21–0.98, respectively). Conversely, large body sizes (6–9) and body size 5 during intermediate school were independently associated with increased odds of developing MS (AOR: 3.04, 95%

CI: 1.01–9.11 and AOR: 4.59, 95% CI: 1.01–20.86, respectively; **Table 3**).

Discussion. In this multicenter matched case–control study, we found that a large body size during intermediate school (ages 13–15) was associated with 3.75 times higher odds of developing MS compared with body size 3. Likewise, body size 5 was associated with 3.75 times higher odds of developing MS than body size 3. Conversely, body size 1 was associated with decreased odds of developing MS. These results suggest that weight during adolescence, rather than during adulthood or childhood, is critical for determining the risk of MS, particularly among girls. This finding is consistent with a study on an American population reporting that obese girls aged 11–18 years had a 78% higher risk of developing pediatric MS with an onset age of less than 18 years.[10] A recent published study found that obese aged 14-16 years had a highest association with MS risk.[11] A Danish prospective cohort study also found a stronger association between obesity and the risk of MS in girls than in boys aged 7–13 years.[12] A matched case–control study conducted at a hospital in Madinah, Saudi Arabia found that the risk of developing MS was significantly higher (8.97 times) among adolescents with large body sizes (7–9) than among those with the smallest body size (1). However, due to its small sample size, that study did not use gender-stratified data in its analysis.[13]

In our study, a large body size during primary and secondary school and university showed no association with the risk of MS, whereas body size 4 among girls during primary school showed lower odds of developing MS. These findings are in line with those from the large longitudinal Nurses' Health Study in the United States, which reported that obese adolescents have an increased risk of MS but found no association between a large body size during childhood or adulthood and the risk of MS.[14]

Although the complete etiology of MS is not well understood, it is known that it is the result of a complex interaction between genetic susceptibility and environmental factors. A case–control study on Swedish and American populations found a significant interaction between obesity during adolescence and HLA-A1*15. Furthermore, obese individuals with HLA-DRB1*15 who were HLA-A*02-negative had a 16 times higher risk of MS than nonobese individuals with no genetic risk factors.[15] In Saudi Arabia, HLA-DRB1*15:01 is the most frequent risk allele in MS patients compared to healthy individuals.[16] A previous study also reported an interaction between adolescent obesity and a history of infectious mononucleosis.[17] Another study reported an interaction between BMI and smoking.[18] Further studies investigating the association between obesity and the risk of MS taking into consideration genetic factors are warranted.

A possible explanation for the connection between obesity and the risk of MS is that obese individuals have lower vitamin D metabolite levels.[19-20] Obesity is associated with lower levels of circulating vitamin D[21,22] and 25-hydroxyvitamin D compared with normal weight. Thus, obesity during childhood may be a strong risk factor for MS. Moreover, obesity is related to a low-grade chronic inflammatory condition and the release of cytokines, which influence immune reactions and possibly increase the risk of MS.[23-25] Furthermore, several adipokines, such as leptin, resistin, visfatin, and adiponectin, that link metabolic status to the immune system may play a role in the pathogenesis of MS.[26,27] In Saudi Arabia, the rates of obesity among male and female students aged 6–16 years are 18.4% and 18%, respectively.[28] Our findings suggest that adolescence and possibly childhood are periods of life during which individuals, especially girls, are particularly vulnerable to exposure to risk factors for MS. A previous study found that exercise reduces the risk of MS.[29] Therefore, interventions against obesity in adolescents, such as encouraging physical activity and maintaining a normal BMI, are needed, especially for girls.

In our study, the response rate was 91% for both cases and controls, which is considered good. Both cases and controls showed a strong interest in contributing to the study. We may attribute this to various reasons, such as an interest in learning the study's results and the prevention of MS in their families and the general population.

Strengths and limitations. To our knowledge, no similar studies with relatively large sample sizes have been conducted in a Middle Eastern country. Thus, the obtained results are useful, as an association between body size and MS has been shown only in Western countries. We recruited patients with MS within 4 years of diagnosis to minimize incidence–prevalence bias. The cases and controls were comparable in terms of demographic characteristics and socioeconomic status. Nevertheless, as this was a case–control study with some exposures referring to previous years, it may be subject to exposure misclassification. However, in assessing obesity, we used school levels rather than age groups to facilitate the participants' recall. Also, because BMIs during different age periods and an MS registry were unavailable, we used the silhouette questionnaire, which is considered a robust tool for distinguishing obese from nonobese status.[30] Although some studies have suggested that each silhouette does not necessarily

directly correspond to a specific BMI, in our study, Stunkard's body silhouettes correlated well with BMI. Furthermore, the body size code at the time of the study was obtained by selecting the body size that most closely matched the participants' body image. Additionally, we used self-reported weight and height to estimate each participant's BMI, and then we calculated the mean BMI for each body size. Therefore, selection bias cannot be excluded, although the controls were selected from the same hospital as the cases; however, the controls may not be representative of the study base that gave rise to cases. Selection bias may also be present because some controls may have had MS with a relatively long latent period; however, this is unlikely, as MS is uncommon in the general population. We sought to minimize the risk of misclassified responses, non-differential in the general population and differential due to MS patients' deteriorating cognitive function. This is another reason why we included only patients diagnosed no more than 4 years previously. On the other hand, although excluding patients with longer-standing MS may have minimized response misclassification, it may have led to selection bias. We did not control for other potential risk factors, such as vitamin D levels and smoking status, which may have resulted in residual confounding. Finally, due to the small sample size of male participants, we did not properly assess interactions by gender; therefore, we could not fully determine whether the associations differed according to gender.

Conclusions. The results of this nationally based case–control study support a link between obesity and MS. Overweight and obesity in adolescent girls of intermediate school age (ages 13–15) are associated with an increased risk of MS. Encouraging physical activity and a healthy diet during this age period is strongly recommended.

References

1. Dobson R, Giovannoni G. Multiple sclerosis - a review. ***Eur J Neurol*** 2019; 26: 27-40.
2. Al Jumah M, Kojan S, Al Shehri AM, Al Balwi M, Al Abdulkarim I, Masuadi EM, et al. HLA class II polymorphism in Saudi patients with multiple sclerosis. ***HLA*** 2018; 91: 17-22.
3. Al Wutayd O, Mohamed AG, Saeedi J, Al Otaibi H, Al Jumah M. Environmental exposures and the risk of multiple sclerosis in Saudi Arabia. ***BMC Neurol*** 2018; 18: 86.
4. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. Multiple sclerosis. ***Lancet*** 2018; 391: 1622-1636.
5. Al Wutayd O. Association of infections with multiple sclerosis in Gulf Cooperation Council countries: a review. ***J Int Med Res*** 2020; 48: 300060519884151.
6. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. ***Nat Rev Neurol*** 2017; 13: 25-36.
7. Hedstrom 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: 1334-1336.
8. Wesnes K, Riise T, Casetta I, Drulovic J, Granieri E, Holmoy T, et al. Body size and the risk of multiple sclerosis in Norway and Italy: the EnvIMS study. ***Mult Scler*** 2015; 21: 388-395.
9. AlJumah M, Bunyan R, Al Otaibi H, Al Towaijri G, Karim A, Al Malik Y, et al. Rising prevalence of multiple sclerosis in Saudi Arabia, a descriptive study. ***BMC Neurol*** 2020; 20: 49.
10. Langer-Gould A, Brara SM, Beaber BE, Koebnick C. Childhood obesity and risk of pediatric multiple sclerosis and clinically isolated syndrome. ***Neurology*** 2013; 80: 548-552.
11. Aa Høglund RA, Meyer HE, Stigum H, Torkildsen Ø, Nina Grytten N, Holmøy T, et al. Association of Body Mass Index in Adolescence and Young Adulthood and Long-term Risk of Multiple Sclerosis: A Population-Based Study. ***Neurology*** 2021; 97: e2253-e2261.
12. Munger KL, Bentzen J, Laursen B, Stenager E, Koch-Henriksen N, Sorensen TI, et al. Childhood body mass index and multiple sclerosis risk: a long-term cohort study. ***Mult Scler*** 2013; 19: 1323-1329.
13. Halawani AT, Zeidan ZA, Kareem AM, Alharthi AA, Almalki H.A. Sociodemographic, environmental and lifestyle risk factors for multiple sclerosis development in the Western region of Saudi Arabia: a matched case control study. ***Saudi Med J*** 2018; 39: 808-814.
14. Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. ***Neurology*** 2009; 73: 1543-1550.
15. Hedström AK, Bomfim IL, Barcellos L, Gianfrancesco M, Schaefer C, Kockum I, Olsson T, et al. Interaction between adolescent obesity and HLA risk genes in the etiology of multiple sclerosis. ***Neurology*** 2014; 82: 865-872.
16. Al Jumah M, Kojan S, Al Shehri AM, Al Balwi M, Al Abdulkarim I, Masuadi EM, et al. HLA class II polymorphism in Saudi patients with multiple sclerosis. ***HLA*** 2018; 91: 17-22.
17. Hedström AK, Bomfim I, Hillert J, Olsson T, Alfredsson L. Obesity interacts with infectious mononucleosis in risk of multiple sclerosis. ***Eur J Neurol*** 2015; 22: e578-e538.
18. Manouchehrinia A, Hedström AK, Alfredsson L, Olsson T, Hillert J, Ramanujam R. Association of pre-disease body mass index with multiple sclerosis prognosis. ***Front Neurol*** 2018; 9: 232.
19. Abbas MA. Physiological functions of Vitamin D in adipose tissue. ***J Steroid Biochem Mol Biol*** 2017; 165: 369-381.
20. Ruiz-Ojeda FJ, Anguita-Ruiz A, Leis R, Aguilera CM. Genetic Factors and Molecular Mechanisms of Vitamin D and Obesity Relationship. ***Ann Nutr Metab*** 2018; 73: 89-99.
21. Goldner WS, Stoner JA, Thompson J, Taylor K, Larson L, Erickson J, et al. Prevalence of vitamin D insufficiency and deficiency in morbidly obese patients: a comparison with non-obese controls. ***Obes Surg*** 2008; 18: 145-150.
22. Konradsen S, Ag H, Lindberg F, Hexeberg S, Jorde R. Serum 1,25-dihydroxy vitamin D is inversely associated with body mass index. ***Eur J Nutr*** 2008; 47: 87-91.
23. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. ***Arch Med Sci*** 2017; 13: 851-863.

24. Shindy S, Cho KW. Adipose tissue dendritic cells: critical regulators of obesity-induced inflammation and insulin resistance. ***Int J Mol Sci*** 2021; 22: 8666.
25. Kumthekar, A, Ogdie A. Obesity and Psoriatic Arthritis: A Narrative Review. ***Rheumatol Ther*** 2020; 7: 447-456.
26. Guerrero-García JD, Carrera-Quintanar L, López-Roa RI, Márquez-Aguirre AL, Rojas-Mayorquín AE, Ortuño-Sahagún D. Multiple sclerosis and obesity: possible roles of adipokines. ***Mediators Inflamm*** 2016; 2016: 4036232.
27. Asghar A, Sheikh N. Role of immune cells in obesity induced low grade inflammation and insulin resistance. ***Cell Immunol*** 2017; 315: 18-26.
28. Al-Hussaini A, Bashir MS, Khormi M, AlTuraiki M, Alkhamis W, Alrajhi M, et al. Overweight and obesity among Saudi children and adolescents: Where do we stand today? ***Saudi J Gastroenterol*** 2019; 25: 229-235.
29. Cortese M, Riise T, Bjørnevik K, Myhr KM. Multiple Sclerosis Conscript Service Database Study Group. Body size and physical exercise, and the risk of multiple sclerosis. ***Mult Scler J*** 2018; 24: 270-278.
30. Lønnebotn M, Svanes C, Igland J, Franklin KA, Accordini S, Benediktsdo´ttir B, et al. Body silhouettes as a tool to reflect obesity in the past. ***PloS one*** 2018: e0195697.

Clinical Practice Guidelines

Clinical Practice Guidelines must include a short abstract. There should be an Introduction section addressing the objective in producing the guideline, what the guideline is about and who will benefit from the guideline. It should describe the population, conditions, health care setting and clinical management/diagnostic test. Authors should adequately describe the methods used to collect and analyze evidence, recommendations and validation. If it is adapted, authors should include the source, how, and why it is adapted? The guidelines should include not more than 50 references, 2-4 illustrations/tables, and an algorithm.