

# Sociodemographic, environmental and lifestyle risk factors for multiple sclerosis development in the Western region of Saudi Arabia

## *A matched case control study*

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### ABSTRACT

**الأهداف:** دراسة العلاقة بين العوامل الديموغرافية الاجتماعية والعوامل البيئية وعوامل الخطر في نمط الحياة خلال سن المراهقة مع حدوث مرض التصلب المتعدد.

**الطريقة:** دراسة لحالات فردية مقترنة بحالات أخرى ضابطة من شهر أكتوبر 2017 إلى يناير 2018. تم الحصول على البيانات من خلال مقابلات وجهًا لوجه مع المشاركين في البحث. عدل الاستبيان وفقا لأهداف الدراسة من استبيان سابق يدرس العوامل البيئية. تم حساب اختبار مربع كاي لاختبار عوامل الخطر المختارة في الدراسة وعلاقتها مع حدوث مرض التصلب المتعدد، وحُدّد مستوى القيمة الاحتمالية عند أقل من 0.05 لكي يعتبر ذا أهمية.

**النتائج:** العينة كانت 80 حالة فردية مصابة بمرض التصلب المتعدد و 160 حالة ضابطة غير مصابة بالمرض، البدء بالتدخين خلال سن المراهقة يزيد من خطورة الإصابة بمرض التصلب المتعدد (نسبة الأرجحية المعدلة = 4.165)، 95% نطاق الثقة (1.449-11.974)، وكذلك وجدنا أن تأثير كيرجيم شكل الجسم (السمنة) بناءً على مقياس للتصنيف يزيد من خطورة الإصابة بالمرض (نسبة الأرجحية المعدلة = 8.970، نطاق الثقة 95% = 1.032-77.983)، وكذلك فإن تاريخ الإصابة بالحصبة يزيد من خطر الإصابة بالمرض (نسبة الأرجحية المعدلة = 3.758، نطاق الثقة 95% = 1.455-9.706) بالإضافة إلى ذلك وجدنا أن التعرض لأشعة الشمس خلال عطلة نهاية الأسبوع أكثر من 4 ساعات باليوم يؤدي إلى تقليل خطورة الإصابة بمرض التصلب المتعدد (نسبة الأرجحية المعدلة = 0.063، نطاق الثقة 95% = 0.006-0.654) وكذلك وجدنا أن أكل السمك أكثر من مرة واحدة بالأسبوع يقلل من خطورة الإصابة بالمرض (نسبة الأرجحية المعدلة = 0.206، نطاق الثقة 95% = 0.055-0.773).

**الخلاصة:** يزداد خطر حدوث مرض التصلب المتعدد زيادة هامة مع التعرض خلال فترة سن المراهقة للعوامل التالية وهي التدخين والإصابة بمرض الحصبة وكبير حجم شكل الجسم (السمنة).

**Objectives:** To examine the association of exposure to sociodemographic, environmental, and lifestyle risk factors during adolescence with the development of multiple sclerosis (MS).

**Methods:** We conducted a case-control study between October 2017 and January 2018 at King Fahd General Hospital (KFH) in Madinah, Saudi Arabia. Data were collected by direct physician-subject interviews. We utilized a questionnaire modified from the environmental risk factors in multiple sclerosis questionnaire (EnvIMS-Q). Chi-square tests were used to examine associations of selected risk factors with the development of MS, a *p*-value of <0.05 was considered significant.

**Results:** A total of 80 cases and 160 controls were enrolled into the study. Smoking during adolescence significantly increased the risk of MS, with an adjusted odds ratio (AOR) of 4.165, and a 95% confidence interval (CI) of 1.449-11.974. Large body size, assessed using a figure rating scale, also increased the risk of MS (AOR=8.970, 95% CI=1.032-77.983), as well as a history of measles infection (AOR=3.758, 95% CI=1.455-9.706). Furthermore, exposure to sunlight during the weekend for more than 4 hours/day decreased the risk of MS (AOR=0.063, 95% CI=0.006-0.654), so did the consumption of fish for more than once per week (AOR=0.206, 95% CI=0.055-0.773).

**Conclusion:** The risk of developing MS is significantly increased by exposure during adolescence to smoking, a history of measles infection, and large body size (obesity).

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Multiple sclerosis (MS) is a chronic immune-mediated disease affecting the central nervous system, characterized by inflammatory demyelination leading to myelin loss and secondary axonal damage. The peak age of onset is approximately 30 years, and the disease affects women more than men, with a female to male ratio of 1.5-2.5.<sup>1</sup> Worldwide, the number of people affected by MS exceeds 2.3 million.<sup>2</sup> The incidence has been increasing rapidly in many countries, including countries of the Arabian Gulf (currently 31-55 per 100000, according to recent studies).<sup>3</sup> Although MS has become more prevalent in Saudi Arabia recently, it remains somewhat under-diagnosed.<sup>4</sup> Other studies also confirm the increasing prevalence of MS in UAE, Kuwait, and Bahrain. For example, in Kuwait, between 2003-2012, the incidence increased by a factor of 3.22 in women and 2.54 in men.<sup>5-7</sup> These changes in prevalence of MS in the Arabian Gulf region may be attributable to changes in lifestyles, environmental factors, diet, or consanguinity.<sup>3</sup>

Recently, several studies have identified variants in multiple genes that increase the risk for developing MS; however, environmental and lifestyle factors are also important, and are not yet fully understood.<sup>8</sup> A major role of environmental factors in the etiology of MS was hypothesized by researchers because of the geographical distribution of MS: the prevalence of MS increases in areas far from the equator.<sup>9</sup> Another hypothesis derives from migration studies, which show changes in the risk of MS in people who migrate between areas that have different environmental risk factors.<sup>1,10</sup> The recent rapid increase in the incidence of MS has mainly been attributed to environmental and lifestyle factors rather than genetic factors.<sup>11,12</sup> In previous studies, Epstein-Barr virus infection (infectious mononucleosis), vitamin D status, and smoking have been identified as the most important risk factors for MS, although obesity in early age may also be implicated.<sup>1,13</sup>

Although many studies on environmental and lifestyle risk factors for MS have been reported, most of these studies have examined MS within populations of predominantly European ancestry.<sup>14</sup> Adolescence is considered to be a vulnerable age for exposure to risk factors associated with the development of MS.<sup>11,15,16</sup> This study sought to expand the existing information regarding risk factors for the development of MS, with

the aim of finding ways to reduce the incidence of MS in the future.

Our objective was to assess the impact of exposure to sociodemographic, environmental, and lifestyle risk factors that might contribute to the development of MS during adolescence (12-17 years of age).

**Methods.** The study used a case-control design, with a case-control ratio of 1:2. Cases were frequency matched with controls for gender and age. For all cases and controls, file numbers were recorded to ensure that no duplications occurred within the sample set.

The study was conducted between October 2017 and January 2018 at King Fahd General Hospital (KFH), Madinah, Saudi Arabia. King Fahd General Hospital (KFH) is the only referral hospital of the Ministry of Health for MS patients within the city of Madinah.

The target population for this study included all recent cases that were diagnosed by neurologists as confirmed cases of MS according to the McDonald criteria,<sup>17</sup> with clinical onset between 2008-2017, and with age 18 years or older at the time of diagnosis. All available cases within the neurology department, together with their file numbers and contact information, were identified as a sample frame, from which the study sample set was recruited. Cases were selected by identifying the individuals with the most recent onset of illness (to minimize recall bias), until we achieved the planned sample size.

Control subjects were recruited to the study from the same base of cases (hospital-based) at KFH. Controls were required to have no history of MS or any other neurological disorder, and to have visited the surgical or emergency department for acute complaints only. Controls were frequency-matched to the cases by age (within a 5-year age group interval) and gender. The selection of controls was performed randomly throughout the week.

The study sample size was calculated using OpenEpi web, based on the following assumptions: the smallest odds ratio expected to be detected was 3.00; the prevalence of exposure in the population was 13% (this was chosen based on previous studies in the same region; and the statistical power was 85%, with 95% confidence intervals.<sup>18</sup> A case-control ratio of 1:2 was chosen for the study. Given these assumptions, the necessary number of cases were determined to be 76 and controls 151.

All variables were directed to the adolescent age period, in both cases and controls. We assessed many variables, including age, gender, marital status, area of residence (rural or urban area), economic status, level of

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education, consanguinity (marriage between first cousins among parents), history of sun exposure (derived from information provided regarding frequency of outdoor activities, frequency of sun exposure during weekends and holidays, and places of activity), self-reported medical history, which was confirmed by verifying physician diagnoses (history of childhood infections, history of tonsillectomy, and history of hypersensitivity), familial history of MS in first or second degree relatives, frequency of food consumption (including milk, eggs, meat, and fish), history of smoking, and physical activity (light or vigorous activity). Additionally, we determined body size (using a figure rating scale) at 15 years of age, specifically as an indicator of elevated body-mass index (BMI) and adulthood obesity. The sample included 80 cases and 160 controls. The outcome variable was the diagnosis of MS, as confirmed by a neurologist. Data were collected in direct, face-to-face interviews. The questionnaire was modified, according to our study objectives, from the Environmental risk factors in multiple sclerosis questionnaire (EnvIMS-Q). The EnvIMS-Q is a validated tool for measuring environmental exposure in case-control studies and is considered to be an acceptable, feasible, and reliable tool for surveying MS patients as well as healthy control subjects.<sup>19</sup> The questionnaire was cross-culturally adapted and modified according to the objectives of the research, and subsequently approved by experts. The questionnaire was translated from English to Arabic by a bilingual translator. We thoroughly searched bibliographic databases such as PubMed, Google Scholar and Embase to identify previous articles that examined the potential risk factors for the development of MS.

The study was ethically approved by the institutional review board of King Fahd Hospital, Madinah, and was conducted in accordance with the principles of the declaration of Helsinki. Informed consent was obtained from all participants in their native languages.

**Statistical analysis.** Data were entered and managed in the field, and subsequently analyzed using SPSS version 20 (IBM Corp., Armonk, NY, USA). Quantitative variables were tested for normality, according to central tendency and dispersion, and median values were calculated. Categorical variables were analyzed by frequencies and percentages, for comparisons between cases and controls. Chi-square tests were used to evaluate the significance of association between the potential risk factors and the development of MS, a *p*-value of <0.05 was considered significant. Confounding factors were included according to their association independently with MS and their relation

with the main significant risk factors (that is, factors belonging to the pathway between the significant risk factors and the outcome MS were not considered as possible confounding factors). The confounding factors analyzed were daily sun exposure, weekend sun exposure, milk consumption, fish consumption, history of measles infection, family history of MS, adult smoking and adult body shape (obesity).

Crude odds ratios (ORs) and adjusted odds ratios (AORs) were determined and used, including 95% confidence intervals (CIs) to control confounding factors and predict potential risk factors.

With the data collected from the cases and controls, in order to determine whether a significant association exists between each of the various risk factors and the development of MS, using binary logistic regression.

**Results.** The socio-demographic characteristics of the MS cases and matched controls are shown in Table 1. The median age of the cases was 32 years (range 19-56), while the median age of the controls was 33 years (range 18-57). The age of onset for the MS cases in our sample was between 20-29 years in 47% of cases, and between 30-39 years in 28.8% of cases. The distributions of cases and controls with respect to marital status, location of residence, economic status, consanguinity, and education level were very similar, with no statistically significant differences.

Table 2 shows the frequencies and percentages for environmental and lifestyle risk factors within the MS cases and controls. It also shows the effect of exposure to various risk factors during adolescence on the development of MS, as determined by univariate analyses. As can be seen in the table, nearly continuous daily exposure to sunlight, relative to limited sunlight exposure, was associated with a significant decrease in the risk of developing MS, while sun exposure during weekend days averaging more than 4 hours daily also decreased the risk of MS, albeit less significantly than continuous daily exposure. The location of daily activities (indoors vs outdoors) was not significantly different between cases and controls, and thus was not associated with the risk of developing MS. Milk consumption more than once per week was found to decrease the risk of developing MS. Likewise, fish consumption more than once per week also decreased the risk of MS. The onset of smoking during adolescence increased the risk of developing MS. Similarly, large body size (for example, obesity), based on a figure rating scale, increased the risk of MS, as did a history of measles infection. Moreover, a family history of MS in a first or second degree relative increased the risk of MS. Other factors, including

**Table 1 -** Socio-demographic characteristics of multiple sclerosis patients and controls (n= 240).

Variables	Cases (n=80)	Controls (n=160)	P-value (Chi-square)
<i>Gender</i>			
Men	28 (35.0)	56 (35.0)	1.000
Women	52 (65.0)	104 (65.0)	
<i>Marital status</i>			
Married	47 (58.8)	101 (63.1)	0.511
Not Married	33 (41.2)	59 (36.9)	
<i>Living area</i>			
Rural	19 (23.8)	33 (20.6)	0.580
Urban	61 (76.2)	127 (79.4)	
<i>Economic Situation</i>			
Poor to moderate	58 (72.5)	130 (81.2)	0.226
Above moderate to less than good	11 (13.8)	18 (11.2)	
Good and above	11 (13.8)	12 (7.5)	
<i>Consanguinity</i>			
Yes	24 (30.0)	46 (28.8)	0.841
No	56 (70.0)	114 (71.2)	
<i>Education level</i>			
Intermediate school or less	9 (11.2)	31 (19.4)	0.280
Secondary school	27 (33.8)	50 (31.2)	
University level or above	44 (55.0)	79 (49.4)	

Values are expressed as number and percentage (%)

physical activity, history of exposure to passive smoking in the home, history of tonsillectomy, history of chicken pox infection, history of hypersensitivity, and a history of vitamin D supplementation during adolescence, showed no statistically significant differences among the cases and controls.

Adjusted ORs for daily sun exposure, weekend sun exposure, milk consumption, fish consumption, history of measles infection, family history of MS, adult smoking, and adult body shape (specifically, obesity) are shown in Table 3. The results following the adjustments showed that sun exposure greater than 4 hours per day during the weekend decreased the risk of MS, as did consumption of fish more than once per week. Adult smoking, adult obesity, and a history of measles infection also increased the risk of MS.

**Discussion.** In this study, 65% of the MS cases were female and 35% were male, and the median age was 32 years. A positive family history of MS in first or second-degree relatives was found in 6.2% of the MS cases. These results are similar to the results reported by a previous study conducted in Saudi Arabia in 2016, in which 71.7% of MS patients were female and 28.3% were male, and 49.1% of the cases were between the ages of 25-35. However, the percentage of

**Table 2 -** Environmental and lifestyle risk factors during adolescent period with univariate crude odds ratio (ORs) and 95% confidence intervals (CIs) for multiple sclerosis (N=240).

Environmental and lifestyle factors	Cases (n=80)	Controls (n=160)	OR	95% CI
<i>Daily sun exposure</i>				
Not that often	18 (22.5)	14 (8.8)	1	Ref
Reasonably often	30 (37.5)	66 (41.2)	0.354	0.156 - 0.804
Quite often	23 (28.8)	41 (25.6)	0.436	0.184 - 1.036
Virtually all the time	9 (11.2)	39 (24.4)	0.179	0.066 - 0.491
<i>Weekend sun exposure</i>				
Never	4 (5.0)	2 (1.2)	1	Ref
1 hour/day	20 (25.0)	28 (17.5)	0.357	0.060 - 2.143
1-2 hours/day	26 (32.5)	61 (38.1)	0.213	0.037 - 1.237
3-4 hours/day	22 (27.5)	23 (14.4)	0.478	0.079 - 2.879
4 hours/day	8 (10.0)	46 (28.8)	0.087	0.014 - 0.556
<i>Daily activities</i>				
Mainly indoor	29 (36.2)	41 (25.6)	1	Ref
Mainly outdoor	23 (28.8)	53 (33.1)	0.614	0.310 - 1.214
Indoors and outdoors	28 (35.0)	66 (41.2)	0.600	0.313 - 1.148
<i>Milk consumption</i>				
Never	13 (16.2)	12 (7.5)	1	Ref
Less than once/month	9 (11.2)	10 (6.2)	0.831	0.252 - 2.743
1-3 times/month	9 (11.2)	6 (3.8)	1.385	0.378 - 5.066
Once/week	19 (23.8)	31 (19.4)	0.566	0.214 - 1.493
More than 1 time/week	30 (37.5)	101 (63.1)	0.274	0.113 - 0.664
<i>Egg consumption</i>				
Never	8 (10.0)	9 (5.6)	1	Ref
Less than once/month	5 (6.2)	5 (3.1)	1.125	0.236 - 5.371
1-3 times/month	7 (8.8)	13 (8.1)	0.606	0.161 - 2.275
Once/week	16 (20.0)	37 (23.1)	0.486	0.159 - 1.489
More than 1 time/week	44 (55.0)	96 (60.0)	0.516	0.186 - 1.426
<i>Meat consumption</i>				
Never	5 (6.2)	15 (9.4)	1	Ref
Less than once/month	7 (8.8)	11 (6.9)	1.909	0.477 - 7.638
1-3 times/month	14 (17.5)	16 (10.0)	2.625	0.759 - 9.076
Once/week	18 (22.5)	41 (25.6)	1.317	0.415 - 4.176
More than 1 time/week	36 (45.0)	77 (48.1)	1.403	0.473 - 4.158
<i>Fish consumption</i>				
Never	12 (15.0)	15 (9.4)	1	Ref
Less than once/month	18 (22.5)	32 (20.0)	0.703	0.271 - 1.825
1-3 times/month	20 (25.0)	31 (19.4)	0.806	0.314 - 2.074
Once/week	24 (30.0)	47 (29.4)	0.638	0.258 - 1.577
More than 1 time/week	6 (7.5)	35 (21.9)	0.214	0.068 - 0.678

Values are expressed as number and percentage (%). \*body silhouettes is from a figure rating scale

patients with a family history of MS was 11.1% in that study.<sup>20</sup> Another study in Qatar found a positive family history in first and second degree relatives in 10.4% of MS patients.<sup>21</sup> In our study, 30% of the MS patients had a history of consanguineous marriages. A study in Kuwait found that 22.5% of MS patient had a history of consanguinity.<sup>14</sup> Evaluation of consanguinity as a risk factor for MS in our study showed no significant difference between cases and controls. Another study conducted in Saudi Arabia by Al Jumah et al found that 16% of MS patients exhibited first degree parental



**Table 2 -** Environmental and lifestyle risk factors during adolescent period with univariate crude odds ratio (ORs) and 95% confidence intervals (CIs) for multiple sclerosis. (MS) (Continued)

Environmental and lifestyle factors	Cases (n=80)	Controls (n=160)	OR	95% CI
<b>Vitamin D supplement</b>				
Yes	3 (3.8)	17 (10.6)	0.328	0.093 - 1.153
No	77 (96.2)	143 (89.4)		
<b>History of tonsillectomy</b>				
Yes	11 (13.8)	25 (15.6)	0.861	0.400 - 1.852
No	69 (86.2)	135 (84.4)		
<b>History of measles</b>				
Yes	16 (20.0)	16 (10.0)	2.250	1.060 - 4.777
No	64 (80.0)	144 (90.0)		
<b>History of chickenpox</b>				
Yes	39 (48.8)	69 (43.1)	1.255	0.732 - 2.150
No	41 (51.2)	91 (56.9)		
<b>Hypersensitivity history</b>				
Yes	25 (31.2)	48 (30.0)	1.061	0.593 - 1.897
No	55 (68.8)	112 (70.0)		
<b>Family history of MS</b>				
Yes	5 (6.2)	1 (0.6)	10.600	1.217 - 92.330
No	75 (93.8)	159 (99.4)		
<b>Smoking</b>				
Yes	19 (23.8)	20 (12.5)	2.180	1.087 - 4.374
No	61 (76.2)	140 (87.5)		
<b>Passive smoking history</b>				
Yes	43 (53.8)	76 (47.5)	1.284	0.750 - 2.200
No	37 (46.2)	84 (52.5)		
<b>Body size</b>				
Body silhouettes* no. 1 (the thinnest)	20 (25.0)	42 (26.2)	1	Ref
Body silhouettes no. 2	16 (20.0)	50 (31.2)	0.672	0.310 - 1.458
Body silhouettes no. 3	13 (16.2)	34 (21.2)	0.803	0.349 - 1.845
Body silhouettes no. 4	8 (10.0)	14 (8.8)	1.200	0.433 - 3.324
Body silhouettes no. 5	9 (11.2)	11 (6.9)	1.718	0.614 - 4.810
Body silhouettes no. 6	8 (10.0)	7 (4.4)	2.400	0.763 - 7.547
Body silhouettes no. 7-9 (obese)	6 (7.5)	2 (1.2)	6.300	1.166 - 34.026
<b>Light physical activity</b>				
Less than one time/week	16 (20.0)	19 (11.9)	0.539	.260-1.116
One time or more/week	64 (80.0)	141 (88.1)		
<b>Vigorous physical activity</b>				
Less than one time/week	40 (50.0)	74 (46.2)	0.860	.503-1.473
One time or more/week	40 (50.0)	86 (53.8)		

Values are presented as number and percentage (%).

\*body silhouettes is from a figure rating scale,

**Table 3 -** Multivariate adjusted odds ratio (OR) and 95% confidence intervals (CIs) for multiple sclerosis (MS).

Variable	Adjusted OR	95% CI
<b>Daily sun exposure</b>		
Not that often	1	Ref
Virtually all the time	.323	.073-1.427
<b>Weekend sun exposure</b>		
Never	1	Ref
>4 hours/day	.063	.006-.654
<b>Milk consumption</b>		
Never	1	Ref
More than 1 time/week	.406	.136-1.212
<b>Fish consumption</b>		
Never	1	Ref
More than 1 time/week	.206	.055-.773
<b>History of measles infection</b>		
No	1	Ref
Yes	3.758	1.455-9.706
<b>Family history of MS</b>		
No	1	Ref
Yes	2.564	.247-26.655
<b>Smoking</b>		
No	1	Ref
Yes	4.165	1.449-11.974
<b>Body size</b>		
Body size	1	Ref
Body silhouette ^ no. 1 (the thinnest)	8.970	1.032-77.983
Body silhouette no.7-9 (obese)		

\*Values are adjusted for daily sun exposure, weekend sun exposure, milk consumption, fish consumption, history of measles infection, family history of MS, adult smoking, and adult body shape. "body silhouette" is from a figure rating scale,

the association was reduced after adjustment.<sup>24</sup> Our study found an insignificant association between socioeconomic status and development of MS, but another multinational EnvIMS-based study concluded that there was a protective effect of low socioeconomic status and MS in Canada; however, the authors recommended further research because the association was inconsistent.<sup>25</sup> Another EnvIMS-based study found a significant association between infrequent outdoor activity and risk of MS. In our study, we found only an insignificant association between the place of daily activity and the development of MS.<sup>26</sup>

Our study revealed that increasing time of exposure to sunlight during the weekend decreased the risk of developing MS, while smoking and adolescent obesity increased the risk. A systematic review published in 2016 found strong evidence of associations between decreased sunlight exposure, low vitamin D, history of smoking, and obesity during adulthood, and the development of MS.<sup>27</sup> Another review by Ascherio and Munge reached to a similar conclusion.<sup>1</sup>

consanguinity, and these individuals were more likely to have familial MS.<sup>22</sup> However, a study in Iran found that those who had a history of parental consanguineous marriage had a lower risk of MS.<sup>23</sup>

Our study found an insignificant association between levels of education and MS development, while another EnvIMS-based study found that higher levels of education decrease the risk of MS, although

Concerning diet, our study found a significant association between fish consumption and a decreased risk of MS development. Another study demonstrated that fish consumption 3 times or more per week decreased the risk of MS (OR=0.55, 95% CI 0.33-0.93).<sup>28</sup> Also, another recent study found that fish consumption in adolescence decreases the risk of MS significantly.<sup>16</sup> This protective effect of fish consumption against MS can be explained by the fact that fatty fish is a source of vitamin D and may compensate for deficiency of it.<sup>29</sup> In our study, there was an insignificant association between vitamin D supplementation during adolescence and development of MS, but another EnvIMS-based study found that self-reported vitamin D supplementation during adolescence decreased the risk of MS development, in comparison to supplementation in childhood, which produced no changes in risk.<sup>30</sup> Another prospective nested case-control study among women concluded that vitamin D deficiency is a risk factor for MS and recommended public health intervention to promote vitamin D levels.<sup>31</sup>

An EnvIMS-based study concluded that vigorous physical activity may decrease the risk of development of MS, but our study found an insignificant association between vigorous physical activity and the development of MS.<sup>32</sup> Another study investigating lifestyle risk factors also found an insignificant association between physical activity and MS.<sup>33</sup> However, a large prospective study using a validated measure of physical activity found weak evidence that higher physical activity may decrease the risk of development of MS.<sup>34</sup> Our study found that a history of measles infection may decrease the risk of MS. Another study found a significant association between measles infection and the development of MS.<sup>35</sup> In a case-control study conducted in 2017 to examine environmental risk factors, a significant association was found between a history of measles or mumps and MS (OR=1.60, 95% CI 1.05-2.45,  $p=0.029$ ).<sup>36</sup> Another study found that a history of infection during childhood (such as measles) increased the risk of MS.<sup>37</sup> The association between MS and measles infection has been studied for a long time, the association postulated as host response to virus infection because virus may cause demyelinating and inflammatory lesions of MS.<sup>38</sup>

A study conducted in Kuwait showed that Bedouin ethnicity and increased daily exposure to sunlight both decreased the risk of MS, while a family history of MS and presence of comorbidities increased the risk of MS. Smoking or wearing usual outdoor clothing were insignificant when comparing all MS participants, but became significant in subgroup comparisons.<sup>14</sup> Thus, we recommend more attention to the implicated risk

factors for development of MS, including reductions in smoking and adulthood obesity, promotion of sun exposure, and fish consumption.

One of the limitations of our study is recall bias, which is an inherent limitation in all case-control studies. Although a longitudinal cohort study design is superior to a case-control study for detecting exposures prior to the onset of disease, it is not feasible to adopt this design for a rare disease such as MS. In this study we used a figure rating scale of standard body images, linked to BMI, to assess obesity in the participants. This is considered a robust technique to classify people as obese or thin; however, body shapes may differ among different ethnicities.<sup>39</sup> Finally, despite the small number of cases, but we attempted to increase the statistical power of the study by increasing the ratio of controls to cases.

In conclusion, the risk of developing MS is significantly increased by exposure to smoking during adolescence, a history of measles infection, and adolescent obesity, but is significantly decreased by increased exposure to sunlight and an increased frequency of weekly fish consumption.

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